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CURRENT STATUS OF ANTIPSYCHOTICS USE PATTERN AMONG OUTPATIENTS WITH SCHIZOPHRENIA IN A TERTIARY CARE HOSPITAL IN NIGERIA

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ABSTRACT

Background: **Previous studies of the prescription pattern of psychotropic medications in patients with schizophrenia have highlighted a high rate of antipsychotic polypharmacy (APP), but data in Northwest Nigerian are sparse. This study seeks to examine the antipsychotic use patterns, prevalence of antipsychotic polypharmacy and its comparison with recommended guidelines in outpatients with schizophrenia in a tertiary health institution in Northwest Nigeria.**

Methods: **One hundred and eighty-five outpatients with schizophrenia who have regular records at a tertiary health center in Nigeria were included in the study. Information about their sociodemographic data and medication were recorded through face-to-face interview and relevant information about their drug use patterns was obtained from their medical files.**

Results: **The mean age was 30.4±10.3 years. Overall, antipsychotic polypharmacy was found in the treatment regimens of 58.4% of the patients. Conventional oral antipsychotics was prevalent, 70.2%. Haloperidol and Trifluoperazine were the prevalent conventional antipsychotics prescribed. The two atypical antipsychotics prescribed were Risperidone and Olanzapine, 8.1% each.**

Conclusion: **Antipsychotic polypharmacy is a prevalent prescribing practice in the management of patients with schizophrenia. It is prescribed for longer durations compared to other developed countries, indicating a significant discrepancy with treatment guidelines which do not advocate the use of any polypharmacy.**

INTRODUCTION

Schizophrenia is a chronic mental illness and pharmacotherapy plays a major role in its management.[1] Pharmacological management of schizophrenia cuts across the various stages of the illness, including first-episode, relapse prevention, and illness that has proved in a few instances refractory to standard treatment.[2] Schizophrenia treatment guidelines emphasize antipsychotic monotherapy as first principle.[3,4] The definition of polypharmacy varies according to the different authors and disciplines. In psychiatry, the use of two or more kinds of antipsychotics is defined as antipsychotic polypharmacy.[5] Antipsychotic polypharmacy (APP) is widely used in clinical practice. Despite the lack of robust evidence, the increased risk of side effects, the possibility of non-compliance with medication and the cost implication.

Antipsychotic polypharmacy prevalence varies widely, from 4 - 92.2%, depending on study design, patient population, diagnosis and geographical region .[6,7] A multicenter study conducted on schizophrenia patients in East Asia reported antipsychotic polypharmacy rate to be 45.7%.[8] In Europe, the rate were reported to be 43.9% in Germany,[9] and in Spain, there was a 13.9% antipsychotic combination. A recently published retrospective cohort study (with 4,156 patients included in the study) in the United States reported that antipsychotic polypharmacy in patients with schizophrenia was 23.3%.[10] In a study in Nigeria polypharmacy of psychotropic agents were reported as 92% for general psychiatric outpatients and 94% in schizophrenia patients.[11]

The current data reported some clinical benefits of antipsychotic polypharmacy in a few cases, such as severe or treatment-resistant schizophrenia. However, polypharmacy may be associated with harmful outcomes, such as an excessively high content of antipsychotic dosage[12,13], extrapyramidal side-effects, cognitive impairment and drug interactions. It can also result in decreases in drug concentrations, thus insufficient treatment and increasing cost, which may be associated with an increased risk of death[14].[6] Chronic use of antipsychotics with a relatively high dose is also shown to be related with a worse outcome in long term recovery than the strategy of dose reduction or discontinuation.[11] The common predictors of polypharmacy are male gender, younger age and being single and unemployed.[15] Other factors are primarily related to clinical severity and poor functionality of the patients, such as having severe psychopathology, residual psychotic symptoms, poor cognitive function, poor insight into the illness, additional psychiatric co-morbidity, in-patients of a psychiatric hospital, involuntary admission, more frequent admissions and the use of depot antipsychotics.[6]

Previous studies of the prescription patterns of psychotropic medications in patients with schizophrenia have highlighted a high rate of antipsychotic polypharmacy, in Europe, the USA and Asia.[8,9,16] Research from Nigeria has focused on psychotropic polypharmacy in general and have not specifically explored APP in schizophrenia patients.[17] However, data on antipsychotic polypharmacy use in schizophrenia in Northwest Nigerian are sparse. This study seeks to examine the antipsychotic use patterns, prevalence of antipsychotic polypharmacy and its comparison with recommended guidelines in outpatients with schizophrenia in a tertiary health institution in Northwest, Nigeria.

METHODS

Design and participants: A cross-sectional study was conducted in July to September 2019. One hundred and eighty- five (185) patients were recruited from the outpatient's clinic of Federal Neuro-Psychiatric Hospital, Kware, Sokoto, Northwest, Nigeria. Patients who were selected fulfilled the diagnostic criteria for schizophrenia according to the ICD-10 or DSM-IV by an attending consultant psychiatrist, aged 18 years and above, gave informed consent and were mentally stable to give relevant information. Background information collected from the case records included age, gender, occupation status, level of education, marital status, duration of illness prior to presentation, duration of use of medications, first or multiple episodes, name of antipsychotic use, type of antipsychotic use (first generation or second generation), use of anticholinergic, use of antidepressants and mood stabilizers. In this study antipsychotic polypharmacy was defined as use of 2 or more types or class of antipsychotics. Psychotropic drugs polypharmacy was defined as use of 2 or more class of psychotropics medications. For examples combination of antipsychotic and mood stabilizers or antipsychotic and antidepressants. Information about their compliance with medications, experience of extrapyramidal side effects, having tardive dyskinesia, patient's perception of treatment efficacy and thought of suicide were obtained through face-to-face interview and supporting information was obtained from their files to confirm their responses. Compliance with medications was rated poor if patients had defaulted from follow up clinic appointment more than 2 times and rated good if none or twice.

Patients whose medical records have incomplete medical, or drug treatment data were excluded from analysis. Three consensus meetings were held with all research assistants before the study to discuss issues related to methodology, such as data collection and uniform data entry. The study was approved by the Research and Ethics Committee of Federal Neuro-Psychiatric Hospital, Kware, Sokoto, Northwest, Nigeria

Statistical analysis: Analyses were performed with the Statistical Package for Social Sciences (SPSS) version 25.0 (SPSS Inc., Chicago, IL, USA). All categorical data were reported in frequency and percentage.

RESULTS

Demographic and clinical characteristics

One hundred and eighty-five patients were interviewed, and case records examined. Table 1 presents the demographic and clinical characteristics of the sample. The mean age was 30.4±10.3 years, majority (83.7%) were aged 18-37 years. The most affected (modal) age was 20years. More than half, 56.8% and 51.4% were male and unemployed respectively. Forty-five (24.3%) presented for treatment within one month of onset of illness, more than half (60.4%) presented for treatment above 6 months to 5 years of having symptoms of schizophrenia and 8.1% more than 5 years of onset of illness. Seventy-five (40.5%) have been on treatment for less than 5 months duration, the same number (40.5%) of patients have been using medications for more than 5 years. One hundred and nineteen (64.3%) had multiple episodes, 81.6% had good compliance with medications, 43.7% had not experience side effects of medications, majority (90.8%) reported that the treatment is efficient, 35.1% reported lifetime suicidal thought, no one reported current suicidal thought.

Table 1

Demographic and clinical characteristics (n = 185)

Demographic and clinical characteristics	Frequency (%)
Age	
18-27	80 (43.2)
28-37	75 (40.5)
38-47	15 (8.1)
≥48	15 (8.1)
Mean ± standard deviation	30.4±10.5
Mode	20
Gender	
Male	105 (56.8)
Female	80 (43.2)
Occupation	
Employed	90(48.6)
Unemployed	95(51.4)
Marital status	
Single/divorced/widow/widower	95(51.4)
Married	90(48.6)
Duration of illness prior to presentation	
Less than 1 month	45(24.3)
1 – 6 months	15(8.1)
Above 6 months – 1 year	65(36.1)
Above 1 year – 5 years	45(24.3)
Above 5 years	15(8.1)
Duration of treatment	
Less than 6 months	75(4.5)
Above 6 months – 1year	15(8.1)
Above 1 year – 5 years	20(10.8)
Above 5 years	75(40.5)
Frequency of episode	
First episode	62(33.5)
Multiple episodes	119(64.3)
Compliance with medications	
Good	151(81.6)
Poor	34(18.4)
Extrapyramidal side effects	
Acute dystonia	27(14.6)
Akathisia	27(14.6)
Parkinsonism	29(15.7)
Tardive dyskinesia	21(11.4)
Nil	81(43.7)
Efficacy of treatment perception	
Yes	168(90.8)
No	17(9.2)
Suicidal thought	

Lifetime	65(35.1)
Current	0
Never	120(64.9)

Pattern and prevalence of antipsychotic and other psychotropic drugs prescription

Table 2 presents the pattern and prevalence of antipsychotic and other psychotropic drugs prescription. Overall, antipsychotic polypharmacy was found in the treatment regimens of 58.4% (n = 108) of the patients. Conventional oral antipsychotics was prevalent, 70.2%. Haloperidol and Trifluoperazine were the prevalent conventional antipsychotics prescribed. The 2 atypical antipsychotics prescribed were Risperidone and Olanzapine, 8.1% each. None of the patients were on Clozapine, Aripiprazole or other types of atypical antipsychotics. Long-acting intramuscular injection were used by 27% of the patients. Majority, 67.6% were on first generation (conventional) antipsychotics. Among the patients on antipsychotic polypharmacy, 16.2% were on combination of first generation (conventional) and second generation (atypical) antipsychotics, 25.9% on 2 or more first generation antipsychotics (FGA), and 16.2 were on 2 or more second generation antipsychotic (SGA). Antidepressant and mood stabilizer combination with antipsychotic were used by 15% of the patients. Majority (83.8%) were also on combination of antipsychotic and anticholinergic (Benzhexol).

Table 2

Pattern and prevalence of antipsychotic and other psychotropic drugs prescription

Pattern and prevalence of antipsychotic prescription	**Frequency (%)**
Types of antipsychotic prescribed	
Chlorpromazine	30(16.2)
Trifluoperazine	50(27)
Haloperidol	50(27)
Risperidone	15(8.1)
Olanzapine	15(8.1)
Clozapine	0
Aripiprazole	0
Others	0
Use of long-acting injection	
Fluphenazine decanoate	30(16.2)
Flupenthixol	20(10.8)
Class of Antipsychotic used	
FGA	125(67.6)
SGA	60(32.4)
Use of combination of both FGA and SGA	
Yes	30(16.2)
No	155(83.8)
Use of more than one FGA	
Yes	48(25.9)

No	137(74.1)
Use of more than one SGA	
Yes	30(16.2)
No	155(83.8)
Use of antidepressant	
Yes	15(8.1)
No	170(91.9)
Use of mood stabilizer	
Yes	15(8.1)
No	170(91.9)
Use of anticholinergic	
Yes	155(83.8)
No	30(16.2)
Antipsychotic polypharmacy	
Yes	108(58.4)
No	77(41.6)

DISCUSSION

This study was conducted among clinically stable schizophrenia patients who showed high rates of antipsychotic polypharmacy, highlighting significant deviation from the recommended guidelines in prescription practice. Polypharmacy was observed among the patients in different combinations; combination of conventional with atypical antipsychotics, 2 or more conventional antipsychotics, 2 or more atypical antipsychotics. Polypharmacy was also identified as combination of antipsychotic and other psychotropic drugs. Some patients were on combination of antipsychotic and antidepressant, antipsychotic and mood stabilizer, while a significant number of patients were antipsychotic and anticholinergic drug (Benzhexol).

According to the data in this study, polypharmacy was considered high because more than half of the patients used different combinations of 2 or more antipsychotics with combination of other psychotropic medications. The high prevalent, 58.4% of antipsychotic polypharmacy are consistent with those reported in the literature.[15] However, this differs from what was reported in a study in the Kingdom of Bahrain in which majority (89.2%) of schizophrenia outpatients were on antipsychotic monotherapy.[18]

It is expected that the rates reported in this study would be higher than those reported elsewhere given that the database consisted of patients with long duration of illness, mostly severe schizophrenia. Such patients would be expected to have higher schizophrenia severity as they would be required to have become dangerous to the family or the community prior to presentation.

It is not impossible that some patients using short-term polypharmacy were misclassified in our study as receiving polypharmacy, causing slightly higher percentages than those in other studies.

This finding is consistent with previous research showing that physicians tend to prescribe multiple antipsychotics before exploring the full dose range of several different single antipsychotic agents.[6,19] Although it is understandable that physicians want to control severe acute symptoms of schizophrenia, particularly early in the course

of disease, long-term use of polypharmacy beginning at an early age may pose additional risk to patients.

The high prevalent (70.2%) of typical antipsychotic use in this study also contradict what was reported in Kingdom of Bahrain (32.3%). [18]Another study reported significant differences between African American and Caucasian schizophrenia patients in the type of prescription filled. Atypical antipsychotics (Clozapine and risperidone) were given more often to Caucasian subjects, whereas typical antipsychotics were given more often to African American subjects.[20] In general, African American subjects were more likely to receive traditional antipsychotic medications. According to another previous study conducted with outpatients in Turkey, the most common antipsychotic use was depot neuroleptics 46.7%, risperidone 45.0% and olanzapine 45.0%.[21] A recently conducted study in the US reported that risperidone was the most frequently used antipsychotic agent and the most frequent combination polypharmacy included FGA, olanzapine and risperidone. In Germany, it was olanzapine[22] and in Korea, it was risperidone and haloperidol but the monotherapy group was olanzapine. In the UK (2007–2011), the primary care setting most commonly prescribed first- and second-generation antipsychotics: olanzapine, risperidone and chlorpromazine, respectively.[23] In Spain, olanzapine and risperidone were reported.[24]

This discrepancy could be due to the higher cost of the atypical antipsychotics. The association of polypharmacy with less use of an atypical antipsychotic further increases and compounds the side-effect burden. To a certain extent, the prescription of these second-generation antipsychotics depends on their availability and affordability. Most of these patients pay out of pockets, virtually none were on National Health Insurance Scheme (NHIS).

In terms of the number of months receiving any type of antipsychotic medication, the duration of therapy reported in this study outrageously contradicts what was reported in US study.[16] Most of the patients in this study have been on antipsychotic for more than 1 year. The study in US reported discontinuation of antipsychotics in less the 1 year of therapy. Discontinuation of antipsychotic could precipitate relapse in some patients. This should be done after detailed psychoeducation of the patients and relatives on the likely outcome of discontinuation of medications. In this study, it was observed that majority of the patients had multiple episodes. This pattern was reported in a previous study.[25] Having multiple episodes could be due to non-compliance with medication which could be related to financial constraint or refusal to accept medication by some patients. Multiple episodes could result in poor prognosis.

There was high rate of compliance with medication in this study. This report may not be reliable because of the high rate of patients with multiple episodes. There is virtually no study in this region to compare the outcome of this study on compliance with medications.

Occurrence of extrapyramidal side effects was high (56.3%) despite concomitant prescriptions of anticholinergic medications. This could be due to longer duration of illness, leading to a longer period of exposure to antipsychotics which could increase the risk towards the development of adverse effects. The increased use of anticholinergic drugs in association with polypharmacy in this study could be for the management and prophylactic treatment of these extrapyramidal effects, although not without its own distressing adverse effects such as urinary retention, constipation and dry mouth. Moreover, the

possibility of drug–drug interactions increases with each added drug and can eventually have a negative impact on treatment adherence, potentially leading to more relapses and rehospitalizations.[20]

Efficacy of treatment was perceived to be good in this study. This report suggested that most patients perhaps achieved remission in the course of their treatment. There was no case of current thought of suicide among the participants. However, lifetime thought of suicide was reported among a few patients. This is consistent with what was reported in previous research.[26] Another study in Malaysia reported higher prevalence of suicidal feelings among schizophrenia patients.[27]

There were some limitations to this study. The formal rating of clinical features such as psychopathology was not performed, the cross-sectional nature of the study did not allow drawing any definite conclusions regarding causality between antipsychotic polypharmacy and its correlates. The findings may not be generalized to patients because the study was conducted in one hospital in Northwest, Nigeria. There is need to conduct a multicentered study within the country. The strengths of the study are that experienced psychiatrists confirmed the diagnoses of the patients and the use of the medication was evaluated by face-to-face interviews instead of a retrospective assessment using prescription records only.

CONCLUSION

Antipsychotic polypharmacy is a prevalent prescribing practice in the management of patients with schizophrenia in Nigeria. It is prescribed for longer durations compare to other developed countries, indicating a significant discrepancy with treatment guidelines (which do not advocate the use of any polypharmacy except for short-term periods when transitioning patients to new antipsychotics). Currently, typical (first generation) antipsychotics are most widely used in schizophrenia outpatients and the most commonly used agents were haloperidol and trifluoperazine. There is need to ensure that the health insurance scheme cover antipsychotic medication so that more patients can benefit in the use of atypical antipsychotic which are more expensive with better tolerance.

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