

## Metabolic Alterations Associated With Antipsychotic Use—A Descriptive Study and Comparison between Haloperidol and Olanzapine in Schizophrenic and Bipolar Patients

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### Abstract

**Introduction:** Antipsychotic drugs are essential to psychiatric health in many conditions, such as schizophrenia and bipolar disorder. However, they present several side effects, such as motor dystonia and “Parkinson-like” behavior (especially in first generation antipsychotics) and metabolic alterations leading to increased body weight, type 2 diabetes and dyslipidemias. Second generation antipsychotics are widely regarded as more damaging in metabolic side effects, though there are few studies comparing if first generation antipsychotics can provoke similar changes in metabolism.

**Methods:** An observational-transversal-descriptive study was conducted in a total of 63 patients in use of their first generation (haloperidol—N=27) or second generation antipsychotic—olanzapine—N=36). Blood samples were collected to assess the following parameters—Fasting Glucose, HDL Cholesterol, LDL Cholesterol, Triglycerides and Basal Insulin. Anthropometric measurements of abdominal and neck circumference, as well as weight were also taken and compared between both groups.

**Statistical analyses:** If variables were considered of normal distribution, the Student *t*-test and variance analyses (ANOVA) were performed to test for significant differences between groups. If samples were considered non-parametric, U Mann-Whitney test, Kruskal-Wallis test, Qui-square for extensive table, or Fish’s test were utilized. Statistical significance was considered 5% on all analyzes ( $p < 0.05$ ).

**Results:** There were no statistically significant differences between both groups using either first and second generation antipsychotics., in relation to anthropometric measurements (abdominal circumference measurements  $p = 0.56$ , U Mann-Whitney test), metabolic status (HOMA index  $p = 0.12$ , HDL cholesterol  $p = 0.27$ , basal glycemia  $p = 0.08$ , BMI  $p = 0.51$ , triglycerides  $p = 0.12$ , Chi-square for extensive tables).

**Discussion:** Metabolic alterations occurred in both groups, which support the literature findings which show a high prevalence of metabolic alteration in antipsychotic medication users.

**Keywords:** Antipsychotic drugs; Schizophrenia; Bipolar disorder; Metabolic syndrome

### Introduction

Schizophrenia and Bipolar Disorder are two psychiatric conditions of great interest in modern times, not only because of their prevalence in psychiatric practice, but because, if untreated by any means, both are associated with higher physical and mental comorbidities, loss in productivity and quality of life and even increase risk of death [1-7].

Bipolar disorder is defined by alterations between episodes depression and mania/hypomania. Depression is characterized by predominant sadness, loss of will and action, weight changes, sleep changes and suicidal ideation. Mania and hypomania are characterized by sudden expansion of affect, mood elevation, inflated self-esteem, decreased need for sleep, increased speed of thought, and psychomotor agitation [1,5]. The exact prevalence is still unknown (considered 2.1% by the World Health Organization). Bipolar disorder normally presents itself in early adulthood, and is correlated with physical and social risks, increasing risk of death by external causes, and suicide by 25% when compared with general population [8].

Schizophrenia is a psychiatric illness defined by changes in course of thought and sense perception, normally presenting itself with delusions and sensory hallucinations. Prevalence is 1% worldwide, generally presenting itself in early adulthood—between 20-30 years of age [2].

### Pharmacological treatments and risk

Treatment for bipolar disorder and schizophrenia may include dopamine receptor antagonists. First appearing in the 1950’s and 60’s, the first generation of dopamine antagonists included chlorpromazine and haloperidol. Both medications were useful for managing agitation, delusional thoughts, and hallucinatory symptoms in psychiatric patients. Side effects included extrapyramidal motor symptoms including tremors and dyskinesia [9,10]. They were also correlated with change in metabolic status, with weight gain and hypercholesterolemia [5-7].

A second generation of dopamine antagonists was introduced in the 1970’s. They offered alternatives for control of both hallucinatory and behavioral symptoms of schizophrenia, and with fewer propensities

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to induce motor side-effects [10]. However, they have been associated greater incidence of metabolic changes such as hypercholesterolemia, hypertriglyceridemia, increased incidence of type 2 diabetes, hypertension and increased general myocardial infarction risk. As documented by many studies, these metabolic alterations collaborate for increased risk of mortality by cardiovascular causes, as well as increased risk of morbidity [5-7,9-11].

There have been few studies comparing the metabolic alterations caused by first and second generation antipsychotics, trying to determine if there is a greater incidence of comorbidities with use of either type of medication [12-15].

## Objective

To determine and compare metabolic status and alterations between two groups of patients: one in current use of first generation antipsychotics and the other second generation antipsychotics in chronic psychiatric treatment for schizophrenia or bipolar disorder.

## Methods

The study was observational-transversal-descriptive, with a total of 63 enrolled patients (N=63), with psychiatric diagnosis of either bipolar disorder or schizophrenia, in use of either typical or atypical antipsychotics drugs for at least 5 years, and enrolled in a municipal service in Santos, São Paulo, specialized in providing consultations and medication—Seção Núcleo de Apoio Psicossocial II. The patients were asked to participate, and gave written consent via form, authorizing blood collection and result divulgence. The study and the consent form were both approved by the Ethics and Human Research Committee of the Santos Prefecture, as well as the Ethics Committee of Centro Universitário Lusíadas.

Exclusion criteria were any psychiatric comorbidities other than those mentioned in inclusion criteria, and current use of any medication to treat diabetes or any form of dyslipidemia. History of metabolic alterations and diseases before onset of psychiatric symptoms (diabetes or hypertriglyceridemia) were also considered exclusion criteria. One single blood collection was performed after patients consented, in which the following parameters were analyzed: fasting glucose, HDL cholesterol, LDL cholesterol, basal insulin and triglycerides in serum concentrations (Figure 1).

The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP-III) criteria were used, and metabolic parameters were considered altered in the following criteria: 1) HDL cholesterol lower than 40 mg/dl for males and lower than 50 mg/dl for females, 2) Triglycerides higher than 150 mg/dl, 3) Fasting glucose higher than 110 mg/dl. LDL cholesterol was considered high if over 130 mg/dl [16].

Basal insulin and fasting glucose were used for calculation of HOMA (Homeostatic Model Assessment) index and Homa Beta Percentage (HOMA B-%), used for measuring type 2 diabetes incidence risk in individual persons (Figure 2). HOMA indexes higher than 1 show increased insulin resistance, and correlated with higher risk for developing type 2 diabetes [17].

Anthropometrics measurements were taken as well, and patients were classified according to WHO BMI Indexes (weight kilograms divided by height in centimeters square), in which patients are classified in straits: *normal weight* if BMI between 18.5 and 25, *overweight* if BMI between 25 and 30, *Obesity type I* if BMI between 30 and 35, *Obesity type II* if BMI between 35 and 40 and *Obesity* for BMI above 40 [18]. The risk for cardiovascular disease is increased directly with increased BMI [19]. Measurements of abdominal circumference were utilized as the main index pointing to greater metabolic risk, and ATP III-NCEP criteria were used as parameters—102 cm for males and 88 cm for females [16] (Figure 3).

Statistical analyses were performed using Kolmogorov-Smirnov (with Lillifors correction) and Shapiro-Wilk tests to test for normal distribution of variables. If variables were considered of normal distribution, the t Student test and variance analyses (ANOVA) were performed to test for significant differences between groups. If samples were considered non-parametric, Mann-Whitney U test, Kruskal-Wallis test, Qui-square for extensive table, or Fish's test were utilized. Statistical significance was considered 5% on all analyzes (p<0.05).

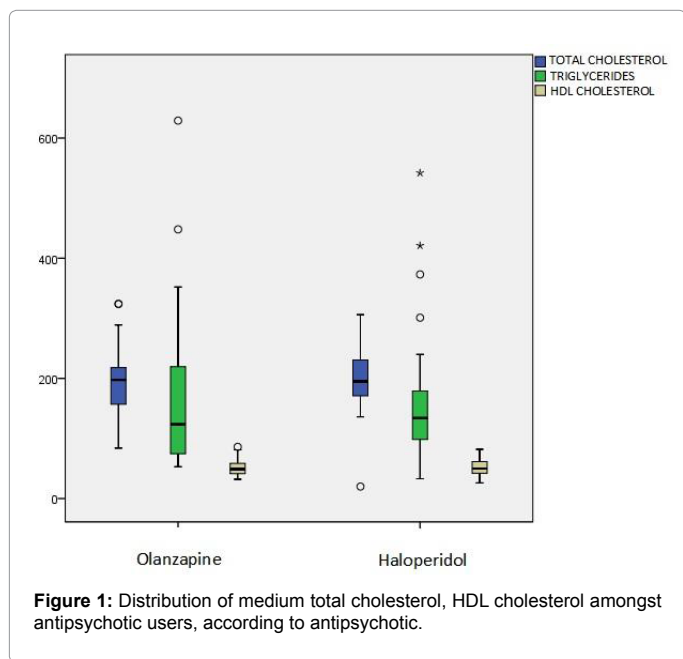


Figure 1: Distribution of medium total cholesterol, HDL cholesterol amongst antipsychotic users, according to antipsychotic.

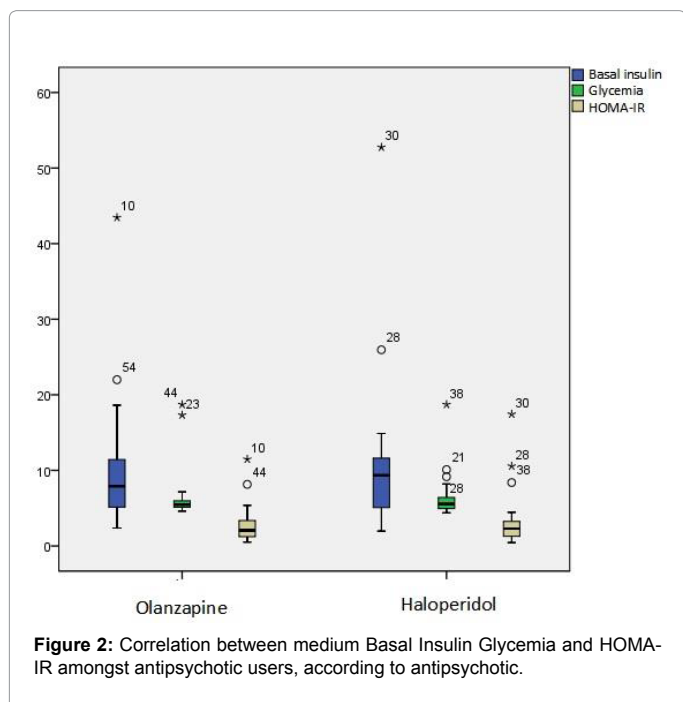
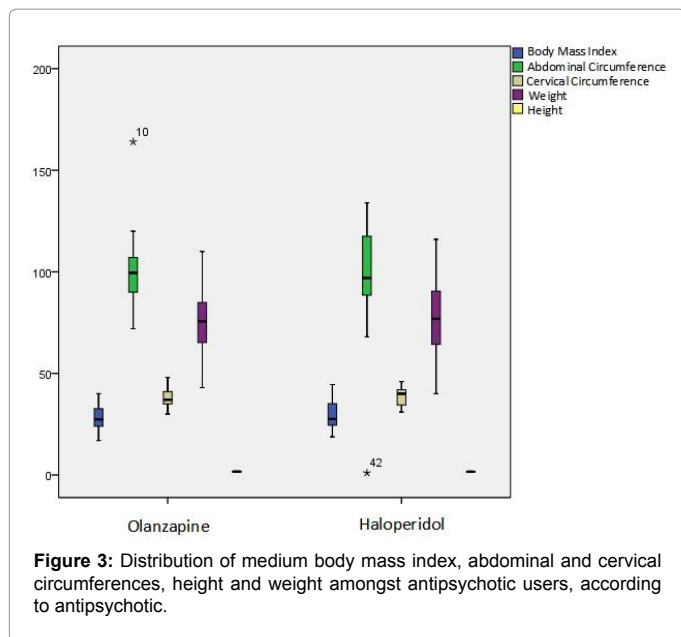


Figure 2: Correlation between medium Basal Insulin Glycemia and HOMA-IR amongst antipsychotic users, according to antipsychotic.



Characteristics	n	%
<b>Gender</b>		
Male	19	30.2
Female	44	69.8
<b>Age (years)</b>		
<40	17	27
40 – 60	38	60.3
>60	8	12.7
<b>Body Mass Index (BMI)</b>		
Eutrofic	20	31.7
Overweight	15	23.8
Obesity I	16	25.4
Obesity II	8	12.7
Obesity III	4	6.3
<b>Diagnosis</b>		
Paranoid schizophrenia (F20)	40	63.5
Bipolar affective disorder (F31)	23	36.5

**Table 1:** Sociodemographic characteristics – gender, age, body mass index and diagnosis of the studied population as a whole (N=63).

## Results

Of the 63 patients in total, N=36 (53.9%) made use of the atypical antipsychotic olanzapine at maximum dose 20 mg daily, and N=27 (46.1%) made use of the typical antipsychotic haloperidol at daily dose of 20 mg daily. There were no statistically significant differences between groups in the following sociodemographic parameters: age, gender, time of use of antipsychotic, smoking or alcohol use in quantity or frequency or significant family history of cardiovascular disease. Other clinical standards were not statistically different between both groups. Olanzapine group: Time of untreated psychosis – 4.23 ± 6.4 years, time of antipsychotic use – 12.1 ± 5 years. Haloperidol group: Time of untreated psychosis – 5.4 ± 4.4 years, time of antipsychotic use – 10.1 ± 3 years. Sociodemographic data can be seen in table 1.

There were, however, no statistical differences between typical and atypical groups in any of the analyzed criteria, as seen in tables 2 and 3, in relation to anthropometric measurements (abdominal circumference measurements p=0.56, Mann-Whitney U test), metabolic status (HOMA index p=0.12, HDL cholesterol p=0.27, basal glycemia p=0.08, BMI p=0.51, triglycerides p=0.12, Chi-square for extensive tables).

## Discussion

The data obtained from this study shows that both groups present metabolic alterations consistent with hypercholesterolemia, hypertriglyceridemia, type 2 diabetes and obesity, however with no significant difference between typical and atypical medication users.

There are limitations to our study, as it does not take into consideration the effect of other psychoactive substances used by bipolar patients (valproate acid, which was the case in our sample) in lipid profile. There is also the possibility that other environmental factors may have played an important role on changing lipid profile: such as antidepressants and mood stabilizers of chronic use.

Second generation antipsychotics present an alternative treatment, as they allow control of behavioral symptoms and less motor side effects when compared with first generation antipsychotics. This leads to better patient adherence and greater improvement in patient outcome [9].

Weight gain and greater cardiovascular risk in antipsychotics-prescribed psychiatric patients, whether it be first or second generation, are shown in many studies as important contributors to higher risk of mortality in this population [4-6].

The goal of modern psychiatry is to improve patient outcome and quality of life. However, results such as shown here demonstrate need to implement new actions of modern health care: the mental health

	Diagnostic-n (%)	
	Schizophrenia (F20)	Bipolar disorder (F32)
<b>Gender</b>		
Male	15 (78.9)	4 (21.1)
Female	25 (56.8)	19 (43.2)
<b>Age (years)</b>		
Less than 40	13 (76.5)	4 (23.5)
More than 40	27 (58.7)	19 (41.3)
<b>IMC</b>		
Eutrofic	10 (50)	10 (50)
Overweight/Obese I-II-III	30 (69.8)	13 (30.2)
<b>HOMA-IR</b>		
Normal	22 (55)	18 (45)
Hyperinsulinemia	18 (78.3)	5 (21.7)
<b>HOMA-Beta</b>		
Normal	32 (59.3)	22 (40.7)
Hyperinsulinemia	8 (88.9)	1 (11.1)
<b>Glycemia</b>		
Normal	22 (61.1)	14 (38.9)
Resistent	18 (66.7)	9 (33.3)
<b>LDL Cholesterol</b>		
Normal	19 (54.3)	16 (45.7)
Elevated	21 (75)	7 (25)
<b>Triglycerides</b>		
Normal	26 (63.4)	15 (36.6)
Elevated	14 (63.5)	8 (36.5)

**Table 2:** Incidence of metabolic alterations according to psychiatric diagnosis (N=63).

	Neuroleptic – n (%)	
	Olanzapine	Haloperidol
<b>Gender</b>		
Male	10 (52.6)	9 (47.4)
Female	26 (59.1)	18 (40.9)
<b>Age (years)</b>		
Less than 40	12 (70.6)	5 (29.4)
More than 40	24 (52.2)	22 (47.8)
<b>IMC</b>		
Eutrofic	12 (60)	8 (40)
Overweight/Obese I-II-III	24 (55.8)	19 (44.2)
<b>HOMA-IR</b>		
Normal	24 (60)	16 (40)
Hyperinsulinemia	12 (52.2)	11 (47.8)
<b>HOMA-Beta</b>		
Normal	33 (61.1)	21 (38.9)
Hyperinsulinemia	3 (33.3)	6 (66.7)
<b>Glycemia</b>		
Normal	22 (61.1)	14 (38.9)
Resistent	14 (51.9)	13 (48.1)
<b>LDL Cholesterol</b>		
Normal	19 (54.3)	16 (45.7)
Elevated	17 (60.7)	11 (39.3)
<b>Triglycerides</b>		
Normal	23 (56.1)	18 (43.9)
Elevated	13 (59.1)	9 (40.9)

**Table 3:** Incidence of metabolic alterations according to neuroleptic use – Olanzapine or Haloperidol (N=63).

professional must not only administer proper medication and manage psychiatric symptoms, but also manage patient cardiovascular risk, whether it is by prescribing proper medication, encouraging eating habit changes and proper exercise routine.

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