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Original Research Article

A Comparative Study of Efficacy and Safety of Conventional Versus Newer Antidepressants in Patients with Depressive Episode in A Tertiary Care Hospital

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Abstract

Background: Depression is a clinical syndrome that is characterised by a cluster of emotional, behavioural, and cognitive features. Depression also poses a significant economic burden to society as it leads to reduced productivity, treatment costs and loss of human life by suicide.

Aims and Objectives: To compare the efficacy and safety of newer antidepressants like Escitalopram and Desvenlafaxine versus conventional antidepressant like Imipramine in patients with Depressive episode.

Material and Methods: An open label, prospective, comparative study was conducted in the Department of Pharmacology, Sri Krishna Medical College (SKMC), Muzaffarpur, Bihar associated with psychiatry outpatient department (OPD), Sri Krishna Medical College and Hospital (SKMCH), Muzaffarpur, Bihar during last 3 months.

Results: 72 newly diagnosed patients of depressive episode according to ICD-10 criteria were divided into three groups of 24 each receiving Imipramine (Group A), Escitalopram (Group B) and Desvenlafaxine (Group C) and followed up for 6 weeks. Efficacy measurement was reduction in MADRS, CGI-S and CGI-I scores. Safety assessment was by number, severity and dropouts due to adverse drug reactions and laboratory investigations. Data was analyzed using ANOVA and Chi square test. Response rate was 51% in Group B, 43% in Group A and 40% in Group C, but this difference was not statistically significant. Initial response was seen as early as 2 weeks in 51% in group B and 40% in group C but none in group A and showed statistical significance. No statistically significant difference was seen in CGI-S and CGI-I scores at the end of 6 weeks.

Conclusion: Newer antidepressants like escitalopram and desvenlafaxine were equally efficacious in treating moderate to severe depressive episode compared to conventional drugs like imipramine however they had an advantage of faster onset of action, better safety and tolerability.

Keywords: Antidepressants, Imipramine, Escitalopam, Desvenlafaxine.

Introduction

Depression is a clinical syndrome that is characterised by a cluster of emotional, behavioural, and cognitive features.

Depression also poses a significant economic burden to society as it leads to reduced productivity, treatment costs and loss of human life by suicide[1]. According to WHO, depression is estimated to affect 350 million people and is the third leading cause for disease burden, with 65.5 million Disability Adjusted Life Years (DALY)[2,3]. India figures among the top ten depressed countries and has fifth highest DALY rates due to depression[4].

Psychotherapy and antidepressants form the mainstay of treatment in depression. Tricyclic antidepressants (TCA) have been the gold standard treatment for years but their major drawback was the high incidence of adverse effects, due to blockade of multiple receptors[5]. Selective serotonin reuptake inhibitors (SSRI) were introduced in 1970s to overcome this drawback[6].Though they had the advantage of higher receptor selectivity, superior tolerability and greater safety in overdose they caused a constellation of side effects like nausea, diarrhea, insomnia, agitation, anxiety, headache and sexual dysfunction. Escitalopram being the newest SSRI is claimed to have better tolerability than the older SSRIs.

Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) like Desvenlafaxine, are novel dual acting antidepressants which ensures enhanced efficacy, and lack of affinity to other receptors and offers better tolerability profile.

Despite the availability of various classes of antidepressants, patient response is not satisfactory, upto 40% fail to show a response to first-line antidepressant, 50% discontinue treatment owing to side effects or insufficient response, and more than 50% fail to achieve remission, even if they initially respond. Moreover, antidepressant drugs tend to lose efficacy over the course of treatment. Lack of comparative studies of such newer drugs with the conventional TCAs and paucity of data in Indian scenario has prompted us to take up this study.

Material and Methods (Experimental Section)

This was a randomized, open label, prospective**,** comparative study conducted in the Department of Pharmacology, Sri Krishna Medical College, associated with psychiatry outpatient department (OPD), SKMCH, Muzaffarpur, Bihar. The study aimed at comparing the efficacy and safety of newer antidepressants like Escitalopram and Desvenlafaxine versus conventional antidepressant like Imipramine in patients with Depressive episode. Clearance from the institution ethics committee of SKMCH was obtained before starting the study. Study duration was one year and six months (November 2018 to May 2020). Ninety patients of either sex aged between 18-65years, who were newly diagnosed with depressive episode according to ICD-10 (International Classification Of Diseases-10, WHO 2007) were included in the study, after obtaining written informed consent[7].Patients with >/= 24 on MADRS (Montgomery Asberg Depression Rating Scale) score were included in the study. MADRS is a ten-item diagnostic questionnaire used to measure the severity of depressive episodes in patients with mood disorders. The questionnaire includes questions on apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts. Each item on this scale yields a score of 0 to 6.

The overall score ranges from 0 to 60, with the usual cut-off points as 0 to 6 – normal, 7 to 19 – mild depression, 20 to 34 – moderate depression, >34 – severe depression[8].

Patients being treated with more than one antidepressant, those with Psychotic depression, Bipolar disorder,

Schizophrenia or Anxiety disorders, current suicidal ideation, serious decompensated medical conditions like Congestive cardiac failure, Renal failure, Hepatic failure, acute gastrointestinal bleeding or on aspirin prophylaxis, ischaemic heart disease, cardiac conduction defects, ECG abnormalities and abnormal liver enzymes, presence of alcohol and substance dependence, epilepsy, mental retardation, mental disorders other than depression, pregnant and lactating women were excluded from the study.

Detailed history recording, thorough clinical examination by a psychiatrist and laboratory investigations were conducted to all patients at the beginning of the study. Study subjects were randomly assigned into 3 groups of 30 patients each using table of random numbers. Group 1 received Imipramine 75-225mg/day orally OD**,** group 2 received Escitalopram 10-20mg/day orally OD and group 3 received Desvenlafaxine 50-100mg/day orally OD.

Follow ups were recorded at 2 weeks, 4 weeks, 8 weeks and 12 weeks from the beginning of the treatment. Primary efficacy parameter was reduction in the total score on MADRS. An initial reduction of MADRS score of 20% or more from the baseline (initial response) was considered as onset of action and the time taken for it was compared in three groups. Response was considered as >50% reduction in MADRS score from baseline and remission was <10 on MADRS score. Number of patients attaining response (response rate) and remission (remission rate) and the time taken to attain them was compared among the three groups.

Secondary efficacy parameters were a) number of patients attaining score 1 (Normal, not at all ill) or score 2 (Borderline mentally ill) on Clinical global impression- severity of illness (CGI-S) and the mean score at the end of 12 weeks b) number of patients attaining score 1 (Very much improved) or score 2 (Much improved) on Clinical global impression-severity of illness (CGI-I) and the mean score at the end of 12 weeks. The CGI scales are commonly used measures of symptom severity, treatment response and the efficacy of treatment. The CGI-S is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment. The CGI-I is a 7 point scale, used to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention[9].

Tolerability was assessed by comparing the number and severity of ADRs and dropouts rate due to ADRs in the three groups. Severity of ADRs was assessed using Hartwig's severity assessment scale[10].According to it, an ADR is termed mild if it did not require change in the treatment or required withdrawal of suspected drug however no antidote or specific treatment was given or did not prolong the hospital stay. Moderate ADRs required withdrawal of suspected drug and specific treatment, and led to admission or prolonged hospital stay by one day.

Severe ADRs required intensive medical care or caused permanent harm to the patient or led to death of the patient. Safety was assessed using laboratory investigations at baseline, 4 weeks, 8 weeks and 12 weeks. Random blood glucose, liver enzymes, serum creatinine and electrolytes, lipid profile, electrocardiogram (ECG) was monitored in all patients. Numerical values were analyzed using ANOVA and categorical values were analyzed using Chi square test or Fisher exact test as appropriate. P value of 0.05 was considered significant.

Ethical Consideration

The study was approved by the Institutional Ethics Committee of SKMCH, Muzaffarpur, Bihar.

Results

A total of 139 patients were screened for inclusion and exclusion criteria out of which 90 patients were included in the

study. Patients with not even a single follow up were excluded from the study and new cases were taken to replace them. Patients with at least a single follow up were considered for analysis by intention to treat using last observation carried forward method. The study consisted of 47 females and 43 males. The P value for gender distribution between the groups was 1 indicating the three groups were gender matched.

Table 1: Baseline characteristics of study subjects in summarized below

Parameters	Group A (Imipramine)	Group B (Escitalopram)	Group C (Desvenlafaxine)	P-value
Age (in years)	43.90±13.88	41.57±14.03	43.33±13.35	0.791
Weight (in kgs)	56.4±1.43	54.3±2.39	57.6±1.43	0.812
Heart Rate (beats per minute)	78.66±3.67	79.36±4.32	82.54±1.35	0.654
SBP (mmHg)	127.29±4.97	130.77±3.89	129.51±2.98	0.701
DBP (mmHg)	84.59±3.71	79.44±3.19	83.71±2.94	0.841
RBS (mg/dl)	103.63±5.91	107.39±6.32	104.59±3.75	0.971
Serum Creatinine (mg/dl)	0.65±0.16	0.59±0.09	0.63±0.17	0.120
ALT (IU/Litre)	22.66±9.02	19.47±7.80	23.87±8.25	0.115
AST (IU/Litre)	31.71±5.71	29.91±3.09	30.52±4.68	0.382
TC (mg/dl)	163.92±8.24	159.82±9.28	166.93±7.02	0.261
LDL (mg/dl)	83.72±6.02	79.47±4.86	85.92±6.92	0.118
MADRS	36.93±8.12	37.23±8.13	37.27±7.21	0.98
CGI-S	4.33±0.96	4.40±0.72	3.97±0.76	0.095

Table 2: Reason for dropouts in three groups

Dropouts	Group A (Imipramine)	Group B (Escitalopram)	Group C (Desvenlafaxine)
ADRs	3	2	1
Physician withdrawal due to ADRs	2	0	1
Inadequate Response	1	0	2
Unknown	3	2	0

Dropout rate in imipramine group was 30% and in escitalopram and desvenlafaxine group it was 13.33% each. Most common reasons for dropouts quoted were ADRs in Group A and Group B and inadequate response in Group C.

Table 3: Efficacy assessment scores in three groups

	MADRS			CGI-S			CGI-I		
	A	B	C	A	B	C	A	B	C
Baseline	36.93	37.23	37.27	4.33	4.40	3.97	-	-	-
2 weeks	34.26	28.86	30.50	4.07	3.50	3.50	3.83	3.17	3.53
4 weeks	27.46	24.3	25.66	3.23	2.97	3.03	3.23	2.86	3.1
8 weeks	22.13	20.66	21.66	2.83	2.63	2.66	2.8	2.56	2.8
12 weeks	18.96	17.33	18.03	2.66	2.13	2.3	2.46	2.2	2.46

All three drugs caused significant decrease in the MADRS score at the end of 12 weeks (P = <0.0001). There was no significant difference in the final MADRS score between the three groups (P = 0.71) however; escitalopram caused the highest

reduction at the end of 2 weeks followed by desvenlafaxine and imipramine, which was statistically significant (P = 0.017). Initial response (>20% reduction in baseline MADRS score) was seen as early as 2 weeks in 19 patients of escitalopram group and 13 patients of desvenlafaxine group but none in imipramine group. This indicates that newer antidepressants lead to early improvement in the patients. Response was seen in 53% patients in imipramine group, out of which 13.3% attained remission. 63% patients in escitalopram group showed response out of which 30% attained remission. 50% patients in desvenlafaxine group, of which 5 (16.66%) attained remission.

However, the difference between the three groups was not significant. There was no difference in the CGI-S score among three groups at the end of 12 weeks; however, the reduction at 2weeks was highest in escitalopram and desvenlafaxine group compared to imipramine, which was significant.

There was no difference in the CGI-I score at the end of the study among three groups, but the reduction was highest with escitalopram followed by desvenlafaxine and imipramine at 2 weeks (<0.001) and 4 weeks (0.007) both of which were statistically significant.

Twenty patients among group B and 18 among group C attained score 1 (Normal), score 2 (Borderline mentally ill) on CGI-S compared to 14 in group A. 19 patients among group B and 16 among group C attained. More number of patients in escitalopram and desvenlafaxine groups attained score 1 (very much improved), score 2 (much improved) on CGI-I compared to 15 in group A. This indicates that the improvement was higher with newer antidepressants. However, the difference was not statistically significant.

Table 4: Adverse drug in study subjects

Adverse effects	Group A (Imipramine)	Group B (Escitalopram)	Group C (Desvenlafaxine)
Dry mouth	4	0	0
Drowsiness	6	0	0
Palpitation	2	0	0
Headache	2	3	3
Nausea	3	5	8
Tremors	6	1	1
Elevated transaminases	1	0	0
Blurred vision	1	0	1
Constipation	6	0	0
Weight gain	4	0	0
Postural hypotension	3	0	0
Anxiety	1	4	0
Difficulty in micturition	1	0	0
Dizziness	3	1	1
Hyperhydrosis	0	0	6
Irraitability	0	1	3
Insomnia	0	4	2
Ejaculation disorder	0	2	1
Increased TC, LDL	0	0	1
Decreased appetite	0	1	2
Weight loss	0	1	3
Vomiting	0	0	1
Diarrhea	0	3	1

Hypertension	0	0	1
Withdrawal syndrome	0	0	1
Erectile dysfunction	0	1	1
Total	43	27	37

A total of 107 ADRs were noted in the study which were of 26 different types. 43 ADRs were noted in imipramine group, 27 in escitalopram and 37 in desvenlafaxine group. Most ADRs in imipramine group (27) were of moderate severity. Most ADRs in escitalopram group (17) and in desvenlafaxine group (21) were mild in severity.

Three patients in imipramine group discontinued the treatment due to ADRs, and 2 patients were withdrawn from the treatment by the physician. One of them had elevated serum transaminases which subsided after the drug was withdrawn and the other patient came with acute urinary retention which was managed by catheterization and administration of antibiotics. ADRs leading to discontinuation were palpitations, excessive drowsiness, dry mouth and constipation.

Two patients in escitalopram group discontinued treatment because of ADRs which were insomnia and ejaculation disorder. One patient in desvenlafaxine group discontinued due to ADR (Erectile dysfunction) and 1 patient was withdrawn from treatment by the physician as she developed hypertension.

Weight gain: There was an increase of 3.22 Kilograms (Kgs) on an average in imipramine group at the end of 12 weeks which was statistically significant (P value 0.041). There was slight increase in overall weight among study subjects in escitalopram group (0.34 Kgs) and desvenlafaxine group (0.21 Kgs) which was not statistically significant.

Blood pressure: There was no statistically significant difference among the study groups or within the groups in blood pressure of the study subjects. However, desvenlafaxine group showed an overall increase in systolic blood pressure (SBP) by 9 mm Hg and diastolic blood pressure (DBP) by 4 mm Hg. One patient in desvenlafaxine group developed significant increase in BP by the end of 2 weeks.

ECG: Two patients developed prolonged PR interval on ECG in imipramine group and complained of palpitations.

None of them developed second degree Atrioventricular block. One patient developed sinus tachycardia on ECG in desvenlafaxine group which returned to normal after reduction in the dose of desvenlafaxine (From 100mg to 50mg). Statistically significant increase in the average RBS level was seen in imipramine group by the end of 12 weeks. Though escitalopram and desvenlafaxine also showed mild increase in average RBS by 12 weeks they were not statistically significant. The difference between imipramine and that of escitalopram and desvenlafaxine was not significant. Statistically significant increase in serum total cholesterol levels was seen with imipramine at 12 weeks. Though there was increase in serum LDL and Triglycerides they were not statistically significant. No significant difference was noted between the three groups. One patient developed increased total cholesterol and LDL after 2 months of treatment with desvenlafaxine and was treated with atorvastatin. No statistically significant difference was noted in liver enzyme levels in any of the three groups. No significant increase in serum creatinine was seen in any of the three groups. Statistically significant decrease in serum sodium was seen with esciatopram by 12 weeks. However, none of the patients showed symptoms of hyponatremia in any group. No significant difference in serum potassium levels were seen in any group. There was overall

decrease in the levels of serum sodium and potassium in all three groups though no patient complained of any symptoms due to hyponatremia or hypokalemia.

Discussion

We enrolled 90 patients into the study who were divided into three groups of 30 each and followed up for a period of 12 weeks after receiving the study drugs. There are numerous similar studies comparing the treatment modalities of an acute episode of depression and most of them have followed up the patients up to 6-8 weeks. However, an episode of acute depression lasts for about 12 weeks and hence we have followed up the patients up to 12 weeks. WHO recommends continuation of the antidepressants for at least 12 months to prevent relapse.

The mean age of patients in this study was 42.93±13.56 years with maximum number of patients between 31-40 years of age group. Kessler et al, noted that the risk for the onset of depression is highest among 18-29 years followed by 30-44 years[11]. This shows that the highest risk of developing depression is between early adulthood to about 40 years. It is clearly established in many studies that women are at a higher risk of developing depression compared to men which was also seen in our study with up to 52% of patients being women.

Most of the patients were unskilled laborers or housewives with a family income of less than ten thousand rupees per month and belonged to the low socioeconomic group. Number of patients who were either currently married or previously married was definitely higher than those who were unmarried. This was similar to the observation done by Kessler et al, who reported that low income and married/ previously married were associated with an elevated risk of developing severe MDD[11].

Response rate for impramine was 53% which was similar to a multicenter randomized trial published by Baca et al who reported 53.7% response rates with imipramine. However the remission rates (MADRS <10) was 25% in our study which was lower compared to 38% reported by Baca et al [12]. Response and remission rates of escitalopram in our study were 63% and 47.3% respectively, which is comparable to a Cochrane review done by Cipriani et al[13].They conducted a review to compare escitalopram with other newer antidepressants and showed a response rate of 60.7%. However, the response and remission rates of desvenlafaxine vary significantly among different studies.

We found the rates to be 50% and 33.33% respectively. Leibowitz et al conducted a meta-analysis of placebo controlled trials and showed that the response rate for desvenlafaxine in depression varied significantly from as low as 39% to as high as 65% and the remission rates varied between 20-37%[14].Though there are significant discrepancies in efficacy parameters of various antidepressants, a meta-analysis conducted by Anderson showed that the efficacy of SSRIs and TCAs are comparable[15]. In a meta-analysis conducted in Canada, SNRIs had the highest efficacy remission rates, and the lowest overall dropout rates, suggesting clinical superiority compared to TCAs and SSRIs, in treating major depression[16].

Initial response was earlier with escitalopram and desvenlafaxine compared to imipramine. Kasper et al conducted a pooled analysis of trials comparing escitalopram with other SSRIs and venlafaxine and concluded that escitalopram was a fast-acting antidepressant with a more rapid onset of effect than the comparators, particularly other SSRIs [17]. Whereas Neirenberg et al reported that dual acting antidepressants like venlafaxine and mirtazapine have early onset of action compared to SSRIs,[18]and Stahl et al also reported that venlafaxine, citalopram and mirtazapine have earlier onset of action[19].Overall our study has demonstrated that newer antidepressants

have an early onset of action compared to conventional TCAs similar to many other studies. This is important because early improvement predicts a better outcome and also improves patient compliance to treatment. Szegedi et al found that improvement in the first 2 weeks in depressed patients treated with antidepressants was highly predictive of a positive response after 6 weeks of treatment[20]. CGI score reduction was also earlier with newer antidepressants in our study. At least 26 different types of ADRs were noted in our study with a total of 107 events during the study period. Commonest ADRs for imipramine were drowsiness, tremors, constipation, dry mouth and weight gain. Antihistaminic and antimuscarinic effects of imipramine are responsible for this. This was similar to a comparative study conducted by Roberto Delle Chiaie who noted that the frequent side effects with imipramine were dry mouth, constipation and tachycardia[21]. Common side effects noted with escitalopram in our study were nausea, insomnia, anxiety and sexual dysfunction. Excessive stimulation of 5-HT in brain and periphery are responsible for this. Anxiety and insomnia were the commonest ADRs for SSRIs in another study conducted in psychiatric outpatients[22]. Nausea, hyperhidrosis, headache and irritability were commonly noted for desvenlafaxine in our study which was similar to other studies. In a study which summarized the adverse drug reactions of antidepressants in the results of the German Multicenter Drug Surveillance Program (AMSP), TCAs had higher ADR rates compared to SSRIs, MAOIs and other newer drugs like venlafaxine and mirtazapine[23]. In SSRI treated patients neurological adverse effects followed by gastrointestinal side effects were common. Venlafaxine was associated with adverse neurological and somatic symptoms. Most of the ADRs caused by escitalopram (63%) and desvenlafaxine (57%) were mild whereas most of the ADRs caused by imipramine (65%) were moderate in severity. Four patients on imipramine showed significant weight gain (>7%) at the end of 12 weeks. Sussmann et al noted that 4.9% of patients treated with imipramine showed 7% or greater body weight increase in acute phase and 24.5% showed weight gain in chronic phase which was significantly higher than newer antidepressants[24].Patients on escitalopram and desvenlafaxine in our study showed a modest increase in weight (0.52 kg and 0.41 kg respectively) at the end of 12 weeks which was not significant.

Anticholinergic side effects like drowsiness, palpitations, dry mouth, constipation and urinary retention were the most common causes for dropouts in Imipramine group. Insomnia and sexual dysfunction (delayed ejaculation) were the causes for discontinuation of the drug in escitalopram group. Erectile dysfunctions lead to discontinuation of the drug in one patient on desvenlafaxine. Desvenlafaxine was withdrawn in another patient by the physician as she developed hypertension. Her blood pressure was normal before the beginning of treatment (126/84 mm Hg) and there was an increase in both systolic blood pressure (142 mm Hg) and diastolic (88 mm Hg) at the end of two weeks. Since the BP was persistently high, desvenlafaxine was stopped and she was switched over to another antidepressant (Sertraline). She was treated with antihypertensives and her BP decreased to 124/84 mm Hg after two weeks. Enhancement of noradrenergic transmission is said to be responsible for this effect of desvenlafaxine.

Imipramine showed significant increase in random blood sugar and total cholesterol by the end of 12 weeks. Though there was mild increase in RBS and TC in both escitalopram group and desvenlafaxine group, none of them were significant. Ghaeli et al noted that patients on imipramine had increase in fasting blood glucose levels whereas this effect was not seen with fluoxetine[25]. Shahsavand et al noted that there was significant increase in total cholesterol and triglycerides by 8

weeks, in patients treated with imipramine[26]. This may lead to the development of metabolic syndrome on prolonged use of TCAs.

Antidepressants are known to cause Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) which constitutes hyponatremia and hypokalemia. This type of dilutional hyponatremia was seen in our study with escitalopram which was statistically significant. However, none of the patients developed symptoms due to hyponatremia. Though imipramine also showed hyponatremia by 12 weeks the levels were not statistically significant, and no patients were symptomatic. Bouman et al noted that there was higher incidence of SIADH in patients on SSRI especially in elderly and hence careful prescription of these drugs is warranted[27].

Conclusion

Newer antidepressants like escitalopram and desvenlafaxine were equally efficacious in treating moderate to severe depressive episode compared to conventional drugs like imipramine however they had an advantage of faster onset of action, better safety and tolerability.

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