THE EFFECTS OF IMIPRAMINE, SERTRALINE AND ESCITALOPRAM ON BLOOD SUGAR AND WEIGHT: AN OBSERVATIONAL STUDY IN DEPRESSIVE PATIENTS IN A TERTIARY CARE HOSPITAL.

Medical Science

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ABSTRACT

Beckground: Antidepressants medications remain a mainstay of treatment for MDD. It is found that psychotropes (antipsychotics, antidepressants, and mood stabilizers) are associated with metabolic syndrome. Mostly of them may cause weight gain over the course of clinical treatment. Antidepressants also affect glucose homeostasis. This open label, prospective and observational study was conducted to analyze the impact of imipramine, sertraline and escitaloprame on body weight and blood glucose level in major depressive patients.

Methodology: A total of 810 such patients meeting the inclusion and exclusion criteria were randomly divided into three groups i.e. group I, II & III containing 270 patients in each group and treated with imipramine, sertraline and escitalopram as per scheduled dose respectively. Body weight and blood sugar parameters during enrolment visit as well as follow up at 4 weeks, 8 weeks, and 12 weeks were recorded and analysed by ANOVA and paired 't' test.

Results: After 12 weeks of treatment mean value of body weight was increased in all groups. Maximum mean value of body weight was increased with imipramine. After 12 weeks of treatment; mean value of fasting blood sugar level was increased in all groups whereas mean value of post prandial blood sugar was found increased in group I only while Group II & group III showed significantly reduction in mean value of post prandial blood sugar.

Conclusion: Mean weight was increased maximum with imipramine whereas it was minimum increased with escitalopram. In terms of weight parameter, escitalopram was found safer than imipramine and sertraline. After 12 weeks of treatment, significant increase in mean fasting blood sugar as well as mean post prandial blood sugar was found with imipramine whereas significant decrease in mean fasting blood sugar as well as mean post prandial blood sugar level was observed with sertraline and escitalopram. We suggest, for sake of patients's safety, monitoring of body weight and blood sugar should be done before initiation of treatment and regularly during treatment with antidepressants especially with imipramine.

KEYWORDS

Depression, blood sugar, body weight and antidepressants.

BECKGROUND: Depression is a major cause of disability worldwide and third leading cause of global disease burden. By 2030 it will become the leading cause of disease burden if current trends continue [1, 2]. Major depressive disorder (MDD), characterized by at least two weeks of low mood that is present across most situations [3]. Antidepressants medications remain a mainstay of treatment for MDD. Mostly, currently prescribed psychotropics (antipsychotics, antidepressants, and mood stabilizers) may cause 2–17 kg of weight gain [4-7] except few psychotropics that are associates with weight loss [8-10] over the course of clinical treatment.

Various reports describe the impact of antidepressants on glucose homeostasis. Psychotropes are associated with metabolic syndrome. Weight and glucose are the important contributing factor for metabolic syndrome [11]. Antidepressant may interfere the metabolism of glucose. In depressed patients, an impaired glucose tolerance is observed [12]. There may an increased risk of diabetes in patients using antidepressants. Present study was conducted to observe the effects of imipramine, sertraline and escitaloprame on body weight and blood glucose level in depressive patients.

Methodology: This open label, observational and comparative study was performed after obtaining the approval from the institutional ethics committee in patients of depressive disorder visiting OPD (Out 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 as per Beck Depression Inventory Scale score and 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 not enrolled for present study.

Study subjects (total- 810, sample size was calculated by ANOVA test) fulfilling the inclusion/exclusion criteria were randomly assigned into three groups. Each group contained 270 patients and 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.

Body weight and blood sugar level was measured during enrolment visit as well as follow up at 4 weeks, 8 weeks, and 12 weeks in study performa and analysed. Blood sugar was measured as per Triender P's. method [13]. Data were analysed as per appropriate statistical method i.e. ANOVA and Tukey HSD test.

Results: It is evident from table no. 1 (a) that there is no statistically significant difference in mean weight was observed among at baseline. However, a significant difference in mean value of weight among groups was observed at week 4, 8 and 12. At both 8 week and 12 week, there is statistical difference observed in weight between Group I and Group II, while there is no significant difference between Group II and group III was observed at 8 & 12 weeks. Table no. 1 (b) compares the mean weight at baseline and at 12 week for all three groups. Paired 't' statistics suggest that there is statistical difference in mean weight observed at baseline and 12 week for all three groups. It is also clear from this table that mean weight at 12 weeks is higher than the same observed at 4 weeks for all groups.

Table-2 (a) showing that at baseline, there were no significant differences observed in mean Fasting Blood Glucose (mg/dl) among groups. However, at all the three follow up intervals, Group I had

significantly higher mean value as compared to Groups II and III.

In Group I, significant increase in mean FBS levels was observed after completion of treatment (at 12 weeks), however, in Groups II and III, a significant decrease in mean FBS levels was observed after completion of treatment as p values are less than 0.001(table-2b).

In table 3 (a), at baseline, there were no significant differences in mean value of Post Prandial Blood Glucose (mg/dl) among groups. However, at all the three follow up intervals, Group I had significantly higher mean value as compared to Groups II and III.

In Group I a significant increase in mean Post Prandial Blood Glucose levels was observed after completion of treatment (at 12 weeks), however, in Groups II and III, a significant decrease in mean Post prandial Blood Glucose levels for all groups were observed (p<0.001) (table 3 b).

DISCUSSION:
Weight:
In many studies it has been confirmed that mostly prescribed psychotropics (antipsychotics, antidepressants and mood stabilizers) may cause 2-17 kg of weight gain over the course of clinical treatment [4-7]. Their broad pharmacodynamic profile, multiple neurotransmitters, receptors and neurocircuits are responsible for drug induced weight gain. In an animal study, it was found that activation of 5-HT2C receptors decrease eating behaviour whereas lacking of this receptor responsible for obese [14]. It is also known that psychotropics with greater ability to block H1 receptors often show greater weight potential [15], possibly through deactivating brain satiety centers. Psychotropics having high affinity to antagonize alpha adrenoreceptor (e.g. TCA) are associated with weight gain whereas those with lower affinities (e.g. SSRI) are not [16]. Another mechanism may be related to blockage of anticholinergic sites, which is associated with appetite stimulation.

In present study, At the end of 12 weeks treatment, weight was increased of 2.82 Kg on an average in group- I whereas it was slightly increased in group II & III (0.52 Kg and 0.35 Kg) respectively. In this study we found that imipramine has more impact on body weight. These finding were very close to previous studies done by divyashree M. et al, Murat Kesim et al [17-18].

Imipramine has 5-HT reuptake inhibition, NE reuptake inhibition, anticholinergic, adrenoreceptor blocking property [19-23]. In our study, this is the most plausible mechanism responsible for more weight gain in comparison to others.

An average 0.52 kg weight was increase in group- II which was statistically significant. Although SSRIs are associated with weight loss at first, on long term use, it is mostly linked to weight gain. When antidepressants is given to depressed person and treatment become effective there might be a situation where someone feels so much better, lot of things suddenly start feeling more pleasurable to them and food is just one of them because of improve mood. This might be a plausible mechanism for minor increase in weight with sertraline therapy.

In present study, there was an average increase of 0.35 kg weight in patients treated with escitalopram. Similar results were also observed in various studies. For example, 0.6 kg mean weight change after 6 month of treatment with escitalopram for depression, [24] 1.4 - 1.8 kg mean weight gain was reported in 8 month trials of escitalopram for depression [25].

Blood Sugar:
Present study shows a significant increase in mean FBS & mean PPS level after 12 weeks of treatment in patients treated with imipramine; whereas it was significantly reduced in patient treated with sertraline and escitalopram. However values of FBS & PPS remain in normal limits till after 12 weeks of treatment. These findings were very close consistent with other study done by Ghaeli P et al, Divyashree M et al and Karun Kumar et al. Ghaeli P et al found that FBG level was decreased in depressive patients' receiving fluoxetine while it was increased in patients treated with imipramine. Divyashree M et al also confirmed a significant increase in average RBS level in patients receiving imipramine by the end of 12 weeks. Karun kumar et al found that there was a significant decline in FBS & PPS level in patients

treated with escitalopram. Dhavale et al also confirmed the reduction in blood sugar level from their baseline values in patient on escitalopram [17, 26-28]. Karaiskos et al and Murat kasim et al also found reduction in glucose level in patients on sertraline therapy but it was statistically insignificant [18, 29].

Various reports describe the impact of antidepressants on glucose homeostatis are diverse: hypoglycaemic, hyperglycaemic and neutral effects [30]. Exact mechanism is not clear, however it is concerned that insulin sensitivity seems to be play an important role in this regard. Blood sugar level is reduced mainly with escitalopram, fluoxetine and sertraline. SSRIs increase the serotonin in synaptic cleft. Serotonin inhibits glucose-induced hyperglycemia and enhanced the increase in serum insulin level elicited by glucose [31]. It was also noted that the autonomic nervous system and metabolic counter regulatory responses to moderate hypoglycaemia were amplified by fluoxetine [32]. Psychotropics are associated with some adverse metabolic effects [11]. As per previous studies, other literature review and present study; it is concluded that for sake of patient's safety, it must take into the account the influence of antidepressants on glucose homeostasis in depressive patients alone or associated with diabetes.

Conclusion: After 12 weeks of treatment, mean weight was found higher than base line in all groups. Maximum mean weight was increased with imipramine whereas it was minimum increased with escitalopram. Present study shows that imipramine has more impact on body weight in comparision to sertraline and escitalopram. In terms of weight parameter, escitalopram was found more safer than imipramine and sertraline. After 12 weeks of treatment, significant increase in mean fasting blood sugar as well as mean post prandial blood sugar was found with imipramine whereas significant decrease in mean fasting blood sugar as well as mean post prandial blood sugar level was observed with sertraline and escitalopram. We suggest, for sake of patients's safety, monitoring of body weight and blood sugar should be done before initiation of treatment and regularly during treatment with an antidepressants especially with imipramine. Further studies are needed to evaluate the effects of imipramine, sertraline and escitalopram on the body weight and blood sugar on long-term use in depressive patients.

Table 1 (a): Inter and between group comparison of Weight

Visits	Group I (n=270)			Group II (n=270)			Group III (n=270)			Statistical significance (ANOVA)		Between Group comparison (Tukey HSD test 'p' value)		
	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	F	'p'	I vs II	I vs III	II vs III
Baseline	270	57.14	2.28	270	57.29	2.14	270	57.39	2.08	0.88	0.416	0.699	0.387	0.867
At 4 wks	246	57.95	2.27	251	57.49	2.16	257	57.52	2.08	3.40	0.033	0.053	0.072	0.989
At 8 wks	207	58.84	2.34	234	57.65	2.19	244	57.65	2.14	20.70	0.000	0.000	0.000	1.000
At12 wks	187	60.02	2.37	228	57.82	2.20	237	57.83	2.16	64.48	0.000	0.000	0.000	0.999

Table- 1 (b) Within Group evaluation of Change among patients completing 12 weeks of treatment

Group	No. of patients completing 12 wks treatment	At Baseline		At 12 weeks		Statistical Significance (Paired 't'-test)	
		Mean	SD	Mean	SD	't'	'p'
I	187	57.20	2.26	60.02	2.37	-324.84	<0.001
II	228	57.30	2.17	57.82	2.20	-198.26	<0.001
III	237	57.48	2.12	57.83	2.16	-107.13	<0.001

Table 2 (a): Inter and between group comparison of Fasting Blood Glucose (mg/dl)

Visits	Group I (n=270)			Group II (n=270)			Group III (n=270)			Statistical significance (ANOVA)		Between Group comparison (Tukey HSD test 'p' value)		
	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	F	'p'	I vs II	I vs III	II vs III

Visits	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	F	p	I vs II	I vs III	II vs III
Baseline	270	89.25	3.20	270	89.29	3.20	270	89.27	3.15	0.011	0.989	0.987	0.997	0.996
At 4 wks	246	92.35	3.31	251	87.78	3.16	257	87.69	3.12	172.54	.000	0.000	0.000	.943
At 8 wks	207	94.86	3.53	234	87.15	3.16	244	86.93	3.13	414.91	.000	0.000	0.000	.737
At12wks	187	96.36	3.54	228	85.77	3.07	237	85.91	3.09	716.28	.000	0.000	0.00	.880

Table 2(b) Within Group evaluation of Change among patients completing 12 weeks of treatment

Groups	No. of patients completing 12 weeks treatment	At Baseline Mean	SD	At 12 weeks Mean	SD	Statistical Significance (Paired 't'-test) 't'	'p'
I	187	89.36	3.28	96.36	3.54	362.18	<0.001
II	228	89.31	3.20	85.77	3.07	397.17	<0.001
III	237	89.25	3.20	85.91	3.09	454.95	<0.001

Table 3 (a): Inter and between group comparison of Post Prandial Blood Glucose (mg/dl)

Visits	Group I (n=270) No.	Mean	SD	Group II (n=270) No.	Mean	SD	Group III (n=270) No.	Mean	SD	Statistical significance (ANOVA) F	'p'	Between Group comparison (Tukey HSD test 'p' value) I vs II	I vs III	II vs III
Baseline	270	127.60	3.52	270	127.64	3.53	270	127.62	3.49	0.009	0.991	0.990	0.998	0.997
At 4 wks	246	130.70	3.62	251	126.159	3.46605	257	126.045	3.45276	142.01	.000	0.000	0.000	.929
At 8 wks	207	133.190	3.84974	234	125.538	3.43762	244	125.276	3.48301	341.37	.000	0.000	0.000	.702
At12wks	187	134.698	3.87586	228	124.143	3.34963	237	124.274	3.44586	588.81	.000	0.000	0.000	.916

Table 3(b) Within Group evaluation of Change among patients completing 12 weeks of treatment

Group	No. of patients completing 12 wks treatment	At Baseline Mean	SD	At 12 weeks Mean	SD	Statistical Significance (Paired 't'-test) 't'	'p'
I	187	127.70	3.63	134.70	3.88	362.18	<0.001
II	228	127.69	3.47	124.14	3.35	397.17	<0.001
III	237	127.61	3.54	124.27	3.45	454.95	<0.001

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