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Second Generation Antipsychotics (SGAs) in Schizophrenic Patients and Bipolar Disorder: Correlation With Metabolic Syndrome (NCEP ATP III(a))

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Abstract

Introduction: The Metabolic Syndrome is a set of diverse clinical situations such as diabetes mellitus, hypertension and dyslipidemia. Patients with mental illnesses such as schizophrenia or bipolar disorder have a higher mortality than the general population attributable in 60% to somatic diseases and metabolic syndrome, where second generation antipsychotics increase the risk of weight gain and insulin resistance. **Objectives**. Correlate the treatment with second generation antipsychotics (SGAs) as a possible predictor for Metabolic Syndrome according to the NCEP ATP III (a) classification.

Methods: Descriptive, cross-sectional correlational study. The sample was of 92 patients, applying an open and convenience sampling due to the mental state of the patients in order to determine their degree of acceptance to the study (Informed Assent) and consent to the legal guardian as the main inclusion criterion. For the analysis, the following variables were considered: blood pressure, weight, height, abdominal circumference, serum levels of triglycerides, glucose and high density lipoproteins. The SPSS 20.0 ® program was used logistic regression analysis with a p-value <0.05 and a confidence level of 95%.

Results: SGAs most used was clozapine (54.3%). The correlation analysis showed that sociodemographic aspects such as personal history, habits, physical activity and paraclinical and anthropometric records correlated with the possible diagnosis of metabolic syndrome ($p < 0.05$), but not with SGAs ($p > 0.05$).).

Conclusion: No correlation was found between the presence of the metabolic syndrome and the type of antipsychotic treatment.

Keywords: second generation antipsychotics, schizophrenic patients, bipolar disorder, metabolic syndrome

1. Introduction

The Metabolic Syndrome (MS) is a current disscusion and issue in the medical community; Its approach is essential because it is related to the diseases that cause the highest mortality worldwide, and its incidence is increasing, characterized by the presence of a set of risk factors such as insulin resistance and compensatory hyperinsulinism associated with disorders of the metabolism of carbohydrates and lipids, high blood pressure levels, and obesity (Menco & Pérez, 2011; Pineda, 2008)

The adoption of behavioral patterns such as unhealthy diet and lack of physical activity have contributed to the high prevalence of hypertension, hypercholesterolemia, diabetes, obesity, and, with this, that cardiovascular diseases are the leading cause of death, disability and premature mortality (Lakka et al., 2002; Park & Lee, 2018). The National Cholesterol Education Program Adult Treatment Panel III (ATPIII), implemented some parameters where three or more of the following criteria must be met: high abdominal perimeter (> 102 cm in men and> 88 cm in women) TG> 150 mg/dl , Low HDL (men <40 mg/dl and women HDL <50 mg/dl), BP> 130/85 mm Hg or receive antihypertensive therapy, glycemia> 110 mg/dl including DM, but in 2004 with the update of the American Diabetes Association, glycemia was modified to 100 mg/dL (Expert Panel on Detection, 2001; Kavey et al., 2003; Grundy et al., 2004). The updated definition of ATPIII (ATPIIIa) is used as the limit of abdominal perimeter the same proposed in the guidelines of the International Diabetes Federation (IDF) for South Americans, that is, 90 cm

for men and 80 cm for women (Alberti, Zimmet, & Shaw, 2006).

Patients with severe mental illnesses such as schizophrenia or bipolar disorder have a higher mortality 2-3 than the general population (Atun et al., 2015; De Hert, Dekker, Wood, Kahl, & Möller, 2009; Levav, Lima, Somoza Lennon, Kramer, & Salvatierra-González, 1989), where according to Newcomer, it is 60% attributable to somatic diseases and metabolic syndrome (Newcomer, 2007a, 2007b). Regarding the metabolic syndrome, the prevalences are two to four times higher than the rest of the population, in the United States, it has been calculated that the average number of years potentially lost in patients with mental illness ranges from 25 to 30 years, compared with the general population where the main cause of death was coronary heart disease (McEvoy et al., 2005; Cortés Morales, 2011; Vancampfort et al., 2015). It is clear that genetic factors and lifestyle have an influence at mental illnesses as well as the presence of metabolic syndrome, where it has not been possible to elucidate in how the interaction of antipsychotic drugs interact with each other, which Somehow, it would explain the differences in the fact that people with mental illness have a greater predisposition to this type of metabolic diseases (Firmann et al., 2008; De Hert et al., 2009; García-García et al., 2008; McEvoy et al., 2005; Muñoz-Calero Franco et al., 2015; Ortiz Lobo & Ibáñez Rojo, 2011; Rojo, Mesa, & Martínez-Ortega, 2014; Lakka et al., 2002).

Second generation antipsychotics (SGAs), as a group can reduce the risk of producing extrapyramidal side effects and hyperprolactinemia when compared with first generation antipsychotics (FGAs) (Martínez, León, Torres, & Crossley, 2017; Cortés Morales, 2011; Pato, Rodríguez, & Valverde, 2017). However, there is scientific evidence suggesting that the interaction of these may increase the risk of significant weight, insulin resistance metabolic homeostasis, hyperglycemia, diabetes mellitus (DM) type 2 and dyslipidemia which could reduce life expectancy in patients who need these drugs as schizophrenic patients and with bipolar disorder (Cortés Morales, 2011).

MS is very frequent in patients with severe mental illnesses, several studies have raised the relationship of schizophrenia with MS, consequently in 240 Canadian subjects showed figures of 42.6% for men and 48.5% for women using the criteria of the National Cholesterol Education Program ATP (ATP III) (Cortés Morales, 2011). In another study conducted with 430 chronic schizophrenic patients in Belgium the presence of MS reached prevalences of 28.4%, and 36%, according to the diagnostic criteria of the ATP III and the International Diabetes Federation, respectively, being more prevalent in female patients (Moreno, González, Fleta, & Pérez, 2006). In Latin America, a study conducted in Brazil also found a higher proportion of women using the criteria of the ATP III (Cortés Morales, 2011).

The objective of the study is correlate the treatment with second generation antipsychotics (SGAs) as a possible predictor for Metabolic Syndrome according to the NCEP ATP III (a) classification.

Objetivo del estudio es correlacionar el tratamiento con antipsicóticos de segunda generación (AP2G) como posible factor predictor para Síndrome Metabólico según la clasificación NCEP ATP III(a).

2. Methods

Descriptive study with a cross-sectional correlational component. The population was 200 inpatients and outpatients of a psychiatric center of the City of Cartagena de Indias/Colombia. The method of sample selection was opened for convenience, for a (n = 92) outcome of patients with schizophrenia and bipolar disorder.

The participating patients gave their informed consent as a way to contribute to their moral development (Autonomy), informed consent was given to the tutors and to patients who demonstrated maturity and independence in the adherence of the treatment as the main inclusion criterion, as a suggestion of the ethics committee of the Corporación Universitaria Rafael Núñez, in addition the patient's data was processed and safeguarded subject to Resolution 8430 of 1993 of Colombia and to the declaration of Helsinki. As exclusion criteria, patients who were not medicated with (SGAs) and patients under 18 years of age did not participate due to the conditions of their mental capacity in relation to the type of pathology.

An instrument validated by experts was applied, in order to obtain sociodemographic, clinical and risk factors information, antipsychotic treatment, cardiovascular and family risk history, among others. Anthropometric parameters were taken, as well as blood sampling. The body mass index (BMI) was calculated by using the measured anthropometric parameters: weight in kilograms and height in meters (Kg/m^2). Likewise, the measurement of the abdominal and hip circumference was made in centimeters with a tape measure, the blood pressure measurement was made using a mercury sphygmomanometer with the patient sitting after five minutes of rest according to the indications of the British Hypertension Society (Williams et al., 2004; Stergiou et al., 2018).

Within the paraclinical studies venipuncture was performed, with a fasting period of 12 hours, to evaluate glucose, total cholesterol, HDL cholesterol and triglycerides. LDL cholesterol was determined by the Friedewald formula. The determinations were made using Fotometer Humalyzer primus (HUMAN), with human serum control level I

and II. For the analysis of the metabolic syndrome, the criteria of (NCEP ATP-III (a)) were considered, considering three or more of the following criteria: abdominal obesity (waist circumference ≥90 cm in men and ≥80 cm in women; 2) Triglyceride values greater than or equal to 150 mg/dl, c-HDL values <40 mg/dl in men and <50 mg/dl in women; 3) values of blood pressure greater than or equal to 130/85 mmHg or carry hypertensive treatment; 4) values of plasma glucose of greater than or equal to 100 mg/dl in the fasted state (including diabetes mellitus) (Thomas et al., 2005; Heng et al., 2006). Through the SPSS 20.0® for Windows, the univariate and multivariate logistic regression analysis was performed. All calculations were made with a 95% confidence level and p-value <0.05.

3. Results

The population was constituted by women (n = 44) and men (n = 48) in equal proportion, between ages of 18 to 76 years with an average of 35.5 years, the great majority are young adults with ages of 23 years (7.6%). (Table 1)

Table 1. Age

Sample	**92**
Mean	38,62
Standard error of the mean	1,590
Median	35,50
Mode	23
Standard deviation	15,252
Variance	232,634
Rank	58
Minimum	18
Maximum	76

In women, a greater distribution of mental illnesses was found in relation to bipolar disorder in a (36.4%). In men the highest percentage was found in schizophrenia compared to women in a (72.9%), however no statistical significance was found between the distribution of the disease between the sexes (P-value> 0.05). (Table 2)

Table 2. Gender versus Diagnosis

		Diagnosis							
		Schizophrenia n (%)	Asperger Syndrome n (%)	Bipolar Disorder n (%)	Mental disorder (Behavior) n (%)	Mixed Disorder n (%)	Acute Psychotic Disorder n (%)	**Total n (%)**	***P Value***
Gender	Female	24 (54,5)	0 (0,00)	16 (36,4)	0 (0,00)	2 (4,5)	0 (0,00)	44 (100)	
	Male	35 (72,9)	1 (2,1)	8 (16,7)	2 (4,2)	0 (0,00)	1 (2,1)	48 (100)	0,94*
Total		59 (64,1)	1 (1,1)	24 (26,1)	2 (2,2)	2 (2,2)	1 (1,1)	92 (100)	

Pearson Chi-square*.

In patients diagnosed with Schizophrenia and Bipolar Disorder, it was found a prevalence of sedentary lifestyle, with a high rate of increasing their tendency to obesity, added to the consumption of alcohol and smoking, which also increases the probability of suffering from hypertension at medium term. (Table 3)

Table 3. Habits and Concomitant Diseases versus Schizophrenia and Bipolar Disorder

Personal History	**Pathologies**					
	Schizophrenia n = 67 (%)		Bipolar Disorder n = 25 (%)		Total n = 92 (%)	
	Yes	No	Yes	No	Yes	No
Hypertension	8 (11.9)	59 (88.1)	5 (20)	20 (80)	13 (14.1)	79 (85.9)
Obesity	13 (19.4)	54 (80.6)	6 (24)	19 (76)	19 (20.7)	73 (79.3)
Sedentary lifestyle	45 (67.2)	22 (32.8)	15 (60)	10 (40)	60 (65.2)	32 (34.8)
Smoker	14 (20.9)	53 (79.1)	3 (12)	22 (88)	17 (18.5)	75 (81.5)
Alcohol Consumer	17 (25.4)	50 (74.6)	7 (28)	18 (72)	24 (26.1)	68 (73.9)

The correlation found between the possible diagnosis of metabolic syndrome and the presence of schizophrenia in personal history was significant in patients with hypertension, which increases in 4.8 times the risk of presenting metabolic syndrome (P-value = 0.044), as well schizophrenic patients with a history of obesity have 3.6 times more risk (P-value = 0.042). (Table 4)

Meanwhile, the results obtained for the case of bipolar disorder patients were less significant than the sociodemographic factors, only the age of the patient with this disorder was correlated with the presence of the syndrome, in at an older age, greater risk of this in 1.06 (P-value = 0.044). As for the habits related to health and the realization of physical activity, the act of dancing was significant, reducing the risk of metabolic syndrome in 0.125 (P-value = 0.049). (Table 5)

Table 4. Logistic regression between the presence of metabolic syndrome and risk factors present in patients with schizophrenia

Dimension	Variables	Schizophrenia	
		Odds Ratio	*P-value*
Personal History	Hypertension	4,889	0,044
	Obesity	3,679	0,042
Habits and Physical Activity	Sports	0,375	0,040
	Perform Exercises	0,267	0.019
	Walks	0,381	0,020
	Fleet	0,333	0,020
Nutrition	Low salt	0,092	0,004
	Fat Consumption	0,423	0,017
	Low in sugar	0,348	0,010
	Consumption of Fruits and Vegetables	0,407	0,012
Anthropometric Paraclinical Records	Glicemia (Mg/Dl)	1,053	0,009
	Hdl (Mg/Dl)	0.888	0,003
	Triglycerides (mg/dl)	1,009	0,018
	weight(Kg)	1,074	0,001
	BMI(Kg/m^2)	1,201	0,002
	Waist Perimeter	1,067	0,002
	Mean Systolic Pressure	1,097	0,001
	Mean Diastolic Pressure	1,106	0,003

Second generation Antipsychotics	Quetiapine	0,844	0,893
	Risperidone	0,711	0,591
	Clozapine	0,030	0,747
	Olanzapine	-	-

Table 5. Logistic regression between the presence of metabolic syndrome and risk factors in patients with Bipolar Disorder

Dimension	**Variables**	**Bipolar Disorder**	
		Odds ratio	P-value
Sociodemographic	Age	1,060	0,044
Habits and Physical Activity	Dancing	0,125	0,049
Anthropometric Paraclinical Records	HDL (mg/dl)	0.752	0,029
	Weight(Kg)	1,121	0,038
	Waist Perimeter	1,075	0,029
Second generation Antipsychotics	Quetiapine	0,420	0,325
	Risperidone	0,933	0,958
	Clozapine	0,643	0,669
	Olanzapine	-	-

Finally, it was observed that none of the second generation antipsychotics used as treatment by schizophrenic and bipolar disorder patients affects the risk of presenting metabolic syndrome (P-value> 0.05).

4. Discussion

In the correlation analyzes, no statistical significance was found between the metabolic syndrome and the second generation antipsychotics, a similar outcome was presented by Estévez and McEvoy, in whose study in whose study throw non-significant values between the mentioned variables (Estévez et al., 2013; McEvoy et al., 2005). These authors argue that a possible cause for the lack of correlation could be the sample size, which in its case was 53, while in the present investigation it was also reduced, but with 92 patients.

Another possible cause for this lack of correlation may originate that metabolic syndrome is not necessarily arising from the effect of antipsychotics, at least in patients with bipolar affective disorder, which were considered in their study, but it is a multisystemic and multifactorial disease, clearly develops from other factors (Jaramillo, Mejía, Velásquez, Palacio, & Zuluaga, 2013). Another study in this regard is that of Almeida et al, cited by Jaramillo, who found that the onset of MS was greater among patients taking lithium than in those taking antipsychotics, which would be a clear indicator that the syndrome is not necessarily related to antipsychotics. At this point it is important to mention that lifestyle also triggers the onset of the syndrome in patients with mental disorders (Jaramillo et al., 2013).

Despite the above, there are studies that do demonstrate the relationship between antipsychotics and the syndrome, in which adverse effects were detected by the use of second generation antipsychotics in patients with chronic schizophrenia, such as weight gain due to the use of olanzapine and from here on with the metabolic syndrome (Aguilar, Coronas, & Caixàs, 2012; Cortés Morales, 2011; De Hert et al., 2009; Estévez et al., 2013; Jaramillo et al., 2013; McEvoy et al., 2005; Muñoz & Gallardo, 2004; Newcomer, 2007a, 2007b; Pato et al., 2017; Vancampfort et al., 2015).

Studies mention that there are high possibilities of presenting the syndrome in patients with physical inactivity and an excess of food intake, which promotes weight gain and obesity, in addition, smoking alters the function of insulin. In the study conducted, sedentary lifestyle was one of the most frequent habits, both in bipolar (60%) and schizophrenic (67.2%) (Jaramillo et al., 2013). Patients suffering from schizophrenia, especially those who have long duration of hospitalization have poor quality of life (Choo et al., 2017). Further research is required to assess the relationship between metabolic syndrome and quality of life in patients suffering from schizophrenia.

Within the personal health history it was found that obesity is present in 19.4% of schizophrenics and in 24% of bipolar patients, something similar happens with hypertension, these two conditions, at least in schizophrenic patients, kept relationship with the presence of the syndrome, and they may increase the risk of suffering from it.

From the above it could be thought that the effect of antipsychotics on the development of metabolic syndrome is indirect, because it affects the risk factors that trigger it, but not the syndrome itself. This statement could be supported by studies that recognize that weight gain is a well-documented side effect of antipsychotics during the acute and maintenance treatment of patients with schizophrenia, in this context, the weight gain is maximum with second-generation antipsychotics such as clozapine and olanzapine, in addition the weight gain becomes rapid during the first weeks, slows gradually and often reaches a plateau after one year of treatment (Correll, Detraux, Lepeleire, & De Hert, 2015; Martinez et al., 2017). The etiology of metabolic syndrome in patients suffering from schizophrenia include genetic factors and inflammation but this study did not measure these biological factors (Ho et al 2014). This is the main limitation of this study.

5. Conclusion

Mental illnesses were differentiated according to gender, in male subjects predominated schizophrenia, while in female ones bipolar disorder. A possible low prevalence of metabolic syndrome was observed in both groups of patients. Of particular attention is that patients with risk factors such as weight gain that can lead to different cardiac pathologies that can be exacerbated with the consumption of antipsychotics, especially in the interaction of these.

It is necessary to promote healthy habits and the realization of physical activities at this population, since it was found a protective effect on the risk of suffering from the syndrome in those patients who perform blood pressure checks, carry out exercises, walks, as well as fleets, and dance sessions (especially bipolar subjects), it is recommended to institutionalize at the psychiatric center a program of physical exercise, aerobic by a person or a group of trained people, understanding that among the physiopathology of the SM and mental disorders such as bipolar there are common elements that can exacerbate any of the two pathologies or even both.

Obesity and hypertension were two of the most common conditions among psychiatric patients, and were discussed as elements that increase the risk of the metabolic syndrome.

It is recommended to design a sustainable and feasible diet, in addition to consider for future studies to include various psychiatric entities so that the study has a greater statistical significance.

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Competing Interests Statement

The authors declare that there are no competing or potential conflicts of interest.

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