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Research Article

Hyperprolactinemia in Psychiatric Patients Taking Antipsychotic Medications: A Longitudinal Study in a Tertiary Hospital in South-South, Nigeria

Emmanuel O Olose[1]*, Chidozie D Chukwujekwu[2], Cecilia O Busari[3] and Monday N Igwe[4]

[1]*Department of Psychiatry, University of Calabar, Cross River State, Nigeria.*

[2]*Department of Psychiatry, University of Port Harcourt, Port Harcourt, Nigeria.*

[3]*Department of Psychiatry, College of Medicine, University of Lagos, Lagos, Nigeria.*

[4]*Department of Psychological Medicine, Faculty of Medicine, Ebonyi State University, Abakaliki, Nigeria.*

ABSTRACT

Hyperprolactinemia is one of the commonest side effects in patients taking antipsychotics, and the tendency of antipsychotics to elevate plasma prolactin level is dose dependent. This study aims to investigate the relationship between use of antipsychotic medications and hyperprolactinemia among mentally ill patients. This is a longitudinal study. From 90 consenting antipsychotic naïve patients and all of whom have met the inclusion criteria, sociodemographic interview schedule was administered. Next, venous blood sample was collected for estimation of serum prolactin level and repeated after 8 weeks. Overall prevalence of hyperprolactinemia is 30%; there is a correlation between hyperprolactinemia and chlorpromazine equivalent dose of antipsychotics ($r = 0.397$; $p < 0.001$); there is no association between hyperprolactinemia and class of antipsychotic, and the greatest predictor of hyperprolactinemia was found to be the dose of antipsychoti c medication used. Hyperprolactinemia may result from the use of typical or atypical antipsychotic medications, and the dose of antipsychotic medication used is the greatest predictor of hyperprolactinemia.

Keywords: Hyperprolactinemia; Psychiatric Patients; Antipsychotics; Longitudinal; Nigeria

INTRODUCTION

Prolactin is a single chain polypeptide with 199-amino acid (23kDa) stabilized by three disulfide bonds [1]. The prolactin gene is found on chromosome 6 [2]. It was first identified as a separate hormone in the early 1970s [1]. It is produced by the lactotrophs of the anterior pituitary gland (the adenohypophysis), and it is excreted in the kidneys [1]. It is secreted regularly throughout life, and there is approximately 100 µg of prolactin available at any time in the human pituitary gland [3]. The prolactin receptor is found widespread in the body [1]. Prolactin is believed to modulate numerous biological effects. However, its main physiological role is in reproductive and homeostatic functions such as breast enlargement during pregnancy and milk production during lactation, inhibition of hypothalamic gonadotropin releasing hormone, and maintenance of proper ovarian function and of progesterone-secreting structures [1,4]. Its secretion follows a circadian rhythm with a peak after about 4 hours of sleep, lowest levels at about 6 hours after waking, and a regular pulsatile release every 95 minutes [4]. The normal plasma level of prolactin varies with age, sex, reproductive status, gravidity, and lactation [5,6]. It is highest at birth then declines gradually to adult levels by 15 years. In women, it reduces after menopause, and it rises by more than 10 times during pregnancy and sustains this level during lactation before gradually returning to normal level over several months in a lactating woman. Without breast feeding, however, after childbirth, it normalizes over 3 weeks [7].

It is important to point out that studies that have compared the prolactin levels in the general population and antipsychotic naïve patients with a psychotic illness have not shown any consistent and significant difference in these populations [4,7]. These studies will

***Correspondence to:** Emmanuel O Olose, Department of Psychiatry, University of Calabar, Cross River State, Nigeria. E-mail: oloseoe@yahoo.com

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then tend to suggest that the psychotic state is not significantly associated with hyperprolactinemia but it could occur as a result of medication use.

Hyperprolactinemia refers to a state where the plasma prolactin level is elevated above the upper limit of normal [7]. The normal plasma level of prolactin varies with age and sex among other factors. The normal plasma range is 2.1–17.7 ng/mL for adult males and 2.8–29.2 ng/mL for nongravid premenopausal adult females [5,6]. It is regarded as the most common pituitary hormone abnormality seen in clinical practice [8].

In any patient, hyperprolactinemia could arise from the use of certain medications such as serotonergic antidepressants, antidopaminergic agents, antihypertensive agents, H2, receptor blockers, protirelin (a thyrotropin releasing hormone), sex hormones, and miscellaneous agents like amphetamines and opiates. Generally, medication-induced hyperprolactinemia typically occurs after about 20 days (the interval may range from 7 to 75 days) after introduction. The onset of hyperprolactinemic symptoms usually occurs a few weeks after the introduction of the offending medication in the absence of signs or symptoms that might suggest a sellar space-occupying lesion and other laboratory tests will be normal [1,4]. Some physiologic states like lactation and pregnancy tend to induce a raise that persists throughout the duration of the state, while sleep, stress, physical exercise, sexual activity, and breast stimulation could induce a raise that is usually slight and transient. In addition, some pathologic conditions are associated with a high level of prolactin such as pituitary diseases like empty sella syndrome, micro-prolactinomas, macro-prolactinomas, and pituitary stalk lesions; hypothalamic diseases like hypothalamic tumors, hypothalamic sarcoidosis, and postencephalitis; some endocrine diseases like acromegaly, Cushing's disease, polycystic ovary syndrome, and primary hypothyroidism; and miscellaneous conditions like chest wall lesions (e.g., trauma, neoplasms), chronic renal failure, liver cirrhosis, ectopic production of prolactin (e.g., by small-cell bronchial carcinoma), and idiopathic type. The cause of hyperprolactinemia could be suggested by the plasma prolactin level. Prolactin levels >150 ng/mL (5000 mU/L) could indicate the presence of a prolactinoma; values of approximately 100–150 ng/mL (3000–5000 mU/L) indicate the presence of a micro- or hypofunctioning prolactinoma, whereas values ranging from 70 to 100 ng/mL (2100–3000 mU/L) are often due to prolactin-raising medications [1,4].

Antipsychotics are broadly classified into two groups which are the first- and the second-generation antipsychotics [9]. The first-generation antipsychotics have higher propensity to cause movement side effect referred to as extrapyramidal side effect [10]. This class consists of mainly the older antipsychotics. They are usually subclassified according to their chemical structure which is very predictive of their therapeutic action and side effects [11]. The prototype of this class is chlorpromazine. It is an aliphatic (or aminoalkyl) derivative of the phenothiazine family. The other derivatives of the phenothiazines are the piperidines (e.g., thioridazine) and the piperazines (e.g., fluphenazine). The aliphatic and piperidine derivatives are associated with a lower incidence of extrapyramidal side effects than the average first-generation antipsychotics but have higher incidence of sedation and autonomic side effect. The piperazines are associated with higher incidence of extrapyramidal side effect but less sedation and autonomic side effect [12]. The thioxanthenes (e.g., flupenthixol), the butyrophenones (e.g., haloperidol), and the diphenylbutylpiperidines (e.g., pimozide) share similar pharmacodynamic properties with the piperazine derivatives of the phenothiazines [12].

The substituted benzamides such as sulpiride and amisulpride have a similar mechanism of action with the first-generation antipsychotics but have a low frequency of associated extrapyramidal side effects which is comparable to the second-generation antipsychotics. Therefore, authorities are not in complete agreement on exactly how to classify them [13].

There are many properties of antipsychotics that could predispose the users to develop hyperprolactinemia. One of such is the affinity D_2 receptor which is a tendency to block (or occupy) the receptor. It has been shown that a critical level of D_2 receptor occupancy must be achieved before the antipsychotic effect can become manifest. Studies have revealed that the extent of D_2 receptor occupancy is directly correlated with the dose of first-generation antipsychotics [13]. This critical level is at 60%–70% of D_2 receptor occupancy as observed from brain imaging studies of the nigrostriatal system using positron emission tomography [14]. Above this range, antipsychotic activity is not further enhanced [14]. The threshold for hyperprolactinemia is at about 72% D_2 receptor occupancy [1,15], while at 80% D_2 receptor occupancy, the incidence of extrapyramidal side effect is increased [1,15]. This is true for all first-generation antipsychotics, while most second-generation antipsychotics are known to achieve antipsychotic effect at a lower D_2 receptor occupancy which could be 5%–10% less compared to first-generation antipsychotics [16]. Clozapine and quetiapine have been found to achieve antipsychotic effect at D_2 receptor occupancy as low as 40% (or lower) [13,14], while aripiprazole, because of its unique mechanism of action, needs more than 85% D_2 receptor occupancy to achieve antipsychotic effect despite causing little or no extrapyramidal side effect [14]. The tendency of antipsychotics to elevate plasma prolactin level is dose dependent [10]. Studies on this area of biological psychiatry are sparse in Nigeria. This study aims to investigate the relationship between use of antipsychotic medications and hyperprolactinemia among mentally ill patients.

Aim of this study

This study is designed to investigate the potential relationship between use of antipsychotic medications and hyperprolactinemia among mentally ill patients.

Specific objectives

1. To determine the prevalence of hyperprolactinemia among psychiatric patients taking antipsychotic medications
2. To determine the correlation between serum prolactin levels and dosage of medications in Chlorpromazine equivalents
3. To determine the association between class of antipsychotic medication and prolactin levels among patients taking antipsychotic medications

4. To determine the predictor of hyperprolactinemia among the variables

MATERIALS AND METHODS

Study location

This study was carried out at Madonna University Teaching Hospital Elele, Rivers State, Nigeria.

Ethical issues

Each patient gave informed consent to participate in the study and for the findings of this study to be published in any journal of the researcher's choice. Approval for the study was given by the ethical committee of Madonna University Teaching Hospital Elele, Rivers State, Nigeria. Discontinuation from the study at any stage of the study does not affect the level of care given to the patient. Cost of the investigations was borne by the authors.

Participants' selection

All new patients attending the weekly psychiatric clinic of the Madonna University Teaching Hospital, Elele, Nigeria within the study period (July–December 2019) who meet the inclusion criteria and who gave voluntary informed consent were recruited into the study until the minimum calculated sample size was recruited.

Inclusion criteria

1. Participants meeting ICD-10 diagnostic criteria for a psychiatric illness.
2. Participants who are antipsychotic naive.
3. Age ≥ 18 years.
4. Those who give informed consent.

Exclusion criteria

1. Medical conditions related to hyperprolactinemia.
2. Previous use of antipsychotic medications.
3. Those who refuse to give consent.
4. Those too sick to give consent.

Sample size determination

The required sample size was calculated by using the relation [9]

$$N = \frac{Z^2pq}{D^2}$$

N = sample size
p = prevalence from a previous study [5]
q = 100-p (the proportion of those without hyponatremia)
Z = confidence interval which is taken to be 1.96
D = degree of confidence (5%)

From the above formula, a minimum sample size of 84 was gotten. Making a 10% allowance for attrition, the sample size was 93.

Procedure

For this study, collection of data was from July to December 2019. The first step was to identify patients diagnosed as having a psychotic illness by the doctor on duty at the emergency room. The nature and purpose of the study was then explained to the patients and their caregivers, and informed consent was then sought to enable them take part in the study. A sociodemographic questionnaire was given to the patient to collect information about age, educational status, occupation, marital status, previous history of psychiatric illness, and history of use of antipsychotic medications. A single venous blood sample was obtained for serum prolactin analysis. A total of 93 patients were approached for enlistment into the study, and at the end of 8 weeks, the serum prolactin level analysis were repeated. At the second assessment, only 90 subjects remained in the study. Three subjects dropped out of the study. Patients were categorized according to the antipsychotics (typical or atypical) that they used in the previous 8 weeks before the second assessment. The attending doctor determined the antipsychotics prescribed for each patient. Any drugs used in the previous 8 weeks were recorded.

Statistical analysis

Data were analyzed using the personal computer version of the Statistical Package for the Social Sciences (SPSS- PC version 22). The subjects were classified according to their serum sodium level, use of antipsychotics and sociodemographic variables. All the antipsychotics used by the index cases were converted to their CPZ equivalent doses. Noncontinuous variables were compared using chi-square test, while the *t*-test was used for continuous variables such as age and sodium levels. For the individual antipsychotics, the mean baseline prolactin values were compared with the respective mean endpoint values by using *t*-test. Binary logistic regression was done to determine the greatest predictor of hyperprolactinemia among the variables. All tests were two-tailed with significance level set at 0.05%.

RESULTS

Sociodemographic characteristics of respondents

Ninety antipsychotic naïve patients who gave consent were recruited into the study and their data analyzed.

The mean age of respondents was 34.08 (±11.82) years and 62% were single. Over two-thirds (61%) of the participants had attained secondary education. More than half (56%) of the participants are employed (Table 1).

Prevalence of hyperprolactinemia

Mean initial prolactin levels for respondents was 7.89 (standard deviation [SD] = 3.37) and mean final prolactin level was 21.73 (SD = 22.73), with a mean change in prolactin level of 13.83 (SD = 21.67). This difference was statistically significant (t = –6.05; df = 89; p ≤ 0.001).Nine (36%) out of the 25 female respondents developed hyperprolactinemia, whereas 16 (24.6%) of the 65 male respondents developed hyperprolactinemia at the end of the study period. Thus overall, 25 respondents developed hyperprolactinemia within the study period giving us an overall prevalence of 36%.

Relationship between dosage of antipsychotics in CPZ equivalents and serum prolactin levels

The mean dose of antipsychotic medication in CPZ equivalents was 456.11 mg (SD = 216.14). There was a significant correlation

Table 1: Sociodemographic characteristics of respondents.

Variables	Frequency (%) N = 90
Age(years)	
10–20	6 (6.67)
21–30	34 (37.78)
31–40	31 (34.44)
41–50	11 (12.22)
51–60	3 (3.33)
61–70	5 (5.56)
Mean age± S.D	34.08±11.82
Marital status	
Single	62 (68.9)
Married	28 (31.1)
Education	
Primary	18 (20)
Secondary	61 (67.8)
Tertiary	11 (12.2)
Employment	
Employed	56(62.2)
Unemployed	34(37.8)

between the final prolactin level and the chlorpromazine equivalent doses of the antipsychotic medications (r = 0.397; p < 0.001).

Association between class of antipsychotic medication and prolactin level

Sixty-two (68.89%) respondents received typical antipsychotics medication out of whom 18 (29.03%) developed hyperprolactinemia. Of the 28 (31.11%) respondents who were placed on atypical antipsychotics, 7 (25%) developed hyperprolactinemia at the end of the study period. This difference was not statistically significant (χ^2 = 0.165; df = 1; p = 0.693; Table 2).

Predictors of hyperprolactinemia

Binary logistic regressions show that the dose of antipsychotic medication used is a better predictor of hyperprolactinemia, than the class of antipsychotic medication taken by the patient (Table 3).

Table 3: Binary logistic regression analysis for predictors of hyperprolactinemia among subjects.

Variables in the equation					
	Wald	df	95%C.I		p value
			Lower	Upper	
Dose	6.391	1	0.995	0.999	0.011
Class of drug	0.29	1	0.319	2.513	0.865
Constant	5.827	1			0.016

DISCUSSION

Prevalence of hyperprolactinemia

The overall prevalence of hyperprolactinemia of 30% found in this study is comparable to the prevalence values reported by some studies [17,18]. Some other studies [17] reported a higher value of up to 70%. These studies were a systematic review of published works. Most of these studies were retrospective in nature, whereas this index study is prospective in design.

This study found the prevalence of hyperprolactinemia to be higher among the females. A British study [19] also found hyperprolactinemia to be higher among the female subjects. Similarly, a study by Kleinberg *et al.* among patients taking risperidone or a first-generation antipsychotic reported an incidence of 60% among female patients versus 40% among the male patients [20]. Nevertheless, Montgomery *et al.* [18] had a contrary finding. Their study differs from the present study because they used the same upper limit of prolactin level for both male and female subjects, but in this study, the upper limit of prolactin level for males and females are different. Additionally, this study is a longitudinal study. Longitudinal studies are known to be more reliable than cross-sectional studies in epidemiological surveys.

Relationship between dosage of antipsychotics in CPZ equivalents and prolactin levels

In this study, there was an association between the dose of antipsychotic dose in CPZ equivalence and hyperprolactinemia. This is similar to the finding in another study [19] among subjects with schizophrenia who were receiving typical antipsychotic medications. However, another study on subjects who were taking atypical antipsychotics did not find any association between dose of antipsychotics and prolactin level [21]. A likely reason for this difference could be the fact that the subjects in the later study [21] were only taking atypical antipsychotics, whereas this present study included subjects who were taking typical and atypical

Table 2: Class of antipsychotic and prolactin level.

Variable (Antipsychotic)	Hyperprolactinemia			χ^2	df	p value
	Cases	Yes	No			
Typical	62	18	44	0.156	1	0.693
Atypical	28	7	21			

antipsychotics. This is worthy of note because several other studies have reported a significant association between level of prolactin and class of antipsychotic medication used.

Association between class of antipsychotic medication and prolactin level

This study found no significant association between class of antipsychotic medication used and prolactin level. A similar finding has been reported in a study by Yen *et al.* [22]. However, an American study [23] by Kinon *et al.* found a significant difference between the prolactin levels of patients taking first- and second-generation antipsychotics. The second-generation antipsychotic studied in the American study was risperidone unlike the present study that recruited other second-generation antipsychotics. Unlike other second-generation antipsychotics, risperidone along with paliperidone and amisulpride are known to significantly raise the prolactin level of subjects [1]. These drugs have a somewhat lower blood–brain barrier penetration and therefore a higher peripheral blood concentration [10,24]. Since the pituitary gland is outside the blood–brain barrier, it might be exposed to higher concentrations of these drugs than other brain areas which might translate to more likelihood of adverse effects from the tuberoinfundibular dopaminergic pathway which regulates the release of prolactin. Furthermore, risperidone was the antipsychotic most associated with high prolactin level in this study. Some studies have reported significant differences in the association of various antipsychotics and the prolactin level of patients [10,14].

Predictors of hyperprolactinemia

The finding in this study is similar to reports in several other studies which have all shown that the dose of antipsychotic medication used is a better predictor of prolactin level than all other variables related to final prolactin level among psychiatric patients using antipsychotic medications.

CONCLUSION

Hyperprolactinemia may result from the use of typical or atypical antipsychotic medications. The dose of antipsychotic medication used is the greatest predictor of hyperprolactinemia. There is no association between class of antipsychotic medications and development of hyperprolactinemia among psychiatric patients using antipsychotic medications.

Additional points

Strengths of this study

1. Exclusion of patients with medical conditions like hypothyroidism, cirrhosis of the liver, chronic kidney failure, prolactinoma, and exclusion of patients taking medications like verapramil, alpha methyl dopa, opioids, cimetidine, hormonal contraceptives, and selective serotonin reuptake inhibitors. This is because these conditions and medications have a propensity to cause hyperprolactinemia. This is to eliminate their effects as confounders.
2. It is a descriptive longitudinal study.
3. The doctors attending to the respondents had the liberty to decide which type of antipsychotic and the dosages to be given to the respondents.

Limitation of this study

The respondents were hospital-based; thus, findings from this study may not be generalizable to the larger population. In spite of these observations, the findings from this study can serve as a reference point for future studies and can add to the epidemiological database of hyperprolactinemia in psychiatric patients.

Disclosure

This study is funded entirely by the authors alone.

Authors' contributions

This work was carried out in collaboration of all the authors. Emmanuel Omamurhomu Olose, Donald Chidozie Chukwujekwu, Cecilia Oluwafumilayo Busari, and Igwe MN designed the study while Emmanuel Omamurhomu Olose wrote the protocol for the study. Emmanuel Omamurhomu Olose, Donald Chidozie Chukwujekwu, and Cecilia Oluwafumilayo Busari collected data. Data analysis was done by Emmanuel Omamurhomu Olose. Emmanuel Omamurhomu Olose, Donald Chidozie Chukwujekwu, and Cecilia Oluwafumilayo Busari did the literature search. Emmanuel Omamurhomu Olose and Igwe MN wrote the initial draft of this publication, Donald Chidozie Chukwujekwu drew the tables, and all the authors made corrections for the final draft of this manuscript.

Competing interests

The authors declare that there is no conflict of interests regarding this study and the publication of its findings.

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