

Weight gain, dyslipidemia and altered parameters for metabolic syndrome on first episode psychotic patients after six-month follow-up

Ganho de peso, dislipidemia e parâmetros alterados para síndrome metabólica em pacientes de primeiro episódio psicótico após seguimento de seis meses

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Abstract

Objectives: Obesity and metabolic abnormalities are frequent in psychotic patients, including first-episode psychosis. We evaluated weight and metabolic parameters in first-episode psychotic outpatients from the First Episode Psychosis Program, Universidade Federal de São Paulo. **Method:** Weight, height, waist and hip circumferences, glucose and lipid levels were measured at baseline and after a six-month period. **Results:** Fifty-seven patients were included and 44 (77.2%) of them finished the study. Patients had a median age of 26.3 years, 60% were men and 43% had a diagnosis of schizophrenia at the endpoint. Weight and BMI values increased significantly during the follow-up ($p < 0.01$). The average weight gain at the follow-up was 10.1% of the baseline weight (SD = 11.9). Only women presented significant waist abnormalities: at the first assessment the waist mean was 79.12 cm (SD = 10.68) and 6 months later it had increased to 89.65 cm (SD = 11.19, $z = -3.182$, $p = 0.001$). After 6 months, the total cholesterol ($p = 0.004$), and triglyceride levels ($p = 0.016$) increased, while HDL-cholesterol levels decreased ($p = 0.025$). During the follow-up period one patient (2.3%) developed diabetes mellitus, one (2.3%) presented altered fasting glucose, 12 (27.2%) patients developed at least two altered parameters for metabolic syndrome and 3 (6.8%) patients developed metabolic syndrome ($p = 0.001$). **Discussion:** The results of this study showed that in a short period of time individuals under antipsychotic treatment had their weight increased significantly and developed important metabolic abnormalities. **Conclusion:** Clinicians should be aware of these risks, choose an antipsychotic that causes less weight gain and should monitor these patients carefully, and recommend prophylactic measures as diet restriction and physical activities.

Descriptors: Psychosis; Primary treatment; Metabolic syndrome X; Obesity; Weight gain

Resumo

Objetivos: Obesidade e alterações metabólicas são freqüentes em pacientes psicóticos, inclusive no primeiro episódio psicótico. Foram avaliados peso e parâmetros metabólicos em pacientes em tratamento no Programa de Episódio Psicótico da Universidade Federal de São Paulo. **Método:** Peso, altura, medida de cintura e quadril, glicemia e perfil lipídico foram avaliados no início do tratamento e após seis meses. **Resultados:** Cinquenta e sete pacientes foram incluídos no estudo e 44 (72%) concluíram o estudo. Os pacientes apresentavam em média 26,3 anos, 60% eram do sexo masculino e, ao final do estudo, 43% apresentavam diagnóstico de esquizofrenia. Houve aumento significativo do peso e índice de massa corporal durante o estudo ($p < 0,01$). Em média, o peso aumentou 10,1% do peso inicial (SD = 11,9). Apenas mulheres apresentaram alterações na medida da cintura: no início, a média da cintura era de 79,12 cm (SD = 10,68) e, após seis meses, houve um aumento para 89,65 cm (SD = 11,19, $z = -3,182$, $p = 0,001$). Após seis meses, houve aumento do colesterol total ($p = 0,004$) e triglicérides ($p = 0,016$), e diminuição dos níveis de colesterol HDL ($p = 0,025$). No período, um paciente (2,3%) desenvolveu diabetes mellitus, um paciente (2,3%) apresentou glicemia de jejum alterada, 12 (27,2%) desenvolveram pelo menos dois parâmetros alterados para síndrome metabólica, e 3 (6,8%) apresentaram síndrome metabólica ($p = 0,001$). **Discussão:** Os resultados deste estudo mostram que em um curto período de tempo pacientes em tratamento com antipsicóticos aumentaram substancialmente o peso e desenvolveram importantes alterações metabólicas. **Conclusão:** Os clínicos devem estar atentos a esses riscos, escolher medicações que causem menor ganho de peso, devendo monitorar esses pacientes cuidadosamente e recomendar medidas profiláticas como restrição dietética e atividade física.

Descritores: Psicose; Tratamento primário; Síndrome X metabólica; Obesidade; Ganho de peso

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Introduction

Antipsychotics had a great impact on psychosis prognosis, and they are considered essential to the treatment of schizophrenia and related disorders.¹ A new generation of antipsychotics has been developed in the last two decades, and the clinicians' concerns about side effects as extrapyramidal symptoms (EPS) and tardive dyskinesia have now been replaced with weight gain and metabolic disturbances such as diabetes, hyperprolactinemia and dyslipidemias.

Patients with schizophrenia were more likely to be overweight or obese, in comparison to the general population² even before the advent of the new antipsychotics, but nowadays, it can be considered one of the main issues in psychosis treatment.

The association between weight gain and some of new antipsychotics was shown in a meta-analysis.³ The weight gain ranged from 0.04 kg with ziprasidone to 4.45 kg with clozapine. Olanzapine and clozapine were associated with a higher weight gain compared to patients taking placebo, who lost, on average, 0.74 kg in ten weeks.

Abnormalities on glucose metabolism are also more common in schizophrenic patients with or without treatment when compared to individuals from general population.⁴ A research based on National Veterans Health Administration data found that, in a period of four months, 38,632 schizophrenic patients received antipsychotic prescriptions, with a percentage of 58.6% of them taking second generation antipsychotics.⁵ These patients presented a higher prevalence of diabetes mellitus, particularly individuals under 40 years old (odds ratio: 1.63, CI 95%: 1.23-2.16).

Metabolic syndrome criteria are hyperinsulinemia, low glucose tolerance, dyslipidemia, hypertension and obesity, and this syndrome represents a major risk of developing cardiovascular diseases.⁶ Having even one or two features of the syndrome associated in one study with increased risk of mortality from coronary heart disease.⁶

The results of an American national multisite prospective trial of antipsychotic effectiveness in patients with chronic schizophrenia (CATIE study) showed that 35.8% (n = 441) of the sample met criteria for metabolic syndrome at baseline.⁷ The prevalence of metabolic syndrome increases with age,⁸ but it might be a concern also in younger patients with psychosis as studies with first episode psychotic patients have shown similar pattern regarding weight gain.^{9,10}

As most of these studies were conducted in developed countries, we decided to investigate the incidence of risk factors for metabolic syndrome in a specialized first-episode psychosis program in São Paulo, Brazil.

Method

The sample was formed by 57 outpatients from a first-episode psychosis program (PEP) in São Paulo, Brazil from August 2003 to December 2004. On admission, these individuals were experiencing their first episode of psychosis and had undergone no more than 3 months of adequate treatment.

This study received approval from the local ethics committee and all participants signed informed consent (n. 1232-03). Completed data for the initial and 6-month assessments were available for 44 patients, 77.8% of the initial sample. At each assessment moment, the weight, height, waist and hip circumferences were measured. Subjects were asked to be present in a 12-hour-fast state for laboratory analysis (glucose and lipid levels). Weight was evaluated without shoes, with the individuals wearing light clothes. Waist was considered at the level of navel.¹¹ The measures were collected by the same

investigator in all assessments.

Table 1 - Antipsychotics at baseline assessment and after 6 months on first episode patients

Drugs	Baseline assessment n (%)	6-month assessment n (%)
No antipsychotic	3 (6.8)	5 (11.4)
Low potency antipsychotics*	6 (13.6)	1 (2.3)
Haloperidol 5-15 mg	9 (20.4)	2 (4.5)
Risperidone 1-6 mg	22 (50.0)	16 (36.4)
Olanzapine 2,5-20 mg	3 (6.8)	7 (15.9)
Aripiprazole 15-30 mg	1 (2.3)	4 (9.1)
Quetiapine	0	2 (4.5)
Ziprasidone	0	1 (2.3)
Research**	0	6 (13.6)
Total	44	44

* Chlorpromazine 100-300 mg, sulpiride 50-200 mg, thioridazine 50-100 mg

** Confidential research using two second generation antipsychotics

The metabolic syndrome definition from the National Cholesterol Education Program (NCEP), 2001, was used, which comprises three or more of the following symptoms: 1) high blood pressure, i.e., $\geq 130/85$ mmHg (or a history of hypertension); 2) abdominal obesity i.e., waist circumference > 102 cm in males and > 88 cm in females; 3) fasting blood glucose ≥ 110 mg/dl (or a history of diabetes mellitus); 4) fasting HDL cholesterol < 40 mg/dl in males and < 50 mg/dl in females; 5) fasting triglycerides ≥ 150 mg/dl.¹²

As this is a naturalistic study, the antipsychotic was not controlled (Table 1). At initial assessment, 26 (59.1%) patients were taking second generation antipsychotics, mainly risperidone (n = 22, 50%) and at the second assessment moment, 34 (81.8%) were on low dose of second-generation antipsychotic.

Data analysis was performed by SPSS 11.5. Weight, BMI and waist were tested using Wilcoxon test, which is a (non) parametric test for continuous data; for categorical data (cholesterol, triglycerides, fasting glucose, altered parameters for metabolic syndrome), Marginal Homogeneity Test – MH, an extension of McNemar test, was used. Mann-Whitney test was performed to compare age between male and female group.

Results

The mean age of the sample was 26.3 years old. Women were significantly older (mean = 32.8, SD = 16.2) than men (mean = 21.9, SD = 4.8; $z = -2.058$, $p = 0.04$). The mean duration of the illness was 187.9 days (SD = 346.5) and at the end of the study, 19 (43.2%) patients had a diagnosis of schizophrenia. Table 2 shows weight, BMI and waist at the baseline and after a 6 months period, separated by gender. As

Table 2 - Weight, BMI and waist at baseline and after 6 months on first episode patients

	Baseline	6-month	Analysis	p
Female (n = 18)				
Weight (mean; SD)	59.8 (13.2)	66.3 (13.9)	Z = -3.267	0.001
BMI (mean; SD)	23.9 (4.9)	26.5 (5.1)	Z = -3.332	0.001
Waist (mean; SD)	79.12 (10.68)	89.65 (11.19)	Z = -3.182	0.001
Male (n = 26)				
Weight (mean; SD)	65.1 (15.5)	70.4 (14.7)	Z = -2.96	0.003
BMI (mean; SD)	21.5 (4.6)	23.2 (4.2)	Z = -2.984	0.003
Waist (mean; SD)	80.08 (12.83)	81.6 (14.50)	Z = -1.008	0.313

Table 3 - Laboratorial tests at baseline and after 6 months on first episode patients

Clinical parameters	Baseline assessment n (%)	6-month assessment n (%)	Analysis	p
Total Cholesterol				
Low (< 200 mg/dl)	37 (88.1)	28 (68.3)	MH = -2.887	0.004
Borderline (200-239 mg/dl)	4 (9.5)	11 (26.8)		
High (> 240 mg/dl)	1 (2.4)	2 (4.9)		
Total	42	41		
LDL Cholesterol			MH = -1.219	0.223
Low (< 100 mg/dl)	25 (59.5)	19 (47.5)		
Normal (100-129 mg/dl)	12 (28.6)	13 (32.5)		
Borderline (130-159 mg/dl)	4 (9.5)	6 (15.0)		
High (160-189 mg/dl)	1 (2.4)	2 (5.0)		
Total	42 (100)	40 (100)		
HDL Cholesterol			MH = 2.236	0.025
Low (< 40 mg/dl)	10 (23.8)	21 (51.2)		
Normal (40-60 mg/dl)	26 (61.9)	15 (36.6)		
High (> 60 mg/dl)	6 (14.3)	5 (12.2)		
Total	42 (100)	41 (100)		
Triglycerides			MH = -2.400	0.016
Low (< 150 mg/dl)	38 (90.5)	32 (80.0)		
Borderline (150-200 mg/dl)	4 (9.5)	1 (2.5)		
High (201-499 mg/dl)	0	7 (17.5)		
Total	42 (100)	40 (100)		
Fasting glucose			MH = -1.342	0.180
Normal	42 (100)	40 (95.2)		
Abnormal	0	1 (2.4)		
Diabetes mellitus	0	1 (2.4)		
Total	42 (100)	42 (100)		

it can be seen, weight and BMI increased significantly during the follow-up period in both male and female ($p < 0.01$). On average, patients gained 10.1% of their initial weight (SD = 11.9), but only women presented significant waist abnormalities: at the first assessment the waist mean was 79.12 cm (SD = 10.68) and 6 months later it had increased to 89.65 cm (SD = 11.19, $z = -3.182$, $p = 0.001$).

At baseline, 88.1% of the sample had the total cholesterol values at normal range, but at the end of the study the percentage decreased to 68.3%, and this difference was statistically significant ($p = 0.004$). As shown on Table 3, the number of patients with low HDL increased from 10 (23.8%) to 21 (51.2%) after the 6-month period ($p = 0.025$). At baseline, no patient had high triglycerides; six months later 7 (17.5%) patients presented triglycerides above 201 mg/dl ($p = 0.016$).

One patient (2.3%) developed diabetes mellitus during the study, and just one (2.3%) presented altered fasting glucose (MH = -1.342, $p = 0.180$).

Although blood pressure was not measured in this study, the number of patients that met criteria for metabolic syndrome was investigated at the beginning and at the end of the study. At baseline, just one patient had metabolic syndrome, but at the end of the follow-up period, 4 patients (9.1%) met the criteria. One patient (7.7%) was taking a first generation antipsychotics (chlorpromazine), and 2 (15.4%) were not taking antipsychotics at the beginning of study; at the endpoint, the same patient taking chlorpromazine was taking haloperidol and all the others were taking second generation antipsychotics.

Thirteen (29.5%) of the patients developed at least two altered parameters for metabolic syndrome (MH, $p = 0.001$). Family history of diabetes was found in 20 (45.5%) patients; 12 (27.3%) patients had a family history of obesity and 9 (20.5%) patients

had a family history of dyslipidemia. There were no significant differences regarding family history of diabetes, obesity and dyslipidemia between those subjects who developed abnormal parameters with those who did not.

Discussion

Weight gain and metabolic abnormalities are side effects more frequently associated to second generation antipsychotics (SGA). Patients presented a significant weight gain during the study, and this is consistent to the literature.³

Dyslipidemia is a side effect of antipsychotics, especially second generation antipsychotics (SGA).⁴ Leitão-Azevedo et al. found a prevalence of 84.7% of dyslipidemia on a cross-sectional study of 124 schizophrenic patients.¹³ In our sample, total cholesterol and triglycerides increased, and HDL cholesterol decreased after treatment, what can cause an increase in cardiovascular diseases.

In this sample of first-episode psychosis patients, the frequency of altered parameters of metabolic syndrome was 29.5% after six months. Twelve patients developed altered parameters for metabolic syndrome, and three patients developed metabolic syndrome. Metabolic syndrome incidence may be underestimated since the blood pressure was not assessed.

Ryan et al. assessed visceral fat distribution on drug-naïve first-episode patients with schizophrenia and compared it to a control group.¹⁴ They selected 19 patients and 19 controls. Patients had three times more intra-abdominal fat (IAF) than matched control subjects, although they were not obese (measured by BMI). Abdominal obesity is a key component of metabolic syndrome, especially in females.¹⁵ In our study, women presented waist to hip ratio altered,

and this data is also seen in other studies.^{14,16} In the last decade, metabolic syndrome prevalence has increased and according to a recent review on gender differences in metabolic syndrome, this increase has been steeper in women, particularly in the young ones,⁸ as we observed in our sample: we found metabolic syndrome in young women (from 14 to 19 years). A literature review on the clinical effects of the new antipsychotics in women has recommended the rational use of sex specific antipsychotic treatment.¹⁷ However, clinical trials of the new antipsychotics have been conducted, for the most part, in male participants,¹⁸ although there have been recent reports about sex differences regarding side effects and subjective tolerability of antipsychotic drugs in psychotic patients.^{19,20}

Prevention is still the most important procedure to avoid weight gain.²¹ Faulkner et al., in a systematic review, evaluated 16 pharmacological and behavioral interventions for weight management in schizophrenic patients.²² The conclusions of the study were the following: only three studies showed at least 5% of body weight reduction; pharmacological studies are restricted because these medications may worsen psychotic symptoms, and it would be necessary to study more behavioral interventions. Weight management programs based on nutritional counseling, physical activity and behavioral interventions have been developed recently^{23,24} and when treating an at-risk patient, physicians need to be vigilant in monitoring antipsychotic medication.²⁵ Collaboration between the psychiatric and diabetology or endocrinologist teams is essential to minimize the risk of diabetes and obesity in patients taking second generation antipsychotics.²⁶

Limitations of the present study are its relatively small sample size, lack of a control group and, as it was a naturalistic study, the treatment was not controlled. Sedentary lifestyle was not assessed during the study, and we know that this is an important factor on prevention of cardiovascular and metabolic diseases.

The losses to the follow-up were relatively low (22.8%), assuming that young patients have more difficulties to comply with treatment.²⁷

Conclusions

The results of this study showed that, in a short period of time, individuals under antipsychotic had their weight increased substantially/significantly and developed important metabolic abnormalities. Health care services should adopt prophylactic measures in order to prevent weight gain and metabolic disturbances.

References

- Nasrallah H. A review of the effect of atypical antipsychotics on weight. *Psychoneuroendocrinology*. 2003;28(Suppl 1):83-96.
- Allison DB, Fontaine KR, Heo M, Mentore JL, Cappelleri JC, Chandler LP, Weiden PJ, Cheskin LJ. The distribution of body mass index among individuals with and without schizophrenia. *J Clin Psychiatry*. 1999;60(4):215-20.
- Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999;156(11):1686-96.
- de Sena EP, Sampaio AS, Quarantin LC, Oliveira IR. Diabetes mellitus e antipsicóticos atípicos. *Rev Bras Psiquiatr*. 2003;25(4):253-7.
- Sernyak MJ, Leslie DL, Alarcon RD, Losonczy MF, Rosenheck R. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry*. 2002;159(4):561-6.
- Khunti K, Davies M. Metabolic syndrome. *BMJ*. 2005;331(7526):1153-4.
- Meyer JM, Nasrallah HA, McEvoy JP, Goff DC, Davis SM, Chakos M, Patel JK, Keefe RS, Stroup TS, Lieberman JA. The clinical antipsychotic trials of intervention effectiveness (CATIE) schizophrenia trial: clinical comparison of subgroups with and without the metabolic syndrome. *Schizophr Res*. 2005;80(1):9-18.
- Regitz-Zagrosek V, Lehmkuhl E, Weickert MO. Gender differences in the metabolic syndrome and their role for cardiovascular disease. *Clin Res Cardiol*. 2006;95(3):136-47.
- Addington J, Mansley C, Addington D. Weight gain in first-episode patients. *Can J Psychiatry*. 2003;48(4):272-6.
- Zipursky RB, Gu H, Green AI, Perkins DO, Tohen MF, McEvoy JP, Strakowski SM, Sharma T, Kahn RS, Gur RE, Tollefson GD, Lieberman JA. Course and predictors of weight gain in people with first-episode psychosis treated with olanzapine or haloperidol. *Br J Psychiatry*. 2005;187:537-43.
- Sistema de Vigilância Alimentar e Nutricional (SISVAN). Manual de Orientações Básicas para a Coleta, Processamento, Análise de Dados e Informação em Serviços de Saúde (2004). [citado 15 fev 2007] Disponível em: www.saude.gov.br/alimentacao/.
- Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-97.
- Leitao-Azevedo CL, Guimaraes R, Abreu MG, Gama CS, Lobato MI, Belmonte-de-Abreu PA. Increased dyslipidemia in schizophrenic outpatients using new generation antipsychotics. *Rev Bras Psiquiatr*. 2006;28(4):301-4.
- Ryan MC, Flanagan S, Kinsella U, Keeling F, Thakore JH. The effects of atypical antipsychotics on visceral fat distribution in first episode, drug-naïve patients with schizophrenia. *Life Sci*. 2004;74(16):1999-2008.
- Sacks FM. Metabolic syndrome: epidemiology and consequences. *J Clin Psychiatry*. 2004;65(Suppl 18):3-12.
- Graham KA, Perkins DO, Edwards LJ, Barrier RC Jr, Lieberman JA, Harp JB. Effect of olanzapine on body composition and energy expenditure in adults with first-episode psychosis. *Am J Psychiatry*. 2005;162(1):118-23.
- Seeman MV. Gender differences in the prescribing of antipsychotic drugs. *Am J Psychiatry*. 2004;161(8):1324-33.
- Chaves AC, Seeman MV. Sex selection bias in schizophrenia antipsychotic trials. *J Clin Psychopharmacology*. 2006;26(5):489-94.
- Barbui C, Nose M, Bindman J, Schene A, Becker T, Mazzi MA, Kikkert M, Camara J, Born A, Tansella M. Sex differences in the subjective tolerability of antipsychotic drugs. *J Clin Psychopharmacol*. 2005;25(6):521-6.
- Aichhorn W, Whitworth AB, Weiss EM, Marksteiner J. Second-generation antipsychotics: is there evidence for sex differences in pharmacokinetic and adverse effect profiles? *Drug Saf*. 2006;29(7):587-98.
- Greenberg I, Chan S, Blackburn GL. Nonpharmacologic and pharmacologic management of weight gain. *J Clin Psychiatry*. 1999;60(Suppl 21):31-6.
- Faulkner G, Soundy AA, Lloyd K. Schizophrenia and weight management: a systematic review of interventions to control weight. *Acta Psychiatr Scand*. 2003;108(5):324-32.
- Menza M, Vreeland B, Minsky S, Gara M, Radler DR, Sakowitz M. Managing atypical antipsychotic-associated weight gain: 12-month data on a multimodal weight control program. *J Clin Psychiatry*. 2004;65(4):471-7.
- Attux C, Araújo C, Roma A, Mateus M, Campagna L, Canguçu D, Bressan R. Brazilian Wellness Program: results from first year. *Int J Neuropsychopharmacol*. 2006;9(Suppl. 1):S156.
- Lieberman JA 3rd. Metabolic changes associated with antipsychotic use. *Prim Care Companion J Clin Psychiatry*. 2004;6(Suppl. 2):8-13.
- Reis AF. Antipsychotic drugs and metabolic syndrome: can we prevent it? *Rev Bras Psiquiatr*. 2007;29(1):9-10.
- Kelly DL, Conley RR, Carpenter WT. First-episode schizophrenia: a focus on pharmacological treatment and safety considerations. *Drugs*. 2005;65(8):1113-38.