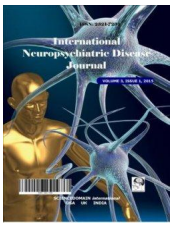

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Weight Gain and Obesity among Out-patients with Schizophrenia on Antipsychotic Medications in Uyo, South-South Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author JHE designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AFUB and EGP managed the analyses of the study. Author EGP managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Treatment of schizophrenia with antipsychotic medications is often associated with increased risks for weight gain, overweight and obesity but the associated risk factors in these patients are not fully known.
Objective: The aim of our study is to determine the prevalence of overweight and obesity in patients with schizophrenia on antipsychotic medications and the risk factors associated with it.
Methods: This was a cross-sectional study. One hundred and six subjects diagnosed with schizophrenia were recruited for the study. Demographic and anthropometric variables, fasting glucose profile and treatment variables were obtained and results analysed using SPSS version 20. Significance was set at *P=.05*.
Result: Study participants had a mean age of 34.67±8.8 years, 55.8% was male, and had a weight gain of 11.92±6.2 and mean BMI of 27.22±3.5. The prevalence of overweight and obesity was 62.3% and 20.8% respectively. The risk of weight gain and obesity in the study population was

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increased for all class of antipsychotic medication (typical or atypical) and was more likely with increased duration of antipsychotic medication use. There was no association of weight gain with age, and duration of illness.
Conclusion: Treatment with antipsychotic medications was associated with a significantly increased risk for weight gain and obesity. There is the need for routine weight monitoring during treatment with antipsychotic medications for management interventions which may include switching of medications.

Keywords: Schizophrenia; antipsychotic medications; overweight; obesity; Nigeria.

1. INTRODUCTION

Schizophrenia is a severe and debilitating major mental disorder characterized by a chronic progressive nature and significant impairment in family, social and occupational functioning [1].

Schizophrenic patients typically have 20% shorter lifespan compared to the general population due in part to a high prevalence of diabetes, coronary artery disease, hypertension, and other chronic medical conditions in this patient population. The unhealthy lifestyle habits of many schizophrenic patients, which include poor diet, smoking, excessive alcohol consumption, and use of illegal substances, are believed to contribute to their higher mortality [2,3].

Antipsychotic medications are typically used to treat nearly all forms of psychosis, including schizophrenia, schizoaffective disorder, affective disorder with psychosis, and psychosis associated with organic mental disorders. These drugs have been classified into classical (also referred to as typical or conventional) antipsychotics and atypical antipsychotics group [4]. Weight gain is a well-known side effect of treatment with psychotropic drugs [5,6]. The rates of obesity and diabetes in patients with schizophrenia are higher than the general population [7]. According to a study, when obesity is defined as a body mass index (BMI) of or greater than 27 kg/m^2, 42% of schizophrenic patients are considered obese as compared to 27% of the general population [8].

The cause for the increased prevalence of obesity in these patients is multifactorial. Antipsychotics, unhealthy diets, inadequate physical activity due to lower socioeconomic status, lower educational level, and sub-optimal living situations and symptoms such as low motivation, apathy and cognitive deficits could all play a role in increased risk of excessive weight gain in this population. Obesity in these patients have been associated with decreased quality of life, non-compliance with antipsychotic medications, a lowered self-esteem, social withdrawal and increased stigmatization [9-12].

It is widely believed that antipsychotic drugs contribute to weight gain via effects mediated by binding to serotonin ($5\text{-}HT_2$), noradenaline, dopamine, and/or histamine receptors. Serotonin activity at receptor sites is a potent satiety signal, with the most implicated receptors being $5\text{-}HT_{1A}$ and $5\text{-}HT_{2C}$. Stimulation of $5\text{-}HT_{1A}$ is associated with an increase in food intake whereas stimulation of $5\text{-}HT_{2C}$ is related to a decrease in food intake. Antagonism of the $5\text{-}HT_{2C}$ receptor can, in turn, lead to an increase in food intake, with most SGAs possessing $5\text{-}HT_{2C}$ antagonist activity [13,14].

In Nigeria, studies on antipsychotic associated weight gain are scanty and few. The present study was designed to determine the prevalence of overweight and obesity in schizophrenia patients under antipsychotic treatment.

2. MATERIALS AND METHODS

2.1 Location of the Study

This study was conducted at University of Uyo Teaching Hospital from November 2017 to February 2018. The hospital is located in Uyo, the capital city of Akwa Ibom State, Nigeria. The hospital is a 450 bed capacity tertiary healthcare centre that offers secondary and tertiary care. It receives referral from primary and secondary healthcare facilities in the state as well as from the neighbouring states. All diagnoses made in the institution were according to the tenth edition of the International Classification of Diseases and health-related disorders (ICD -10) criteria. [15] Clinically generated data for each subject enrolled were matched to the ICD -10 criteria.

2.2 Subjects

The sample size was calculated using a public domain software available on-line

(www.statpages.org) [16] using a prevalence of obesity as determined from previous Nigerian studies (12.4%) [17]. The sample consisted of one hundred and ten participants but only one hundred and six (n=106) subjects with schizophrenia were included in the analysis because 4 subjects had incomplete data. A subject is enrolled if he/she met the following inclusion criteria: a diagnosis of schizophrenia as confirmed by a consultant psychiatrist using the ICD 10 criteria, who has been receiving anti-psychotic medications for at least one year prior to study entry, adults above the age of 18years, and who granted consent. The exclusion criteria were: refusal to participate in study and florid psychopathology that could impair response to questions.

2.3 Procedure

Approval for the study was obtained from the Research and Ethical Committee of the University of Uyo teaching Hospital. Informed consent was obtained from patients or their accompanying family members. Patients who met the inclusion criteria were consecutively recruited into the study after a comprehensive psychiatric evaluation and diagnosis by resident doctors in psychiatry. The Mini International Neuropsychiatric Interview (MINI) English Version 5.0.0 [18] was further used to confirm the diagnosis of schizophrenia in the participants. The MINI was designed as a brief structured interview for the major Axis 1diagnosis in the Diagnostic and Statistical Manual (DSM-IV) and ICD-10.

2.4 Measures

2.4.1 Socio-demographic characteristics

A socio-demographic questionnaire designed by the authors was used to obtain information Measures evaluated includes socio-demographic details (age of the patient and family member, gender, educational status, marital status, religion) illness related variables (total duration of illness) and medication related variables (type of medication, doses and the chlorpromazine equivalence of the antipsychotic medications).

2.4.2 Medication profile

The medication profile of each individual patient was obtained through chart review of the medication record files domiciled in the hospital. Data recorded include: The number of antipsychotic medicines on the patients' current treatment regimen. Exposure to antipsychotic medication was measured as 1.class of antipsychotics used 2, duration of antipsychotic use 3, doses of medication used. All the antipsychotics used by the test subjects were converted to their chlorpromazine equivalent doses.

2.4.3 Body mass index

The height of the subjects was measured (to the nearest 0.1 cm) using an improvised wooden stadiometer mounted on a vertical wall with the respondent standing erect against the wall on a horizontal floor without shoes. The head was placed so as to ensure that the external auditory meatus and the angle of the eye were on a horizontal line. The Weight of the participants was measured in kilograms to the nearest 0.5kg using a Hanna-calibrated bathroom scale. Each subject was weighed wearing light clothing without shoes or stocking. BMI was computed as the weight (kg)/(height[m])2 (ie kg/m2) [19]. The BMI was classified according to World Health Organization(WHO) classification which defines normal as <25.0 mg/m2, overweight as BMI of 25.0 kg/m2 – 29.9 kg/m2 and obesity as a BMI of > 30.0 kg/m2 [20].

2.5 Data Analysis

Descriptive statistics such as frequencies, mean and standard deviation were computed for socio-demographic and clinical characteristics of the participants and other variables as appropriate. Relevant inferential statistics such as chi-square, t-test, ANOVA, Pearson's correlation were used as appropriate. The statistical package for social sciences (SPSS) version 20 was used for analysis. Significance was computed at $P < .05$.

3. RESULT

One hundred and six participants were included in the study. The mean age of the participants was 34.52 ± 8.9 years (range 20-60 years). More than half of them were females (58.5%). The majority (79.2%) was never married and about 72.1% of them had formal education to at least secondary school level and 72.6% of them were unemployed.

The mean duration of illness was 6.96±6.2 years and the mean duration of use of antipsychotic drugs 5.71±2.4 years. Mean weight gain of participants was 11.92±6.2 kg (Table 1).

Table 1. Socio-demographic and clinical characteristics of the participants

Variables	N (%)
Age in years (mean ±SD)	34.52±8.9
Age	
>40 years	72(67.9)
≤40 years	34(32.1)
Sex	
Male	44(41.5)
Female	62(58.5)
Marital status	
Single/separated	84(79.2)
Married	22(20.8)
Educational level	
Primary	6(5.7)
Secondary	68(64.2)
Tertiary	32(30.2)
Employment status	
Employed	29(27.4)
Unemployed	77(72.6)
Duration of illness	
≤10 years	76(71.7)
>10 years	30(28.3)
Mean duration of antipsychotic use (years)	5.71 ±2.4
Duration of antipsychotic use	
≤5 years	37(34.9)
>5 years	69(65.1)
Class of antipsychotic medication	
Conventional	12(11.3)
Atypical	28(26.4)
Combination	66(62.3)
Body Mass Index (BMI)	
Normal	31(29.2)
Overweight	53(50.0)
Obese	22(20.8)

3.1 Distribution of the Antipsychotic-Related Variables

About 11.3% of subjects were on conventional antipsychotics and the three most commonly prescribed first generation antipsychotics were: haloperidol (48.6%) stelazine (22.3%) chlorpromazine (15.5%). The remaining 13.6% were on thioridazine, long acting injectables like Fluphenazine decanoate or Flupenthixol decanoate.

26.4% of the subjects were on atypical antipsychotics. The most commonly prescribed serotonin dopamine antagonists (SDAs) were olanzapine (36.8%), risperidone (55.6%). The remaining 7.6% of subjects were on clozapine (2.5%), quatiepine (3.8%) aripiprazole (1.3%). About 62.3% of the subjects were on combination therapy and the most common combinations were: Two conventional antipsychotics or conventional antipsychotics and atypical and any class of antipsychotics and long acting injectables. The dosing frequency of 45% of the subjects was at least twice per day and 28% were on once daily dose regimen.

The mean daily dosage per day in milligram for subjects on chlorpromazine was 320 mg/day. The subjects on haloperidol had 15.45 mg/day mean value while those prescribed stelazine 12.85 mg/day. The mean chlorpromazine equivalent dosage was 512.82. and 256.0 mg for those on haloperidol and stelazine respectively.

The mean daily dosage for olanzepine was 18.40±2.5. mg/day. Subjects on risperidone received a mean daily dosage of 3.85±1.3 mg/day The chlorpromazine equivalent dosage for patients on olanzapine and risperidone was 368.0 mg and 385mg respectively.

3.2 Antipsychotic Usage and Weight Gain

The mean weight gain of the subjects on antipsychotic medication was 11.92±6.17 kg over a mean 5 year period of antipsychotic medication use. The mean weight of subjects before commencement of antipsychotic medications was 62.13±11.74kg. At one year of antipsychotic medication use, the mean weight was 68.25±8.9kg. After a mean 5 years period of antipsychotic medications mean weight of subjects was 73.00±10.53 kg (*ANOVA (F)=13.05, P=<.001*). This implies that 56.3% of the weight gain of subjects occurred within the first year of antipsychotic medication use.

There was poor correlation between period of antipsychotic use and weight gain (*r=0.23, P=.03*). There was no association found between mean weight gain of subjects (determined as the difference between weight at first presentation before commencement of antipsychotic medications and weight at study entry) and age, duration of illness, class of antipsychotic medication. The mean weight gain in kg of four individual antipsychotic medications after mean 5 year duration of antipsychotic medication use was stelazine 9.89±3.5 kg, haloperidol 11.62±6.8 kg, risperidone 11.74±5.5 kg and olanzepine 14.34±6.9 kg. There was no significant difference among the individual medications on their propensity to cause weight gain among

participants (*ANOVA (F)=1.76,P=.14)*. By class of antipsychotic medication, the mean gain by conventional antipsychotics was 10.57±5.4 kg and the mean gain caused by atypical medications was 13.08±6.5 kg (*t=-1.40*, *P=1.17*) This implies that the conventional antipsychotic medications were as likely to cause increased weight gain as the second generation antipsychotics in our treatment setting.

3.3 Patient Characteristics and Body Mass Index

At presentation to our treatment facility before commencement of antipsychotic medications, the prevalence rates of normal weight, overweight and obesity were 72.6%, 24.5% and 2.8% respectively. At study entry, after a mean 5 year period of treatments with antipsychotic medications, the prevalence of overweight and obesity were 62.3% and 20.8% respectively showing significant differences from values before commencement of antipsychotic medication (x^2*=11.23, P=.02*). Gender was a factor in the propensity to gain weight. Relative to men, women were more likely to become overweight and obese following antipsychotic use (*p=.04*). Increasing duration of antipsychotic use was associated with increased tendency for overweight and obesity among study participants (*P=.04*). There was no association found between BMI values and age of participants, employment status, and class of antipsychotic medication. Also, no association was detected with duration of illness and marital status (see Table 2).

Table 2. Demographic and clinical characteristics by body mass index classification

Variables	Normal or low weight n (%)	Overweight n (%)	Obesity n(%)	Statistics	P-value
Sex					
Male	12(66.7)	25(37.9)	6(27.3)	x^2=6.89	**.04**
Female	6(33.3)	41(62.1)	16(72.7)	df 2	
Age					
≤40 years	11(61.1)	31(47.0)	13(59.1)	x^2=1.7	.43
>40 years	7(38.9)	35(53.0)	9(40.9)	df=2	
Marital status					
Married	1(5.6)	16(24.2)	5(22.7)	x^2=3.07	.22
Single	17(94.4)	50(75.8)	17(77.3)	df=2	
Employment					
Employed	6(33.3)	18(27.3)	5(22.7)	x^2=0.56	.76
Unemployed	12(66.7)	48(72.7)	17(77.3)	df=2	
Duration of antipsychotic use					
≤5years	11(61.1)	18(27.3)	8(36.4)	x^2=6.89	**.03**
>5years	7(38.9)	48(72.7)	14(63.6)	df=2	
BMI before treatment					
Normal	15(83.3)	51(77.3)	11(50.0)	x^2=11.23	**.02**
Overweight	2(11.1)	15(22.7)	9(40.9)	df=4	
Obesity	1(5.6)	0(0)	2(9.1)		
Class of antipsychotics					
Conventional	2(11.1)	5(7.6)	5(22.7)	x^2=5.63	.26
Atypical	3(16.7)	18(27.3)	7(31.8)	df=4	
Combination	13(72.2)	43(65.1)	10(45.5)		
Duration of illness					
≤10 years	13(72.2)	46(69.7)	17(77.3)	x^2=1.67	.43
>10 years	5(27.8)	20(30.3)	5(22.7)	df=2	
Hyperglycaemia					
No	14(77.8)	55(83.3)	12(54.5)	x^2=7.6	**.03**
Yes	4(22.2)	11(16.7)	10(45.5)	df=2	

3.4 Body Mass Index and Glycaemic Status

According to the American Diabetes Association (ADA) any individuals with fasting glucose level of 100-125 mg/dl (5.6-6.9 mmol/l) or glucose level of 140-199 mg/dl (7.8-11 mmol/l) two hours after 75-g oral glucose tolerance test or hemoglobin A(1c) 5.7%-6.4% be classified as prediabetic, indicating increased risk for the emergence of diabetes [21]. In this study, when a subject had pre-diabetes (fasting plasma glucose 100–125 mg/dl) or diabetes (fasting plasma glucose ≥126 mg/dl), he/she was considered to have hyperglycaemia. The glycaemic status of study participants showed 11 subjects representing 16.7% of subjects within overweight range had hyperglycaemia compared to 10 subjects representing 45.5% participants in the obesity range with hyperglycaemia (*P=.03*). (see Table 2)

4. DISCUSSION

In this study, the prevalence of overweight and obesity among patients with schizophrenia under antipsychotic medications were 50% and 20.8% respectively. These rates are relatively high compared to the rate reported in a previous Nigerian study of subjects under antipsychotic medications, which found obesity rate of 7.3% [17]. In our sample, the proportion of study participants in the overweight range is high compared to the findings reported in the general Nigerian adult population study in which overweight rate of 8.1-22.2% was obtained [22]. For patients who never received antipsychotic medications and presenting for the first time for treatment in our facility, the prevalence rate of overweight and obesity were 24.5% and 2.8% respectively. However, at study entry, after a mean five year period of treatment with various antipsychotic medications, the prevalence of obesity in our sample (20.8%) had significantly increased from initial value of 2.8%. The prevalence of obesity found in this study differs from findings from other developing countries such as Ghana and Indonesia which reported lower rates of 5.91% and 5.0% respectively [23,24]. The high obesity prevalence rate in this study compared to rates from other developing countries may be attributed to patients' characteristics in our sample. A high proportion of our study participants are unemployed resulting in low economic placements and limiting their capacity for healthy lifestyle choices and pursuits. The low employment and economic opportunities among participants also has the potential to promote increased redundancy and reduced physical activities participation resulting in a more sedentary life style which can lead to significant weight increases.

Worldwide, the prevalence rate of obesity in the present study is in agreement with several studies from high income countries which have reported similar prevalence [25,26]. Increasingly, more patients in our treatment setting are prescribed the second generation atypical antipsychotic medications as first line medications as reflected in the high proportion (about 55%) of patients on these medications either as monotherapy or in combination with conventional antipsychotics. This may partly explain the proximity of the obesity rate found in this study to the prevalence rates reported from some advanced industrialised nations.

The atypical antipsychotic medications have been reported to contribute more to drug-induced weight gain compared to the conventional antipsychotics. In this study however, we did not observed a significant differential class effect of medications on the risk of weight gain by study participants. Weight gain is a well-established side-effects of both first and second generation antipsychotic medications [8] and has been cited as an important reason for medication non-adherence [13,27,28]. The mean weight gain of our sample in kg significantly increased by 56.3% from the weight at onset of treatment to a period of one year after commencement of antipsychotic medication treatment. This represents a 10% increase on the initial body weight at presentation to our treatment facility within one year of antipsychotic medication treatment. This finding is consistent with a study by Hummer et al. [29] who reported that after 1 year of treatment, 36% of patients treated with clozapine had gained more than 10% of their initial body weight. Previous studies have reported significant contributions by both classes of antipsychotic medications, especially the second generation atypical antipsychotic medications, to the prevalence of obesity in the medicated schizophrenic population, with current estimates ranging from 40 to 60% versus 30% of the general adult population [30,31]

The role of demographic factors in promoting weight gain and obesity following treatments with antipsychotic medications was explored in the study. Socio-demographic variables like age, marital status and employment status have not

been consistently predictive of weight gain and obesity in this population of patients and our study is generally in support of studies which did report significant association with these variables. In the current study, women were significantly more likely to be overweight and obese compared to the male subjects. This is in agreement with previous studies which have reported similar findings [19,32]. The gender differences in the prevalence of overweight and obesity between male and female participants on antipsychotic medications have partly been attributed to events such as pregnancy, oral contraceptives therapy and menopause [33,34].

The impact of treatment duration and the risk for significant weight increases and obesity in patients on antipsychotic medications have been reported in previous studies [29,35,36]. In this study, weight increases and obesity was significantly related to the duration of antipsychotic medication treatment. Treatments with atypical antipsychotics had resulted in a higher mean weight gain for study participants compared to the weight gain attributed to conventional antipsychotic medications use. The differential weight gain effect of the class of antipsychotic medications was not observed in this study and therefore in agreement with studies which reported such findings [19,31].

We found a significant statistical association between obesity and the risk of developing hyperglycaemia. The impact of antipsychotic medications on the risk of developing hyperglycaemia and diabetes mellitus in patients with schizophrenia on antipsychotic medications has long been recognised. Previous studies have reported that the tendency for antipsychotic medication to cause hyperglycaemia and type 2 diabetes mellitus is related in part to their ability to cause weight gain and obesity [37,38]. Both typical and atypical antipsychotics have been associated with increased risk of weight gain and diabetes mellitus in patients with schizophrenia. Recent reports suggest that second generation atypical antipsychotic medications contribute more to clinically significant hyperglycemia than the conventional antipsychotics [39]. In this study the risk of developing hyperglycaemia following antipsychotic medications was increased for study participant within the obesity range. The clinical implication of this observation is the need for routine weight and glycaemic status monitoring and to institutes management measures which may include switching medication for at individuals with significant weight gain as recommended by the American Diabetes Association [21].

This study has some limitations. The cross-sectional nature of the study cannot confirm associations between the factors studied, the value must be limited to the descriptive and its exploratory nature. Also, confounding variables such as nutritional status, sedentary status and genetic influences were not objectively measured, controlled and accounted for in this study.

5. CONCLUSION

Patients on antipsychotic medication for schizophrenia or other illnesses should be considered a high-risk group for significant increases in weight gain and obesity. There in the need for regular and routine monitoring of all patients on antipsychotic medication for necessary management measures and interventions to prevent excessive weight gain during treatment.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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