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# COMPARATIVE STUDY OF SAFETY AND EFFICACY OF DESVENLAFLEXINE VERSUS SERTRALINE : A RANDOMISED CONTROL TRIAL

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## ABSTRACT

Desvenlaflexine (SNRI) and Sertraline (SSRI) were compared to evaluate the safety in mild to moderate depressive disorder. A 6 Inter departmental work between psychiatry and pharmaology was carried out in, ajkiya Medical College Ambedkarnagar (U.P) and N.SCB Medical College Jabalpur,(M.P) (n= 60 patients) on patients suffering from depression single episode (▲ F 32.0 or ▲F 32.1 A/T ICD X), recurrent depressive disorder (▲ F 33.0 or ▲F 33.1 A/T ICD X) was conducted. Scoring on MADRS was kept as primary end point. Subjects were randomly assigned (1:1) into two different groups (Desvenlaflexine 50-100 mg/day (flexibly dosed) and to sertraline 50-1000mg/day) i.e. Group A and Group B with the step-up dosing pattern. Change in score of MADRS was main determinant of the study during its tenure and a greater proportion of sertraline-treated patients completed the 6-week study compared with desvenlaflexine - treated patients. At week 6, Desvenlaflexine treatment resulted in slightly lesser improvement, more drop outs, and more adverse effects compared with sertraline, however the differences were not clinically significant. These findings suggest that SSRI, Sertraliune is better tolerated and at least as effective as the SNRI, Desvenlaflexine in the treatment of major depressive disorder with mild to moderate severity.

**KEYWORDS: Desvenlaflexine, Sertraline, Depression, Antidepressants**

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# 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 44years. 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≤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 Desvenlaflexine versus selected SSRIs are limited. So in the current study we aim to compare the efficacy and safety of Desvenlafaxine and Sertraline in mild to moderate depressed patients.

# MATERIALS 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, Rajkiya Medical College Ambedkarnagar after clearance from Institutional Ethical Committee. This study was done as joint collaboration between Pharmacology departments of Rajkiya Medical College Ambedkarnagar and Netaji Subhash Chandra Bose medical college Jabalpur. 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 Rajkiya Medical College Ambedkarnagar . 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 Desvenlafaxine or Sertraline group. The sample size consisted of 30 patients for each mild to moderate depressed patients which were drawn from OPD, Department of Psychiatry Rajkiya Medical College Ambedkarnagar. A sample group was taken up for the study. Subjects above 18 years of age of either gender, diagnosed to be suffering from depression (▲ F 32.0 or ▲F 32.1 as per ICD -10)(International classification of Diseases) with or without somatic symptoms or recurrent depressive disorder (▲ F 33.0 or ▲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(Clinical global impression )>3 and <5 on 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 centre 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 incapicitaing 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 and Blood Urea) were carried out. Dosage Schedule was random allocation of Desvenlafaxine 100mg (Group A) and Sertraline 100mg (Group B) belonging to study population were done.Dosage was one capsule twice daily (50mg of Desvenlafaxine for first 2 weeks and 100mg of Desvenlafaxine for next 4 weeks) and Sertraline 50mg in the morning for first two weeks and 100mg 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

- Semistuctured proforma for socio demographic details.
- Details of psychiatric history and examination
- Montgomery As berg Depression Rating Scale (MADRS)[8]
- Clinical global impression (CGI-I)[9]
- Dosage Record Treatment Emergent Symptom Scale (DOTES)[10]

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%.

## 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. Side effects assessed by DOTES are presented in table-6. Side effect either reported by the patient, observed by the clinician or elicited by the therapist are presented in table -7.

**Table 1**

***Summarizing the events from the point of screening to randomization of patients***

| | | |
|---|---|---|
| 1 | TOTAL NO. OF PATIENTS WITH TENTATIVE DIAGNOSIS OF DEPRESSION SCREENED IN O.P.D | 185 |
| 2 | NO. OF PATIENTS EXCLUDED<br>REASONS FOR EXCLUSION | 113 |
| I | Not fulfilling the diagnostic criteria | 85 |
| II | Unwilling to give informed consent | 08 |
| 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 |
| 3 | NO. OF PATIENTS INCLUDED IN THE STUDY | 72 |
| 4 | TOTAL NO. OF DROP OUT PATIENTS DURING STUDY | 12 |
| A | In Desvenlafaxine group | 09 |
| VII | Did not report on the scheduled day/absent | 00 |
| VIII | Refused to Continue in the study due to any cause(side effect,poor compliance,etc | 07 |
| IX | Did not report on assigned visit or follow the systems of medication | 02 |
| B | In SERTRALINEGroup | 03 |
| 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 |
| 5 | NO. OF PATIENTS WHO COMPLETED THE TRIAL | 60 |
| a | Desvenlafaxine group | 30 |
| b | In Sertraline Group | 30 |

**Table 2**

***Depicts the sociodemographic variables of the 60 subjects enrolled in the study***

| VARIABLES | DESVENLAFAXINE GROUP (n=30) | | SERTRALINE GROUP (N=30) | | $X^2$ | d.f.,p |
|---|---|---|---|---|---|---|
| | N | % | N | % | | |
| **AGE (in yrs)** | | | | | | |
| Upto 30 | 3 | 10.0 | 1 | 3.3 | 0.02 | 1,0.89 |
| 31-45 | 27 | 90.0 | 29 | 96.7 | | |
| **SEX** | | | | | | |
| Male | 12 | 40.0 | 15 | 50.0 | 0.61 | 1,0.43 |
| Female | 18 | 60.0 | 15 | 50.0 | | |
| **MARITAL STATUS** | | | | | | |
| Married | 28 | 93.3 | 28 | 93.3 | 0.00 | 1,1.00 |
| Single | 2 | 6.7 | 2 | 6.7 | | |
| **RELEGION** | | | | | | |
| Hindu | 25 | 83.3 | 23 | 76.7 | 0.42 | 1,0.52 |
| Muslim | 05 | 16.7 | 07 | 23.3 | | |
| Others | 00 | | 00 | | | |
| **INCOME GROUP (in Rs. /month)** | | | | | | |
| > 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 | 53.5 | | |
| **EDUCATION** | | | | | | |
| 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 | | |
| **OCCUPATION** | | | | | | |
| Housewives | 16 | 53.3 | 14 | 46.7 | 0.29 | 2,0.86 |
| Farmers/Manual labourers /Skilled labourers | 10 | 33.3 | 11 | 36.6 | | |
| Clerical | 04 | 13.3 | 05 | 16.7 | | |

Regarding socio demographic variables like age, sex, marital status ,distribution as per religion, and income distribution, education and occupation both Desvenlafaxine and Sertralline 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.

**Table 3**
***Shows different clinical variables considered in the study***

| VARIABLES | DESVENLAFAXINE GROUP (N=30) | | SERTRALINE GROUP (N=30) | | $X^2$ | d.f.,p |
|---|---|---|---|---|---|---|
| | N | % | N | % | | |
| **DURATION** | | | | | | |
| <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 | | |
| **ONSET** | | | | | | |
| Insidious | 14 | 46.7 | 13 | 43.3 | 0.07 | 1,0.79 |
| Acute | 16 | 53.3 | 17 | 56.7 | | |
| **EPISODE** | | | | | | |
| $1^{ST}$ | 24 | 0.0 | 23 | 76.7 | 0.10 | 1,0.75 |
| >1 | 06 | 0.0 | 07 | 23.3 | | |
| **FAMILY HISTORY OF SIMILAR ILLNESS** | | | | | | |
| Present | 06 | 20.0 | 08 | 26.7 | 0.37 | 1,0.54 |
| Absent | 24 | 80.0 | 22 | 73.3 | | |

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 and family history between the two groups.

**Table 4**
***Mean change in MADRS score from baseline in two groups***

| Change from baseline | DESVENLAFAXINE (n = 30) | | SERTRALINE (n = 30) | | Significance 't' d.f. p |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| 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.***

Changes in mean in MADRS scores in the Desvenlafaxine 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 Sertraline 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 Desvenlafaxine group however not clinically significant. (p=0.421).

**Table 5**
***Change in CGI Score from Baseline***

| Change from baseline | Desvenlafaxine (n = 30) | | | Sertraline (n = 30) | | | |
|---|---|---|---|---|---|---|---|
| | Same | Decrease | Increase | Same | Decrease | Increase | |
| N<br>After2weeks<br>% | 12<br><br>40.0 | 16<br><br>53.3 | 2<br><br>6.7 | 12<br><br>40.0 | 16<br><br>53.3 | 2<br><br>6.7 | $X^2$= 0.00<br>d.f.=1<br>p=1.00 |
| N<br>After4weeks<br>% | 7<br><br>23.3 | 21<br><br>70.0 | 2<br><br>6.7 | 5<br><br>16.7 | 24<br><br>80.0 | 1<br><br>3.3 | $X^2$=0.52<br>d.f.=1<br>p=0.4 |
| N<br>After6weeks<br>% | 7<br><br>23.3 | 23<br><br>76.7 | --<br><br>-- | 2<br><br>6.7 | 28<br><br>93.3 | --<br><br>-- | $X^2$=3.22<br>d.f.=1<br>p=0.07 |

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

Overall there was more reduction in CGI scores in Sertraline group as compared to Desvenlafaxine group at the end of 4 and 6 weeks however it was not statistically significant (p=0.07). Patient discontinued more in desvenlafaxine group as compared to escitalopram group.Pertaining to Central Nervous System side effects Insomnia, headache was more in desvenlafaxine group. Somnolence,, tremors, lethargy, dream abnormality and yawning, orgasmic abnormality , ejaculation disorder was more in sertraline group. Pertaining to G.I.T and autonomic. Symptoms; Constipation, increased sweating ,nausea, hot flushes , weight gain , decreased appetite, hot flushes , increased salivation , vomiting , blurred vision, palpitation were more increased in desvenlafaxine group. Sertraline is having a better tolerated drug as compared to desvenlafaxine. In the present study on initial dosage of study medication less side effect were reported but on increasing dosage more subjects in desvenlavaxine group. (73.3% vs 63.3%) had side effects however didn't reach point of clinical significance. Concomitant medication-Lorazepam 2 m.g. was required in 04 patients in Sertraline group and in 06 patients in Desvenlafaxine group as insomnia was more in duloxetine group.

**Table 6**
***Side effects assessed by DOTES***

| | **Desvenlafaxine(N=30)** | | | | **Sertraline(N=30)** | | | |
|---|---|---|---|---|---|---|---|---|
| | **DAY** | | | | **DAY** | | | |
| | 0 | 14 | 28 | 42 | 0 | 14 | 28 | 42 |
| **a. BEHAVIOURAL TOXICITY** | | | | | | | | |
| 1. Toxic confessional state | - | - | - | - | - | - | - | - |
| 2. Excitement/ Agitation | - | - | - | - | - | - | - | - |
| 3. Increased Motor activity | - | - | - | - | - | - | - | - |
| 4. Decreased Motor activity | - | - | - | - | - | - | - | - |
| 5. Insomnia | - | 1 | 2 | 6 | - | 1 | 2 | 4 |
| 6. Drowsiness | - | - | - | - | - | - | - | - |
| 1. Abnormal Urine Test | - | - | - | - | - | - | - | - |
| **b. NUROLOGICAL** | | | | | | | | |
| 1. Rigidity | - | - | - | - | - | - | - | - |
| 2. Tremors | - | 1 | 1 | 1 | - | - | - | - |
| 3. Dystonic symptoms | - | - | - | - | - | - | - | - |
| 4. Akathisia | - | - | - | - | - | - | - | - |
| **c. AUTONOMIC and GIT** | | | | | | | | |
| 1. Dry mouth | - | 1 | 1 | 1 | - | 1 | 1 | 1 |
| 2. Nasal Congestion | - | 1 | 1 | 2 | - | - | - | - |
| 3. Blurred vision | - | - | 1 | 2 | - | - | - | - |
| 4. Constipation | - | 1 | 2 | 3 | - | - | 1 | 1 |
| 5. Increased Salivation | - | - | - | - | - | 1 | 1 | 2 |
| 6. Sweating increased | - | - | 1 | 2 | - | - | - | - |
| 7. Nausea | - | 2 | 4 | 4 | - | 2 | 3 | 2 |
| 8. Diarrhoea | - | 1 | 2 | 1 | - | 1 | 2 | 1 |
| **d. OTHERS** | | | | | | | | |
| 1. Dermatologic | | | | | | | | |
| 2. Weight gain | - | - | 1 | 1 | - | - | - | - |
| 3. Weight loss | - | - | - | - | - | - | - | - |
| 4. Anorexia/decreased appetite | - | - | 1 | 1 | - | - | - | - |
| 5. Tardive dskinesia | - | - | - | - | - | - | - | - |

**Table 7**
***Side effect either reported by the patient, observed by the clinician or elicited by the therapist***

| Side Effects observed | Desvenlafaxine (N=30) | | | | Sertraline (N= 30) | | | |
|---|---|---|---|---|---|---|---|---|
| | DAY | | | | DAY | | | |
| | 0 | 14 | 28 | 42 | 0 | 14 | 28 | 42 |
| 1. Flatulence | - | - | - | - | - | 1 | 1 | 1 |
| 2. Paresthesia | - | - | 1 | 2 | - | - | - | - |
| 3. Somnolence | - | - | - | - | - | 1 | 1 | 2 |
| 4. Decreased libido | - | - | 1 | 1 | - | - | 1 | 1 |
| 5. Anxiety | - | - | - | - | - | - | 1 | 1 |
| 6. Orgasmic Abnormality | - | 1 | 1 | 1 | - | 1 | 2 | 3 |
| 7. Lethargy | - | - | - | - | - | 1 | 1 | 1 |
| 8. Dream Abnormality | - | - | - | - | - | 1 | 1 | 1 |
| 9. Yawning | - | - | - | - | - | 1 | 1 | 1 |
| 1. Vomiting | - | - | 1 | 1 | - | - | 1 | 3 |
| 2. Palpitation | - | - | - | - | - | 1 | 1 | 1 |
| 3. Hot Flushes | - | - | 1 | 1 | - | - | - | - |
| 4. Mucosal dryness | - | - | - | - | - | - | - | - |
| 5. Indigestion | - | - | 1 | 1 | - | - | 1 | 1 |
| 6. Abdominal Pain | - | - | 1 | 1 | - | - | 1 | 1 |
| 7. Influnza like symptoms | - | - | - | - | - | 1 | 1 | 2 |
| 8. Hypertension | - | - | - | - | - | - | - | - |
| 9. Fatigue | - | 1 | 1 | 2 | - | - | 1 | 2 |
| 10. Ejaculation Disorder | - | 1 | 1 | 2 | - | 1 | 2 | 3 |
| 11. Impotence | - | - | 1 | 1 | - | - | 1 | 1 |
| 12. Anorgasmia | - | - | 1 | 1 | - | 1 | 1 | 1 |
| 13. Rhinitis | - | - | 1 | 1 | - | - | 2 | 2 |
| 14. Snusitisi | - | - | - | - | - | - | 1 | 1 |
| 15. Dizziness | - | 1 | 2 | 3 | - | - | 1 | 2 |
| 16. Decreased appetite | - | - | 1 | 1 | - | - | 1 | 1 |
| 25.Headache | - | 3 | 5 | 8 | - | 1 | 2 | - |

***Note: Number in the table indicates the number of patients complaining of side effects***

# DISCUSSION

Studies comparing SSRI and SNRIs conclude dual re-uptake inhibition confers greater efficacy than inhibition of serotonin re-uptake alone[11,12,13,14]. Studies have demonstrated that desvenlafaxine is a significantly more potent norepinephrine reuptake inhibitor than venlafaxine. Controlled clinical trials of escitalopram in depressed outpatients have established its efficacy in depression significantly, desvenlafaxine has evidence of efficacy in a primary care study[15,16] . Selective serotonin reuptake inhibitors (SSRIs) have broadly replaced the older tricyclic antidepressant-type drugs as the first-line treatment for depression.. They combine good efficacy with their key advantage, a favourable adverse event profile This study did not compare the long term efficacy or safety of Desvenlafaxine and Sertraline . 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 showed significantly greater improvement on the primary efficacy measure.Sleep subscale of the MADRS which deteriorated with desvenlafaxine. There were more drop outs in the desvenlafaxine group as compared to escitalopram group.Sertraline is better tolerated and at least as effective as the serotonin-norepinephrine reuptake inhibitor desvenlafaxine in the treatment of major depressive disorder.

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