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Prevalence and correlates of antipsychotic polypharmacy among outpatients with schizophrenia attending a tertiary psychiatric facility in Nigeria

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Abstract

Background: The study aimed to determine the prevalence, pattern and correlates of antipsychotic polypharmacy (APP) among outpatients with schizophrenia attending a tertiary psychiatric facility in Nigeria.

Method: A cross-sectional study of 250 patients with schizophrenia attending the outpatient clinic of a regional tertiary psychiatric facility in Nigeria was undertaken. They were administered a sociodemographic questionnaire, the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning (GAF) scale and the Liverpool University Side Effects Rating Scale (LUNSERS).

Results: Of the 250 subjects interviewed, 176 (70.4%) were on APP. APP was significantly associated with higher prescribed chlorpromazine equivalent doses of antipsychotics ($p < 0.001$), increased frequency of dosing ($p < 0.001$), negative symptoms ($p < 0.01$), poorer functioning ($p = 0.04$) and greater side-effect burden ($p = 0.04$).

Conclusion: The APP rate reported from this study is high. Clinicians should be mindful of its impact on dosage and side-effect profiles as APP use is associated with negative symptoms and poor psychosocial functioning.

Keywords: antipsychotic, correlates, Nigeria, polypharmacy, prevalence, schizophrenia

Introduction

Schizophrenia is a chronic mental disorder with a prevalence of 1.4–4.6 per 1000 and a global incidence of about 1% [McGrath *et al.* 2008; World Health Organization, 2014]. It contributes about 1% to the global burden of disease [World Health Organization, 2000].

Antipsychotics have been a cornerstone in schizophrenia treatment since their discovery. When used appropriately, they have been shown to reduce positive symptoms in 75% of acutely ill schizophrenia patients [Dixon *et al.* 1995], and recent meta-analytic reports found significant efficacy of second-generation antipsychotics (SGAs) with negative symptoms [Darba *et al.* 2011].

Antipsychotics are ideally used as monotherapy, as recommended in countries where treatment guidelines exist [Gaebel *et al.* 2011]. However, polypharmacy prescriptions involving the concurrent use of two or more antipsychotics in schizophrenia treatment are increasingly common, even in settings where treatment guidelines are available [Ranceva *et al.* 2010; Gallego *et al.* 2012]. Globally, prevalence rates between 4% and 70% for antipsychotic polypharmacy (APP) have been reported [Fleischacker and Uchida, 2014]. Patterns incorporate a wide spectrum of antipsychotics giving rise to varying combinations [Correll *et al.* 2009; Clark *et al.* 2002]. Factors associated with higher rates of APP among patients with schizophrenia include treatment resistance, 'arrested' medication switching, attempts at avoiding high-dose monotherapy, insomnia and utilization of antipsychotics in the control of acute exacerbations of psychosis [Langan and Shajahan, 2010]. Other reports

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have associated APP with in-patient care, severity of illness, physician preference and use of depot antipsychotic preparations [Xiang *et al*. 2007; Gallego *et al*. 2012; Tungaraza *et al*. 2011].

Clinicians may prescribe multiple antipsychotics when treating schizophrenia in a patient, citing better treatment outcomes, especially in treatment-resistant cases [Kotler *et al*. 2004; Cipriani *et al*. 2009]. Positive and negative symptoms, functioning and health-related quality of life have been shown to improve following antipsychotic combinations [Shiloh *et al*. 1997; Ascher-Svanum *et al*. 2012]. Reports showing benefits of APP contrast with other studies reporting greater burden of side effects, including extrapyramidal side effects and metabolic changes [Gallego *et al*. 2012], as well as increased costs of treatment compared with monotherapy [Zhu *et al*. 2008; Centorrino *et al*. 2004; Cipriani *et al*. 2009].

There are few studies on APP use in schizophrenia from Africa, with one study reporting APP rate of 28.6% from South Africa [Koen *et al*. 2008]. Previous research from Nigeria has focused on psychotropic polypharmacy in general and have not specifically explored APP in schizophrenia patients [Famuyiwa, 1983; Adeponle *et al*. 2007], hence the rationale for this study.

Methods

Study design and location

The study design was cross-sectional. All patients were recruited from among attendees of the Consultant Out-Patient Department (COPD) of the Federal Neuro-Psychiatric Hospital, Benin City, Nigeria. The hospital is a 230-bed facility which provides in-patient and out-patient care, as well as emergency services to mentally ill persons.

Study participants

A total of 250 participants were recruited for the study. To be eligible, a patient must have been aged 18–64 years, diagnosed with schizophrenia by an attending consultant psychiatrist according to the ICD-10 criteria, must have given their written informed consent to participate in the study and were currently mentally stable, to be able to understand the nature and purpose of the study. Such patients should also have had an illness duration and antipsychotic treatment of at least 1 year before being recruited into the study.

Operational definition of polypharmacy

This study regarded subjects on APP as those who were on two or more antipsychotics, including a combination of parenteral (depot) and oral antipsychotics at the time of the study and were not undergoing a medication switch.

Measures

Sociodemographic questionnaire. Designed by the researchers, this was used to obtain data on age, gender, educational and marital status. Clinical variables including type of antipsychotic medication, dosing regimen, duration of illness, as well as the presence of physical comorbidity were also obtained.

Assessment of illness severity, functioning and medication side effects. The Positive and Negative Syndrome Scale (PANSS) was used to rate positive, negative and general psychopathology symptoms [Kay *et al*. 1987]. The Global Assessment of Functioning (GAF) scale was used to rate overall functioning across psychological, social and occupational domains as at the time of an interview [Spitzer *et al*. 1996].

The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) was used to obtain information on medication-related side effects. This instrument is a 51-item self-report questionnaire on adverse effects of antipsychotic treatment. Respondents are asked to rate their experience of symptoms during the previous month on a five-point Likert scale from 'not at all' = 0 to 'very much' = 4 points. Total score range is 0–164 for females, and 0–156 for males [Day *et al*. 1995].

Procedure

The study spanned a 10-week period (August–October 2013). Over this period, patients with schizophrenia who satisfied the study criteria were consecutively recruited to participate in the study. A total of 355 patients with schizophrenia attended out-patient clinics over the study period, 262 satisfied the study criteria of which 250

consented to participate. Study participants were interviewed by one of the researchers who administered the sociodemographic questionnaire, PANSS, GAF and LUNSERS.

Data on antipsychotic prescription patterns were extracted from case files of respondents and prescribed daily doses (PDD) of antipsychotics were calculated and converted to their chlorpromazine equivalents according to guidelines of the *British National Formulary* (BNF) [BMJ, 2012], and recommendations of the schizophrenia Patient Outcome Research Team (PORT) [Buchanan *et al.* 2010].

Ethical considerations

The study protocol was reviewed and approved by the Ethics and Research Committee of the Federal Neuro-Psychiatric Hospital, Benin City. Participants who agreed to participate after the study process and purpose were explained, signed a written informed consent form. Voluntariness and anonymity were assured.

Data analysis

The data collected were analysed using the Statistical Package for the Social Sciences, version 20. Results are displayed in tables and figures. The chi-square test was used to investigate the relationships between categorical variables and differences between two groups were calculated using Student's *t* test. Comparisons between individuals on polypharmacy and those on monotherapy were performed concerning sociodemographic and clinical variables to determine factors associated with polypharmacy. Significant associations between presence of APP (dependent variable) and independent variables (categorical and continuous) were entered into a logistic regression model to identify predictors or correlates of polypharmacy. Statistical significance was set at $p < 0.05$.

Table 1. Sociodemographic characteristics of participants.

Variable	Frequency (n = 250)	Percentage (%)
Age class, years		
18–30	67	26.8
31–40	91	36.4
41–50	56	22.4
51–60	29	11.6
61–64	7	2.8
Mean ± SD	37.85 ± 10.57	
Gender		
Female	102	40.8
Male	148	59.2
Marital status		
Married	57	22.8
Not married	193	77.2
Employment status		
Employed	111	44.4
Unemployed	139	55.6
Highest educational qualification		
No formal education	8	3.2
Primary	75	30.0
Secondary	112	44.8
Tertiary	53	21.2
Postgraduate	2	0.8
Location of residence		
Rural	30	12.0
Urban	174	69.6
Semi-urban	46	18.4
Source of income/allowance		
None	64	25.6
Family support/ stipend	78	31.2
Paid employment	55	22.0
Self-employed	53	21.2
Income range ($)		
<18,000	183	73.2
18,000–99,999	62	24.8
100,000–300,000	5	2.0

SD, standard deviation.

Results

Sociodemographic characteristics of participants

Table 1 shows the sociodemographic characteristics of participants. There were 148 (59.2%) males and almost 40% of the study population was aged 31–40 years. About 4 in 10 respondents (44.4%) were employed with the majority (73.2%) earning below the national minimum wage of $90 per month. A total of 193 (77.2%) participants were unmarried and only 22% of them had a university (college) level of education.

Table 2. Clinical characteristics of participants.

Variable	Frequency (n = 250)	Percentage (%)
ICD-10 diagnostic category of schizophrenia		
Paranoid	108	43.2
Undifferentiated	95	38.0
Hebephrenic	32	12.8
Others	15	6.0
Course of illness (PANSS)		
First episode	92	36.8
Intermittent	69	27.6
Progredient	29	11.6
Chronic	60	24.0
Physical comorbidity present?		
Yes	43	17.2

PANSS, Positive and Negative Syndrome Scale.

Table 3. Pattern of antipsychotic prescriptions and dosing schedule of interviewed participants.

Variable	Frequency (n)	Percentage (%)
Antipsychotic therapy class		
Monotherapy	74	29.6
Polypharmacy	176	70.4
Polypharmacy (oral-only combinations)	31	12.0
Pattern of antipsychotic prescription		
Oral FGAs monotherapy	37	15.2
Oral SGAs monotherapy	34	13.6
i.m. FGAs monotherapy	3	1.2
Combination of oral FGAs	30	12.0
Oral FGAs + oral SGAs	1	0.4
i.m. FGAs + oral FGAs	111	44.0
i.m. FGAs + oral SGAs	34	14.0
Total SGAs prescriptions	69	27.6
Dosing schedule		
Once daily	92	36.8
Twice daily	13	5.2
Monthly depot	3	1.2
Once daily + monthly depot	106	42.4
Twice daily + monthly depot	34	13.6
Thrice daily + monthly depot	2	0.8

FGA, first-generation antipsychotic; i.m., intramuscular depot injection; SGA, second-generation antipsychotic.

Clinical characteristics of participants

Table 2 shows the clinical characteristics of participants. A total of 108 (43.2%) met the ICD-10 diagnostic criteria for paranoid schizophrenia, while 38% had undifferentiated schizophrenia; 92 (36.8%) were having the illness for the first time. The duration of illness ranged between 13 and 517 months, and 17.2% of participants had a physical comorbidity, mostly hypertension (10.8%).

Pattern of antipsychotic prescribing and polypharmacy

Table 3 shows results from the analysis of antipsychotic drug-related factors. The first-generation antipsychotics (FGAs) prescribed study participants were trifluoperazine, haloperidol, chlorpromazine and thioridazine. A total of 34 patients (13.6%) were taking second-generation antipsychotics (SGAs) in monotherapy; risperidone or olanzapine. Risperidone was the most commonly prescribed SGA. A total of 145 patients (58%) were prescribed depot FGAs, restricted only to fluphenazine decanoate injection or flupenthixol decanoate injection in 52.4% (n = 131) and 5.6% (n = 14) of the total sample, respectively.

Polypharmacy as defined in the study context was found in 70.4% (n = 176) of participants. The most common form of polypharmacy comprised a combination of a FGA depot antipsychotic plus FGA oral antipsychotic and was found in 44.4% of participants. Although trifluoperazine was the most frequently prescribed oral antipsychotic in polypharmacy combinations, chlorpromazine was the most frequently used in oral-only combinations. A total of 69 participants (27.6%) were receiving a SGA. Risperidone was the only SGA that was being used in an oral-only combination: one patient was receiving it simultaneously with chlorpromazine.

Some patients on monotherapy received their medication in divided doses; there were twice as many patients on oral monotherapy receiving their medication as a single once-daily dose than those on oral-only polypharmacy. More

Table 4. Comparison of participants on antipsychotic monotherapy or polypharmacy on the basis of symptom profile, CPZeq, side-effect profile and functioning.

Variable	Polypharmacy Mean (SD)	Monotherapy Mean (SD)	*t*/*U*	*p*
PANSS-P	11.54 (6.25)	11.16 (6.84)	−0.424	0.67
PANSS-N	16.18 (8.49)	13.19 (5.93)	− 2.760	**0.01**
PANSS-G	28.06 (11.47)	25.66 (10.21)	− 1.559	0.12
PANSS-T	55.73 (22.98)	49.91 (19.39)	− 1.912	0.06
GAF	66.91 (23.03)	73.49 (21.41)	−2.104	**0.04**
LUNSERS				
Total	18.87 (12.40)	15.43 (11.22)	2.056	**0.04**
Extrapyramidal	4.96 (4.93)	4.54 (5.40)	0.60	0.55
Anticholinergic	1.21 (2.02)	1.51 (2.01)	−1.09	0.28
Other autonomic	1.78 (2.55)	1.32 (1.93)	1.40	0.17
Allergic reactions	0.52 (1.58)	0.28 (0.91)	1.19	0.24
Psychic	5.30 (4.61)	4.99 (4.51)	0.50	0.62
Hormonal	1.32 (1.84)	1.70 (2.15)	−1.43	0.15
Miscellaneous	1.57 (1.79)	1.47 (1.63)	0.42	0.68
Prescribed daily dose (CPZ Eq.)	838.21 (471.58)	288.18 (216.93)	12.62	**0.001**

GAF, Global Assessment of Functioning Scale; LUNSERS, Liverpool University Side Effects Rating Scale; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.
Statistically significant values are highlighted in bold font.

patients on polypharmacy were on depot antipsychotics being prescribed on a monthly basis. These differences were statistically significant. ($p < 0.001$)

Correlates of APP. Analysis did not reveal any significant associations between sociodemographic characteristics of participants and APP. Patients on monotherapy compared with those on polypharmacy did not differ regarding pattern of diagnosis ($p = 0.165$), age of onset ($p = 0.273$) and duration of illness ($p = 0.10$).

As shown in Table 4, patients on APP scored significantly higher on the negative syndrome subscale of the PANSS compared with those on monotherapy ($t = -2.76$; $p < 0.006$); differences observed between overall PANSS scores of patients on monotherapy and those on polypharmacy fell short of being significant ($t = 1.91$; $p = 0.057$). Patients on polypharmacy had significantly lower mean GAF scores compared with patients on monotherapy ($t = 2.104$; $p = 0.036$).

The mean PDD of antipsychotic in chlorpromazine equivalent was significantly higher among patients on polypharmacy than those on monotherapy ($p < 0.001$). Moreover, study participants receiving 500 mg or less in chlorpromazine equivalent dose of antipsychotic were twice likely to be on only one antipsychotic compared with patients on multiple antipsychotics. This difference was statistically significant ($p < 0.001$).

When the PDD of antipsychotics received by patients on polypharmacy regimen that had a depot antipsychotic included were compared with those that had only oral antipsychotics in the combination, 50 patients on polypharmacy were found to be on doses above the BNF limit of 1000 mg chlorpromazine equivalent; only one of these was on an oral-only combination. This difference was statistically significant ($p< 0.001$).

The side-effect profile of participants on monotherapy and those on polypharmacy on the basis of their scores on the LUNSERS were compared. Participants on polypharmacy had a significantly higher side-effect profile compared with those on monotherapy ($t = 2.056$; $p = 0.041$).

A bivariate logistic regression model of the significant continuous variables (total daily dose of chlorpromazine, LUNSERS scores, GAF scores and scores on the negative subscale of the PANSS) on the dichotomous dependent variable of polypharmacy or monotherapy retained total daily dose of antipsychotic in chlorpromazine equivalent (Wald = 52.03; $p < 0.001$), GAF scores (Wald = 6.767; $p = 0.008$) and negative subscale of the

PANSS (Wald = 4.152; $p = 0.042$) as significant predictors of polypharmacy

Discussion

Prevalence of APP

This study found a prevalence rate of 70.4% for APP among schizophrenia outpatients. With depot antipsychotics excluded the prevalence of APP from this study dropped to 12.0% which approximated with earlier reports [Ranceva *et al.* 2010; Ganguly *et al.* 2004; Gallego *et al.* 2012, Koen *et al.* 2008]. The study also showed that negative symptoms, lower social functioning, higher PDD of antipsychotics and increased burden of side effects were significant correlates of APP.

The higher rate of APP from this study in contrast to reports from North America and Europe is accounted for by the frequent use of depot antipsychotics in combination with oral medications (58.4% of polypharmacy in the present sample). High rates of depot use may be because patients or carers often believe that parenteral forms of antipsychotics are more potent when compared with oral medications, poor medication adherence and absence of locally relevant treatment guidelines for clinicians. Of the 176 patients on APP, 82% ($n = 146$) had at least a second antipsychotic as a depot preparation.

Participants in this study were outpatients who are usually less severely ill compared with hospitalized patients. Polypharmacy rates were expected to be lower as studies have also reported a direct correlation between the severity of illness and polypharmacy prescription [Langle *et al.* 2012]. However, patients in this present study were all attendees in a specialist psychiatric hospital facility. Specialist or tertiary care facilities care for clientele that are usually more severely ill at baseline compared with those in general hospital settings [Sim *et al.* 2004] warranting prescription of multiple antipsychotics which are retained even after symptoms remit [Tapp *et al.* 2003; Tungaraza *et al.* 2011].

Pattern of APP

As regards patterns of APP, one hundred and sixty-five (93.8% of the study sample) were on a combination that included only two antipsychotics; the remainder (6.8%) had combinations that included three antipsychotics, including a depot preparation. This compared with an Austrian study where 8% of patients received prescriptions for three concurrent antipsychotics [Rittmannsberger *et al.* 1999].

Unlike studies in Europe and North America, the majority of participants on APP in this study were on a combination of FGAs, which are relatively cheaper and therefore more readily available compared with SGAs. Health care in Nigeria is mainly financed out-of-pocket by patients and their relatives; it is unsurprising therefore that clinicians and relatives would opt for FGAs. Such economic considerations are further evidenced by the fact that unlike studies from North America and Europe where oral APP frequently contain combinations of SGAs and FGAs [Tapp *et al.* 2003; Ranceva *et al.* 2010; Gallego *et al.* 2012], only one patient (0.4%) in this study was on such combination, in this case risperidone plus chlorpromazine. Again, the high rate of depot antipsychotic use notwithstanding, only the relatively cheaper fluphenazine and flupenthixol decanoate were identified in this study.

The finding from this study that chlorpromazine was the most frequently prescribed antipsychotic in oral-only combinations may derive from pharmacodynamic considerations. Chlorpromazine is a low-potency antipsychotic with a relatively higher affinity for non-D2 receptors, including histaminergic, conveying sedative properties to this antipsychotic. This suggests its use possibly to facilitate or enhance sedation; there may also be a failure to withdraw the drug even when patients have clinically improved.

No participant was on any combination comprising only SGAs although such combinations formed 2% of APP in Europe and America [Gallego *et al.* 2012; Bruggermann *et al.* 2008]. This may likely be due to issues of availability and cost as has been suggested in an earlier study [Sim *et al.* 2004]. Availability as a factor in the frequency of use of SGAs in this study is reinforced by the absence of any participant on such SGAs as aripiprazole or quetiapine none of which is a readily available antipsychotic in Nigeria.

In this study, APP was associated with higher dosage, higher scores on the negative subscale of the PANSS and reduced functioning. Though the cross-sectional nature of the study would not permit a discussion on causality, it needs to be determined from future research whether physicians

are prescribing multiple antipsychotics in order to optimize outcomes for those with negative symptoms or whether negative symptoms are due to neuroleptic side effects of prescribed antipsychotics. A more frequent use of depot preparations was also associated with APP.

Patients receiving two or more antipsychotic drugs were on doses that were up to three times more than their monotherapy counterparts, and were in some cases up to three times higher than the recommended BNF dose limit of 1000 mg chlorpromazine equivalent. The association found between high doses, depot use and APP brings to the fore the necessity for regulation of antipsychotic use among clinicians. With depot prescriptions, it may be relatively easy to inadvertently exceed recommended doses; standard regulation/guidelines on the use of depot and antipsychotic combinations is therefore essential to prevent unwholesome use of these medications, particularly since APP was significantly correlated with a greater side-effect burden. None of the observed differences in sociodemographic variables between participants on monotherapy and those on polypharmacy was statistically significant, unlike in some earlier studies.

This study had some limitations. Its cross-sectional nature did not allow us to draw any definite conclusions regarding causality between APP and its correlates. Reasons for clinicians prescribing APP were not explored and the outcome of antipsychotic use in study participants was based on case records without an articulated set of outcome criteria. The possibility of some participants being on other forms of treatment, such as herbal remedies (a common feature in this study setting) was not factored, and this may have affected the outcome of this study. Patients with treatment-resistant schizophrenia were not specifically factored and there was no information about adherence with treatment, since that will determine whether or not all of the side effects and impact of medication on symptoms will be evident.

In conclusion, this study provides evidence from sub-Saharan Africa of the high prevalence of APP among patients with schizophrenia. APP is also associated with higher dosage, poorer psychosocial functioning, and greater symptom burden. Future studies employing a longitudinal design are required to explore cause–effect relationships and bridge the identified gaps in the current study.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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