RESEARCH ARTICLE

A COMPARATIVE STUDY OF THE INFLUENCE OF MOOD STABILIZERS AND/OR ATYPICAL ANTIPSYCHOTICS ON METABOLIC DISTURBANCES

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ABSTRACT

Recent literature has shown that people with mental disorders are more likely to suffer from metabolic syndrome. The question is to what extent is the metabolic syndrome a result of the side effects of medications used in the treatment of bipolar disorder. The aim of this study was to compare various components of metabolic syndrome in patients receiving mood stabilizer alone, with that of combination of mood stabilizer and atypical antipsychotic. The study consisted of 63 bipolar I disorder patients attending OPD and/or admitted for treatment of acute mood episodes. Socio-demographic and clinical variables were noted and metabolic parameters, included body mass index (BMI), fasting plasma glucose, fasting total cholesterol and fasting triglycerides.Among the 63 patients included in the study, metabolic syndrome according to NCEP ATP III set criteria at end of 26 weeks of drug treatment was 6 (9.52%) and 4 (6.35%) in the combination group and mood stabilizer group respectively. Mean changes in weight (t=-6.541, p=0.000), BMI (t=-6.515, p=0.000) and waist (t=-4.498, p=0.000) were highly significant. In our study we noticed that patients on combination therapy of mood stabilizer with atypical antipsychotic had higher metabolic consequences than those receiving mood stabilizers alone. There was significant increase in weight gain in both the groups but it was higher in the combination group. In both the groups there were no statistically significant changes in blood sugar, blood pressure, and serum lipids; however blood pressure, serum triglycerides and cholesterol levels were raised above normal in some patients.

Keywords: Atypical antipsychotics, Bipolar I disorder, Metabolic syndrome, Mood stabilizers

INTRODUCTION

Metabolic syndrome is a constellation of interrelated risk factors of metabolic origin—metabolic risk factors—that appear to directly promote the development of atherosclerotic cardiovascular disease (ASCVD). It is of particular significance in psychiatric community, because of frequent association of its individual components with several psychiatric disorders [1].

Recent literature shows a higher prevalence of metabolic syndrome in patients with bipolar disorder than that expected for age- and gender- matched controls in general population [2], [3]. Research linking mental disorders and metabolic syndrome is in its early stages, especially when it comes to

bipolar disorder. Insight into the complexity of the issues on bipolar disorder and metabolic syndrome includes different factors through a variety of variables: constitutional factors, development conditions, premorbid state, and degree of maturity, emotional stability, intelligence and interaction in etiopathogenesis. A number of investigations focused on association of treatment with mood stabilizers or/and antipsychotics and metabolic syndrome in patients with bipolar disorder. The question is in what extent is metabolic syndrome a result of side effects of medications applied in the treatment of bipolar disorder [4].

MATERIALS AND METHODS
Study design

The present study is a prospective study undertaken at a tertiary care psychiatric hospital in Goa. Permission to conduct the study was obtained from the Institutional ethical committee and Medical Superintendent of IPHB (Institute of Psychiatry and Human Behaviour). Treatment naïve patients diagnosed as Bipolar I disorder, meeting ICD-10 criteria in age group 18-59 years were included in the study. Inpatients as well as outpatients coming for regular follow-ups were a part of this study. Sixty three patients formed the study sample. There were 24 patients on mood stabilizer alone and 39 on a combination of a mood stabilizer and an atypical antipsychotic.

At baseline, a full clinical examination and metabolic screening of the patients was performed. The metabolic screening consisted of fasting blood sugar and lipid profile after an overnight fast to maintain uniformity. During the clinical examination, blood pressure and anthropometric measurements (weight, height and waist

circumference) were obtained by the use of standard protocols and techniques. The same was repeated at 4 weeks, 12 weeks and at the end of 26 weeks.

National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III) guidelines with the following five components of the MetS (Metabolic Syndrome) were used.

1.Abdominal obesity: waist circumference >102 centimetres (40 inches) in men and >88 centimetres (35 inches) in women.

2.Hypertriglyceridemia: >150 mg/dl (1.69 mmol/L).

3.Low high-density lipoprotein (HDL) cholesterol: <40 mg/dl (1.04 mmol/L) in men and <50 mg/dl (1.29 mmol/L) in women.

4.High blood pressure: ≥130/85 mmHg.

5.High fasting plasma glucose: ≥110 mg/dl (≥6.1 mmol/L).
Of these at least three are required for diagnosis of MetS.

Inclusion criteria

Patients of either gender in age group of 18-59 years, diagnosed as Bipolar I disorder, meeting ICD-10 criteria, who were treatment naïve with normal baseline laboratory investigations.
Exclusion criteria
Patients with co-morbid organic psychiatric disorders, substance abuse, pregnant and lactating patients, patients with family history of diabetes, hypertension or any other significant medical condition. Diagnosed patients of diabetes mellitus, hypertension, renal impairment and

hypothyroidism as well as patients suffering from any other significant chronic or life threatening medical or surgical disorders.

Statistical analysis

Change in weight, BMI, waist circumference, blood sugars, serum triglycerides and total serum cholesterol of the 2 groups were compared using independent students t-test. P< 0.05 was considered significant and p< 0.01 as highly significant.

RESULTS AND DISCUSSION

In the present study the effect of metabolic disturbances was studied on bipolar I disorder patients who received medication for a period of 26 weeks. The patients were divided into two groups, one group receiving only mood stabilizer agents and the other group receiving combination of mood stabilizer with atypical antipsychotics (Combination group). It was found that maximum number of patients in the study sample belonged to the age group of 30-39 years. Maximum numbers of patients were prescribed combination therapy out of which Lithium+Risperidone (25.4%) was the most commonly prescribed drug combination.

The mean weight gain in the present study was found to be 2.94 kg in mood stabilizer group and 5.64 kg in combination group. Weight gained ranged from 1 to 5 kg and 1.5 to 9 kg in the above mentioned groups respectively. The dispersion of weight gain is given below in Table 1.

Table 1: Range of weight gain (kilograms) in two groups

| Range of weight gain (kg)	Mood Stabilizer Group Number of patients		Combination Group Number of patients			
	L	V	L+R	V+R	Ox+R	V+Ol
0-1	-	1	-	-	-	-
1-2	2	2	-	-	2	-
2-3	2	4	-	-	2	-
3-4	1	7	1	4	2	-
4-5	2	-	5	3	1	-
5-6	-	-	4	2	-	1
6-7	-	-	2	1	-	-
7-8	-	-	2	2	-	2
8-9	-	-	2	1	-	-

(L:Lithium, V:Valproate, L+R:Lithium+Risperidone, V+R:Valproate+Risperidone, Ox+R:Oxcarbamazepine+Risperidone, V+Ol: Valproate+ Olanzapine)

In this study we found that combining a mood stabilizer with atypical antipsychotic would increase the risk of more weight gain than that would have been caused by mood stabilizer alone (t=-6.541, df=61, p<0.0001). Similar finding were noted in three small placebo controlled studies comparing weight gain caused by drug treatment by Tohen et al [5], Sachs et al [6], Yatham et al [7].

In the present study significant weight gain (7% or more of baseline) at end of 26 weeks of medication was observed in 3.18% and 39.68% of mood stabilizer group and combination group respectively.

Figure 1 shows dispersion of percentage of weight gain at end of 26 week of medication. Weight gain as percentage of body weight ranged from 2 to 7.81 % in mood stabilizer group and 5.79 to 18.37 % in combination group. These findings are in accordance with the findings of Tohen et al [8], noted a weight increase of 2 kg over a 18-month relapse prevention phase with combination olanzapine and divalproex/lithium, compared with weight loss of 1.8 kg in the monotherapy divalproex/lithium group. Clinically relevant increases in weight (≥7% change from baseline) were greater for patients who received combination therapy (27%) versus monotherapy (6%).

Figure 1: Percentage of weight gain in the two groups at end of 26 weeks.
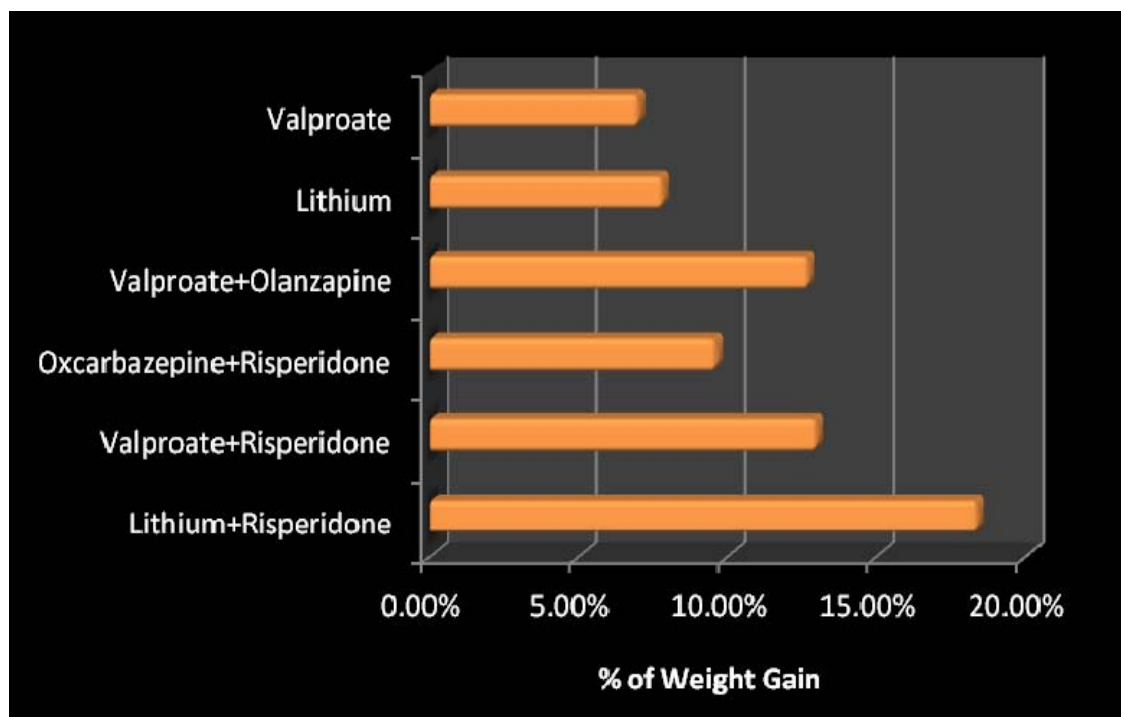
In a prospective 18 month double-blind study conducted by Sachs et al[9] in patients with bipolar I disorder analyzed ≥7% weight change (increase, decrease, fluctuation) treated with lamotrigine (n=227), lithium (n=166) and placebo (n=190). The percentages of patients with a ≥7% weight gain, during randomized treatment, were 10.9%, 7.6% and 11.8% for the lamotrigine, placebo, and lithium groups, respectively. The percentages of patients with a ≥7% weight loss, during randomized treatment, were 12.1%, 11.5%, and 5.1% for the lamotrigine, placebo, and lithium groups,

respectively. The percentage of patients with a ≥7% weight loss did not significantly differ between lamotrigine and placebo but was significantly higher with lamotrigine than lithium. The incidences of ≥7% weight changes and of weight changes reported as adverse events were comparable between active treatments and placebo.

In the present study we also observed that at baseline 19.05 % and 38.1 % of patients in mood stabilizer group and combination group respectively had normal BMI scores according to WHO classification of BMI. At end of 26 week of medication only 12.7 % and 20.64 % of patients in the above mentioned group respectively had their BMI within normal levels. The mean change in BMI of patients in mood stabilizer group was 1.19±0.43 and combination group was 2.19±0.67. Dispersion of BMI at baseline level and after 26 weeks of medication in subjects is as below in table 2.

Table 2: BMI change in the two groups

BMI	Combination Group		Mood Stabilizer Group	
	At baseline	**After treatment**	**At baseline**	**After treatment**
18-24.9	24 (38.1%)	13 (20.64%)	12 (19.05%)	8 (12.7%)
25-29.9	13 (20.64%)	22 (34.92%)	8 (12.7%)	12 (19.05%)
30-34.9	2 (3.18%)	3 (4.76%)	4 (6.35%)	4 (6.35%)
35-39.9	-	1 (1.59%)	-	-
>40	-	-	-	-

McIntyre et al [10], in a cross-sectional study examining effect of valproate on weight gain, and reproductive hormone changes. The study showed an increase in weight and BMI in 38 women being treated for bipolar I or bipolar II disorder with valproate (VPA) or lithium over a mean of 26 months. The mean BMI of those taking VPA was 31.1kg/m^2, slightly greater than those taking lithium.

Fagiolini et al [11], in a study of obesity and weight during acute (4 weeks) and maintenance (12 months) treatment with lithium (N=47), valproate (N=12) and others in bipolar I disorder patients reported that during acute treatment, 14 subjects (28%) gained at least 5% of their baseline BMI. Six subjects (12%) gained more than 10% and 2 (4%) gained more than 15%. Using a paired t-test by BMI classification, they observed that both the normal and overweight group gained a significant amount of weight during acute treatment (normal weight, t=2.25, df=14, p<0.05; overweight, t=2.96, df=17, p<0.01). The median weight gained by normal weight subjects was 4.1% of BMI (5.0 lb). The median weight gained by overweight subjects was 2.9% of BMI (5.5 lb). During the 1st 12 months of maintenance treatment, 13 (26%) of the subjects gained more than 5% of the BMI, but only 3 individuals (6%) gained more than 10%. No subject gained more than 15%. There was a

significant increase in normal weight group only (t=3.07, df=14, p<0.01).

In the CATIE study conducted by Lieberman et al [12], means of increased glucose and percentage of glycated hemoglobin (adjusted for drug exposure time) were 13.7 mg/dl and 0.40% for olanzapine, 7.5 mg/dl and 0.04% for quetiapine, 6.6 mg/dl and 0.07% for risperidone, 5.4 mg/dl and 0.09% for perphenazine and 2.3 mg/dl and 0.11% for ziprasidone. Glycated hemoglobin values for the olanzapine group were significantly higher than for the others; the same did not occur with means of increased glucose [25].

Although the above mentioned study has shown impaired fasting blood sugar, our study failed to show any significant impairment in the two comparisons groups. The mean changes in FBSL were 9.17±6.83 and 8.31±7.55 in mood stabilizer and combination group respectively.

We also found that at baseline all the patients had triglycerides and cholesterol levels in normal range but at end point, 4.76% of patients in mood stabilizer group and 6.35% of patients in combination group had triglycerides values above cut-off limit (>150mg %). The mean change in triglycerides was 30.13±10.92 and 31.82±12.57 in mood stabilizer group and combination group respectively. Cholesterol values were raised in 3.18% and 4.76% of patients in mood stabilizer group and combination group respectively. The mean change in cholesterol values was 26.08±10.71 and 33.89±19.12 in above mentioned groups respectively.

Figure 2 shows the mean changes in the laboratory parameters (blood sugars, serum triglycerides, and serum cholesterol) in the mood stabilizer group and combination group at end of 26 weeks of drug therapy.

Figure 2: Mean changes in lab values with drugs
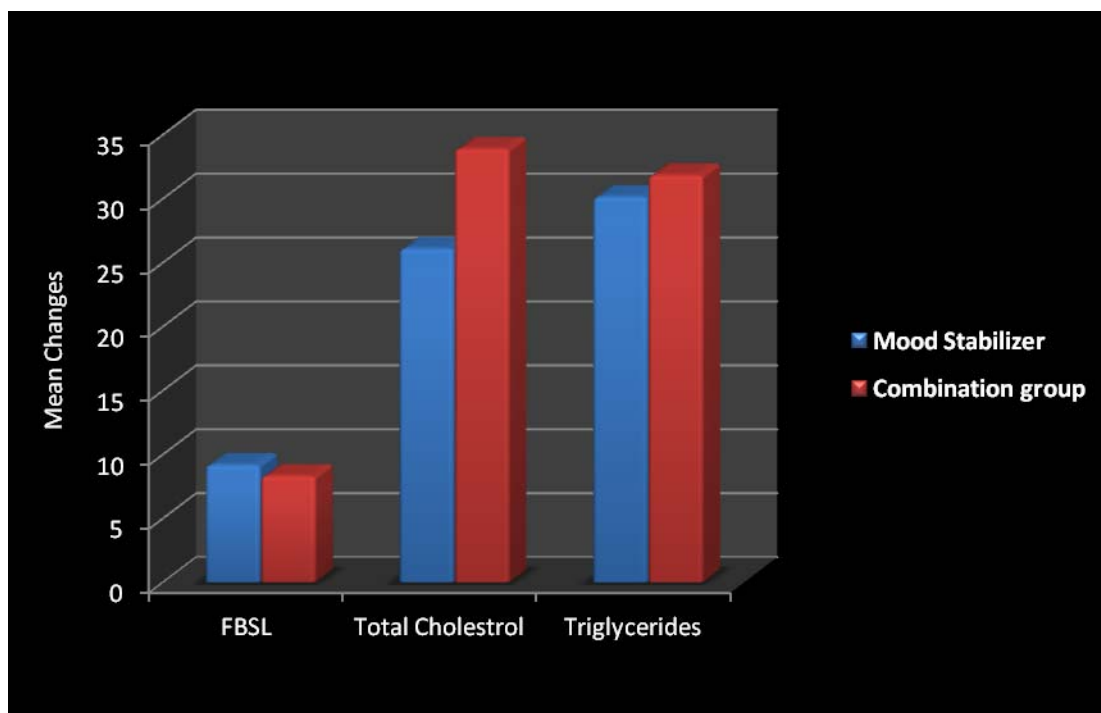
Kim et al [13], conducted a cohort study assessing metabolic abnormalities in patients of bipolar I disorder (N=184) at initiation of acute phase treatment found that 38 (20.7%) had hypercholesterolemia, with 2 (1.1%) receiving cholesterol lowering agents. However, no statistically significant variable was associated with hypercholesterolemia. McIntyre et al [10], in a cross-sectional study of women with BD taking lithium (n = 20) and valproic acid (n = 18), found that total cholesterol, LDL, HDL and triglyceride levels did not significantly differ from mean normal range or between both groups.

In the CATIE study conducted by Lieberman et al [12], the means of increased total cholesterol and serum triglycerides (adjusted for drug exposure time) were 9.4 mg/dl and 40.5% for olanzapine, 6.6 mg/dl and 21.2% for quetiapine, -1.3 mg/dl and -2.4% for risperidone, 1.5 mg/dl and 9.2% for perphenazine and -8.2 mg/dl and -16.5% for ziprasidone. Difference between drugs was significant for both means; however, which one was responsible for such difference was not informed.

Chang et al [14], in a cross-sectional study that included 117 patients diagnosed with bipolar disorder and treated with lithium, valproate or both showed that 36.8% and 53.0% of the patients met the criteria for hypertriglyceridemia and low high density lipoprotein cholesterol (HDL-C), respectively. The prevalence of metabolic abnormalities was significantly higher in patients who have been co-treated with second-generation antipsychotics (SGAs).

Our findings were also similar wherein 6 (9.52%) and 4 (6.35%) of patients in combination group and mood stabilizer group had metabolic syndrome according to NCEP ATP III set criteria.

Considering all the above facts it would be prudent for clinicians to monitor patients taking mood stabilizer especially those receiving combination of mood stabilizer with atypical antipsychotic for weight increase and related metabolic changes, particularly in the first several months of treatment.

To identify and monitor patients with a cardiovascular and metabolic risk, several countries have introduced guidelines for a regular monitoring of the cardiovascular and metabolic risk of patients with psychotic disorders [15]. Based on these guidelines, patients should be screened once a year and more often after antipsychotic drug treatment has been newly started. Long-term follow-up of patients screened on a regular basis will give information on the course of the metabolic syndrome and the specific risk factors associated with the disease.

In the light of the findings in this study and others, psychiatrists should consider measuring BP and waist circumference, two components of the metabolic syndrome, as well as monitoring of weight which are easily assessed in the clinic setting, in addition to measuring fasting glucose, and lipids levels. This is important for early intervention to reduce the high rates of cardiovascular morbidity in severely mentally ill patients.

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