

A clinical study to compare efficacy of duloxetine versus escitalopram in patients suffering with depression

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ABSTRACT

Duloxetine (SNRI) and Escitalopram (most selective SSRI) were compared to evaluate the efficacy in mild to moderate depressive disorder. This was a 6-week, double blind, randomized, parallel-group study in collaboration with Departments of pharmacology and psychiatry, E.L.M.C. Lucknow. Patients suffering from depression single episode, recurrent depressive disorder were included for the study. Scoring on Montgomery-Asberg depression rating scale (MADRS) was kept as primary end point. Subjects were randomly assigned into two different groups (Duloxetine 40-60 mg/day and to escitalopram 10-20mg/day). The primary efficacy variable was assessed by the change from baseline at week 6 in MADRS total score. A significantly greater proportion of escitalopram-treated patients completed the 6-week study compared with duloxetine-treated patients. At week 6, duloxetine treatment resulted in lesser improvement, more drop outs as compared to escitalopram treated patients. However the differences were not statistically significant. These findings suggest that Escitalopram is at least as effective as the Duloxetine in the treatment of major depressive disorder with mild to moderate severity.

Key words: Duloxetine, Escitalopram, Depression, Antidepressants

1. INTRODUCTION

Depression is a complex diagnostic construct, applied to individuals with a particular set of symptoms among which the essential ingredients are depressed mood and loss of interest [1, 2]. Across the world, 10.07% of disability can be attributed to unipolar major depression. It contributes to nearly 20% of disease in women aged from 15 to 44 years. W.H.O. expects that by the year 2020, unipolar major depression will be the second leading cause disease burden in the world. Aggregate burden of disability associated with depression of mild severity may be greater than the disability associated with the smaller number of people with the more severe depression [3]. Depressive symptoms are not recognized in around 50% of attending patients and aggregate disability is more in them, so sample was drawn from mild to moderate depressed patients [4].

Antidepressants that act via modifying both serotonergic and noradrenergic neurotransmission SNRIs may have an advantage compared with antidepressants that primarily affect only one of these neurotransmitter systems like SSRIs, particularly in patients with both

depression and physical symptoms. Depressive disorders are also associated with a constellation of physical or somatic symptoms and the link between depression and somatic symptoms which resolve better with SNRIs. Studies have demonstrated significantly greater remission (HAM-D \leq 7) rates with the SNRI venlafaxine as compared with SSRIs [5,6,7]. There is controversy whether the newer, better tolerated, and safer Serotonin norepinephrine reuptake inhibitors are more efficacious than SSRIs. The studies related to comparison of Duloxetine versus selected SSRIs are limited. So in the current study we aim to compare the efficacy and safety of Duloxetine and Escitalopram in mild to moderate depressed patients.

2. MATERIAL AND METHODS

This study was a randomized, comparative and step up dosing design and was carried out in outdoor patients in the department of Psychiatry, Era's Medical College and Hospital, Lucknow after clearance from Institutional Ethical Committee. Systematic Random Sampling was applied and concealment was done by envelop method. Statistician had generated allocation sequence and assigned participants to their

respective groups. Psychiatrist had enrolled participants, administered scales and assessed the clinical outcomes. Side effect monitoring was done by a pharmacologist and a psychiatrist. The patients were included in the study after fulfilling the inclusion/ exclusion criteria and only after obtaining full informed consent as diagnosed in psychiatry OPD of Era's Medical College. All subjects gave informed consent for the study. The patients diagnosed to be suffering from depression as per diagnostic criteria of ICD-10 were randomly allocated to either Duloxetine or Escitalopram group. The sample size consisted of 30 patients for each mild to moderate depressed patients which were drawn from OPD, Department of Psychiatry, Era's Medical College and Hospital, Lucknow. A sample group was taken up for the study. Subjects above 18 years of age of either gender, diagnosed to be suffering from depression (Δ F 32.0 or Δ F 32.1 as per ICD -10) (International classification of Diseases) with or without somatic symptoms or recurrent depressive disorder (Δ F 33.0 or Δ F 33.1 as per ICD -10) with or without somatic symptoms, duration of current depressive episode is to be between 4 weeks to 12 months, and scoring >6 and ≤ 34 on MADRS (Montgomery Asberg Depression Rating Scale), CGI-S >3 and <5 (Clinical global impression-severity) the initial visit were enrolled in the study. Patients having Axis I or Axis II disorder other than depressive disorder, scoring > 4 on MARDS items number 10 (suicidal thoughts) at screening or baseline, history of non response to an adequate (6 week) trial of three or more antidepressant (with or without mood stabilizers) during the current episode, with imminent risk of suicide or injury to self, others, or property, pregnant, lactating women or women not using medically accepted method of contraception were excluded. Besides patients with current clinically significant neurological, metabolic (including type1 diabetes), hepatic, renal hematological, pulmonary, cardiovascular, gastrointestinal, and / or urological disorder such, as unstable angina, congestive heart failure (uncontrolled), or central nervous system (CNS) infection that would pose a risk to the subject if they were to participate in the study or that might confound the results of the study, subjects with human immunodeficiency virus (HIV) seropositivity (or history of seropositivity), history of malignancy, or any chronic incapacitating illness were excluded. Besides subjects with history of substance abuse excluding tobacco use were excluded. Patients satisfying the selection criteria and eligible were provided with informed consent form and those who were desirous were enrolled in the study. A detailed baseline assessment was done as per the semi structured

proforma which included psychiatric and medical history, physical examination and detailed mental status assessment. Baseline investigations (Hb, TLC, DLC, ESR, Blood Sugar, Liver Function Tests & Blood Urea) were carried out. Dosage Schedule was random allocation of Duloxetine 60mg (Group A) and Escitalopram 20mg (Group B) belonging to study population were done. Dosage was one capsule twice daily (20mg of Duloxetine for first 2 weeks and 30mg of Duloxetine for next 4 weeks) and Escitalopram 10mg in the morning for first two weeks and 20mg for next four weeks and 1 capsule in the evening which was placebo. However the investigator would not know the type of capsule being given to the patient due to double blind nature of the study. Patients were evaluated every second week as per schedule mentioned earlier. Concomitant medication like Lorazepam 2 mg were given as and when required (only night time), records of which were maintained. The addition of Lorazepam, in the depressive symptom study was considered for the final analysis. Instruments used were

- Semistructured proforma for socio demographic details.
- Details of psychiatric history and examination
- Montgomery Asberg Depression Rating Scale (MADRS) [8]
- Clinical Global Impression (CGI) [9]

At every visit depressive symptoms were measured by using Montgomery-Asberg Depression Rating Scale (MADRS). At initial visit severity of symptoms were assessed by CGI-S. At visits space between every two weeks Clinical global impression – improvement (CGI-I) were given to the subjects. Adverse effects were also either recorded by the patient, reported by the patient, observed by the therapist or either elicited by the therapist on each visit. Drug naive patients were taken in the study. If the patients were on any medication, then they were kept drug free for a period of at least 15 days for complete elimination of the drug from the body prior to randomization. Treatment with prior psychotropic medications (e.g., antipsychotic agents, antidepressants and mood stabilizers) were discontinued as tolerated and clinically appropriate at least 15 days prior to randomization. Prior to the study the power of the study estimated was about 90% but during the execution of the study the power came out be (Calculated using G*Power software) 92.9%.

3. RESULTS

Table.1 summarizes the events from the point of screening to randomization of patients. Sociodemographic variables of the subjects

enrolled in the study are presented in table 2. Different clinical variables considered in the study are presented in table.3. Mean change in MADRS score from baseline in two groups are present in table.4. Change in CGI Score from baseline among the patients are presented in table.5.

Table .1 Table summarizing the events from the point of screening to randomization of patients

| | |
|--|-----|
| TOTAL NO. OF PATIENTS WITH TENTATIVE DIAGNOSIS OF DEPRESSION SCREENED IN O.P.D | 175 |
| NO. OF PATIENTS EXCLUDED | 103 |
| REASONS FOR EXCLUSION | |
| I. Not fulfilling the diagnostic criteria | 80 |
| II. Unwilling to give informed consent | 03 |
| III. Unwilling to come for Scheduled follow up visits | 04 |
| IV. Unwilling to accept oral drugs | 02 |
| V. Already taken antidepressant for the current episode | 12 |
| VI. Did not report to collect the drugs after screening | 02 |
| NO. OF PATIENTS INCLUDED IN THE STUDY | 72 |
| TOTAL NO. OF DROP OUT PATIENTS | 12 |
| A In Duloxetine group | |
| I. Did not report on the scheduled day/absent | 0 |
| II. Refused to Continue in the study due to any cause(side effect,poor compliance,etc | 07 |
| II. Did not report on assigned visit or follow the systems of medication | 02 |
| B. In Escitalopram Group | |
| I. Did not report on the Scheduled scheduled day/absent | 00 |
| II. Refused to continue in the study due to any cause(side effect,poor compliance,etc | 02 |
| III. Did notreport on the assigned visit or follow the system of medication | 01 |
| NO. OF PATIENTS WHO COMPLETED THE TRIAL | 60 |
| Duloxetine group | 30 |
| In Escitalopram Group | 30 |

Regarding socio demographic variables like age ,sex, marital status ,distribution as per religion, and income distribution, education and occupation both Duloxetine and Escitalopram groups had no significant difference in the age, sex marital status, religion of the two groups ,education and occupation i.e. both the populations were similar in nature.

Pertaining to clinical variables like duration of illness, type of onset, episodicity and family history of similar illness statistical analysis revealed there was no significant different in duration, onset, episode & family history between the two groups Changes in mean in MADRS scores in the Duloxetine group biweekly from the base line revealed significant reductions in MADRS score at end of 2 ,4 and 6 weeks (p=0.000). Similarly mean reduction in MADRS scores in the Escitalopram group from base line i.e. Also had significant reduction of MADRS score at the end of 2, 4 and 6 weeks (p=0.000).When comparison was drawn between the two groups with consideration of MADRS scores, Escitalopram group had slightly more reduction of MADRS scores than Duloxetine group however not clinically significant. (p=0.421).

Overall there was more reduction in CGI scores in Escitalopram group as compared to Duloxetine group at the end of 4 and 6 weeks however it was not statistically significant (p=0.07).

4. DISCUSSION

Earlier studies which compared SSRI and SNRIs confers greater efficacy of SNRIs than inhibition of serotonin re-uptake alone. [10,11,12,13] .Controlled clinical trials of escitalopram in depressed outpatients have established its efficacy in depression. escitalopram has evidence of efficacy in a primary care study[14]. Selective serotonin reuptake inhibitors (SSRIs) have broadly replaced the older tricyclic antidepressant-type drugs as the first-line treatment for depression. Escitalopram is the most selective antidepressant[15]. Significantly greater proportion of escitalopram-treated patients completed the 8-week study compared with duloxetine-treated patients[16]. MADRS total scores with Escitalopram had significantly greater improvement compared with duloxetine with significantly fewer escitalopram-treated patients discontinued because of adverse events compared with duloxetine (2% vs 13%, respectively; p < 0.01).

Pigott et al.,(2007) concluded that both drugs demonstrated similar remission rates over the course of the study, however the entire 8-month study, discontinuation rates differed significantly for duloxetine (62%) compared with escitalopram (55%; p = 0.02). [17]

Nierenberg et al.,(2007) concluded that there is no differences between duloxetine, escitalopram, and placebo rates of remission or response at 8 weeks. Adverse events that occurred significantly

Table -2: depicts the sociodemographic variables of the 60 subjects enrolled in the study

| VARIABLES | DULOXETINE GROUP (n=30) | | ESCITALOPRAM GROUP (N=30) | | X ² | d.f.,p |
|---|----------------------------|------|------------------------------|------|----------------|--------|
| | N | % | N | % | | |
| <u>AGE(in yrs)</u> | | | | | | |
| Upto 30 | 3 | 10.0 | 1 | 3.3 | 0.02 | 1,0.89 |
| 31-45 | 27 | 90.0 | 29 | 96.7 | | |
| <u>SEX</u> | | | | | | |
| Male | 12 | 40.0 | 15 | 50.0 | 0.61 | 1,0.43 |
| Female | 18 | 60.0 | 15 | 50.0 | | |
| <u>MARITAL STATUS</u> | | | | | | |
| MARRIED | 28 | 93.3 | 28 | 93.3 | 0.00 | 1,1.00 |
| SINGLE | 2 | 6.7 | 2 | 6.7 | | |
| <u>RELEGIION</u> | | | | | | |
| HINDU | 25 | 83.3 | 23 | 76.7 | 0.42 | 1,0.52 |
| MUSLIM | 05 | 16.7 | 07 | 23.3 | | |
| OTHERS | 00 | | 00 | | | |
| <u>INCOME GROUP (in Rs./month)</u> | | | | | | |
| > 5000 | 6 | 20.0 | 3 | 10.0 | 2.74 | 2,0.25 |
| 5000-7499/- | 14 | 46.7 | 11 | 36.7 | | |
| 7500 and above | 10 | 33.3 | 16 | 53.3 | | |
| <u>EDUCATION</u> | | | | | | |
| Primary - | 8 | 26.7 | 6 | 20.0 | 0.47 | 2,0.79 |
| Secondary - | 12 | 40.0 | 12 | 40.0 | | |
| Higher Secondary/PUC | 10 | 33.3 | 12 | 40.0 | | |
| <u>OCCUPATION</u> | | | | | | |
| Housewives - Farmers/Manual labourers /Skilled labourers - Clerical - | 16 | 53.3 | 14 | 46.7 | 0.29 | 2,0.86 |
| | 10 | 33.3 | 11 | 36.6 | | |
| | 04 | 13.3 | 05 | 16.7 | | |

Table -3: shows different clinical variables considered in the study

| VARIABLES | DULOXETINE GROUP (N=30) | | ESCITALOPRAM GROUP (N=30) | | X ² | d.f.,p |
|--|-------------------------|------|---------------------------|------|----------------|--------|
| | N | % | N | % | | |
| <u>DURATION</u> | | | | | | |
| <1 Months | 08 | 26.7 | 06 | 20.0 | 0.39 | 2,0.82 |
| 1-6 Months | 16 | 53.3 | 17 | 56.7 | | |
| > 6 Months | 06 | 20.0 | 07 | 23.3 | | |
| <u>ONSET</u> | | | | | | |
| INSIDIOUS | 14 | 46.7 | 13 | 43.3 | 0.07 | 1,0.79 |
| ACUTE EPISODE | 16 | 53.3 | 17 | 56.7 | | |
| <u>1ST</u> | | | | | | |
| | 24 | 80.0 | 23 | 76.7 | 0.10 | 1,0.75 |
| <u>>1</u> | | | | | | |
| | 06 | 20.0 | 07 | 23.3 | | |
| <u>FAMILY HISTORY OF SIMILAR ILLNESS PRESENT</u> | | | | | | |
| | 06 | 20.0 | 08 | 26.7 | 0.37 | 1,0.54 |
| <u>ABSENT</u> | | | | | | |
| | 24 | 80.0 | 22 | 73.3 | | |

Table - 4: Mean change in MADRS score from baseline in two groups

| Change from baseline | Duloxetine (n = 30) | | Escitalopram (n = 30) | | Significance | | |
|----------------------|---------------------|------|-----------------------|-------|--------------|------|-------|
| | Mean | SD | Mean | SD | 't' | d.f. | p |
| After 2 weeks | 4.93 | 2.15 | 5.30 | 15.79 | 0.76 | 58 | 0.450 |
| After 4 weeks | 8.90 | 4.03 | 9.83 | 2.95 | 1.02 | 58 | 0.312 |
| After 6 weeks | 13.36 | 6.20 | 14.50 | 4.52 | 0.81 | 58 | 0.421 |

Significant at p< 0.05 (d.f = 58), hence above stated values are not significant

Table - 5: Change in CGI Score from Baseline

| Change from baseline | Duloxetine (n = 30) | | | Escitalopram (n = 30) | | | Significance |
|----------------------|---------------------|----------|----------|-----------------------|----------|----------|---|
| | Same | Decrease | Increase | Same | Decrease | Increase | |
| After 2 weeks | N 12 | 16 | 2 | N 12 | 16 | 2 | X ² = 0.00 d.f.=1 p=1.00 |
| | % 40.0 | 53.3 | 6.7 | % 40.0 | 53.3 | 6.7 | |
| After 4 weeks | N 7 | 21 | 2 | N 5 | 24 | 1 | X ² =0.52 d.f.=1 p=0.4 |
| | % 23.3 | 70.0 | 6.7 | % 16.7 | 80.0 | 3.3 | |
| After 6 weeks | N 7 | 23 | - | N 2 | 28 | - | X ² =3.22 d.f.=1 p=0.07 |
| | % 23.3 | 76.7 | - | % 6.7 | 93.3 | - | |

Significant at p< 0.05 (d.f = 1), hence above stated values are not significant

more frequently among duloxetine-treated patients when compared with those receiving escitalopram were nausea, dry mouth, vomiting, yawning, and irritability. The rate of discontinuation due to adverse events did not differ significantly between treatment groups. Lack of placebo arm, however, earlier studies have concluded that Escitalopram and Duloxetine have higher efficacy than placebo.^[18]

Present study did not compare the long term efficacy of Duloxetine and Escitalopram. Finally, the study population is typical of the patient population recruited for the outpatient clinical studies in MDD, and the result may not generalize to the patients with MDD in an outpatient clinical practice who have co morbid medical or psychiatric condition that would have excluded them from participation in this study that is generalizability of the results to real world clinical practice can be a potential concern because of exclusion criteria as it was randomized control trial. Future studies that compare dual action antidepressants with SSRIs should probably start at the best tolerated initial dose and increase to maximally tolerated safe and effective dose should be undertaken. Concluding, both the drugs showed significantly greater improvement on the primary efficacy measure. There were more drop outs in the duloxetine group as compared to escitalopram group.

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