

Increased dyslipidemia in schizophrenic outpatients using new generation antipsychotics

Dislipidemia aumentada em pacientes esquizofrênicos ambulatoriais em uso de antipsicóticos de nova geração

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Abstract

Objective: First and second generation antipsychotics are associated with metabolic disturbances. A cross-sectional study was designed to follow outpatients at the Schizophrenia and Dementia Program at a major teaching hospital in Porto Alegre, Brazil (Hospital de Clínicas de Porto Alegre) in order to verify whether second generation antipsychotics were associated with higher glucose and lipid levels regardless of age and gender. **Method:** Four metabolic parameters (cholesterol and fractions, glucose and triglycerides) and anthropometric measures were obtained from 124 consecutive adult outpatients diagnosed with schizophrenia by DSM-IV and ICD-10 with the Operational Criteria Checklist for Psychotic Disorders system using the same antipsychotic drug for at least 9 weeks. **Results:** Most patients had elevated BMI (76.6%) and dyslipidemia (84.7%). Clozapine users had lower HDL levels compared to first generation antipsychotics users. Both groups had elevated body mass index ($p = 0.033$; $OR = 3.3$; $95\%CI = 1.1-9.8$) and second generation antipsychotics ($p = 0.021$; $OR = 3.5$; $95\%CI = 1.1-11.2$) showed significant effect, adjusted for age and gender in the logistic regression for dyslipidemia, and significant age effect for hyperglycemia ($p = 0.030$; $OR = 1.1$; $95\%CI = 1.0-1.1$). **Discussion:** There was statistically significant association between the use of second generation antipsychotics and dyslipidemia. It raises the issue of increased vulnerability of second generation antipsychotics-treated patients, regardless of age, as well as the need for assertive treatment for overweight and dyslipidemia in schizophrenia in order to reduce the risk of diabetes and cardiovascular disease.

Descriptors: Schizophrenia; Lipids; Dyslipidemias; Obesity; Antipsychotics agents

Resumo

Objetivo: Antipsicóticos de primeira e de segunda geração estão implicados em alterações metabólicas. Foi elaborado este estudo transversal para verificar se os antipsicóticos de segunda geração estavam associados a maiores níveis de glicose e lipídeos, independente de idade e sexo, em pacientes atendidos no Programa de Esquizofrenia e Demência do Hospital de Clínicas de Porto Alegre. **Método:** Foram obtidos colesterol e frações, glicose e triglicérides séricos, e medidas antropométricas em 124 pacientes esquizofrênicos, encaminhados consecutivamente, diagnosticados pelo DSM-IV e CID-10 pelo sistema Operational Criteria Checklist for Psychotic Disorders, e em uso do mesmo antipsicótico por, no mínimo, nove semanas. **Resultados:** A maioria dos pacientes apresentou IMC elevado (76,6%) e dislipidemia (84,7%). Os usuários de clozapina apresentaram níveis de colesterol-HDL mais baixos que os de antipsicóticos de primeira geração. O índice de massa corporal elevado ($p = 0,033$; $OR = 3,3$; $IC95\% = 1,1-9,8$) e antipsicóticos de segunda geração ($p = 0,021$; $OR = 3,5$; $IC95\% = 1,1-11,2$) mostraram efeito significativo, ajustado para idade e sexo, na regressão logística para dislipidemia, e efeito significativo de idade para hiperglicemia ($p = 0,030$; $OR = 1,1$; $IC95\% = 1,0-1,1$). **Discussão:** Houve associação estatisticamente significativa entre o uso de antipsicóticos de segunda geração e dislipidemia. Isto levanta a questão da vulnerabilidade aumentada dos usuários de antipsicóticos de segunda geração, independente de idade, e a necessidade do tratamento adequado de sobrepeso e dislipidemia em esquizofrenia para reduzir o risco de diabetes e doenças cardiovasculares.

Descritores: Esquizofrenia; Lipídeos; Dislipidemias; Obesidade; Agentes antipsicóticos

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Introduction

Antipsychotics are the most effective treatment for schizophrenic patients. Nevertheless, the use of both, first generation (FGAs) and second generation (SGAs) antipsychotics, involves important adverse effects, such as weight gain, lipid profile disturbances and glucose metabolism, resulting in metabolic and cardiovascular risk increase.¹⁻²

Obesity became a serious public health problem due to its growing prevalence around the world.³ Its association with the development of comorbidities such as type II diabetes mellitus (DM), hypertension and dyslipidemia is well-known.³

Recent studies have identified high prevalence of hyperglycemia and dyslipidemia in patients treated with SGAs, showing higher association mainly with clozapine and olanzapine.⁴⁻⁵ A review by Allison et al., in 1999, using several antipsychotics, evidenced, weight ranging from 0.39 kg loss with molindone to 4.45 kg gain with clozapine after 10 weeks of treatment.¹ Moreover, schizophrenic patients showed higher risk for morbidities associated with sedentary lifestyle, tobacco use and poor diet.⁵

Based on clinical experience, supported by recent publications relating antipsychotic drugs and weight gain and atherogenic lipid profile,² this cross-sectional study was designed to verify whether SGAs were associated with increased blood glucose and lipid levels in chronic schizophrenic outpatients, regardless of gender or age.

Method

1. Subjects

The study included 124 adult schizophrenic outpatients. Patients were consecutively recruited from March 2003 to August 2005 at a major teaching hospital in Porto Alegre, Brazil (Hospital de Clínicas de Porto Alegre - HCPA). The subjects simultaneously met the schizophrenia diagnosis criteria of DSM-IV and ICD-10 assessed by the OPCRIT system.⁶ No patient had evidence of neurological disorder or current abuse of psychoactive substances. All had been stable under antipsychotic medication for at least 9 weeks. All patients and family members gave written informed consent to participate in this study which was approved by the Ethics Research Committee and Graduation Program of HCPA (# 05-212).

2. Data collection

Patients received standardized assessments: 1) Body mass index (BMI = kg/m²) and body fat percentage (BF%) were used for the anthropometric assessment. Eutrophic status was defined as BMI from 18 to 24.9 kg/m², overweight from 25 to 29.9 kg/m², and obesity over 30 kg/m².⁷ Weight was collected through a calibrated electronic digital scale. Height was obtained through an anthropometer. BF% was assessed by a body fat monitor and classified as normal (women < 30% and men < 20%) and above normal (women ≥ 30% and men ≥ 20%); 2) Biochemical assessment: was measured after a 12-hour fasting period. Dyslipidemia was defined by one or more abnormal blood levels⁷ (total cholesterol > 200 mg/dL, HDL-cholesterol < 50 mg/dL for women and < 40 mg/dL for men, cholesterol-LDL > 160 mg/dL and triglycerides > 150 mg/dL). Pre-diabetes was defined by fasting glucose level between 100-125 mg/dL and DM by fasting glucose level ≥ 126 mg/dL or current use of anti-diabetes medication.⁸

Current medication was obtained from the patients' medical records. Antipsychotic use was divided into four categories: SGAs without clozapine (risperidone, clozapine, olanzapine, amisulpride and ziprasidone), clozapine, FGAs (haloperidol, pimozide, sulpiride, thioridazine, levomepromazine and chlorpromazine) and combination (simultaneous use of two kinds of treatment). All categories included subjects that could be using more than one antipsychotic drug within the same

generation. In the clozapine group, subjects could be using other SGAs.

Tobacco use and physical activity data were obtained from medical records and/or patient's self-reports. Individuals whose records and/or self-reports were positive for tobacco use were considered smokers. The number of cigarettes a day was not assessed. Sedentary-lifestyle was defined by less than 30-minute exercises three times a week.

3. Statistical treatment

The sample size was based on a pilot study of 30 patients. A total of 124 patients were obtained for 80% power, 5% significance level and a 22% difference between prevalence of dyslipidemia between the groups (SGAs and FGAs). The quantitative and qualitative variables were respectively described as mean and standard deviation (SD) or median (25th-75th percentiles) and absolute and relative frequencies. Analyses of variance (ANOVA) or the Kruskal-Wallis were used to compare medication according to quantitative variables. The Pearson's chi-square test was used to study the groups related to qualitative variables. Student's *t* test or the Mann-Whitney non-parametric test were used to compare the variables related to dyslipidemia and hyperglycemia. All variables with *p* < 0.25 in the bivariate analysis were included in the multiple logistic regression model in order to assess possible dyslipidemia and hyperglycemia predictors. The data analysis used SPSS 10.0.

Results

Table 1 describes demographic and clinical characteristics of the total sample and the 4 groups of antipsychotic drug treatment: SGAs without clozapine, clozapine, FGAs and combination. There was statistically significant difference between the groups regarding age and cholesterol-HDL. FGA users were significantly older than the combination group.

Clozapine users had lower cholesterol-HDL than FGA users. All groups showed elevated BMI and around 3/4 (76.6%) were overweight. Fasting glucose level was similar in the groups, except for SGAs without clozapine, showing a pre-diabetes status (≥ 100 mg/dL).

The logistic regression model assessing the predictor variables for dyslipidemia evidenced above normal BMI (*p* = 0.033), with adjusted odds ratio of 3.3 and 95% confidence interval (95%CI) ranging from 1.1 to 9.8. There was also a significant difference in the use of SGAs compared to FGAs (*p* = 0.031), with adjusted odds ratio of 3.5 (95% CI = 1.1-11.2).

Age was the only variable associated with increased glucose levels, with adjusted odds ratio of 1.1 (95% CI = 1.0-1.1), i.e., schizophrenic patients had a 10% increase in the risk of hyperglycemia as they get one year older.

Discussion

In the sample, the percentage of patients presenting BMI above normal was nearly twice as much as the general population in Brazil (76% versus 40%),⁹ and this result is in accordance with foreign authors.¹ There was predominance of overweight tending to obesity and excess body fat in all groups, with increased prevalence of dyslipidemia (84.70%).

There was significant difference between cholesterol-HDL levels in our study, which was not found in Mackin's study.¹⁰ Patients under clozapine had lower cholesterol-HDL levels when compared to FGA users. Likewise, for the other blood levels (cholesterol-LDL and triglycerides), both studies failed to show significant difference between the treatments.

In the logistic regression model, two risk factors appeared as strong predictors of dyslipidemia: BMI above normal and SGAs.

Remarkably, in our study, age was not a predictor for dyslipidemia, since FGA users were older and showed lower

Table 1 – Demographic and clinical characteristics of schizophrenic outpatients under different antipsychotic treatments - HCPA/2005

Characteristics	Total sample (n = 124)	Type of medication				P
		SGAs without clozapine ^d (n = 18)	Clozapine (n = 52)	FGAs (n = 41)	Combination (n = 13)	
Gender – n (%)						
Male	93 (75.0)	11 (61.1)	41 (78.8)	32 (78.0)	9 (69.2)	0.441*
Female	31 (25.0)	7 (38.9)	11 (21.2)	9 (22.0)	4 (30.8)	
Age (years) – Mean ± SD	35.8 ± 9.8	34.9 ± 9.5	35.5 ± 10.0	38.4 ^a ± 9.3	29.9 ± 9.3	0.050**
Weight (Kg) - Mean ± SD	83.8 ± 16.9	86.1 ± 17.7	84.7 ± 17.3	81.2 ± 16.4	84.8 ± 16.6	0.684**
BMI (Kg/m²) - Mean ± SD	28.8 ± 5.5	30.0 ± 5.5	28.8 ± 5.4	28.4 ± 6	28.8 ± 4.3	0.789**
BF% - Above normal – n (%)	99 (79.8)	15 (83.3)	42 (80.8)	32 (78.0)	10 (76.9)	0.603*
Triglycerides - Median (25th-75th %ile)	193.5 (111.0-292.0)	127.0 (80.8-270.3)	234.5 (120.3-324.3)	183.0 (106.0-252.0)	149.0 (76.0-232.5)	0.134***
Total cholesterol - Mean ± SD	211.3 ± 51.0	206.8 ± 45.7	221.3 ± 50.9	205.3 ± 48.5	197.3 ± 58.6	0.299**
HDL - Below normal – n (%)	60 (48.4)	12 (66.7)	30 ^b (57.7)	12 (29.3)	6 (46.2)	0.019*
LDL - Mean ± SD	122.2 ± 37.4	131.5 ± 36.8	123.2 ± 33.9	117.4 ± 37.1	120.0 ± 50.6	0.682**
Glucose - Mean ± SD	104.3 ± 41.4	92.7 ± 10.7	105.8 ± 36.5	108.1 ± 57.6	102.3 ± 14.1	0.627**
Dyslipidemia – n (%)	105 (84.7)	16 (88.9)	48 (92.3)	30 (73.2)	11 (84.6)	0.080*
Time using the drug (weeks) - Median (25th-75th %ile)	72.0 (19.5-161.0)	47.5 (21.0-93.8)	75.0 (27.0-161.0)	93.0 (19.0-161.0)	29.5 (9.3-60.0)	0.063***
Tobacco use – n (%)	43 (34.7)	5 (27.8)	6 (11.5)	17(41.5)	3 (23.1)	0.880*
Physical activity – n (%)	11 (8.9)	1 (5.6)	6 (11.5)	4 (9.8)	0 (0.0)	0.514*

SGAs: second generation antipsychotics; FGAs: first generation antipsychotics; BMI: body mass index; BF %: body fat percentage; HDL: high-density lipoprotein;

LDL: low-density lipoprotein

^a risperidone (n = 7); olanzapine (n = 6); ziprasidone (n = 2); olanzapine + amisulpride (n = 1); olanzapine + risperidone (n = 1); ziprasidone + risperidone (n = 1)

*Chi-square test

** Variance analysis (ANOVA)

*** Kruskal-Wallis test

^a vs Combination

^b vs FGAs

rates of dyslipidemia. In this context, it is assumed that, rather than age, drug use is a more important predictor factor for dyslipidemia.

Similar results were found in a recent cross-sectional study with 62 schizophrenic patients, in which increased BMI was associated with dyslipidemia.¹¹ There are several hypotheses explaining the increased dyslipidemia in schizophrenia. Obesity and weight gain are clearly associated with increased lipid profile in the general population.³ Therefore, it is expected that, once SGAs are likely to be more responsible for weight gain in schizophrenic patients,⁴ they will also be correlated with increased lipid levels.

The association between antipsychotic drugs, altered insulin metabolism and increased diabetes in schizophrenic patients has been reported for several decades. Recent studies confirmed the association of antipsychotic use with increase new onset diabetes.¹²

We found high prevalence of altered glucose profile (40.34%), considering the 100 mg/dL cut-off point. Others have also found high prevalence of hyperglycemia using different cut-off points.^{11,13}

There are descriptions of a progressive relationship between hyperglycemia and cardiovascular events, such as heart attack or stroke, with the risk beginning with glucose levels under diabetes cut-off points. Regular monitoring of blood glucose levels in antipsychotic users has been recommended.¹²

The final model of logistic regression showed increased effect of age. We identified a similar association in a previous study with 194 schizophrenic patients where subjects with DM and reduced glucose tolerance were significantly older than the ones with normal glucose profile.¹⁴ Mukherjee et al., in a prospective study of 95 schizophrenic patients, failed to find age difference between diabetic and non-diabetic patients. However, there was no difference in DM prevalence in the age group under 50 years old, although it showed a 12.9% increase in those between the ages of 50 and 59 and a 18.9% increase in those between the ages of 60 and 69.¹⁵

The greatest limitation of this study is its cross-sectional design, which does not allow for the identification of the putative risk factors before illness onset. Cultural and social variables involving eating habits were not controlled, as well as genetic and psychological variables potentially associated with the regulation of food consumption. The study failed to assess sub-phenotypes, such as family history of schizophrenia, diabetes, hypertension and dyslipidemia.

Despite the limitations, it is important to highlight that the findings of increased dyslipidemia in schizophrenic patients show the necessity of developing a comprehensive multidisciplinary approach to this group aiming to reduce DM and cardiovascular risk.

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