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Antipsychotic Medication in  
a Tertiary Hospital in South-  
South, Nigeria

HATASO, USA

# Hyponatremia among Psychiatric Patients Using Antipsychotic Medication in a Tertiary Hospital in South-South, Nigeria

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## Abstract

The aim of this study was to determine the prevalence of hyponatremia among psychiatric patients taking antipsychotics, to determine the correlation between serum sodium levels and dosage of medications as well as to determine the association between class of antipsychotic medication and serum sodium levels among patients taking antipsychotic medications. This is a longitudinal study. From 92 consenting antipsychotic naïve patients who met the inclusion criteria, sociodemographic interview schedule was administered. Thereafter, a single venous blood sample was obtained for serum electrolyte analysis and repeated after 6 weeks. Prevalence of hyponatremia was 19.4%, there was a correlation between hyponatremia and dose of antipsychotic in chlorpromazine equivalent ( $r = -0.354$ ;  $p = 0.01$ ), and there is an association between typical antipsychotic use and hyponatremia. The use of both typical and atypical antipsychotic medications can lead to hyponatremia. This is in keeping with previous reports.

**Keywords:** Hyponatremia; Psychiatric patients; Antipsychotics.

## 1. INTRODUCTION

Hyponatremia occurs commonly in psychiatry but usually as a side effect of prescribed medications or following polydipsia [1], and it is a very common electrolyte disorder seen among in-patients. The reported prevalence is between 5 and 30% depending on the clinical setting [2]. Hyponatremia refers to a serum sodium concentration that is below the normal range. The range of normality for serum sodium is between 135 and 145 mEq/L. Therefore, a serum sodium level of less than 135 mEq/L is hyponatremia, with levels below 125 mEq/L described as severe.

In a retrospective in-depth analysis of hyponatremia cases in a large unselected population of psychiatric in-patients within a 3-year period, it was reported that hyponatremia may be due to the syndrome of inappropriate antidiuretic hormone (ADH) secretion, as shown by low serum osmolarity in the studied population. In addition to advanced age and female gender, treatment with specific drugs (not drug classes) confers substantially greater risk.

In a Canadian study [3], atypical antipsychotic usage was shown to be associated with a modest increase in the 30-day risk of hospital admission resulting from hyponatremia. The association was less than that described with other psychotropic medications.

Hyponatremia occurs as a rare and clinically important adverse reaction to treatment with different psychotropic medications, such as selective serotonin reuptake inhibitors and antiepileptic drugs. Previous published studies have reported the development of hyponatremia in association with antipsychotic drug treatment [4]. The incidence of hyponatremia induced by antipsychotic medications may likely be far higher than is presently conceptualized. It should be noted that the use of typical and atypical antipsychotics has been reported to be associated with the occurrence of hyponatremia as a side effect. Psychiatrists, physicians generally and indeed all healthcare workers, should be aware of the risk of hyponatremia occurring with the use of antipsychotics [4].

Quite a number of psychiatric patients taking neuroleptics may have polydipsia and polyuria without identifiable underlying medical causes. Hyponatremia developing in some patients with polydipsia may progress to water intoxication and may lead to symptoms such as confusion, lethargy, psychosis, and even seizures or death. This syndrome may be appropriately referred to as "psychogenic polydipsia" or "self-induced water intoxication." Even though the underlying pathophysiological etiological basis of this condition is unclear, some factors have been identified to be playing key roles in the etiology of polydipsia with hyponatremia, especially among patients presenting with symptoms. These include a probable dysfunction of the hypothalamus as well as a dysfunctional secretion of ADH as is unequivocally seen in the syndrome of inappropriate secretion of ADH (SIADH) and use of a neuroleptic medication [5]. SIADH may be suspected in any patient presenting with hyponatremia, hypo-osmolality, and a urine osmolality of less than 100 mOsm/kg. It causes hyponatremia by inhibiting the excretion of ingested water [6].

In a retrospective study of over 20,000 patients with schizophrenia receiving in-patient treatment, a 5.8% incidence of hyponatremia was reported [7]. It has been suggested that the syndrome of psychosis, intermittent hyponatremia, and polydipsia (PIP), which is seen among psychiatric patients especially in patients with schizophrenia [1], may be due to compulsive water drinking [2]. This compulsive water drinking behavior in turn may be due to central thirst dysregulation [1,3], endogenous opioid system [5], and neuroleptic drug therapy that leads to an altered thirst sensation [3].

Most studies on the effect of antipsychotic medication use on serum sodium levels in Nigeria are cross sectional and retrospective in design. Longitudinal studies are needed to determine the exact nature of the relationship between the use of antipsychotic medication and hyponatremia. This study aims at determining the potential relationship between the use of antipsychotic medications and hyponatremia among psychiatric patients.

### 1.1. Aim of Study

The design of this study was to investigate the potential relationship between use of antipsychotic medications and hyponatremia among psychiatric patients.

### 1.2. Specific Objectives of This Study

- (1) To determine the prevalence of hyponatremia among psychiatric patients using antipsychotic medications
- (2) To determine the correlation between serum sodium levels and dosage of medications in CPZ equivalents
- (3) To determine the association between class of antipsychotic medication and serum sodium levels among patients taking antipsychotic medications

## 2. METHODS

### 2.1. Study Location

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

### 2.2. Ethical Issues

Each patient and their relatives voluntarily gave informed consent to participate in the study as well as for the findings of this study to be published in any journal of the researcher's choice. The Ethical Committee of Madonna University Teaching Hospital, Elele, Rivers State, Nigeria, approved this study. Discontinuation from the study at any stage does not affect the level of patient care. Costs of the investigations were borne by the researchers.

### 2.3. Sample Size Determination

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

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

$N$  = 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 20% allowance for attrition, the minimum sample size was 105.

### 2.4. Inclusion Criteria

- (1) Participants meeting ICD-10 diagnostic criteria for a psychiatric illness
- (2) Participants who are antipsychotic naive
- (3) Age  $\geq$  18 years
- (4) Must give informed consent

### 2.5. Exclusion Criteria

- (1) Medical conditions related to hyponatremia (e.g., hypothyroidism and severe alcoholism)
- (2) Taking medications related to hyponatremia (e.g., carbamazepine, thiazide diuretics, and antidepressants)
- (3) Those who refuse to give consent

## 2.6. Procedure

Data collection took place from April to December 2016. First, all patients diagnosed as having any psychotic illness by the doctor on duty at the emergency room were identified. The nature and purpose of the study are 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 is then given to the patient to collect information about age, educational status, occupation, and family history of hyponatremia or severe alcoholism or hypothyroidism.

A single venous blood sample was obtained for serum sodium and electrolyte analysis. All blood samples were processed by the same laboratory scientist. At the end of 6 weeks, the serum sodium and electrolyte analysis were repeated. At the second assessment, 92 subjects remained in the study. Thirteen subjects withdrew from the study. Patients were grouped according to the class of antipsychotics (typical or atypical) that they used in the previous 6 weeks before the second assessment. The attending doctor determined the antipsychotics prescribed for each patient. Any drugs used in the previous 6 weeks were recorded.

## 2.7. Statistical Analysis

The personal computer version 22 of the statistical package for social sciences (SPSS) was used for the data analysis. The subjects were classified according to their serum sodium level, use of antipsychotics, and sociodemographic variables. Doses of all the antipsychotics used by the cases were converted to their chlorpromazine equivalent doses. Noncontinuous variables were compared using Chi-square test, while the *t*-test was used for continuous variables of age and sodium levels. For the individual antipsychotics, the respective mean baseline serum sodium values were compared with the mean endpoint values using *t*-test. All tests were two-tailed, and level of significance level was set at 0.05%.

## 3. RESULTS

### 3.1. Sociodemographic Characteristics of Respondents

A total of 92 patients completed the study. Sixty-six (71.7%) of the respondents were males, while 26 (28.3%) were females (Table 1).

**Table 1: Sociodemographic characteristics of respondents.**

<b>Variable</b>	<b>Frequency</b>
	<b>N(%)</b>
	<b>N = 92</b>
<b>Gender</b>	
Male	66(71.7)
Female	26(28.3)
<b>Age (years)</b>	
18-27	26(28.3)
28-37	38(41.3)
38-47	15(16.3)
48-57	5(5.4)
58-67	8(8.6)
<b>Mean age</b>	<b>34.13(11.86)</b>
<b>Marital status</b>	
Married	28(30.4)
Single	64(69.6)
<b>Employment</b>	
Employed	36(39.2)
Unemployed	48(52.2)
Student	8(8.6)
<b>Education</b>	
Primary	19(20.7)
Secondary	61(66.3)
Tertiary	12(13)

**Table 2: Association between class of antipsychotic and hyponatremia.**

Variable (antipsychotic)	Cases	Hyponatremia		$\chi^2$	df	p-value
		Yes	No			
Typical	66	16	50	84.60	42.0	< 0.01
Atypical	26	2	24			

**3.2. Prevalence of Hyponatremia**

Mean initial sodium level was 139.78 (SD = 1.57), df = 91, and  $t = 849.19$ , and mean final sodium level was 136.70 (SD = 5.09). This difference was statistically significant. df = 91,  $t = 258.23$ ,  $p \leq 0.001$ .

Eighteen (19.6%) of the total of 92 participants had hyponatremia (final serum sodium levels below 135 mEq/L).

**3.2.1. Correlation between dose of antipsychotic medication and hyponatremia**

Mean antipsychotic dosage in chlorpromazine equivalent was 463.58 mg (219.62). There was a correlation between the final sodium level and antipsychotic dosage in CPZ equivalent ( $r = -0.354$ ;  $p = 0.01$ ).

**3.3. Association between Class of Antipsychotic Medication and Hyponatremia**

Sixty-six (71.7%) cases received typical antipsychotics medications out of which 16(17.4%) cases developed hyponatremia, whereas 26 (28.3%) used atypical antipsychotic medications and only 2(2.2%) developed hyponatremia. This difference is statistically significant ( $\chi^2 = 84.60$ , df = 42,  $p < 0.01$ ) (Table 2).

Among those who used atypical antipsychotic agents, the mean change in sodium level was 1.08 mEq/L, while the mean change in sodium level for those who used typical antipsychotic medication was 4.27 mEq/L. This difference is statistically significant ( $t = 2.32$ , df = 30,  $p = 0.02$ ).

**4. DISCUSSION****4.1. Prevalence of Hyponatremia**

The prevalence of hyponatremia in this study (19.4%) is very striking because some studies [7] have reported lower values. Although some studies have reported lower prevalence, a systematic review [4] article aptly observes that "the incidence of antipsychotic induced hyponatremia may be markedly higher than is currently believed." These studies were population-based studies and also had longer follow-up periods compared to present study. Nevertheless, the finding in this study is still tenable as it is comparable to prevalence values reported in several other studies. One American study [2] noted that "the majority of cases of hyponatraemia (34.1%) were associated with medication use." Furthermore, the prevalence of hyponatremia has been observed to be as high as 30% in several other studies [8-10] depending on the criteria for diagnosis, the clinical setting, and the patient population. It is noteworthy that these studies with higher prevalence values did not exclude patients taking medications known to have the propensity to cause hyponatremia. These medications include carbamazepine, thiazide diuretics, and antidepressants. The present study excluded patients using these medications, and this may explain our lower value.

**4.2. Correlation between Dose of Antipsychotic Medication and Hyponatremia**

This study found that there is a correlation between dose of antipsychotic in CPZ equivalent and hyponatremia. Nevertheless, a systematic review [4] of published evidence reports that overall correlational analysis showed no significant correlations between defined daily CPZ-equivalent dosages and serum sodium levels. It must be noted that majority of the publications (91 out of a total of 95 publications) used in the previously mentioned systematic review article were case reports and case series and thus of weaker scientific strength in terms of hierarchy of scientific evidence when compared to our study which has a prospective longitudinal design.

**4.3. Association between Class of Antipsychotic Medication and Hyponatremia**

This study shows an association between use of antipsychotic medication and development of hyponatremia. This is in harmony with the finding in a population-based Canadian Cohort study [3] on atypical antipsychotic medications and hyponatremia which reported that the use of newer generation antipsychotic drugs is associated with significant increase in the 30-day risk of a hospital admission from hyponatremia. It further noted that the association was less than that described with other psychotropic medications.

In addition, a systematic review of published evidence [4] revealed that both the newer atypical antipsychotics and the older typical antipsychotics have some association with the development of hyponatremia.

In this study, both typical and atypical antipsychotic medications use led to the development of hyponatremia. This is similar to reports in a recent study [11] which reported that compared with no antipsychotic use, atypical and typical antipsychotics were associated with an elevated risk of hyponatremia, after adjustment for chronological age, gender, and physical comorbidities. Use of carbamazepine also carries a significant risk for hyponatremia ( $p < 0.05$ ).

## 5. CONCLUSIONS

### 5.1. Strengths of This Study

(1) Use of antipsychotic drug naive patients as previous use of antipsychotic medications may mask metabolic effects. (2) Exclusion of patients with medical conditions related to hyponatremia (e.g., hypothyroidism and severe alcoholism) and patients taking medications related to hyponatremia (e.g., carbamazepine, thiazide diuretics, and antidepressants). This is to eliminate their effects as confounders. (3) It is a prospective longitudinal study. (4) The type and dosage of antipsychotic used were determined by the attending doctors.

### 5.2. Limitations of This Study

(1) The duration of follow-up was only 6 weeks. (2) Findings from hospital-based studies such as this 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.

### Authors' Contributions

This work was carried out with the collaboration of all the authors. E.O. Olose, D.C. Chukwujekwu, M.N. Igwe, and M.C. Aguocha designed the study. E.O. Olose wrote the protocol for the study. In addition, E.O. Olose, C.O. Busari, M.N. Igwe, D.C. Chukwujekwu, and S.K. Opara did the literature search, and M.C. Aguocha was in charge of the data analysis. E.O. Olose wrote the initial draft of this publication, D.C. Chukwujekwu prepared 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 interest regarding this study and the publication of its findings.

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