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EVALUATION OF EFFICACY OF IMIPRAMINE, SERTRALINE AND ESCITALOPRAM IN DEPRESSIVE PATIENTS: AN OBSERVATIONAL STUDY.

Medical Science

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ABSTRACT

Background: Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and sense of well – being. Depression is a major cause of disability worldwide. Various studies demonstrated the efficacy of antidepressant drugs by using various rating scales available to measure the depth of severity of depression. e.g. Hamilton Depression Rating Scale , Montgomery-Asberg Depression Rating Scale, Raskin Depression Rating Scale, Beck Depression Inventory (BDI), Geriatric Depression Scale (GDS), Zung Self-Rating Depression Scale and Patient Health Questionnaire (PHQ) sets etc. BDI is one of the most widely used instruments for measuring the severity of depression.

Method: This open label, prospective and observational study was conducted to evaluate the efficacy of imipramine, sertraline and escitalopram in major depressive patients. DSM –V criteria was used to diagnose the depressive patients. A total of 810 such patients were randomly divided into three groups i.e. group I, II & III containing 270 patients in each group. Patients of these groups were treated with imipramine, sertraline and escitalopram respectively as per schedule dose. Base line parameter such as heart rate, blood pressure and BDI score were recorded and follow up at 4, 8 and 12 weeks. Data were analyses with appropriate statistical methods.

Results: We found that female patients were more than male. A total of 187 patients in group I, 228 in group II and 237 patients in group III completed this study. During study period, all the three groups showed a significant increase in mean values of heart rate as 'p' values are less than 0.05. However in groups; mean value were within normal range at all followup intervals. A total of 9 patients were drop out in imipramine group due to tachycardia whereas it was 6 and 4 in sertraline and escitalopram group respectively. In all groups systolic as well as diastolic BP was progressively increased at 4, 8 and 12 weeks but it was within normal range. Group III showed maximum efficacy whereas it was minimum with group I after 12 weeks of treatment.

Conclusion: Escitalopram showed maximum efficacy whereas imipramine possess least after 12 weeks of treatment. Response rate of escitalopram and sertraline was almost similar whereas it was seen least with imipramine, so overall escitalopram was found better than sertraline and imipramine.

KEYWORDS

Depression, BDI, Antidepressants

Introduction: Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and sense of well - being [1, 2]. Recently conducted world mental health surveys indicate that major depression is experienced by 10-15% people in their lifetime [3] and about 5% suffer from major depression in any given year [4]. In Indian context, a recent large sample survey with rigorous methodology reported an overall prevalence of 15.9% for depression[5].

There are various rating scales available to measure the depth of severity of depression. BDI is one of the most widely used instruments for measuring the severity of depression. It is a 21-question multiple-choice self report inventory created by Aaron T. Beck [6].

The W.H.O. mhGAP Intervention Guide has outlined the treatment options for depression, which consist of basic psychosocial support combined with antidepressant medication or psychotherapy [7].

Antidepressant medication is recommended as an initial treatment choice in people with mild, moderate, or severe major depression, and should be given to all patients with severe depression unless ECT is planned [8].

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 [9]. Selective serotonin reuptake inhibitors (SSRI) were introduced in 1970s to overcome this drawback [10].

Of the SSRIs currently on the market, escitalopram has the highest selectivity for the serotonin transporter (SERT) compared to the norepinephrine transporter (NET), making the side-effect profile relatively mild in comparison to less-selective SSRIs [11]. Hence, most clinical guidelines consider the newer generation antidepressants to be first-line medications for MDD [12-14].

Paucity of comparative studies of such newer drugs in Indian scenario prompts us to take up this study.

Aims & Objectives: Main aim of this study was to evaluate and compare the efficacy of Escitalopram, sertraline and imipramine in patients with depressive disorder.

Methodology: This open label, prospective and comparative observational study was conducted after obtaining the approval from the institutional ethics committee & approval from Rajasthan University of Health Sciences, Jaipur (RUHS).

Source of data: Patients of depressive disorder visiting OPD (Out Patient Department) of psychiatric department of JLN Medical College & Associate group of Hospitals, Ajmer (Rajasthan). Patients were included since August 2016 as per inclusion and exclusion criteria of this study.

Inclusion criteria included the patients of either sex aged between 18-65 years suffering from depressive disorder, Newly diagnosed patients of depressive episode fulfilling the criteria of DSM-V, Patients with >/= 14 to 28 on BDI (Beck Depression Inventory Rating Scale- BDI-II) score, Patients giving written informed consent.

Exclusion Criteria involves such patients who do not fulfil the inclusion criteria, patients being treated with more than one antidepressant, patients with psychotic depression, bipolar disorder, schizophrenia or anxiety disorders, patients with current suicidal ideation, patients with serious decompensated medical conditions like congestive cardiac failure, renal failure, and Hepatic failure, patients with ischeamic heart disease, cardiac conduction defects and arrhythmias, patients with ECG abnormalities and abnormal liver enzymes, presence of alcohol and substance dependence, epilepsy, mental retardation, mental disorders other than depression, pregnant and lactating women, Non complying patients who are unable to give consent for the study.

Sample size: Sample size was calculated by ANOVA test using statistical analysis software Primer version 6.0. At power of 80 % and α error of 0.05, taking 10 % attrition rate, we obtained a number of 802 [{729 + 729x10%}=801.9]. For convince a total of 810 patients with depressive disorder meeting the inclusion and exclusion criteria were selected and 270 patients out of this were selected in each group studied as follows:

Group I: Study subjects were treated with imipramine orally in a dose of 75 mg BD.

Group II: Study subjects were treated with sertraline orally in a dose of 150 mg daily (i.e. 50 mg in morning and 100 mg in night)

Group III: Study subjects were treated with escitalopram orally in a dose of 10 mg BD.

Demographic profile, efficacy and side effect profile was assessed during enrolment visit as well as follow up at 4 weeks, 8 weeks, and 12 weeks. Data were analysed as per appropriate statistical method. Efficacy profile was evaluated by measuring the BDI score.

Results: A total of 187 patients in group I, 228 in group II and 237 patients in group III completed this study; rest of the patients were withdraw from present study due to adverse effects or unknown reasons. All participants were in a range of 18-70 years with a mean age of 41.56 ± 13.58 yrs. Mean age ± SD for Group I, Group II and Group III is 39.96±13.59, 44.6±12.97 and 40±13.71 respectively. 'p' value of F statistic suggests that there is significant difference among group (p=0.000) (Chart-1). Female patients were more than male (female-no. 433, 53.46% and male-no. 377, 46.54%). In Groups I, II and group III, majority of patients were females (Chart-2). Chi square test = 1.915328, p value=0.38, indicates that there is no significant difference in number of males and females among different groups.

Heart rate profile is described in **Chart 3 (a) & 3 (b)**. It is observed that at baseline as well as at all the three follow up intervals, mean values are significantly different among groups. At baseline, 4 week and 8 week intervals mean heart rate for Group III is statistically less than mean heart rate of Group I and Group II. At 8 week interval mean heart rate of Group III is significantly greater than mean heart rate of Group II, while it is significantly less than mean heart rate of Group I. During the study period, all the three groups showed a significant increase in mean values of heart rate as p values are less than 0.05.

At baseline as well as all the three follow up intervals, no statistically significant intergroup differences in Systolic Blood pressure (SBP) values of different groups were observed as p values for all three groups are greater than 0.05 [Chart 4 (a)].

In all the three groups a systematic increase in SBP values were observed. Owing to same SD values at baseline and 12 weeks intervals, the statistical evaluation of change could not be done. This implies that the change in SBP values was universal and did not have any chance error [Chart 4 (b)].

Chart 5 (a) shows that at baseline and all the three follow up intervals, Group III had significantly lower mean value of Diastolic Blood pressure DBP as compared to Groups I and II. Statistically, no significant difference was observed between Groups I and II at all the four measurements.

In all the three groups a systematic increase in DBP values were observed. Owing to same SD values at baseline and 12 weeks intervals, the statistical evaluation of change could not be done. This implies that the change in DBP values was universal and did not have any chance error [(Chart-5 (b)].

It is evident from chart 6 (a), At baseline, there was no significant difference in mean BDI values of three groups (p>0.05). However, at subsequent intervals, Group I showed maximum value and Group III showed minimum values. At all the three follow-up intervals, all the three between group differences were significant statistically as p values are <0.05.

All the three groups showed a significant decline in mean BDI values at the completion of study (12 weeks) as p values are less than 0.001 [(chart-6 (b)].

Discussion: Depression is a major cause of disability worldwide. Gender difference in the prevalence of unipolar depression has been well established [15-17]. Major depression is almost twice as common in women as in men, although it is unclear why this is so [18]. In present study, female patients (No. 433/ 53.45%) more than male (No. 377/ 46.54%) were enrolled. In all groups, majority of patients were female (char-2). Similar results were also observed in previous studies [19]. In Indian context educational status of females is less in comparison to male. In some areas they are married in early age. So in some context poverty, illiteracy and early marriage may also be responsible for depression more in females.

People are most likely to develop their first depressive episode between the ages of 30 and 40. All the participants were in a range of 18-70 years with a mean age of 41.56 ± 13.58 yrs. Mean age was found quite similar to previous studies [20-21].

Heart rate & B. P.

Heart rate per min. is described in Chart-3 (a) & 3 (b). After treatment mean values were 67.11, 66.78, 66.39 rate per minute in Imipramine, sertraline and escitalopram group respectively. However during study period, all the three groups showed a significant increase in mean values of heart rate as 'p' values are less than 0.05 (This may be due to anticholinergic and NE reuptake inhibition property of imipramine [22] and MAO inhibition property in sertraline [23]. It is shown that in all groups; mean value were within normal limits at all followup intervals. A total of 9 patients were drop out in imipramine group due to tachycardia whereas it was 6 and 4 in sertraline and escitalopram group respectively.

Chart 4 (a & b) and 5 (a & b) shows inter and between group comparision of systolic & diastolic blood pressure. In all groups systolic as well as diastolic BP was progressively increased at 4, 8 and 12 weeks but it was within normal range.

In all groups we observed same SD values at baseline and 12 weeks intervals, therefore statistical evaluation of change could not be done for systolic & diastolic blood pressure.

Our study findings are very similar to study carried by Divyashree M et al and Murat Kesim et al[19,24].

BDI: There are various rating scales available to measure the depth of severity of depression. e.g. Hamilton Depression Rating Scale , Montgomery-Asberg Depression Rating Scale, Raskin Depression Rating Scale, Beck Depression Inventory (BDI), Geriatric Depression Scale (GDS), Zung Self-Rating Depression Scale and Patient Health Questionnaire (PHQ) sets etc.

BDI is one of the most widely1 used instruments for measuring the severity of depression. It is a 21-question multiple-choice self-report inventory created by Aaron T. Beck. The BDI was originally developed to provide a quantitative assessment of the intensity of depression. Because it is designed to reflect the depth of depression, it can monitor changes over time and provide an objective measure for judging improvement and the effectiveness or otherwise of treatment methods. There are three versions of the BDI- the original BDI, BDI-1A, and the BDI-II.

Like the BDI, the BDI-II also contains 21 questions, each answer being scored on a scale value of 0 to 3. Higher total scores indicate more severe depressive symptoms. The standardized cut-offs used differ from the original [25] are as:

- 0–13: minimal depression
- 14–19: mild depression
- 20–28: moderate depression
- 29–63: severe depression.

Only mild-to-moderate depressive patients (BDI score ≤ 28) was included for this study. Reduction in total score on BDI was considered as primary efficacy parameter in present study.

It is evident from chart 6 (a) that at baseline there was no significant difference in mean BDI score among study group, (p value is >0.05). At subsequent intervals, group III showed maximum reduction in BDI score whereas minimum reduction was seen with group I. After 12 weeks of treatment, all three groups showed a statistically significant

decline in mean BDI value as p values are leass than 0.05 [chart 6 (b)].

It is evident from chart 6 (b) that group III showed maximum efficacy whereas it was minimum with group I after 12 weeks of treatment (p value is <0.05).

In term of response rate (≥ 50 % reduction in BDI score from baseline), least response rate was seen in group I, whereas group II and group III showed almost similar response. In imipramine group, only 75 patient showed ≥ 50 % reduction in BDI score from baseline whereas it was 113 & 115 for sertraline and escitalopram group [(chart 6(c)]. In term of efficacy, our study results were very close to previously studies done by Divyashree et al, Ventura D et al and Cipriani A et al [19,26,27].

Various biochemical studies explain the mechanism responsible for it's maximum efficacy. There are two binding sites on serotonin transporter protein, i.e. a high affinity, primary binding site that mediates the inhibition of serotonin reuptake and a low affinity site that allosterically modulate the affinity of ligands at the primary site [28 -29]. Escitalopram uniquely binds to both the primary and allosteric sites [30] leading to enhanced serotonergic neurotransmission and subsequent downstream effects on synaptic plasticity and neurogenesis [31 -33]. The additional allosteric mechanism of escitalopram, which appears to be unique among SSRI antidepressants [34] may be plausible mechanism for its efficacy advantages in patients of MDD.

Conclusion: We found that Group III (patients treated with escitalopram) showed maximum efficacy whereas imipramine possess least after 12 weeks of treatment (p value is <0.05). Tolerability and safety was also found better with escitalopram when compared with sertraline and imipramine, because maximum number of patients completed this study in group III, whereas it was least within group I. Response rate of escitalopram and Sertraline was almost similar whereas it was seen least with imipramine, so overall escitalopram was found better than sertraline and imipramine. Based on previous studies and our study results we suggest that escitalopram is far better than sertraline and imipramine however further studies are needed to evaluate the antidepressant efficacy of imipramine, sertraline and escitalopram on long-term use in depressive patients.

Chart 1- Age wise distribution of patients in study groups

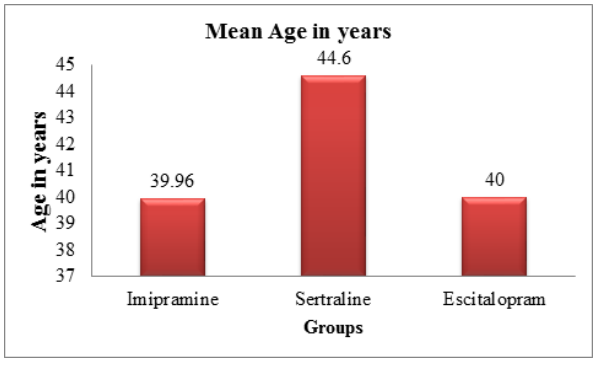


Chart 2- Gender wise distribution of patients in study groups

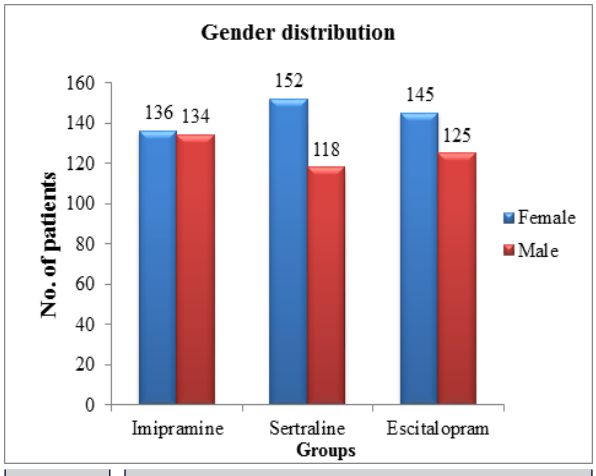


Chart 3 a: Inter and between group comparison of Heart Rate

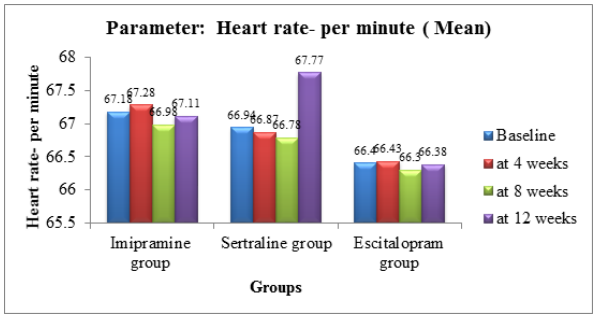


Chart 3 b: Within Group evaluation of Change among patients completing 12 weeks of treatment

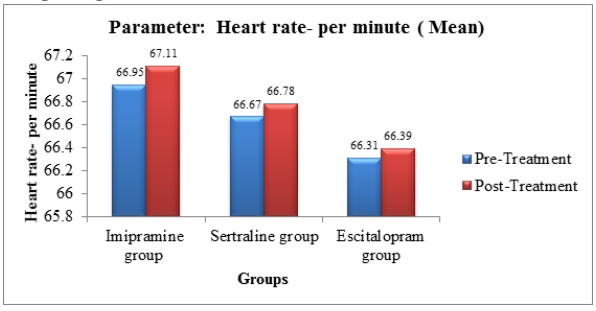


Chart 4 (a): Inter and between group comparison of Systolic Blood Pressure

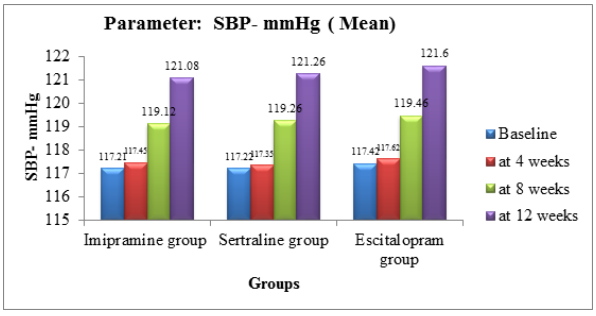


Table 4(b) Within Group evaluation of Change among patients completing 12 weeks of treatment

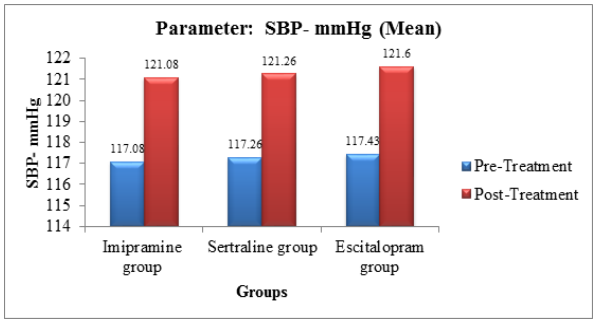


Chart 5 (a): Inter and between group comparison of Diastolic Blood Pressure

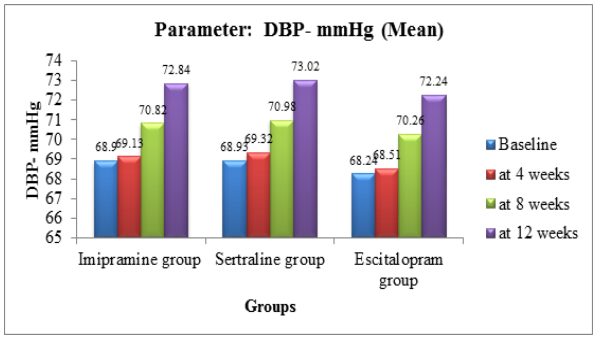


Chart 5 (b) Within Group evaluation of Change among patients completing 12 weeks of treatment

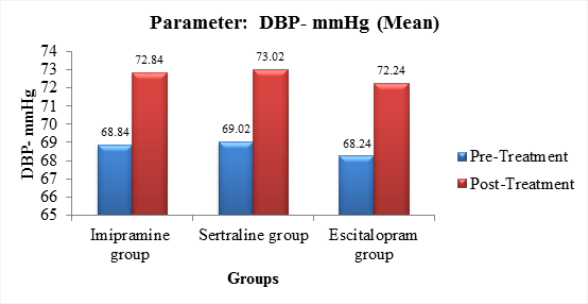


Chart 6 (a): Inter and between group comparison of BDI

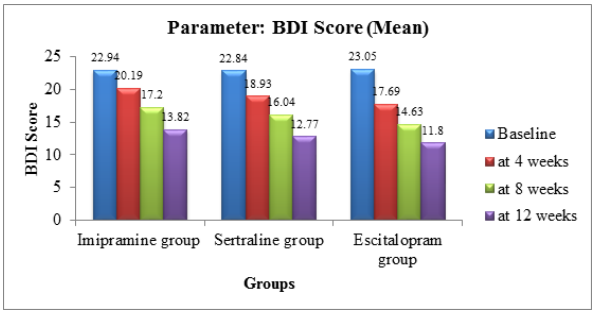


Chart 6 (b): Within Group evaluation of Change among patients completing 12 weeks of treatment

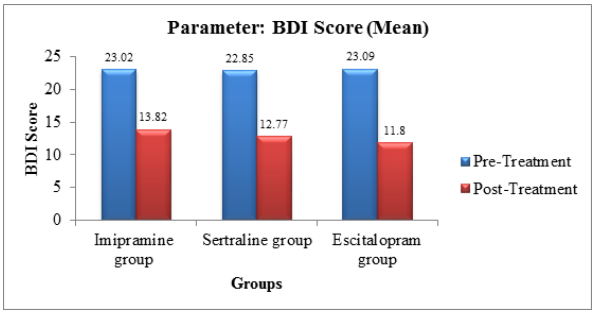
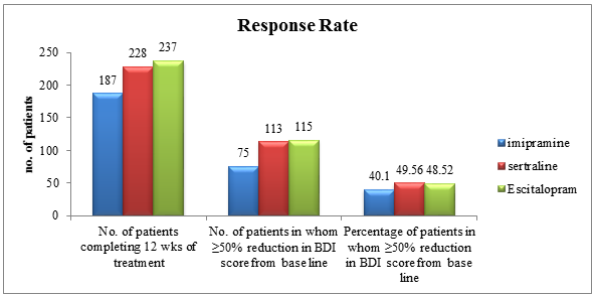


Chart 6 (c): Showing Response Rate



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