Original article

Overweight and obesity in schizophrenic patients taking clozapine compared to the use of other antipsychotics

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INTRODUCTION

Antipsychotics have been crucial for the treatment of schizophrenic patients, allowing them to stay with their families, thus reducing number and time of hospitalizations and improving their acceptance by the community.[1] Among the drugs for the treatment of schizophrenia, both clozapine and most second-generation antipsychotics (atypical) display the peculiar profile of less extrapyramidal effects and lower prolactin increase, with higher treatment adherence and relatively higher recurrence prevention. However, these drugs are more associated with weight gain and metabolic disturbances,[2,3] such as type II diabetes mellitus and atherogenic lipid profile, although both antipsychotics, typical (first generation) and atypical, are associated with these clinical complications.[4-7] Despite these adverse effects, only clozapine, among all antipsychotics, presents evidence of clinical effect in antipsychotic-refractory or treatment-resistant patients, representing about 20% of all cases.[1]

Increase in body weight was observed in more than 50% of schizophrenic patients who receive antipsychotic drugs in general.[8] Body mass index (BMI) is significantly higher in schizophrenic patients compared to psychiatric patients with other diagnosis and to the general population.[3] Additionally, increased body weight is also associated with reduced self-esteem, treatment dropout,[2,9] and increased risk of comorbid conditions.[10] Data from the Brazilian Ministry of Health show a prevalence of 32% for overweight and 8% for obesity in the general population.[11]

The national survey of the Ministry of Health (2002-2003) and the Brazilian National Cancer Institute (INCA), covering 15 Brazilian capital cities and in Distrito Federal, showed a prevalence of 27.99% of overweight and 10.26% of obesity in the general population. In Porto Alegre, the rate of excess body weight (overweight + obesity) is as high as 43.1%.[12] Although that population-based study failed to identify schizophrenic patients, it suggested a double effect on nutritional morbidity in schizophrenia (epidemic increase in the general population added to drug effect in this special group). This “double effect” causes an additional threat to patients, added to higher disability rate, early retirement, and lower quality of life. Excessive body weight

substantially increases mortality and morbidity of several clinical disorders, such as hypertension, dyslipidemia, type II diabetes mellitus, heart diseases, gallbladder diseases, osteoarthritis, sleep apnea, respiratory problems, and endometrial, breast, prostate and colon cancer,[13] thus reducing survival and quality of life of schizophrenic patients. Studies show that these patients present three-fold higher mortality rate than the general population, due to higher prevalence and severity of clinical status,[14,15] with consequent cardiovascular risk.[4]

Magnitude of weight gain varies according to drugs and dosage, with some drugs evidencing gains from 1.5 to 8.8 kg.[4,16,17] Several studies have provided evidence of significant weight gain after short- and long-term administration of atypicals, compared with typical antipsychotics.[3,4,6,17,18]

With regard to the use of atypical antipsychotics, a review study has shown that subjects taking sertindole, risperidone and ziprasidone presented lower weight gain compared to patients taking clozapine and olanzapine.[4] Another study found similar results, with clozapine and olanzapine being responsible for higher weight gain than risperidone and sertindole.[17]

In addition to weight increase, hyperlipidemia and diabetes have also been associated with significant complications in these patients. Most studies suggest the prevalence of diabetes and obesity among individuals with schizophrenia and affective disorders is approximately 1.5-2 times higher than in the general population.[7]

Increased frequency of type II diabetes mellitus and obesity has been associated with the growing use of antipsychotics, although it is difficult to determine whether the prevalence of these complications would be specific, or independent of specific drug selection. Most of the data came from studies with schizophrenic patients; even under these conditions, evidence is quite limited. It is important to stress that there is evidence that first-episode schizophrenic patients who have not received specific medication have three-fold higher visceral adiposity,[19,20] less tolerance to glucose, and more resistance to insulin than healthy controls.[21]

Environmental factors involving lifestyle may predispose to mortality and morbidity associated with weight gain and endocrine and cardiovascular diseases. Smoking, alcohol use,

inadequate diet, and sedentary lifestyle all increase mortality in the general population. Besides high rates of smoking (50-90%) and alcohol abuse in this population, studies also show evidence of high fat consumption and low levels of fibers in diet than the reference population. Additionally, there is also an association of antipsychotic drug use with increased appetite and carbohydrate craving. Sedentary lifestyle, also present in schizophrenic patients, may be partly due to the negative symptoms of the disease and the sedative effects of antipsychotics, besides long periods in hospital beds.[22]

Some researches suggest that, besides sexual hormones, thyroidal hormones are also involved in changes of lipid profile and cardiovascular risk.[23-26] Other metabolic changes secondary to antipsychotic drug use are hyperprolactinaemia[27] and subsequent changes on reproductive hormones, such as estradiol and testosterone. Besides menstrual irregularities, hormone changes are associated with galactorrhea, sexual disorder, infertility, weight gain, and mood changes.[28] In addition, increase in cortisol has also been shown in psychiatric patients and is associated with visceral obesity, insulin resistance, and diabetes.[29]

Considering the complexity of obesity and overweight, with the interaction of genetic factors under multifactorial conditions related to the environment, there is a need for better understanding of this interaction.[30] Recent researches have addressed the understanding of the association between use of antipsychotics and weight gain.[8,17,31] Regulation of body weight is a complex mechanism, involving food consumption, energy expenditure, satiety, and other factors still unidentified in appetite control. In general, antipsychotic agents act on different neurotransmitter systems, and atypical antipsychotics particularly have a wide range of action on these multiple systems regulating body weight. Among the different mechanisms previously identified, weight gain has been associated with higher affinity of atypical antipsychotics to histamine, serotonin and dopamine receptors.[18] A preliminary study by our group, with a 1-year follow-up of Brazilian female adolescents exposed to psychoactive drugs, clearly showed the effect of antipsychotics on weight gain, compared with antidepressants and anticonvulsants. This study is

being currently expanded to explore differences among psychiatric diagnoses (schizophrenia and other psychotic disorders) and types of antipsychotics used.[32]

Despite the lack of understanding of the causes of these physical changes, a common finding is excessive body weight and its associated morbidities. Therefore, schizophrenic patients also seem to present an increased risk for clinical changes related to obesity, such as type II diabetes and cardiovascular disease,[4] even before the use of antipsychotics, although their use predisposes to risk increase.

Based on the extensive evidence of weight gain associated with antipsychotic drug use and on the lack of specific studies in schizophrenic patients in Brazil, a cross-sectional study was carried out for the assessment of differences in weight and obesity among schizophrenic patients exposed to clozapine and other antipsychotics.

METHOD

The study included adult patients, aged 18 years or older, of both genders, receiving regular care at the Outpatient Clinic of the Schizophrenia Program (PRODESQ) at Hospital de Clínicas de Porto Alegre (HCPA). The program is supported by the Brazilian Unified Health System (SUS), with universal access, with no restriction of class, gender or ethnicity for residents at the catchment of Porto Alegre Metropolitan Area (RS).[33] Patients were consecutively included, and had to meet the DSM-IV and ICD-10 diagnostic criteria for schizophrenia without evidence of neurological disease and current psychoactive drug abuse.

The sample was composed of 121 patients. Of these, 53 were treatment-refractory (using clozapine alone and/or combined with other typical and/or atypical antipsychotics), and 68 were non-refractory. Non-refractory patients were subdivided into 50 patients who were only taking typical antipsychotics (alone and/or combined with haloperidol, pimozide, sulpiride, thioridazine, levomepromazine, and chlorpromazine) and into18 patients taking atypical antipsychotics other than clozapine (alone and/or combined with risperidone, olanzapine, amisulpride, and ziprasidone).

In the latter group, the patients could also be taking typical antipsychotics concomitantly. Both groups included patients who were receiving other drugs, such an anticonvulsants, benzodiazepines, mood stabilizers, and antidepressants.

All these patients were submitted to standardized psychiatric and anthropometric evaluations, as follows:

a) Standardized psychiatric evaluation: consisted of four psychiatric interviews performed by an interviewer (psychiatrist or psychologist) using the diagnostic system Operational Criteria Checklist for Psychotic Illness (OPCRIT),[34,35] recording at least three information sources (patient, family and medical charts) about the occurrence of psychiatric symptoms throughout the patient's life. All patients and family members received a semi-structured interview with OPCRIT guidelines, by previously trained interviewers.[36]

b) Anthropometric evaluation: obtained by data collection on weight and height by nutritionists, calculating BMI (weight/m^2). For this calculation, weight was measured using an electronic digital scale, gauged by the Brazilian National Institute of Metrology, Standardization and Industrial Quality (INMETRO), with a 50-g variation and maximum capacity of 150 kg. Patients were placed standing at the center of the scale base, without shoes and wearing light clothes, which were subtracted using the standard estimate previously standardized by the researchers. Height was obtained with a wall anthropometer, with a 0.1 cm variation. Individuals were placed standing, without shoes, ankles together, flat back, and arms stretched along the body. The BMI classification followed the criteria of the Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults,[37] with overweight defined as BMI from 25 to 29.9 kg/m^2, and obesity as BMI over 30 kg/m^2. Obesity was divided into three classes: grade I (mild), with BMI from 30 to 34.9 kg/m^2; grade II (moderate), with BMI from 35 to 39.9 kg/m^2; and grade III (severe), with BMI equal or higher than 40 kg/m^2.

All patients and family members signed an informed consent, approved by the Ethics Commission of HCPA (GPPG), and the National Research Ethics Committee (CONEP).

Statistical treatment

Data analysis was performed using the software Statistical Package for Social Sciences (SPSS 8.0).

According to the Kolmogorov-Smirnov test for normality, the quantitative variables presented normal distribution and were described through average and standard deviation (SD). For the qualitative variables, description was made using absolute and percentage frequencies. The chi-square test was used to verify the association between neuroleptic resistance, BMI and gender. The Student's *t* test for independent samples was used to study the association of age with antipsychotic resistance. To verify the association between age and BMI, we used Pearson's linear correlation. Multiple linear regression was used to control confounding variables and to test whether a variable would change the effect of another variable present in the model over the outcome of BMI. The chi-square test was used to compare BMI between the studied sample and the Brazilian population. Significance level was set at 5%.

RESULTS

Patients' mean age was 34.46 years (SD ± 9.14). Mean weight obtained in the sample was 82.15 kg (SD ± 16.63), and mean BMI was 28.19 kg/m^2 (SD ± 5.58).

Qualitative variables were described in absolute and percentage frequencies, with a predominance of males (78.5%). There was a higher prevalence of overweight and all three obesity degrees when analyzed together (72.73%), in relation to "below normal" and "normal" ranges, also grouped in the analysis, with 27.27% of the total ($\chi^2 = 25.0$; $p < 0.001$). An equivalent percentage was seen in both categories of the variable "use of clozapine" (table 1).

Table 1 - Distribution of adult patients with schizophrenia diagnosis (DSM-IV and ICD-10) at HCPA, according to gender, BMI category and use of antipsychotics (2004)

Variables	**n**	**%**
Gender		
Male	95	78.50
Female	26	21.50
BMI category		
Below normal – below 18.5 kg/m^2	2	1.65
Normal – 18.5 to 24.9 kg/m^2	31	25.61
Overweight – 25 to 29.9 kg/m^2	48	39.67
Obesity (total)	40	33.06
Grade I – 30 to 34.9 kg/m^2	27	22.31
Grade II – 35 to 39.9 kg/m^2	9	7.44
Grade III – 40 kg/m^2 or more	4	3.31
Use of clozapine		
Present*	53	43.80
Absent**	68	56.20

BMI = body mass index.

* Use of clozapine alone and/or combined with other typical and/or atypical antipsychotics.

** Subdivided into 18 patients taking atypical antipsychotics, except clozapine (alone and/or combined with themselves and/or with typical antipsychotics), and 50 patients taking typical antipsychotics (alone and/or combined with themselves).

In the group of patients taking clozapine, there was an overweight and obesity percentage of 77.4%, whereas in the other group it was 69.1%; this difference was not statistically significant (p =

0,421). Similarly, there was no BMI difference between typical and atypical antipsychotic use (p = 0.440) and between males and females (p = 0.769).

However, there was a directly proportional association between age and BMI. This association is represented in figure 1.

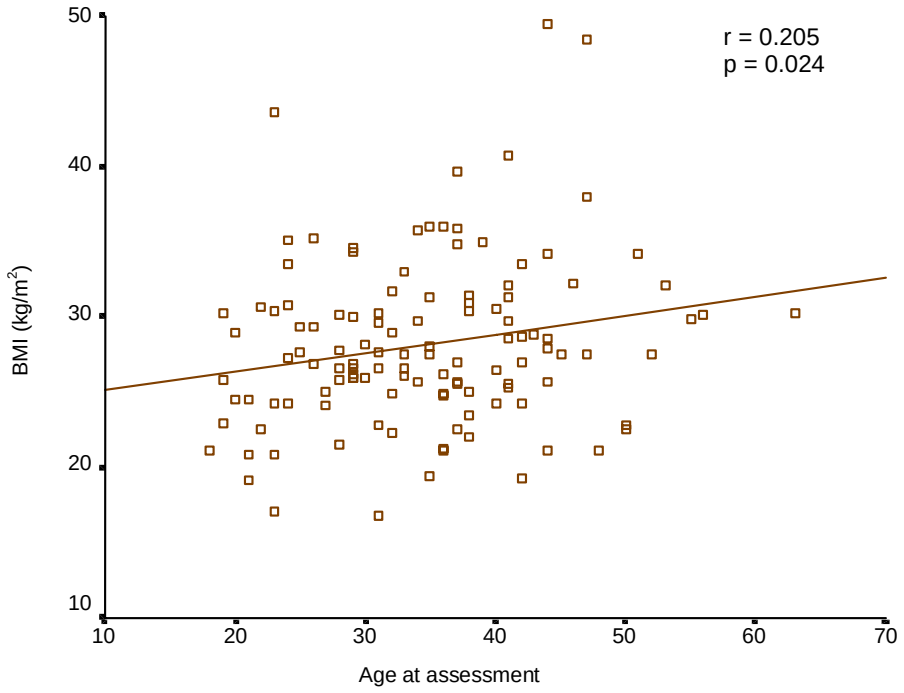

Figure 1 - Correlation between age and BMI of schizophrenic patients at HCPA (2004).BMI = body mass index.

Table 2 shows the linear regression model for BMI according to age and use of clozapine. Age was the only predicting variable significantly associated with BMI. The interpretation for the beta coefficient related to age would be that, at each increase in 1 year of age, patients increase in average 0.17 kg/m^2 in BMI.

Table 2 - Linear regression of age and use of clozapine as predictors of BMI in 121 schizophrenic patients at HCPA (2004)

	B	SE	ß	t	p
Constant	22.23	2.65		8.40	0.000
Age	0.17	0.07	0.27	2.23	0.028
Use of clozapine	3.63	3.94	0.33	0.92	0.358
Use of clozapine *versus* age	- 0.09	0.11	- 0.29	- 0.80	0.428

BMI = body mass index; B = angular coefficient; SE = standard error; ß = standardized coefficient; t = Student's *t* test.

DISCUSSION

The main finding of this study shows that the BMI of refractory patients (taking clozapine) and of patients taking other antipsychotics is in the overweight/obesity range, without statistically significant differences between groups. Similarly, the BMI of patients taking typical antipsychotics is similar to patients taking atypical antipsychotics.

Obesity is associated with several comorbid conditions and with increased mortality,[7] and these patients present an increased risk for the development of clinical conditions related to cardiovascular diseases, such as dyslipidemia, hypertension, type II diabetes mellitus and metabolic syndrome.[22]

Sample results show that the overweight and obesity problem affects both patients taking clozapine and those taking other antipsychotics. This aspect is apparently in opposition to several studies showing increased weight gain with the use of second-generation antipsychotics, compared to first-generation antipsychotics.[3,4,6,7,17,18] Most evidence reported in the literature is based on case-control studies, pharmacovigilance and database reviews. Many of them present disadvantages, such as their retrospective nature, heterogeneous methodology, presence of systematic assessment errors and lack of adequate or well-characterized controls.[7]

Antipsychotics, both typical and atypical, produce weight gain,[4] although it is difficult to differentiate weight gain patterns between these drugs. Although weight gain represents a collateral effect commonly reported for antipsychotic drugs, it seems to be more common in patients taking atypical antipsychotics.

Meta-analyses, literature reviews, data from clinical trials and clinical experience show that some patients present a significant weight gain while taking antipsychotics. An extensive meta-analysis, including more than 80 studies and more than 30,000 measurements, has associated clozapine, as well as olanzapine, with more weight gain compared with other antipsychotics (typical and atypical).[4] Wirshing et al.,[17] in a retrospective analysis of 92 schizophrenic male patients, have noted a higher weight gain with clozapine and olanzapine, compared with risperidone, haloperidol and sertindole. Covell et al.,[39] in an open randomized clinical trial (n = 227), obtained a higher weight gain with clozapine, compared to other typical antipsychotics. It is interesting to remark that, in that study, other second-generation antipsychotics were not available yet. Furthermore, since patients had already been taking first-generation antipsychotics for several years, and many of them presented initial weight gain at the beginning of the study, the authors considered that the additional weight gain could not be attributed to a specific medication or to a cumulative effect of all the years taking antipsychotics.

In our study, the lack of differences on BMI of patients taking clozapine and other antipsychotics may probably reflect the study design, which does not allow for cause and effect inferences, only associations. Although we could not measure the attributable risk of weight gain association with antipsychotics drugs and the differential risks between classes of drugs could not be quantified in this study, there is clear evidence that overweight and obesity are predominant in both groups. It is thought that the sample size would have a low probability of markedly influencing the association between BMI and use of clozapine, due to high sample descriptive level ($p = 0.421$). If this level had borderline significance, that would be more likely.

Weight gain is a common collateral effect of several drugs, including most antipsychotic agents. Patients taking antipsychotics often make concomitant use of other parallel drugs to treat psychiatric symptoms and/or clinical events common to the general population. When patients receive multiple agents that cause weight gain, the effects can be addictive and lead to obesity. Among them, antidepressants stand out, reported in the literature as being related to weight gain, as well as mood stabilizers and anticonvulsant drug use, with a well-documented weight gain potential.[18] The treatment itself, combining atypical antipsychotics, seems to have an additional effect that induces weight gain.[18]

The present study controlled the effect of age on BMI using the linear regression, showing that the positive association between age and BMI did not change the lack of association between clozapine use and BMI. BMI increased according to age reinforces the findings by Grundy (1998) about the tendency of gradual weight gain with age in the general population. The same study also stresses that weight gain in maturity is associated with factors such as reduction in baseline metabolism rate, resulting from loss of muscle mass, reduction in physical activity and increase in food consumption.[38]

Since the patients from our sample were all covered by SUS, an additional study was performed using data of adult population from the Brazilian Ministry of Health.[12] This comparison evidenced that the BMI distribution of schizophrenic patients from our sample significantly differed from the BMI of Brazil and general population in Porto Alegre. We found increased overweight and obesity among our patients, with odds ratio of 4.29 of being overweight than the Brazilian general population, and 3.51 times of being overweight than the adult population in Porto Alegre. This is consistent with evidence from the literature, which shows, in average, higher levels of BMI in schizophrenics taking antipsychotics than in the general population.[3,4,8]

Due to the study design, there are limitations associated with cross-sectional studies collecting data from chronic patients with long lasting illnesses using different drugs throughout the treatment and with poor medical records about weight before antipsychotics drug use and

progressive weight changes over exposure to drugs. Additionally, drug type, dose and duration of use were not specified, neither there was any control of cultural, social, genetic and psychological variables associated with eating behavior, consumption and energy expenditure.[40]

Despite the limitations, it is important to stress that the findings in this study allow us to state that schizophrenic patients, under continued use of antipsychotics are at higher risk for obesity and deserve clinical, nutritional, psychiatric and psychological attention, since obesity is a risk factor for several health problems that increase morbidity and mortality rates.

In this context, the authors warn about the necessity of more detailed studies, including higher number of subjects and with better information about previous treatment, in order to disentangle the process and magnitude of weight gain between different neuroleptics, with the identification of interactions with other drugs, especially anticonvulsants and antidepressants, and assessment of the residual effect of a drug over the subsequent one.

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ABSTRACT

Background: *The use of antipsychotics has been crucial in the treatment of schizophrenic patients. However, clozapine, as well as most atypical antipsychotics, may lead to higher weight gain and metabolic changes.*

Objective: *To compare the frequency of overweight and obesity between schizophrenic patients exposed to clozapine to the prevalence of patients exposed to other antipsychotics.*

Method: *This study assessed 121 schizophrenic outpatients aged 18 years or older, both genders, consecutively referred to an outpatient clinic for schizophrenia and dementia at Hospital de Clínicas de Porto Alegre, a public hospital in Porto Alegre, Brazil. Anthropometric measures of 53 patients taking clozapine and of 68 taking other antipsychotics were assessed. All patients met DSM-IV and ICD-10 diagnostic criteria for schizophrenia.*

Results: *There was no significant difference in body mass index between schizophrenic patients taking clozapine and patients taking other antipsychotics. Analyses showed high frequency of overweight and obesity (72.7%).*

Discussion: *Due to higher frequency of overweight in the schizophrenic population, it was possible to confirm a higher risk of vascular and metabolic disorders in the sample. Absence of a significant difference with regard to the use of clozapine, compared to other antipsychotics, provides evidence for the need of prospective studies in order to determine the magnitude of weight gain and risk increase related to specific exposure to each antipsychotic drug.*

Keywords: *Schizophrenia, obesity, antipsychotics.*

Title: *Overweight and obesity in schizophrenic patients taking clozapine compared to the use of other antipsychotics*

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