Original Article

Analysis of Side Effects in Major Depressive Patients receiving Imipramine, Sertraline and Escitalopram therapy.

Arun Kumar Sharma*, Sunil Kumar Mathur**
**Senior Demonstrator, **Senior Professor & Head,*
Department of Pharmacology, JLN Medical College, Ajmer (Raj.)

ABSTRACT

Beckground: Depression is a major cause of disability worldwide and third leading cause of global disease burden. Antidepressants medications remain a mainstay of treatment for major depressive disorder (MDD). Antidepressant side effects included insomnia, sleepiness during the day, restlessness, muscle spasm, dry mouth, profuse sweating, sexual disorders, nausea, constipation, diarrhoea, weight gain and dizziness. After obtaining the approval from the institutional ethics committee, this open label, observational and comparative study was conducted in patients of depressive disorder visiting OPD (Out Patient Department) of psychiatric department of JLN Medical College & Associate group of Hospitals, Ajmer (Rajasthan). Study subjects (total- 810, sample size was calculated by ANOVA test) meeting the inclusion/exclusion criteria were randomly assigned into three groups containing, 270 patients in each group were treated with imipramine, sertraline and escitalopram respectively as per scheduled. Tolerability was assessed and analysed by observing the side effects in above study patients at 4 weeks, 8 weeks, and 12 weeks.

We observed that imipramine and sertraline had relatively and significantly higher side effects as compared to escitalopram. Dropout cases were maximum seen with imipramine therapy while it was seen minimum with escitalopram.

Conclusion: Escitalopram appears to be the best tolerated SSRI because of its additional mechanism (allosterically modulate the affinity of ligand at the primary site) which makes it unique among SSRI antidepressants. Overall it is concluded from present study that escitalopram is more tolerable in comparision to imipramine and sertraline.

Key words: *Depression, imipramine, sertraline and escitalopram.*

Beckground: Depression is a major cause of disability worldwide and third leading cause of global disease burden [1]. Antidepressants medications remain a mainstay of treatment for major depressive disorder (MDD). Various class of antidepressants posses some degree of adverse events. Antidepressant side effects included insomnia, sleepiness during the day, restlessness, muscle spasm, dry mouth, profuse sweating, sexual disorders, nausea, constipation, diarrhoea, weight gain and dizziness [2]. Gastrointestinal disturbance are the most frequently reported side effects [3]. The efficacy of selective serotonin reuptake inhibitors (SSRIs) is comparable to that of tricycle antidepressants (TCA) but having fewer side effects [4]. This was confirmed by finding that patients taking SSRIs therapy discontinued because of adverse effects fewer than did those taking TCAs [5]. Based on tolerability profile, SSRIs are a significant advancement over the TCAs for the treatment of depression [6]. In present study we analysis the adverse effects profile in study patients taking antidepressants i.e. imipramine, sertraline and escitalopram.

Methodology: After obtaining the approval from the institutional ethics committee, this open label, observational and comparative study was conducted in patients of depressive disorder visiting OPD (Out

Corresponding Author : ***Dr. Sunil Kumar Mathur, Senior Professor & Head, Department of Pharmacology, JLN Medical College, Ajmer (Raj.), Mob. 9414008259, Email: pharma.sharm@yahoo.in, sunrinty@gmail.com***

Patient Department) of psychiatric department of JLN Medical College & Associate group of Hospitals, Ajmer (Rajasthan).

Inclusion/exclusion criteria:

Patients of either sex aged between 18-65 years suffering from mild to moderate depressive disorder who gave their written consent for this study were enrolled since August 2016. Patients being treated with more than one antidepressant, having any other medical conditions / disorder, pregnant and lactating and any other patients who do not fulfil the inclusion criteria were excluded from present study.

Study subjects (total- 810, sample size was calculated by ANOVA test) meeting the inclusion/exclusion criteria were randomly assigned into three groups containing, 270 patients in each group were treated 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.

Tolerability was assessed and analysed by observing the side effects in above study patients at 4 weeks, 8 weeks, and 12 weeks.

Results: A total of 1026 ADRs were noted which were of 13 different types. 506 ADRs were noted in imipramine group, 401 in sertraline group and 119 in escitalopram group. At 4 and 8 weeks maximum proportion of patients with side effects was seen in Group I followed by Group II and then Group III. At 12 weeks, side effects were maximum in Group II (81.1%) followed by Group I (77.8%) and then in Group III (28.3%). Statistically, the difference among groups was significant at all the three follow up intervals ($p<0.001$) (Table-1). However, as compared to Group III, Groups I and II had relatively and significantly higher side effects.

A total of 158 patients were dropout from our study. 83 patients in group I, 42 in Group II and 33 in group III were dropout from present study. 105 patients were dropout due to ADRs whereas 53 patients were dropout due to unknown reasons (Table-2).

Discussion: In present study tolerability was assessed by comparing the number and severity of ADRs and drop-outs due to ADRs in study groups.

A total of 1026 ADRs were noted which were of 13 different types. 506 ADRs were noted in imipramine group, 401 in sertraline group and 119 in escitalopram group. Moderate ADRs were noted in 43 patients in group I, 36 in group II and 26 in group III. Rest of the ADRs were belonging to mild category.

Dry mouth was most common ADR observed in group I & II whereas in group III it was flatulance.

Common side effects noted were dry mouth, constipation, headache, nausea, anorexia which were similar to other studies. These side effects due to anticholinergic properties in TCA. Divya shree et al also found that TCAs had higher ADR rates compared to SSRIs, MAOIs and other newer ones [7].

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QT prolongation, tachycardia, sexual side effects and diarrhoea were most common causes for dropout in group III and group II patients. Tachycardia, constipation and dry mouth were most common causes for dropout in group I. ECG changes were within normal limits in rest of the patients.Severity of ADRs was assessed using Hartwig's severity assessment scale [8]. 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.

In present study all reported ADRs were of mild category except ADRs found in dropout cases which were of moderate type.

Maximum dropouts due to ADRs and unknown reason were in Group I whereas it was minimum in group III. These results are in accordance with Divya Shree et al 2014 and Esmaeil Shahsavand Ananloo et al 2013 [7, 9].

Above observed side effect occurs due to interaction of antidepressants (mainly TCA -Imipramine) on multiple receptors such as histamine, cholinergic, dopaminergic and noradrenergic. SSRIs show improved tolerability due to absence of interaction with these receptors [10]. SSRIs causes inhibition of serotonin reuptake therefore most SSRIs side effects are dose related and can be attributed to serotonergic effects [3]. Overall escitalopram appears to be the best tolerated SSRI because of its additional mechanism (allosterically modulate the affinity of ligand at the primary site) which makes it unique among SSRI antidepressants [11]. Overall It is concluded from present study that escitalopram is more tolerable in comparision to imipramine and sertraline.

We suggest that major depressive patients on antidepressants should be watch for any side effect carefully.

Table 1: Group wise analysis of various side effects

Sr. No.	Side effects	Group-I (Imipramine group)		Group-II (Sertraline group)		Group-III (Escitalopram group)	
		No.	Percentage	No.	Percentage	No.	Percentage
1	Anorexia	22	8.14	14	5.18	2	0.74
2	Anxiety	21	7.77	20	7.4	6	2.22
3	Constipation	60	22.22	27	10	3	1.11
4	Diarrhoea	19	7.03	47	17.4	0	0
5	Dry mouth	162	60	70	25.92	17	6.29
6	ECG Changes-						
	(QT Prolongation)	0	0	0	0	13	4.81
7	Flatulance	11	4.07	22	8.14	28	10.37
8	Headache	81	30	68	25.18	24	8.88
9	Insomnia	33	12.22	64	23.7	8	2.96
10	Nausea	48	17.77	37	13.7	3	1.11
11	Sexual side effects	0	0	8	2.96	5	1.85
12	Tachycardia	22	8.14	7	2.59	4	1.48
13	Urinary retention	27	10	17	6.29	6	2.22
	Total	506	49.32	401	39.08	119	11.59

Table 2: VISITWISE DROP OUT CASES

Visits	Group - I (Imipramine group)			Group - II (Sertraline group)			Group - III (Escitalopram group)			Grand total
	Due to adverse effects	Due to unknown reason	Total	Due to adverse effects	Due to unknown reason	Total	Due to adverse effects	Due to unknown reason	Total	
at 4 weeks	17	7	24	19	0	19	13	0	13	56
at 8 weeks	26	13	39	17	0	17	13	0	13	69
at 12 weeks	0	20	20	0	6	6	0	7	7	33
Total	43	40	83	36	6	42	26	7	33	158

References:

1) Ustun TB, Ayuso-Mateos JL, Chatterji s, et al. Global burden of depressive disorders in the year 2000. British Journal of Psychiatry 2004; 184:386-92.

2) Bet PM, Hugtenburg JG, Penninx BW et al. Side effects of antidepressants during long term use in a naturalistic setting. Eur Neuropsychopharmacol. 2013; 23(11):1443-1451.

3) Goldstein BJ, Goodnick PJ. Selective serotonin reuptake inhibitors in the treatment of affective disorder, 3: tolerability, safety and pharmacoeconomics. J Psychopharmacol 1998; 12 (suppl B): S55-S87.

4) Anderson IM. SSRIs versus tricyclic antidepressants in depressed patients: A meta-analysis of efficacy and tolerability. Depress Anxiety 1998; 7 (suppl 1):11-17.

5) Edwards JG, Anderson I. Systemic review and guide to selection of selective serotonin reuptake inhibitors. Drugs 1999; 57: 507-533.

6) Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. Primary Care Companion J Clin Psychiatry 2001 (Feb); 3:22-27.

7) Divyashree M, Jayanthi CR and Chandrashekar H. A comparative study of efficacy and safety of conventional versus newer antidepressants in patients with depressive episode in a tertiary care hospital. Journal of Chemical and Pharmaceutical Research, 2014; 6(2):516-524.

8) Hartwing SC, Siegel J and Schneider PJ. Preventability and severity assessment in reporting adverse drug reaction. Am J Hosp Pharma, 1992; 49: 2229-32.

9) Shahsavand Ananloo E, Ghaeli P, Kamkar MZ, et al. Comparing the effects of fluoxetine and imipramine on total cholesterol, triglyceride, and weight in patients with major depression. DARU Journal of Pharmaceutical Sciences, 2013; 21:4.

10) Nelson JC. Safety and tolerability of the new antidepressant. J Clin Psychiatry 1997; 58 (suppl 6):26-31.

11) Chen F, Larsen MB, Neubauer HA, et al. Characterization of an allosteric citalopram-binding site at the serotonin transporter. J Neurochem, 2005; 92:21-28.