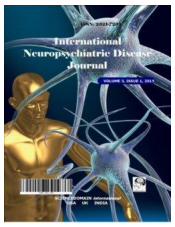

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A Cross-Sectional Study of the Impact of Antipsychotic Medications on the Hematological Profile of Patients with Schizophrenia in a Tertiary Health Facility in Uyo, South-South, Nigeria

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Authors' contributions

This work was carried out in collaboration between both authors. Author HEJ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author TAE contributed significantly to acquisition and review of data, analysis and interpretation of data, revising the draft manuscript for important intellectual content. We both read and approved the final version of the manuscript to be published.

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ABSTRACT

Objective: Antipsychotic drugs have been implicated as a potential cause of haematological toxicity. However, the seemingly mild and asymptomatic presentation is perhaps responsible for it not being frequently investigated. The aim of this study, therefore, was to determine the effect of antipsychotic drugs on the hematological profile of patients with schizophrenia.
Methods: This was a descriptive cross-sectional study involving 100 participants i.e. 60 subjects and 40 controls. 2.5 mls of blood was obtained from each participant for determination of full blood counts. Clinical data of subjects including their demographic characteristics, classes of antipsychotics, and duration of antipsychotic usage were obtained from their respective case files. Data was analysed using Statistical Package for Social Sciences for Windows Version 17. Significant level was set at $p<0.05$.

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Results: The mean of the hematological parameters including haemoglobin concentration, absolute neutrophil counts and platelet counts were significantly lower among the subjects than the controls p=0.001, 0.04 and 0.001 respectively. Similarly, there was statistically significant differences in the mean platelet count, MPV and PCT of subjects and controls with p<0.001, 0.001 and 0.04 respectively. However, there was no association between the mean age and gender of subjects and absolute neutrophil count p=0.24 and 0.46 respectively.
Conclusion: Significant reduction in haematological parameters of subjects compared to the controls may suggest some degree of haemato-toxicity most likely attributable to the antipsychotic drug. Furthermore the absolute neutrophil count though significantly lower in the subjects did not show age or sex differences. Therefore, there is need to regularly monitor haematological indices of psychiatric patients during treatment with antipsychotics.

Keywords: Antipsychotics; psychiatry; neutropaenia; blood dyscrasias.

1. INTRODUCTION

Drug-induced blood dyscrasias/abnormalities is a relatively common occurrence in clinical medicine including psychiatry. The underlying mechanism is thought to be one or a combination of the following including; direct toxicity of the drug on the haemopoietic cells resulting in marrow suppression, immune-mediated via antibodies directed at the haemopoietic cells in the bone marrow or mature blood cells in the peripheral circulation and less commonly inborn errors of metabolism [1]. Depending on the site of hematopoietic cell damage and the underlying mechanism, a single or multi-lineage blood dyscrasia may occur [1].

Almost all classes of antipsychotic medication have been reported to cause blood dyscrasia [2]. Agranulocytosis is probably the most important and the most common blood dyscrasia associated with antipsychotic drug use [3].

The phenothiazine due to their cumulative effect in the body, tend to cause bone marrow suppression especially in patients on maintenance therapy [1,3]. Clinical symptoms usually manifest within 40-days after the commencement of therapy and bone marrow examination often reveals hypocellular marrow elements [1].

Similarly, the atypical antipsychotics like clozapine have equally been implicated in blood dyscrasias. Clozapine-induced agranulocytosis selectively affects the precursors of polymorphonuclear leucocytes in the bone marrow [4]. The mechanism of action is unknown, but evidence of immunologically mediated reaction has been suggested [5]. Studies from western countries shows that clozapine carries a 0.8% and 2.7% risk of causing agranulocytosis and neutropaenia respectively in the first year of therapy [6]. Death resulting from neutropenic sepsis following antipsychotic medication have equally been reported [4,7]. It has been shown that patients who developed agranulocytosis on one antipsychotic medication are more likely to develop same when taking other types of antipsychotics especially the atypical antipsychotics [7]. Furthermore, the risk of agranulocytosis have been shown to increase with age and higher among females [6].

Red cell dyscrasias from antipsychotic use is a rare occurrence. The incidence of anaemia in patient taking clozapine was reported to be less than 0.1% [1]. Wasti et al. [8] in their study on the haematological, morphological and serum iron indices in schizophrenic patients who were on haloperidol, reported a significant reduction in erythrocyte count, haemoglobin, and packed cell volume of these patient compared with the controls. They also reported significant alteration in the red cell morphology with more than 10% of the red cells in the peripheral blood smear being hypochromic and microcytic. Furthermore, the study also reported an inverse correlation in the level of serum iron and ferritin with increased total iron binding capacity (TIBC) level among the subjects compared with the controls.

Thrombocytopenia resulting from antipsychotic use is equally quite rare. Among the conventional antipsychotics, the incidence is more common with the phenothiazine while clozapine is more often implicated among the atypical antipsychotics [2,9]. A study in Italy reported only 2 cases of thrombocytopenia among 2,404 patients (0.08%) who received clozapine [10]. A similar finding was reported in a joint study conducted in England and Ireland in which only 6 patients developed thrombocytopaenia out of the

over 6000 patients reviewed in the course of treatment [11]. In both studies, the thrombocytopenia was asymptomatic and the patients recovered almost spontaneously upon the discontinuation of the drug [10,11]. However, slow recovery of platelet has been reported by some authors following discontinuation of the medication [12].

The mean platelet volume (MPV) has been reported in several studies as an independent risk factor for venous thromboembolism (VTE) and cardiovascular risk [13,14]. MPV is a measure of platelet size and a maker of platelet function [14,15]. Increased MPV is associated with increased platelet reactivity. This is because large platelets contain denser granules and are metabolically more active. They also have a higher thrombotic potential and expresses higher levels of p-selectin than small platelets [14,15]. Antipsychotic medication have been reported to induce both cardiovascular and metabolic abnormalities in psychiatric patients with increase thrombotic risk than the general population [14,16]. Hence, serial MPV measurement a component of complete blood count from haematology auto-analyser may serve as useful tool in monitoring both thrombotic and cardiovascular risk in schizophrenic patients on antipsychotic drugs.

Whilst the occurrence of blood dyscrasias resulting from antipsychotic use is relatively common, the relatively mild nature and asymptomatic presentation in most patients perhaps is responsible for its under-reporting especially in a centre like ours where to the best of our knowledge research on this subject have not been previously reported. Therefore, this study sought to determine the effect of antipsychotic drugs on the hematological profile of patients with schizophrenia and also to determine if any, association between the classes of antipsychotics, duration of its use and body mass index of the subjects on their haematological indices. We believe that this study will create the much need awareness among psychiatrists and other physicians alike on the need to monitor patients on this medication closely as well as add to the existing body of knowledge on this subject.

2. MATERIALS AND METHODS

2.1 Study Site

This study was conducted at University of Uyo Teaching Hospital from February to June, 2017. The hospital is located in Uyo, the capital city of Akwa Ibom State, Nigeria. The hospital is a 500 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 [17]. Clinically generated data for each subject enrolled were matched to the ICD -10 criteria.

2.2 Study Design/ Recruitment of Subjects and Controls

This was a cross-sectional descriptive study designed to achieve the above set objective.

Patients were consecutively recruited into the study after a comprehensive psychiatric evaluation and diagnosis of schizophrenia was made by a consultant psychiatrist. The Mini International Neuropsychiatry Interview (MINI) Version 5.0.0 was further used to confirm the diagnosis of schizophrenia among the subjects. The Mini was designed as a brief structured interview for the major Axis 1 diagnosis in the Diagnostic and Statistical Manual (DSM IV) and ICD-10 [17].

Sixty schizophrenic patients who were either on atypical or conventional antipsychotic medication and who were attending regularly, the Mental Health Clinic of the Hospital were recruited into the study. Forty age and sex matched individuals who presented at the blood Donor Clinic of the Hospital were also consecutively recruited into the control arm of the study. Recruitment of subjects and controls lasted about 5 months (February-June 2017). All participants were assured of strict confidentiality in all aspect of the study.

2.3 Inclusion and Exclusion Criteria

Subjects who were 18 years of age and above, diagnosed with schizophrenia using above criteria and had received antipsychotic medication for at least 6 months. A written informed consent was obtained, either from the patients or their relatives before enrolment in the study. Patients who were taking medications that could impact on their haematological parameters such as carbamazepine, those with co-morbidities e.g. obesity, diabetes mellitus, renal impairments among others and those who did

not give a written informed consent were excluded from the study.

The controls subjects were individuals who presented at the blood donor clinic of the hospital for blood donation. Only donors certified fit to donate were recruited. A written informed consent was obtained from each eligible donor before enrolment in the study.

2.4 Specimen Collection/Analytical Procedure

Two and half millilitres (2.5 mls) of free flowing venous blood was collected from each of the participants (subjects and controls) into a pre-coated ethylene diamine-tetra-acetic acid (EDTA) vacutainer tubes. These samples were used to determine the complete blood count (CBC) of each participant using the Sysmex KX 31 Haematology auto-analyser. CBC analysis was done within 2 hours of sample collection. Samples that could not be analysed immediately were stored in the refrigerator at 2-6°C till analysis was done. From the CBC results the following parameters were extracted including, Haemoglobin concentration, Haematocrits, Red cell indices, Leucocyte count and its differentials as well as Platelet counts and its indices. Information on the socio-demographic characteristics of the subjects including age, gender, educational status, employment status, type/class of antipsychotics and the duration of its use were obtained from each subject's case-notes and recorded in a profoma designed for the study.

2.5 Data Analysis

Data was analysed using Statistical Package for Social Sciences for Windows Version 17 (SPSS Inc., Chicago, IL, USA). The results were presented in simple tables. Descriptive and inferential statistics such as student t-test, ANOVA, Pearson's correlation were used as appropriate. The level of significance was set at $p< 0.05$

2.6 Ethical Consideration

Ethical approval was obtained from the Health Research Ethics Committee (IHREC) of the hospital before the commencement of the study.

3. RESULTS

One hundred participants, comprising 60-test subjects and 40-controls were included in the study. The mean age of the test subjects was 37.61 ± 11.8 years (range 20-60 years) while that of the controls was 37.93 ±12.4 years. ($t = 0.52$; $p = 0.82$). More than half of the subjects were males (60%), majority (61.7%) were not married, and 61% had formal education to at least secondary school level whilst 46.7% were unemployed. More than 50% of the subjects had normal BMI (Table 1).

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

Variables	ns (%)
Age in years (mean ±SD) Subjects	39.25±12.20
Age in years (mean ±SD) Controls	37.93±12.4 (*P*=0.82)
Age	
≤40 years	36(60.0)
>40 years	24(40.0)
Sex	
Male	36(60.0)
Female	4(40.0)
Marital status	
Single	37(61.7)
Married	23(38.3)
Educational level	
Primary	6(10.0)
Secondary	31(51.7)
Tertiary	23(38.3)
Employment status	
Employed	32(53.3)
Unemployed	28(46.7)
Body Mass Index (BMI)	
High	28(46.7)
Normal	32(53.3)

BMI was dichotomised at the median score

The mean duration of illness was 8.00±7.8 years while the mean duration of antipsychotic drug use was 2.9±1.35 years. About 26.7% of subjects were on conventional antipsychotics. The three most commonly prescribed first generation antipsychotics were; haloperidol (42.3%) trifluoperazine (25.4%) chlorpromazine (22.6%). The remaining 9.7% were on (Thioridazine) long acting injectables like fluphenazine decanoate or flupenthixol decanoate. 28.3% of the subjects were on atypical antipsychotics. The most commonly prescribed serotonin dopamine antagonists (SDAs) were olanzapine (46.6%), risperidone (40.5%) quatiepine (9.1%) and clozapine (1.2%). More than 45.0% of the subjects were on polytherapy and the common combinations were; combination of two conventional antipsychotics,

combination of a conventional and atypical antipsychotics or combination of any class of antipsychotics and a long acting injectable form. The dosing frequency of 40% of the subjects was at least twice per day while 20% were on once daily dose regimen (Table 2).

The mean of the various red cell parameters were significantly lower in the subjects compared with the controls $P< 0.001$ in all cases except for the MCHC. In the white blood cells parameters, the mean of the absolute neutrophil count (ANC) was significantly lower among the subjects compared to the controls $P<0.04$. Similarly, there was statistically significant differences in the mean platelet count, MPV and PCT of subjects and controls with $P<0.001$, 0.001 and 0.04 respectively (Table 3).

Table 2. Distribution of the antipsychotic classes among subjects

Variables	Frequency
Duration of illness	
< 10 Years	**36 (60)**
>10 Years	**24 (40)**
Mean duration of annipsychotic use	**2.90± 1.35**
Classess of antipsychotics	
Conventional antipsychotics	**16 (26.7)**
haloperidol	7 (43.7)
trifluperazine	4 (25.0)
chlorpromazine	4 (25.0)
thioridazine	1 (6.3)
Atypical antipsychotics	**17 (28.3)**
olanzapine	8 (47.1)
risperidone	7 (41.2)
clozapine	2 (11.7)
Combination antipsychotics	**27 (45.0)**

Table 3. Comparison of the mean haematological parameters of subjects and controls

Variables	Subjects	Control	Test statistics	*p*-value
RBC	4.21±0.56	4.94±0.39	t =7.42	0.001
HGB	123.57±12.19	136.73±9.84	t = 5.97	0.001
HCT	0.386±0.04	0.439±0.03	t = 7.92	0.001
MCV	82.39±2.99	89.70±3.28	t =11.28	0.001
MCH	26.34±1.41	28.41±0.95	t =8.78	0.001
MCHC	319.75±8.69	322.50±7.32	t =1.717	0.89
RDWCV	0.13±0.04	0.16±0.04	t =4.28	0.001
RDWSD	56.77±13.72	46.09±9.58	t =4.43	0.001
WBC	5.91±1.72	6.54±2.91	t =1.26	0.21
Neu	2.92±1.23	3.70±2.24	t =2.10	0.04
Lym	2.46±0.67	2.19±1.06	t =1.44	0.15
Mon	0.22±0.11	0.26±0.23	t =1.06	0.29
Eos	0.26±0.23	0.34±0.45	t =1.10	0.28
Bas	0.03±0.02	0.046±0.03	t =2.05	0.04
Platelet indices				
PLT	194.5±59.8	338.8±159.07	t =5.60	0.001
MPV	9.4±0.84	8.7±1.05	t =3.34	0.001
PDW	16.16±0.42	15.72±1.77	t =1.55	0.13
PCT	1.80±0.54	2.61±1.68	t =2.99	0.04

HBG: Haemoglobin; HCT: Haematocrit; MCH: Mean cell haemoglobin; MCV: Mean cell volume; MCHC: Mean cell haemoglobin concentration; RDWCV: Red cell distribution width coefficient of variation; RDWSD: Red cell distribution width standard deviation

PLT: Platelet; MPV: Mean platelet volume; PDW: Platelet distribution width, PCT: Plateletcrit; Neu: Neutrophil; Lym: Lymphocyte; Mon: Monocyte; Eos: Eosinophil; Bas: Basophils

Table 4. Comparison of the mean neutrophil count of subjects by gender and age

Variables	Mean value	test-statistics	*P*-value
Gender			
Male	0.47±0.10	t = 0.75	*P*= 0.46
Female	0,49±0.92		
Age			
≤40	0.45±0.10		*P* = 0.24
>40	0.50±0.95	t =1.19	

Table 5. Association between Independent variables and outcome variables (RBC, PLT & WBC) among test subjects

Independent variables (Test subjects)	Outcome measures		
	RBC	**WBC**	**Platelets**
Duration of antipsychotic use	Pearson's r = -0.17 *P*=0.29	Pearson's r= -0.27 *P*=0.09	Pearson's r=- 0.28 *P*=0.08
BMI	Pearson's r = -0.13 *P*=0.44	Pearson's r = 0.05 *P*=0.76	Pearson's r = -0.19 *P*=0.25

There was no association between the mean absolute neutrophil count and the mean age or gender of subjects. p=0.24 and 0.46 respectively. (Table 3)

There was also no significant association between independent variables (class of antipsychotic drug use, duration of antipsychotic drug use, and BMI) and outcome variables (RBC, WBC parameters and platelets activity indices) Table 5.

4. DISCUSSION

Drug induced hematological abnormalities or blood dyscrasias occur occasionally during treatment with antipsychotic drugs. Both the conventional and the atypical antipsychotic agents have been implicated to various extent in this abnormalities [2]. In majority of the cases, these abnormalities are often mild and clinically irrelevant. However in a small proportion of patients a potentially life threatening outcome have been observed [18].

This study shows that the mean RBCs, hematocrit, haemoglobin and red cell indices of the subjects was significantly lower than that of the controls (p=0.001) except MCHC. This finding was contrary to the report by Akanni et al. [19] who reported a significant increase in the red cell indices of the subjects but not in their mean haematocrit and haemoglobin levels when compared with controls. The increased red cell indices among the subjects was attributed to increased activity of the liver enzymes. Henderson et al. [20] reported an increase in the hepatic enzyme activity following antipsychotic medication. Harold et al. [21] on the other hand, observed that increased level and activity of liver enzymes following hepatic stimulation, result in increased haematological indices. The effect is on the on the red cell morphology, causing some degree of macrocytosis and eventual increase in the red cell indices. The significantly lower red cell indices among the subjects compared with the controls in this study may be attributed to the low RBCs, haematocrit and haemoglobin levels of the former. The red cell indices are directly derived from these parameters [22].

Agranulocytosis (neutropenia) has been a consistent observation by various authors as a direct adverse effect of antipsychotics on haematologic profile of schizophrenic patients [1,2]. The atypical antipsychotics are associated with significant higher risk of agranulocytosis than the conventional antipsychotics [3,6].

In this study, the absolute neutrophil count (ANC), was significantly lower than that of the control group (p=0.04) and consistent with findings from previous studies [3,6,7]. Alvir JM et al. [7] in their study reviewed a total of 11,555 patients on clozapine over a 15 month period. Out of this number, 76 had neutropaenia, two of whom died of neutropenic sepsis. The onset of neutropenia was found to occur within 3 months of commencement of therapy in affected persons. However, few documented case reports have reported late onset in some patients [23,24]. Furthermore, of the known risk factors of agranulocytosis such as increasing age and female gender, none had any influence on the

ANC of subjects in this study. This contrast the findings from other authors who reported higher risk of agranulocytosis and neutropenia with increasing age and among women [6,7]. None of our subject had neutropaenia, despite the observed reduction in the mean ANC of the subjects. Perhaps, the small size of subjects reviewed in this study may have accounted for this observed differences.

Also, a significant reduction in the mean platelet count of the subjects compared to the controls was observed in this study. Few studies have reported thrombocytopaenia (0.01% and 0.1% respectively) among schizophrenic patients taking clozapine and risperidone [10,11]. A joint Prospective studies in England and Ireland and another in Italy reported similar observations. [10,11] with a reversal of the effect (thrombocytopenia) upon discontinuation of the medication [7]. In addition, Holt RJ [25], reported that phenothiazine have higher risk of inducing thrombocytopaenia than the other antipsychotics. Immunological mechanism has been largely suggested as the basis for the thrombocytopaenia [26].

In addition, the MPV was significantly higher among the subjects than controls. Semiz et al. [13], also reported a significantly higher MPV levels in schizophrenic patients on antipsychotics than in those who were not on medication. MPV have been reported in several studies as an independent risk factor for venous thromboembolism (VTE) and cardiovascular risk [14]. MPV a measure of platelet size, is a maker of platelet function [14,15]. Increased MPV is associated with increased platelet reactivity. Large platelets contain denser granules and are metabolically more active. They equally have a higher thrombotic potential and express higher levels of p-selectin than small platelets [14,15]. Antipsychotic medication have been shown to induce both cardiovascular and metabolic abnormalities in psychiatric patients with increase thrombotic risk than the general population [14,16]. Hence, serial MPV measurement may serve as useful tool in monitoring the risk of cardiovascular events in psychiatric patients on antipsychotic drugs.

Furthermore, there was no significant association between the independent variables (duration of antipsychotic use and body mass index of subjects) and the outcome variables (haematological indices; Hb, WBC, Platelet). Atkn et al. [11], reported that the risk of agranulocytosis and neutropaenia from clozapine use is highest within the first 6 to 18 months of commencing therapy. Flanagan et al. [3] posit that this adverse effect may likely be genetic as well as dose related rather than duration of treatment. The mean duration of antipsychotic use in this study was 2.90±1.35 years. Similarly Holt RJ [25] in his study on the incidence of thrombocytopenia in psychiatric patients receiving different antipsychotics did not demonstrate any significant difference between the duration of drug use and occurrence of thrombocytopaenia. Perhaps the occurrence of thrombocytopaenia may largely be dose related as suggested by Flanagan et al. [3]

Obesity is highly prevalent among patients with schizophrenia [27]. Atypical antipsychotics like clozapine are particularly more culpable than other agents [28]. In a recent systemic review, the highest prevalence of metabolic syndrome in schizophrenic patients was among those on clozapine [29]. Though, there was no association between the high BMI and haematological indices of subjects, studies among non-psychiatric patients have reported otherwise [30,31]. Some researchers in Brazil demonstrated an association between the lipid and haematological profiles and body adiposity in obese adolescents [30]. Perhaps the small sample size of this study may have accounted for this observed difference.

5. CONCLUSION

The hematological indices of subjects in this study were significantly lower than that of the controls thus indicating some degree of haemato-toxicity perhaps due to the effects of the antipsychotics. Furthermore, the absolute neutrophil count though significantly lower in the subjects than controls did not show age or sex differences. Therefore there is need to regularly monitor haematological indices of schizophrenic patients during treatment with antipsychotic medications and equally to be aware of the potential hazard of combining several drugs with a known risk of haemato-toxicity.

6. LIMITATION OF STUDY

Due to the fact that some patients were on combination antipsychotics medication we were unable to determine the effect of each drug or classes of drugs on the haematological indices of patients. Also the number of patients recruited in our study were relatively small compared to that

of other studies, hence incidence of anaemia, neutropaenia and thrombocytopaenia could not be ascertain from this study.

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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