

# CONVENTIONAL AND ATYPICAL ANTIPSYCHOTICS; CHANGES IN GLUCOSE AND CHOLESTEROL LEVELS

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**ABSTRACT.. Objective:** The objective of the study was to compare changes in fasting blood glucose and serum cholesterol levels following initiation of conventional and atypical antipsychotics in patients of psychosis. **Study Design:** An Interventional Comparative design was used. **Place and Duration of Study:** The study was conducted at Department of Psychiatry, Military Hospital Rawalpindi from August 2007 to August 2008. **Patients and Methods:** A total of 110 patients were assigned to treatment with haloperidol (n=35), risperidone (n=36) and olanzapine (n=39). Fasting blood glucose and serum cholesterol levels were recorded at baseline and subsequently repeated at 02nd week, 06th week and 08th week of treatment. In all the subjects, all the blood samples were drawn as a fasting sample in early morning. **Results:** ANOVA analyses indicated that changes in mean fasting glucose and cholesterol levels reached significance in period 2 (from 2nd week to 6th week) but not in period 1 (from 0 to 2nd week) and period 3 (from 6th week to 8th week). The increase in mean fasting glucose and cholesterol levels over time reached statistical significance in the olanzapine group after 6 weeks. No significant change in glucose was detected in the haloperidol and risperidone groups. **Conclusions:** There is a higher risk of hyperglycemia and hypercholesterolemia with olanzapine treatment as compared to risperidone and haloperidol in the study population. These changes appear between 2 to 6 weeks after starting treatment.

**Key words:** Atypical antipsychotics, Metabolic changes

## INTRODUCTION

Abnormalities in glucose regulation have been reported in schizophrenia before and after the introduction of antipsychotic medications. Hyperglycemia in the context of treatment with atypical antipsychotic medications has been documented in several series of uncontrolled case reports, and olanzapine has been implicated more frequently than risperidone. Complicating this issue is the observation that patients with schizophrenia are more likely to develop diabetes mellitus than the general population, regardless of antipsychotic use.

Large epidemiological studies have provided conflicting information regarding the relative risk of diabetes and exposure to different antipsychotics<sup>1</sup>. Case reports have linked treatment with clozapine and olanzapine to hyperlipidemia that disappears when antipsychotic medications are discontinued<sup>2-4</sup>. Medical record reviews further support a connection between clozapine and olanzapine and the increased risk of hypertriglyceridemia<sup>5,6</sup>. In one case-control study, olanzapine and clozapine, but not risperidone or combination therapy, were associated with a significantly increased risk of hyperlipidemia<sup>7</sup>.

Clinical epidemiological studies provide a second line of

evidence linking treatment with antipsychotic medications to an increased risk of hyperlipidemia<sup>7,8</sup>. Prospective research further suggests that antipsychotic medications may adversely affect serum lipids. In one randomized double-blind controlled trial, olanzapine and clozapine resulted in significant increases in total serum cholesterol<sup>9</sup>. In a 4-week trial, olanzapine and risperidone in combination with divalproex were associated with statistically non significant increases in total serum cholesterol<sup>10</sup>. However, the true incidence of both hyperglycemia and hypercholesterolemia induced by different typical or atypical medications is not known in Pakistan at this time.

## OBJECTIVE

The objective of the study was to compare changes in fasting blood glucose and serum cholesterol levels following initiation of conventional and atypical antipsychotics in patients of psychosis.

## PATIENTS AND METHODS

### Study Design

It was an interventional comparative study, which was carried out at Department of Psychiatry, Military Hospital Rawalpindi.

**Sample Size and Technique**

A total of 110 patients were assigned to treatment with haloperidol (n=35), risperidone (n=36) and olanzapine (n=39). Patients diagnosed with psychosis reporting to the facility and consenting for participation in the study were randomly assigned to the three groups of antipsychotics using random number table.

**Inclusion Criteria**

Indoor patients and their next of kin consenting to participate for 8 weeks of indoor treatment with antipsychotics were included in the study.

**Exclusion Criteria**

Patients with history of failure to respond to risperidone, history of olanzapine, risperidone, or haloperidol intolerance, depot antipsychotic treatment within 30 days before random assignment to one of the three drugs and substantial medical illness were excluded from the study.

**Data Collection**

Patients and their next of kin were told about the nature & purpose of the study & their consent was sought. The sample was drawn from the patients reporting to the tertiary care mental health facility of Military Hospital Rawalpindi.

A total number of 110 patients diagnosed with psychosis according to the ICD-10 criteria were taken as the sample and were randomly split into the 3 groups. Those patients who were on antipsychotics were admitted and taken off the medication and a ‘wash-out’ period of 72 hours was observed. An initial early morning, fasting blood sample was obtained for the measurement of fasting blood glucose levels and serum cholesterol levels prior to the administration of antipsychotic medication – conventional (Haloperidol) and atypical (Risperidone and Olanzapine). These were recorded as “baseline levels”.

Fasting blood sugar, serum cholesterol levels and weight were repeated at 02nd week, 06th week and 08th week of treatment. In all the subjects, all the blood samples were drawn as a fasting sample in early morning.

The patients in the study were aware of the medication

they were receiving and thus were not blinded. Those doing the measurements were not blinded as well.

**Data Analysis**

All analyses were carried out with the help of computer software, which include Statistical Package for Social Sciences (SPSS-13). The variables involved in the study were a. Age

- b. Gender
- c. Blood Glucose Fasting
- d. Serum Cholesterol

Values of weight, Blood Glucose Fasting and Serum Cholesterol at baseline, 2nd week, 4th week and 6th week of treatment were fed in the SPSS. Mean values of Blood Sugar Fasting and Serum Cholesterol for all the three groups were calculated for baseline, 2nd week, 6th week and 8th week. Means were compared by using ANOVA. Statistical significance (p<0.05) was noted.

**RESULTS**

The mean age of the study group was 35.45 years (SD=10.21). 73 patients were men, and 37 were women.

| Table-I. Mean Ages of the Study Groups |          |                    |
|--|----------|--------------------|
| Medication                             | Mean Age | Standard Deviation |
| Haloperidol (N=35)                     | 33.77    | 10.34              |
| Risperidone (N=36)                     | 35.11    | 9.94               |
| Olanzapine (N=39)                      | 37.28    | 10.31              |

**Change in Glucose Levels Over Time**

ANOVA analyses indicated that differences among treatment groups reached significance in period 2 (from 2nd week to 6th week) but not in period 1 (from 0 to 2nd week) and period 3 (from 6th week to 8th week). The increase in mean glucose blood levels over time reached statistical significance in the Olanzapine group after 6 weeks (p=0.04). No significant change in glucose was detected in the Haloperidol and Risperidone groups.

**Change in Cholesterol Levels Over Time**

Differences among treatment groups reached significance after 6 weeks. The increase in the olanzapine group reached statistical significance after 6 weeks (p=0.04). No significant change over time in

| Table-II. Gender Distribution of the Study Groups |                    |                    |                   |               |
|---|--------------------|--------------------|-------------------|---------------|
| Gender  | Antipsychotic Used |                    |                   | Total (N=110) |
|   | Haloperidol (N=35) | Risperidone (N=36) | Olanzapine (N=39) | Total (N=110) |
| Male  | 23 (65.7%)         | 24 (66.6%)         | 26 (66.6%)        | 73 (66.3%)    |
| Female  | 12 (34.3%)         | 12 (33.3%)         | 13 (33.3%)        | 37 (33.6%)    |

Fig-1. Change in Mean Glucose from Baseline Over Time

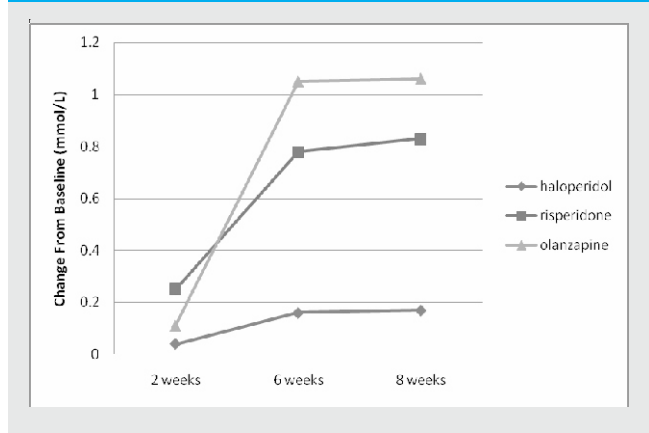
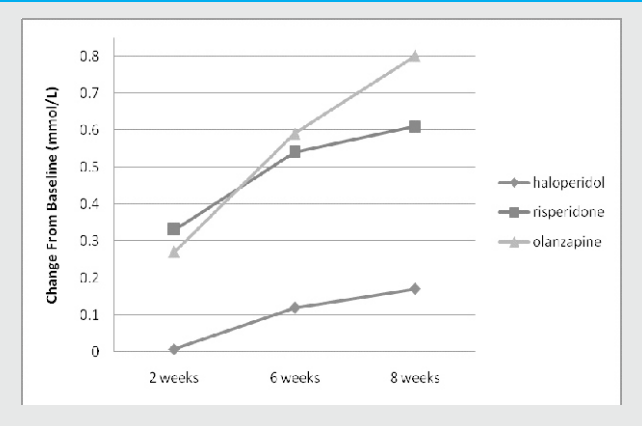


Fig-2. Change in mean cholesterol from baseline over time



cholesterol was detected in the haloperidol and risperidone groups.

**DISCUSSION**

Our study shows that olanzapine is associated with significantly elevated mean glucose levels after 6 weeks of treatment and that risperidone and haloperidol were not associated with significant increases. The mean increases were modest and remained within clinically normal ranges, but 6.3% of patients (six given olanzapine and one given risperidone) developed abnormally high glucose levels (>6.1 mmol/l) during the course of their treatment. Changes in glucose levels were independent of weight increase in all three treatment groups, despite significant weight gains, which were highest for olanzapine, followed by risperidone.

In a nonrandomized study that compared the atypical and typical antipsychotics as our study, similar results were found for olanzapine<sup>11</sup>. When challenged with a modified glucose tolerance test, the olanzapine-treated group had significant elevations in post load glucose levels at all time points compared with untreated control

subjects and haloperidol- treated patients.

Among the traditional neuroleptics, chlorpromazine<sup>12</sup> and thioridazine<sup>13</sup> are the agents most closely associated with diabetes mellitus, although the associations are weaker than those with olanzapine or clozapine. In our study, the typical antipsychotic haloperidol was associated with an elevation of mean glucose levels within a clinically normal range. Haloperidol has been reported to increase insulin resistance and to be associated with higher fasting glucose levels in obese women compared with control subjects<sup>14</sup>. Haloperidol has also been reported to be associated with higher glucose levels in schizophrenia subjects than control subjects during the glucose tolerance test<sup>15</sup>. Increased insulin resistance in peripheral tissues can be caused by hyperprolactinemia<sup>16</sup> and may be involved in the mechanism underlying hyperglycemia in patients treated with typical antipsychotics.

The second important finding of our study is that increase in mean cholesterol levels over time reached statistical significance in the olanzapine group after 6 weeks. There was no significant elevation in cholesterol levels with

risperidone and haloperidol. A similar association between elevated cholesterol and olanzapine treatment was reported by Kinon et al<sup>17</sup>. Our findings are consistent with open-label and retrospective data demonstrating a greater association of olanzapine treatment than risperidone treatment with increases in cholesterol<sup>18</sup>. Henderson et al. found significant increases in both fasting cholesterol and triglycerides in a group of 81 patients treated with clozapine<sup>19</sup>. It appears that the more pronounced effect of antipsychotic treatments on lipid metabolism may be on triglycerides,<sup>20</sup> which were not measured in the present study.

## CONCLUSIONS

Risk of development of hyperglycemia and hypercholesterolemia is significantly high in patients treated with olanzapine.

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Words without actions are the  
assassins of idealism.

*Herbert Hoover (1874 - 1964)*