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ORIGINAL RESEARCH

Weight gain, metabolic disturbances, and physical health care in a Brazilian sample of outpatients with schizophrenia

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Background: In the last few decades, a large number of studies have produced compelling evidence that patients with schizophrenia are at increased risk for developing several medical conditions and diseases, including obesity, metabolic disturbances, and cardiovascular diseases. Several protocols have been designed with the aim of reducing such risk.

Objective: To investigate current physical health status in a population of outpatients with schizophrenia.

Methods: A cross-sectional study was conducted in our outpatient clinic, selecting subjects who met DSM-IV diagnosis criteria for schizophrenia. Data were collected regarding clinical characteristics, lifestyle, medication in use, and biometric and laboratory parameters.

Results: A total of 261 patients were included. We found a high prevalence of elevated body mass index (BMI $>$ 25) (70%), dyslipidemia (73.2%), and metabolic syndrome (28.7%). Patients' ages were associated with worsened lipid profiles, but other variables, such as disorder duration or type of antipsychotic in use, were not associated with any metabolic disturbance. Despite the increased prevalence of these conditions, only a small portion of the sample was under regular medical treatment.

Conclusion: Outpatients with schizophrenia show signs of poor physical health conditions. These findings reinforce the need for an intensive and appropriate approach to assure that these patients receive adequate clinical referral and treatment.

Keywords: psychosis, obesity, public health, antipsychotic drugs, cardiovascular disorders

Introduction

Patients with schizophrenia are at increased risk for several physical morbidities, including respiratory, infectious, metabolic, and cardiovascular diseases (CVDs).[1] Many factors contribute to increase the risk for such conditions, and most of them are intertwined. First, the onset of mental disorder is correlated with the adoption of a series of behaviors that are implicated in an increased risk for such diseases, including smoking, inadequate diet, and sedentarism.[2,3] Those behaviors both aggravate and lead to other clinical conditions also prevalent among patients with schizophrenia, such as obesity, hypertension, diabetes mellitus, dyslipidemia, and cancer.[2,4–6] The use of antipsychotic drugs is also known to be strongly correlated with increased risk for medical diseases in patients with schizophrenia.[7–9]

Although antipsychotic medications are currently the gold-standard treatment for schizophrenia, both first-generation (FGAs) and second-generation antipsychotics (SGAs) are associated with increased risk for the aforementioned physical morbidities, with CVDs being the most studied and having the most replicated studies.[10,11]

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In fact, there is evidence that SGAs, despite having demonstrated a higher efficacy in the treatment of schizophrenia and fewer adverse effects,[12] are associated with higher risk for CVDs than are FGAs.[13–15] It has been speculated that this effect, added to the increasing prescription of these medications, might be responsible for an even higher burden for this population of patients and for health services in decades to come.[2]

The objective of the present study was to investigate the current physical health of a sample of outpatients with diagnoses of schizophrenia regarding metabolic disturbances and cardiovascular risk using clinical history and biometric and laboratorial parameter assessment.

Methods

All outpatients of the Schizophrenia Research Program (PROJESQ) at the Institute of Psychiatry, Clinics Hospital, Faculty Of Medicine, University of São Paulo, Brazil (Instituto de Psiquiatria do Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo), who were willing and able to give a written informed consent, were included in this research, carried out in 2008. The inclusion criteria were a diagnosis of schizophrenia, both sexes, and age between 18 and 70 years. The diagnosis of schizophrenia was made after clinical interview, followed by discussion and agreement of the specialized team psychiatrist, in accordance to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV criteria for schizophrenia.[16] The study was approved by the Research Ethics Committee of HC-FMUSP.

Data regarding clinical and demographical information, as well as information on patients' habits (whether the patient currently smoked and performed regular physical activities) and medical treatment at the time of investigation (whether the patient was under any medical treatment other than psychiatric), were collected through interviews. The biometric data were collected through physical examination and involved weight, height, waist, and hip circumference measures, and blood pressure. Laboratory analysis was conducted by the hospital's laboratory of clinical analysis (Divisão de Laboratório Central, HC-FMUSP), and included blood glucose and lipid profile (total cholesterol, fractions, and triglycerides). Overweight was defined as body mass index (BMI) equal to or higher than 25 kg/m^2. Glucose intolerance, diabetes mellitus, dyslipidemia, and metabolic syndrome were defined according to the National Cholesterol Education Program (NCEP), National Institutes of Health (NIH).[17,18]

The collected data were statistically analyzed using SPSS software (v 14.0; SPSS Inc, Chicago, IL). The statistical methods include descriptive statistics, correlation analysis, chi-square test, Mann–Whitney test, variance analysis, and post hoc analysis for comparison between groups (Tukey's honestly significant difference test). During the data analysis, patients were divided into four groups according to the current antipsychotics in use: 1) FGAs, 2) SGAs, 3) clozapine, and 4) polypharmacy (association of two or more antipsychotics).

Results

We included 261 patients who met the inclusion criteria and agreed to participate in the study.

General features

The descriptive analysis of the sample revealed important characteristics of the population under treatment. Our patients had a broad variance of age (mean age 35.6 years; standard deviation [SD] ± 10.1) and duration of disorder (mean duration 13.8 years; SD ± 8.2), though it would be possible to affirm that it consisted mostly of chronically ill patients (27.2% had more than 20 years of disorder). Some indirect data suggested that a significant proportion of the patients presented with a severe form of the disorder, since approximately half of the patients needed at least one psychiatric hospital admission, and 18 had more than five admissions. Almost 40% of the sample were using clozapine as monotherapy, 10% in association with another antipsychotic (in the majority of cases, due to refractoriness of the disorder).

Concerning life habits, we found a high prevalence of smoking (55.2%), mainly among men. Sedentariness was also very prevalent (95%). The demographics, habits, biometrics, and laboratorial information are summarized in Table 1.

Use of medications other than antipsychotics

The use of antidepressants was found in almost 30% of the sample; no association was found concerning its use and weight gain or other metabolic disturbances. The association of valproate with clozapine was the most common association of mood stabilizers and antipsychotics in this sample ($\chi^2 = 25.6$, $P = 0.012$, df = 12), mainly indicated for prevention and control of seizures related to high doses of clozapine. This association was not found to be significantly correlated with any metabolic disturbances analyzed. Table 2 summarizes information on the use of antipsychotic drugs and other medications.

Table 1 Demographic and clinical features of the sample

Demographics	Total n = 261	Men n = 182 (69.7%)	Women n = 79 (30.3%)	P
Age (years), mean ± SD	36.5 ± 10.1	35.8 ± 9.42	37.9 ± 11.6	0.293
Duration of disease (years), mean ± SD	13.48 ± 8.1	13.9 ± 8.3	12.4 ± 7.6	0.221
Hospital admissions, mean ± SD	1.91 ± 2.6	1.92 ± 2.5	1.9 ± 3.1	0.468
Life habits				
Smoking, n (%)	144 (55.2%)	118 (64.8%)	26 (32.9%)	<0.000*
Physical activity, n (%)	14 (5.4%)	8 (4.4%)	6 (7.6%)	0.292
Biometric and laboratory data				
Body mass index, mean ± SD	27.9 ± 5.5	27.7 ± 5.4	28.3 ± 5.6	0.287
Waist–hip ratio, mean ± SD	–	0.94 ± 0.08	0.9 ± 0.12	–
Systolic blood pressure (mmHg), mean ± SD	118.2 ± 15.7	119.4 ± 15.7	115.4 ± 15.4	0.014
Diastolic blood pressure (mmHg), mean ± SD	76.7 ± 10.8	77.1 ± 10.0	75.75 ± 12.5	0.285
Total cholesterol (mg/dL), mean ± SD	198.3 ± 42.4	194.2 ± 42.9	207.7 ± 40.7	0.045*
HDL (mg/dL), mean ± SD	48.5 ± 16.9	45.3 ± 14.1	55.8 ± 20.3	<0.000*
LDL (mg/dL), mean ± SD	115.6 ± 38.5	114.1 ± 34.8	119.1 ± 40.2	0.292
Triglycerides (mg/dL), mean ± SD	178.8 ± 25.5	185.7 ± 23.4	163.0 ± 29.6	0.048*
Blood glucose (mg/dL), mean ± SD	101.7 ± 40.2	101.0 ± 39.5	103.2 ± 42.1	0.624
Clinical data				
Overweight, n (%)	182 (69.7%)	124 (68.1%)	57 (72.2%)	0.518
Obesity, n (%)	82 (31.4%)	54 (29.7%)	28 (35.4%)	0.356
Glucose intolerance, n (%)	61 (23.3%)	58 (31.9%)	23 (29.1%)	0.659
Diabetes mellitus, n (%)	20 (7.6%)	11 (6%)	9 (11.4%)	0.136
Dyslipidemia, n (%)	191 (73.2%)	131 (72%)	60 (75.9%)	0.506
Metabolic syndrome, n (%)	75 (28.7%)	50 (27.5%)	25 (31.6%)	0.494

Note: *$P < 0.05$.
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

Metabolic profile

We found that a high proportion of patients had BMIs above normal limits (70%), and 31.4% were considered obese. The fasting blood glucose was found to be above normal limits in 30.9% of the sample, suggesting a high prevalence of glucose intolerance and diabetes mellitus that were either inadequately controlled or undiagnosed, and hence not being treated.

Table 2 Medications in use

Antipsychotics	
Total	261 (100%)
FGAs	17 (6.5%)
SGAs	97 (37.2%)
Clozapine	99 (37.4%)
Polypharmacy	48 (18.4%)
Antidepressants	
Total	72 (27.6%)
Tricyclic	11 (4.2%)
SSRIs	61 (23.4%)
Mood stabilizer	
Total	44 (16.9%)
Lithium	13 (5.0%)
Valproate	25 (9.6%)
Carbamazepine	6 (2.3%)
Other medications	
Total	15 (5.7%)
Antihypertensives	3 (1.1%)
Thyroid hormones	2 (0.8%)
Others	10 (3.8%)

Abbreviations: FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics; SSRIs, selective serotonine reuptake inhibitors.

Some parameters of lipid profile (such as total cholesterol and low-density lipoprotein (LDL) were correlated with patients' ages (Pearson correlation = 0.191, $P = 0.002$ and Pearson correlation = 0.157, $P = 0.011$, respectively, for total cholesterol and LDL). However, there was no correlation with the duration of disorder or type of antipsychotic in use ($P = 0.296$, df = 3). BMI showed no correlation with patient age or duration of disorder, but was correlated with total cholesterol and LDL (respectively $P < 0.001$ and $P = 0.002$), and inversely correlated with high-density lipoprotein (HDL) ($P = 0.011$), which was an expected finding.

We did not find any significant correlation between dyslipidemia and patient age or duration of disorder (Pearson correlation = 0.068, $P = 0.148$ and Pearson correlation = 0.042, $P = 0.285$, respectively), nor with use of any type of antipsychotic ($\chi^2 = 1.554$, $P = 0.460$). Applying the same method for metabolic syndrome, we found an association between age and metabolic syndrome, which was more prevalent in older patients (Pearson correlation = 0.138, $P = 0.029$); however, that was not true for duration of the disorder (Pearson correlation = 0.074, $P = 0.234$), nor for use of any type of antipsychotic ($\chi^2 = 0.382$, $P = 0.826$).

Even after dividing the sample in two groups having extremely different durations of disorder, separating those with less than 3 years of disorder (n = 22) and those with more than 20 years of disorder (n = 71), we still could not find any significant difference between those groups concerning clinical parameters, prevalence of diabetes melitus, dyslipidemia, or metabolic syndrome.

Only 5.7% of the sample was under pharmacological medical treatment. There was no association between metabolic disturbances and pharmacological medical treatment or appropriate lifestyle habits (not smoking and being physically active).

Association between metabolic profile and types of antipsychotics

There was no significant difference between the samples of different types of antipsychotics regarding risk factor or metabolic disturbances, except for LDL parameters ($P = 0.032$, CI 95%: 0.59–35.4). Nevertheless, after a post hoc evaluation (Scheffe's test) only a trend for significance remained ($P = 0.07$) between the polypharmacy and FGA groups. There was no significant difference between the other groups of antipsychotics. Table 3 shows information regarding the association between the types of antipsychotics and metabolic parameters in this sample.

Discussion

Our analysis suggests that this is a population with high rates of comorbidities, both mental and physical. The high number of patients under antidepressant treatment might indicate an increased prevalence of depression, which is a phenomenon often observed in samples of patients with schizophrenia.[19]

The high prevalence of tobacco smoking and sedentariness, despite also being frequent among those patients, raises serious concerns, since both habits are implicated in increased risk for CVDs. In fact, we found a high prevalence of several other risk factors for CVDs in our sample, including a large number of overweight patients, inadequate lipid profiles, and high levels of fasting blood glucose. Such increased prevalence of risk factors for CVDs is highlighted when contrasted with findings from the healthy Brazilian population, as described in a large epidemiologic study.[20] In this sample, the prevalence of obesity was 11.3% among men and 11.2% among women, whereas in our sample, such proportions were 29.7% and 35.3%. Also, the prevalence of dyslipidemia was 16.5%, whereas in our sample, its prevalence was 73.2%.

This significant increase in risk factors was also found in a similar population in Brazil, in a study conducted by the Federal University of Rio Grande do Sul, Porto Alegre, Brazil.[21] Another Brazilian study also addressed the prevalence of metabolic disorders among patients with psychiatric disorders and showed elevated rates of this condition (31.8% in schizophrenic disorder, 38.3% in bipolar disorders, and 48.1% in depression), though neither the psychiatric diagnosis nor the use of antipsychotics was associated with metabolic syndrome after logistic regression analysis, which was probably due to the small sample size.[22]

Patients on different types of antipsychotics showed no difference regarding metabolic risk, nor with the use of polypharmacy, as suggested by other studies.[23] The nonsignificant lower levels of LDL seen in patients using polypharmacy in comparison with the FGA patients ($P = 0.07$) might be explained by patients with polypharmacy having a more severe form of the disorder in comparison with

Table 3 Antipsychotic medication and metabolic parameters

	FGAs n = 17	SGAs n = 97	Clozapine n = 99	Polypharmacy n = 48	*P*
BMI, mean ± SD	27.6 ± 5.1	28.7 ± 5.5	27.5 ± 5.3	27.4 ± 5.9	0.397
Total cholesterol (mg/dL), mean ± SD	196.7 ± 42.3	204.8 ± 42.2	196.4 ± 39.6	189.5 ± 47.4	0.207
HDL (mg/dL), mean ± SD	47.9 ± 15.5	46.5 ± 13.6	49.9 ± 19.7	49.7 ± 17.2	0.516
LDL (mg/dL), mean ± SD	120.0 ± 37.2	123.8 ± 42.5	111.6 ± 34.1	105.8 ± 36.9	0.032*
Triglycerides (mg/dL), mean ± SD	157.1 ± 80.0	172.4 ± 127.3	187.4 ± 107.8	164.5 ± 114.4	0.578
Blood glucose (mg/dL), mean ± SD	100.0 ± 39.9	102.4 ± 46.6	103.9 ± 38.2	95.8 ± 29.8	0.709
Overweight, n (%)	12 (70.5%)	74 (76.2%)	65 (65.6%)	30 (62.5%)	0.272
Obesity, n (%)	6 (35.3%)	39 (40.2%)	24 (24.2%)	13 (27%)	0.095
Glucose intolerance, n (%)	5 (29.4%)	30 (30.9%)	34 (34.3%)	12 (25%)	0.719
Diabetes mellitus, n (%)	2 (5.6%)	8 (19.8%)	8 (33%)	2 (7.3%)	0.728
Dyslipidemia, n (%)	13 (76.4%)	69 (71.1%)	78 (78.7%)	31 (64.5%)	0.296
Metabolic syndrome, n (%)	4 (23.5%)	30 (30.9%)	30 (30.3%)	11 (22.9%)	0.714

Note: *$P < 0.05$ (post hoc Scheffe's test showed no significant differences except a trend [$P = 0.07$] between polypharmacy and FGAs).

Abbreviations: BMI, body mass index; FGAs, first-generation antipsychotics; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; SGAs, second-generation antipsychotics.

patients with FGAs, which might imply more-frequent clinical appointments and evaluations, hence more attention and lifestyle counseling (diet, exercises, etc), and thus decreased risk factors for CVDs.

Although worse lipid profiles were associated with patient age, which is expected in the general population,[24] the duration of the disorder was not associated with different lipid profiles or BMI. Some studies have revealed that the metabolic alterations due to use of antipsychotics (especially lipid profile changes and weight gain) occur in a matter of months, reaching a plateau after approximately 9 months of use.[25,26] Concerning the analysis of an early event in a sample of chronically ill patients, it comes as no surprise that we found no association between metabolic parameters and duration of the disorder. Nevertheless, it is clear that the exposure to antipsychotic medications is a risk, in this population, for development of metabolic disorders at a very early stage, resulting in a large population of individuals chronically exposed to several risk factors for CVDs and other diseases.[27]

It is important to notice that only a small proportion of patients in our sample was under pharmacological treatment for physical diseases, which, given the high prevalence of metabolic disorders and increased risk for CVDs, suggests poor access to medical or health care and/or poor compliance with treatment. This phenomenon is extensively described in the scientific literature as a worldwide problem concerning patients with schizophrenia.[2,28,29]

The main limitation of our study is its cross-sectional design, which did not allow any conclusions regarding causal effects of the variables analyzed. Furthermore, we did not include a control group, and some variables had only a few subjects allocated, such as "physically active" or "pharmacological medical treatment," making the analysis difficult. A better investigation on the matter might be done by choosing the sample and controlling it using physical activities as a parameter, as was done in other studies with positive results.[30,31] However, we believe that the naturalistic nature of the present study and the relatively large sample might create a reliable portrait of the population of outpatients under treatment, revealing a high prevalence of cardiovascular risk factors, physical comorbidities, and the need for clinical assessment and liaison with the general practitioner for adequate clinical treatment. This reinforces the results found in the study by Leitão-Azevedo et al.[21]

Conclusion

Patients with schizophrenia, regardless of age or type of antipsychotic medication in use, were found to be at increased risk for many physical disturbances, including weight gain, dyslipidemia, and increased risk for CVDs; and may benefit from clinical evaluation and adequate treatment, as recommended by international protocols. We suggest that an intensive and appropriate approach should be taken to assure that these patients receive adequate clinical referral and treatment.

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Disclosure

The authors report no financing or other conflicts of interest.

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