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Association of Obesity with Antipsychotic Drugs in Rural Population, India

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ABSTRACT

To describe the association between obesity and the use of antipsychotic drugs (APDs) in adult outpatients followed-up on in rural center. A longitudinal, retrospective design study carried out between January 2010 and June 2011, in patients who were included in a claim database and for whom an APD treatment had been registered. A body mass index (BMI), 30 kg/m2 was defined as obesity. The main measurements were: use of APDs, demographics, medical background and co-morbidities, and clinical parameters. Logistic regression analysis and ANCOVA with Bonferroni adjustment were applied to correct the model. A total of 110 subjects (mean age: 48.8 (18.4) years; women: 56.5%; obesity: 28.3% [95% confidence intervals (CI), 27.9%–28.7%]) were analyzed. A total of 1.8% of the patients were receiving APDs, without statistical differences in distribution by type of drug (typical: 48.8%; atypical: 51.2%). Obesity was associated with the use of APDs [OR = 1.7 (CI: 1.5–1.9)], hypertension [OR = 2.7 (CI: 2.5–2.9)], diabetes [OR = 1.5 (CI: 1.3–1.8)] and dyslipidemia [OR = 1.3 (CI: 1.2–1.4)], p = 0.0001 in all cases. BMI was significantly higher in subjects on APDs; 29.4 vs. 27.5 kg/m2, p = 0.002, and remained higher after adjusting by age and sex (mean difference 0.5 (CI: 0.2–0.8), p = 0.01). After adjusting by age, sex and the Charlson index, obese subjects generated higher average annual total costs than nonobese subjects; 821 (CI: 797–845) vs. 684 (CI: 668 –699), respectively, p = 0.001. Obesity was associated with the use of APDs, regardless of the type of drug, and with the presence of hypertension, diabetes and dyslipidemia. Obesity was also associated with substantially higher health care costs.

Keywords: Obesity, retrospective study, antipsychotic use, rural setting, health care costs.

INTRODUCTION

Metabolic disorders such as obesity, diabetes or dyslipidemia increase the risk of cardiovascular events [1]. Specifically, obesity exerts an unquestionable impact on population health, due to its high associated morbidity-mortality [1,2]. Its prevalence in the general population ranges between 6% and 20% (Andhra Pradesh, India), with an increased presence in females and a trend to increase with age, reaching a peak in the decade of 40–50 years. The use of antipsychotic drugs (APDs) has been increasing considerably during recent years, not only as a result of growth in the population that uses such substances, but also because of expanded use of such medication in other

clinical situations in which they are considered to be of potential benefit for patients. However, the evidence to date suggests that antipsychotics, or at least some of the most widely used APDs, are associated with a considerable increase in patient body weight (7%) and with the development of glucose and lipid metabolic alterations. This in turn can imply an increased risk of premature death among such patients due to cardiovascular events [3,4,5]. These repercussions are more notorious in the case of second generation APDs (atypical drugs), though the level of risk tends to vary according to the different drug substances used [6,7,8]. These drugs increase the activity of AMP kinase within the hypothalamus, blocking the activity of the H1 histamine receptors. In this way, a link is established between weight gain and atypical APD use. Although the typical or classical APDs also induce this side effect, the precise mechanism involved in this case is not known [3]. Nevertheless, considerable controversy is found among different authors. As an example, clozapine and olanzapine, in addition to the known increases in body weight, can also elevate cholesterol and triglyceride concentrations [9-12] or increase the risk of developing diabetes mellitus [13,14] Similar results have also been recorded in patients treated with risperidone, though the negative effects upon the health of these subjects are somewhat more controversial. Unfortunately, the role and importance of each of them are often difficult to assess, and it is likewise difficult to determine whether certain biological alterations are the cause or effect of the excess body weight [15,16,17,3,12,18,19]. The present study further evaluates previously observed associations between obesity and typical and atypical APD use, and explores its influence upon health care resource utilization in adult outpatients followed-up on by five rural health centers in the Indian population setting.

MATERIALS AND METHODS

A retrospective study was conducted based on the medical records of adult patients monitored on an outpatient basis and under normal clinical practice conditions. The study population was seen by Primary Care teams at Bhaskar General Hospital, Yenkapalli, India. It involves a recruitment of about 110 patients (15.5% over 64 years of age). The designated population is predominantly rural, with middle to low socioeconomic level. The study included all patients seen between January 2010 and June 2011, meeting the following criteria: a) age over 18 years; b) initiation of pharmacological treatment with APDs; and c) inclusion in the chronic prescriptions program with regular patient reports for the programmed visits to obtain the corresponding medical prescriptions (with registry of the daily dose, time interval and duration of each treatment). Patients failing to report to the center were excluded, as were those displaced or outside the zone, and those presenting disabling mental disorders. Obesity was defined as the presence of excess body weight secondary to the accumulation of adipose tissue, with a body mass index (BMI, kg/m2) of over 30 [20]. Information was collected on the prescription of APDs (atypical: amisulpiride, clozapine, olanzapine, quetiapine, risperidone and ziprasidone; typical: chlorpromazine, fluphenazine, haloperidol, perphenazine, pimozide, thioridazine), reflected in the computer-based case histories, according to the recommendations of the prescribing physician[21]. Quantifi cation was made of the number of health problems attended per patient/year (comorbidity), considered as a diagnosis-equivalent disease care problem (International Classification of Primary Care, ICPC) [22]. The personal antecedents were the following: arterial hypertension, dyslipidemia, diabetes mellitus, active smoking, alcoholism, ischemic heart disease, cardiac ischemia with angina, acute myocardial infarction, coronary ischemia, cerebrovascular accident, cardiovascular event, chronic obstructive pulmonary disease, chronic airflow obstruction and bronchial asthma. The Charlson Index was quantified as an estimation of morbidity burden (severity), and the following clinical Neuropsychiatric Disease and Treatment. Obesity and the use of antipsychotic drugs parameters were documented (medical records): systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg), baseline blood glucose (mg/dl), triglycerides (mg/dl), total cholesterol (mg/dl), low density lipoprotein cholesterol (LDL-c, Friedewald in mg/dl) and high density lipoprotein cholesterol (HDLc) in mg/dl. The consumed health care resources, documented from the registries of each center, comprised the visits or appointments with the rural center, referrals to the reference specialists, requests for supporting complementary tests, and drug prescriptions charged to CatSalut occurring during the study period of evaluation. Visits made were defined as appointments programmed between the professional team and the patient due to a health demand or problem, in the center or in the home of the patient. A statistical analysis was made, with calculation of the mean and standard deviation (SD), and corresponding 95% confidence intervals (CI). Parametric tests (chi-square and Student t-test) were used for the relationship between variables in the bivariate analysis. A logistic regression analysis (forward step procedure) was performed to correct the model, including the variables according to significance of the results in the bivariate analysis and their clinical significance (dependent variable: obesity). The SPSSWIN version 12 statistical package was used, accepting statistical significance for p 0.05.

RESULTS

A total of 110 subjects (mean age: 48.8 (18.4) years; women: 56.5%; obesity: 28.3% [95% confidence intervals (CI), 27.9%–28.7%]) were analyzed. A total of 1.8% of the patients were receiving APDs, without statistical differences in distribution by type of drug (typical: 48.8%; atypical: 51.2%). Obesity was associated with the use of APDs [OR = 1.7 (CI: 1.5–1.9)], hypertension [OR = 2.7 (CI: 2.5–2.9)], diabetes [OR = 1.5 (CI: 1.3–1.8)] and dyslipidemia [OR = 1.3 (CI: 1.2–1.4)], $p < 0.0001$ in all cases. BMI was significantly higher in subjects on APDs; 29.4 vs. 27.5 kg/m2, $p < 0.002$, and remained higher after adjusting by age and sex (mean difference 0.5 (CI: 0.2–0.8), $p < 0.01$). After adjusting by age, sex and the Charlson index, obese subjects generated higher average annual total costs than nonobese subjects; 821 (CI: 797–845) vs. 684 (CI: 668 –699), respectively, $p < 0.001$.

Table 1: Overall characteristics of patients included in the study according to the use of antipsychotic drugs (APDs)

General Concepts	NO APDs N=100	APDs N=110	P-Value
Characteristics Sex – Male Female	 54.5% 45.5%	 55.5% 44.5%	NS
Mean age(SD), years	52.8(19.4)	56.4(18.5)	<0.001
Body Mass Index (SD), Kg/m^2	27.2(5.1)	28.9(5.8)	<0.001
Mean visits/year(SD)	9.2(8.5)	14.8(11.4)	<0.001
Mean episodes/year(SD)	5.8(3.6)	6.9(4.2)	<0.001
Mean Charlson index (SD)	0.4(0.65)	0.5(0.7)	<0.001

Values are given as percentage or mean; Abbrevations: SD= Standard deviation; NS= Nonsignificant.

Table 2: Overall characteristics of patients included in the study according to the use of antipsychotic drugs (APDs)

General Concepts	NO APDs N=100	APDs N=110	P-Value
Clinical Parameter Systolic blood pressure (SD), mm Hg	130(15.5)	128(15.2)	NS
Diastolic blood pressure (SD), mm Hg	76(9.6)	75(9.4)	NS
Baseline blood glucose (SD), mg/dl	98.6(27.4)	103.1(35.1)	<0.006
Serum triglycerides (SD), mg/dl	121.2(81.1)	138.8(90.8)	<0.001
Total cholesterol (SD), mg/dl	205.6(40.5)	208.5(42.2)	NS
HDL- cholesterol (SD), mg/dl	46.8(13.2)	43.8(12.8)	<0.001
LDL- cholesterol (SD), mg/dl	138.8(35.6)	139.2(34.5)	NS

Values are given as percentage or mean; Abbrevations: SD= Standard deviation; NS= Nonsignificant.

DISCUSSION

The results of this study show obese patients seen in the rural setting to represent 25.3% of the total. Compared with the general population, this markedly high percentage can be explained in part by the fact that the attended patients are not representative of the general population, and because young individuals less commonly resort to health care services. Nevertheless, the lack of knowledge of the specific etiology of the disorder and the scant therapeutic resources available, lead to a limited percentage treatment success that is often followed by recovery of the initial body weight. The above suggests that treatment and preventive activities targeting obesity are inefficient in the rural setting. This in turn generates a certain relaxed approach to this risk factor, and a reluctance to dedicate major efforts to solve the problem – in contrast to other disorders which are more amenable to effective medical intervention.

In the logistic model, obesity was associated with the use of APDs and the presence of hypertension, diabetes and dyslipidemia, and with patient age and sex. These results are similar to those reported in the consulted literature [13,23,3,2,4), though the impact of obesity upon health requires the adoption of a preventive approach that can only be achieved through the generalization of educative and preventive activities [3]. These data reflect the importance of preventing weight gain in such patients, with adequate treatment in each case, and posterior supervision of the patients that receive APD therapy – particularly among those presenting a high cardiovascular risk or those who are already obese [3,5]. This may be due to patient selection bias, a statistical artifact, or limited statistical power as a result of the small number of patients in each group [14]. Likewise, the possibility that a modification in APD treatment regimen may have altered our findings cannot be ruled out.

In studies of the use of psychoactive drugs, and in coincidence with our own observations, a larger proportion of treatments were seen to correspond to women – this possibly being due to the greater tendency among women to visit Rural centers [24,25]. It therefore would be interesting to conduct similar studies in the future, to confirm this possibility. This coincides with the literature, where in general psychiatric patients are seen to seek care more often, and do so more in Rural centers than in psychiatric clinics [26]. In this context, in a study of the epidemiology and use of health care resources related to mental health in Primary Care, reported that these patients present higher consulting rates than those individuals without mental disease [27]. The highest consulting rates were likewise associated with the demographic variables of patient sex (female) and age.

The results obtained can be explained not only by the different geographical composition of the study sample (a factor clearly associated to patient age), but also by other differences implicated in the studies consulted, and which could be explained in part by different health or dietary habits [28, 29]. Particularly as relates to obesity, the question emerges as to what other factors could be playing a relevant role in the fact that metabolic syndrome is more prevalent among these patients. In this context, unhealthy living habits could play an important role. In this sense, the role of diet seems to be confirmed, in view of the observed high prevalence of obesity, dyslipidemia, and hypertriglyceridemia. These observations, attributable to diet, lifestyle, or other conditioning factors, appear to coincide with the tendency of schizophrenic patients to accumulate fat and intraabdominal adipose tissue [30]. Regardless of the effect of lifestyle and health-damaging habits, attention should also focus on the role of the APDs used as treatment – some of which have been shown to exert a direct influence upon weight gain and lipid and carbohydrate metabolic disorders [31, 32]. Although controversy exists surrounding this, such substances could be making an important contribution to the appearance of metabolic disorders with an increased risk of cardiovascular disease. Other possible causes, such as certain alterations of the hypothalamic-pituitary-adrenal neuroendocrine axis inducing increased blood cortisol levels with genotypic expression in the form of abdominal obesity among patients receiving APDs, or the possible effects upon hippocampal volume, are aspects requiring further study and confirmation as potential cardiovascular risk factors in patients of this kind [33]. Other limitations require caution in generalizing the results, including the inherent observational design of the obesity and the use of antipsychotic drugs study (data underestimation), the possible variability among professionals in the different centers, the coordination of levels (health care continuum), and the lack of prescribed dose adjustment [4]. Nevertheless, such reformed centers present a very similar intervention organizational and protocol model – thus ensuring a common and homogeneous health care level. In future, new studies will be needed to confirm the consistency of the results obtained, and to evaluate strategies designed to reduce the cardiovascular risk factors. Likewise, it is important to continue advancing in treatment compliance and the achievement of objectives, in order to ensure more cost-effective interventions [4].

CONCLUSION

In conclusion, obesity is an important cardiovascular risk factor significantly associated with the use of APDs in the presence of hypertension, diabetes and dyslipidemia, and with patient age and sex as nonmodifiable factors, leading to an increased consumption of health care resources. Further research under normal clinical practice conditions will be needed to reinforce the consistency of these results.

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