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Medication-related factors of non adherence among patients with schizophrenia and bipolar disorder: Outcome of a cross-sectional survey in Maiduguri, North-eastern Nigeria

Ibrahim, A.W.[1*], Pindar, S.K.[1], Yerima, M.M.[1], Rabbebe, I.B.[2], Shehu, S.[3], Garkuwa, H.A.[4], Bashir, I.Y.[5], Wakil, M.A.[1] and Yahya, S.J.[6]

[1]Mental Health Department, College of Medical Sciences, University of Maiduguri, Borno State, Nigeria.
[2]Clinical Services Department, Federal Neuropsychiatric Hospital, Maiduguri, Borno State, Nigeria.
[3]Department of Psychiatry, Bayero University Kano, Kano State, Nigeria.
[4]Clinical Services Department, Abubakar Tafawa Balewa, University Teaching Hospital, Bauchi State, Nigeria.
[5]Clinical Services Department, Federal Teaching Hospital, Gombe, Gombe State, Nigeria.
[6]Community Medicine Department, College of Medical Sciences, University of Maiduguri, Borno State, Nigeria.

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Pharmacotherapy is the cornerstone in the symptomatic treatment of schizophrenia and bipolar disorder, but non-adherence to the medications constitutes major obstacles to optimal outcome in their management. This study assessed the prevalence of and exclusively x-rayed medication-related factors of non-adherence among patients with these disorders in a resource-poor setting. Three hundred and fifty eight (358) patients with schizophrenia and bipolar disorder were randomly enrolled and interviewed at the out-patient department of the Federal Neuropsychiatric Hospital, Maiduguri in North-eastern Nigeria. Data were collected using an anonymous sociodemographic questionnaire, clinical proforma and the Hausa version of the 8-item Morisky Medication Adherence Scale (MMAS-8). The overall prevalence of non-adherence was 54.2%, while the rates were 62.5% and 45.8% for subjects with schizophrenia and bipolar disorder respectively. The independent medication-related predictors of non-adherence were: multiple dosing frequency (Odds Ratio (O.R) = 7.843, 95% C.I = 4.537 to 13.557, P ≤ 0.001), presence of side effects (O.R = 6.823, 95% C.I = 3.900 - 11.937, p ≤ 0.001), cost of medications (O.R. = 4.009, 95% C.I = 2.555 to 6.921, p ≤ 0.001), and polytherapy (O.R. = 2.317, 95% C.I = 1.363 to 3.940, p = 0.002). This study therefore, recommends the use of guidelines that encourage rational pharmacotherapy based on monotherapy, consider routine lower dosing prescriptions, and integrating side effects surveillance and early intervention in clinical practice.

Key words: Non-adherence, schizophrenia, bipolar disorder, North-eastern Nigeria.

INTRODUCTION

Schizophrenia and bipolar disorder are characterized by chronic, and sometimes relapsing and remitting courses that impact negatively on the premorbid functioning and quality of life of sufferers (Harding et al., 1987; Rietschel et al., 2009; Saarni et al., 2010; Latalova et al., 2011; Aloba et al., 2013). The use of medications, in conjunction

with other psychosocial interventions constitutes the cornerstone in the management of these disorders (Barnes et al., 2011; Goodwin et al., 2009). Therefore, adherence to the various therapeutic modalities, most especially, pharmacotherapy is critical for an optimal outcome. In spite of this, research evidences have shown that nonadherence to the prescribed medical treatments among patients with different disorders constitutes a major problem of public health significance (van Dulmen et al., 2007; Dilla et al., 2013).

Wide variations have been reported on non-adherence figures among psychiatric patients due presumably to differences in the targeted population, definitions and measurement methods (Kane et al., 2013). Nonadherence rates among patients with schizophrenia and bipolar disorder ranged between 30 and 65% (Yang et al., 2012; Demoz et al., 2014). In a review of studies published between 1980 and 2000, Lacro et al. (2002), reported an unweighted mean non-adherence frequency of 40.5% among patients with schizophrenia. The reported nonadherence rate for bipolar disorder is estimated to be between 34 and 48.1% (Baldessarini et al., 2008; Sajatovic et al., 2007; Sajatovic et al., 2006). Further research evidence indicated that 55% of people with schizophrenia who did not adhere to their antipsychotic regimen will relapse over the course of 1 year compared to 14% of those who adhered to their medications (Adam and Scott, 2000). In bipolar disorder, the relapse rate is 60% for noncompliant patients who were presented with manic episode (Keck et al., 1996).

Factors that negatively influenced adherence to medications range from patient-related to treatment-related variables, as well as socio-economic-related factors (American Pharmacists Association, 2013). The principal treatment-related correlates of non-adherence are attributable to the medications used in the treatment of most of these disorders. These medication-related factors include dosing regimen, side effect profiles, fear of addiction potentials, and concerns about drug-drug interactions (Weiden and Miller, 2001; DiBonaventura et al., 2012; Higashi et al., 2013; Caldeira et al., 2014; Eticha et al., 2015). Most studies conducted in sub-Saharan that addressed nonadherence among patients with psychiatric disorders principally assessed patient-related and socio-economic factors, with little or no attempt made at looking at the medication-related factors as significant correlates of nonadherence.

This is the first study that addressed this topical issue among patients with schizophrenia and bipolar disorder in North-eastern Nigeria. This study ascertained; theprevalence of nonadherence to medications among patients with schizophrenia and bipolar disorder and determined the medication-related factors associated with nonadherence among the subjects.

METHODOLOGY

Study design and setting

This was a hospital-based cross-sectional study conducted at the outpatient department of the Federal Neuropsychiatric Hospital, Maiduguri, Borno State, Nigeria. As a matter of policy, 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. Clinically generated data for each subject enrolled were matched to the ICD -10 criteria by two consultant psychiatrists for quality assurance purposes.

Participants

The minimum sample size was computed using a prevalence of 34.2% reported by Danladi et al. (2013) in Jos, North-central Nigeria for non-adherence among patients with schizophrenia, which was set at 95% confidence interval with a corresponding critical value (Z) of 1.96 and 0.05 degree of precision. This yielded a minimum sample size of 345 respondents but in order to increase the power of the study, 380 subjects were interviewed at the end. The subjects consisted of 190 subjects each with the diagnoses of schizophrenia and bipolar disorders. Subjects were randomly selected using the table of random numbers during their respective clinic visitations. A subject is enrolled if the following eligibility criteria were met: a diagnosis of schizophrenia or bipolar disorder, had been on medications for at least 6 months, adults above the age of 18years, and who granted consent. The exclusion criteria were: current florid psychopathology capable of impairing response, and comorbid psychoactive substance use or physical disorders. Comorbid psychoactive substance is excluded in this study, because its presence confers dual diagnosis on the subjects as reported by Okpataku et al. (2015) and thus serves as a confounder while this study considered only subjects with discrete diagnosis of either schizophrenia or bipolar disorder. For the purpose of screening out those with significant psychopathology, mental state examination was conducted on all the participants at the index contact. For the purpose of this study, florid psychopathology is defined as the presence of any positive or negative symptom(s) that make(s) engagement in an interview impossible on clinical evaluation. While the exclusion of those with a comorbid physical disorder was based on previous clinical documentation, symptoms at presentation, general physical and relevant systemic examinations. All of the above clinical processes were independently conducted by two of the investigators.

Measures

Data collection spanned between February and August, 2014, and the following assessment tools were used:

1) Sociodemographic questionnaire designed by the authors that solicited for age, sex, marital status and years of education.
2) Subjects' clinical records to check for the documentation of extrapyramidal symptoms such as rigidity, tremors, bradykinesia, upward rolling of the eyes, etc or the prescription of an anti-

*Corresponding author. E-mail: ibrahimabdu55@gmail.com.

cholinergic drug (example, Trihexiphenidyl) for the subjects. The definition of the presence of extrapyramidal side effects (EPSE) for the purpose of this study include: clinically documented EPSE symptoms, verbally reported EPSE symptoms at any stage of treatment and/or prescription of anticholinergics. Other side effects such as hyperprolactinaemia, undue sedation and others such as sexual dysfunction and blurring of vision, etc were also extracted from the subjects' medical records or verbally elicited. In this study, hyperprolactinaemia is entertained by the presence of one or more of the following symptoms; galactorrhoea (which is not physiological such as during breastfeeding), menstrual irregularities or gynaecomastia (particularly in males).

3) Clinical proforma that sought for other vital information such as type of medication, cost of medication per day (in the Nigerian currency which is converted to the dollar equivalent), dosing frequency, drug combination(s) such as polytherapy or monotherapy and other side effects that were verbally volunteered but were not captured in the medical records. The medication cost is dichotomized into; below and above $1 per day based on its use as a benchmark for purchasing power parity by the United Nations. (United Nation Development Group, 2003). The definition of polytherapy adapted for this study is the use of more than one psychotropic medication irrespective of the class or the clinical indication, apart from ones used for treating medications-induced side effects such as anticholinergics for EPSE.

4) The Morisky medication adherence scale (MMAS-8) which is an 8-item instrument developed by Donald Morisky was used to assess medication adherence among patients with different clinical conditions. In this study, the Hausa version was used because it is the local language understood by majority of the respondents. The instrument was translated using iterative back-translation method; in the first stage of the translation, the English version of the MMAS-8 was translated into Hausa independently by two native speakers. The two translated versions were then synchronized, maintaining precise semantic and idiomatic equivalents as far as possible to have a final version. The final version was then back-translated to English by another set of native Hausa speakers and compared to the original MMAS-8 and was found to have inter-item correlation of 0.903. The internal consistency of the overall final Hausa version has a Cronbach's alpha of 0.708 which was considered satisfactory. Cronbach's α values of ≥ 0.70 are usually categorized as good to excellent (George and Mallery, 2003). The copyright permission to translate and use the instrument was granted by Donald Morisky. In interpreting the outcome, the scores were graded as follows: <6 is low adherence, 6 to <8 is medium adherence and high adherence is equal to 8 (Morisky et al., 2008). For the purpose of this study, non-adherence is defined as MMAS-8 score of less than 8 while score of 8 is considered adherent. Similar cut-off score was adopted for non-adherence among hypertensive outpatients with comorbid psychiatric conditions in Ghana (Kretchy et al., 2014).

Ethical consideration

Ethical clearance was obtained from the ethics and research committee of Federal Neuropsychiatric Hospital, Maiduguri. Written informed consents were also obtained from all the participants. In order to ensure confidentiality, codes were used for data entry and analysis.

Data analyses

The data were analyzed using statistical package for social sciences (SPSS) version 20. Descriptive statistics were used to represent the characteristics of the participants. Bivariate analyses were used to explore the associations between the medication-related variables and medication non-adherence among the subjects. Binary logistic regression was then conducted to determine the independent predictors of non-adherence among the subjects. Non-adherence was used as the independent variable while the factors found to be significant on bivariate analyses were used as covariates. Significance was computed at $p < 0.05$, two-tailed.

RESULTS

At the end of the study, the data of 358 subjects were finally analyzed yielding an overall response rate of 94.2%. This consisted of 181 and 177 subjects with the diagnoses of schizophrenia and bipolar disorder respectively. The data of 22 subjects were not analyzed due to: refusal to grant informed consent (n = 7), presence of florid psychopathology (n = 4), comorbid psychoactive substance use (n = 3), presence of physical disorders (n = 2), and those whose questionnaires could not be analyzed due to missing data (n = 6).

Sociodemographic characteristics of the respondents

Males constituted 55.3% of the subjects. Over 73% of the subjects were below 40 years with an average age of 35.03 years (SD±9.592) which ranged between 18 and 63 years. Over 70% of them had less than 12 years of education and over 51% were unmarried. The average duration lived with the illness was 3.45 years (SD±1.477) with a range of between 1 and 16 years. The findings are presented in Table 1.

Distribution of the medication-related variables

Over 56% of the subjects spent ≤ $1 per day [equivalent to N200 (Nigerian currency)] on their medications. About 53% of them were on conventional antipsychotics and the three most commonly prescribed first generation antipsychotics were: Trifluoperazine (36.3%), Chlorpromazine (33.5%) and Haloperidol (23.1%). The remaining 7.1% were on either Thioridazine, Fluphenazine decanoate or Flupenthixol decanoate (the last two are depot preparations). About 30% were on mood stabilizers and the only prescribed ones were Carbamazepine (63.1%) and Sodium Valproate (36.9%). Over 10% were on atypical antipsychotics. The most commonly prescribed serotonin dopamine antagonists (SDAs) were Olanzapine (62.3%), Risperidone (29.4%) and Clozapine (8.1%). Over 53% of the subjects were on polytherapy and the most common combinations were: any class of antipsychotics and mood stabilizers, conventional antipsychotics and depot injections, and combination of two conventional antipsychotics. The dosing frequency of 46% of the subjects was at least thrice per day. Approximately 63% of the subjects had

Table 1. Sociodemographic characteristics of the respondents.

Variables	Schizophrenia (%)	Bipolar disorder (%)	Total (%)
Gender (N = 358)			
Male	111 (61.3)	87 (49.2)	198 (55.3)
Female	70 (38.7)	90 (50.8)	160 (44.7)
Age (Mean = 35.03 years + 9.592 SD, Range = 18 - 63years)			
≤ 40 years	130 (71.8)	133 (75.1)	263 (73.5)
> 40 years	51 (28.2)	44 (24.9)	95 (26.5)
Years of education			
≤ 12 years	139 (76.8)	115 (65.0)	62 (35.0)
> 12 years	42 (23.2)	62 (35.0)	104 (29.1)
Marital status			
Married	86 (47.5)	89 (50.3)	175 (48.9)
Single	86 (47.5)	52 (29.4)	110 (30.7)
Widowed	13 (7.2)	11 (6.2)	24 (6.7)
Divorced	24 (13.3)	25 (14.1)	49 (13.7)
Duration of illness (Mean = 3.45 years + 1.477 SD, Range = 1 - 16years)			
≤ 2 years	64 (35.4)	54 (30.5)	71 (40.1)
3 - 4 years	53 (29.2)	52 (29.4)	105 (29.3)
≥ 5 years	64 (35.4)	71 (40.1)	135 (37.7)

medications-related side effects while 37% reported no medication-induced side effects. The details are depicted in Table 2.

Levels of adherence of the subjects

In terms of their levels of adherence based on the stratification used for this study, over 43% of the subjects were categorized as having low adherence, while 10.6% were categorized as having medium adherence. One hundred and sixty four (45.8%) were classified as having high adherence. The overall prevalence of non-adherence was 54.2% using an MMAS cut-off score of <8 adapted for this study. The findings are depicted in Table 3.

Medication-related variables found to be associated with non-adherence in the subjects

On bivariate analysis, all the variables explored, namely; cost of medications (χ^2 = 38.23, df = 1, p = <0.001), class of the psychotropic medications used (χ^2 = 11.593, df = 1, p = <0.001), drug combination(s) (χ^2 = 13.008, df = 1, p = <0.001), dosing frequency (χ^2 = 86.034, df = 1, p = <0.001), and side effect profiles (χ^2 = 69.855, df = 1, p = <0.001) were all found to have statistically significant associations with non-adherence in the subjects. These findings are shown in Table 4.

Logistic regression analysis for variables associated with non-adherence

Logistic regression analysis revealed the following; cost of medications [Odds ratio (O.R.) = 4.009, p = <0.001, 95% C.I. = 2.555 - 6.921], drug combinations [O.R. = 2.317, p = <0.001, 95% C.I. = 0.931 - 1.488], side effects [O.R. = 6.823, p = <0.001, 95% C.I. = 3.900 - 11.937] and dosing frequency [O.R. = 7.843, p = <0.001, 95% C.I. = 4.537 - 13.557] as the independent predictors of nonadherence among the subjects. The details are presented in Table 5. The Pearson's correlation coefficient for polypharmacy and side effects was 0.77, p = <0.001.

DISCUSSION

This study estimated the prevalence rate of non-adherence, and determined the medication-related correlates of non-adherence among subjects with schizophrenia and bipolar disorder. Though, previous studies by Adewuya et al. (2009) and Adeponle et al. (2009) looked at these pertinent issues among patients

Table 2. Distribution of medication-related variables in the subjects.

Variables	Schizophrenia (%)	Bipolar disorder (%)	Total (%)
Cost of medications (N = 358)			
≤ $1 per day	123 (68.0)	78 (44.1)	201 (56.1)
> $1 per day	58 (32.0)	99 (55.9)	157 (43.9)
Class of medications			
Conventional antipsychotics	127 (70.2)	62 (35.0)	189 (52.8)
Antidepressants	9 (5.0)	14 (7.9)	23 (6.4)
Mood stabilizers	18 (9.9)	89 (50.3)	107 (29.9)
Atypicals	27 (14.9)	12 (6.8)	39 (10.9)
Drug combination			
Polytherapy	97 (53.6)	95 (53.7)	192 (53.6)
Monotherapy	84 (46.4)	82 (46.3)	166 (46.4)
Dosing frequency			
Once per day	50 (27.6)	54 (30.5)	104 (29.1)
Twice per day	34 (18.8)	55 (31.1)	89 (34.9)
Thrice or more per day	97 (53.6)	68 (38.4)	165 (46.0)
Side effects profile			
Extrapyramidal side effects	47 (26.0)	30 (16.9)	77 (21.5)
Hyperprolactinaemic	9 (5.0)	9 (5.1)	18 (5.0)
Sexual	23 (12.7)	21 (11.9)	44 (12.3)
Anticholinergic	16 (8.8)	22 (12.4)	38 (10.6)
More than one side effect	24 (13.3)	24 (13.6)	48 (13.4)
No side effect	62 (34.2)	71 (40.1)	133 (37.2)

Table 3. Levels of adherence of the respondents.

Variables	Schizophrenia (%)	Bipolar disorder (%)	Total (%)
Level of adherence (N = 358)			
Low adherence	104 (57.5)	52 (29.4)	156 (43.6)
Medium adherence	9 (5.0)	29 (16.4)	38 (10.6)
High adherence	68 (27.5)	96 (54.2)	164 (45.8)

with mental illnesses in this part of the African sub-continent, this is the first study to the best of our knowledge that strictly looked at medication-related factors as predictors of poor adherence among patients with the two diagnostic entities analyzed. This is important considering our socio-economic peculiarities and the therapeutic options available at the disposal of mental health clinicians in sub-Saharan Africa.

Analysis of the levels of adherence revealed that 43.6, 10.6 and 45.8% of the subjects had low, medium and high adherence respectively. However, using the MMAS total of <8 adapted in this study for the definition of nonadherence, it means 54.2% of the subjects were non-adherent. For the individual diagnostic entities, the non-adherence rates were 62.5 and 45.8% for subjects with schizophrenia and bipolar disorder respectively. This roughly translates to every four and every six out of ten subjects with bipolar disorder and schizophrenia were nonadherent, while overall, over five subjects out of ten across the diagnostic groups were nonadherent. This overall non-adherence rate falls within the range of 30 to 65% reported in previous studies by Yang et al. (2012) and Kassis et al. (2014). The reported higher rate of non-adherence among subjects with schizophrenia than among those with bipolar disorder might be attributed to: higher rate of the prescription of conventional anti-

Table 4. Bivariate analyses of medication-related variables in the subjects.

Variables	Non-adheren (%)	Adherent (%)	Total (%)	Statistics
Cost of medications (N = 358)				
≤ $1 per day	80 (41.2)	121 (73.8)	201 (56.1)	χ^2 = 38.23, df =1, p=<0.001**
> $1 per day	114 (58.8)	43 (26.2)	157 (43.9)	
Class of medications				
Conventional	111 (57.2)	78 (47.6)	189 (52.8)	
Antidepressants	10 (5.2)	13 (7.9)	23 (6.4)	χ^2 =11.59, df = 3, p=<0.001**
Mood stabilizers	61 (31.4)	46 (28.0)	107 (29.9)	
Atypical	12 (6.2)	27 (16.5)	39 (10.9)	
Drug combination				
Polytherapy	121 (62.4)	71 (43.3)	192 (53.6)	χ^2 = 13.01, df = 1, p=<0.001**
Monotherapy	73 (37.6)	93 (56.7)	166 (46.4)	
Dosing frequency				
≥ Thrice per day	133 (68.6)	32 (19.5)	165 (46.1)	χ^2 = 86.03, df = 1, p=<0.001**
≤ Twice per day	61 (31.4)	132 (80.5)	193 (53.9)	
Side effects				
Side effects present	160 (82.5)	65 (39.6)	225 (62.8)	χ^2 = 69.86, df = 1, p=<0.001**
Side effects absent	34 (17.5)	99 (60.4)	133 (37.2)	

**Statistically significant findings.

Table 5. Logistic regression analyses of variables.

Variables	Standard error	Exp (B) odds ratio	95 C.I. Lower - Upper	P - value
Medication cost	0.341	4.009	2.555 - 6.291	<0.001**
Class of medications	0.120	1.177	0.931 - 1.488	0.174
Drug combination(s)	0.271	2.317	1.363 - 3.940	0.002**
Dosing frequency	0.279	7.843	4.537 - 13.557	<0.001**
Side effect profile	0.285	6.823	3.900 - 11.937	<0.001**

**Statistically significant findings.

psychotics and their attendant side effects such as the extrapyramidal ones which may encumber adherence, and probable lower levels of insight and residual psychopathology among the schizophrenic subjects in comparison to their bipolar disorder counterparts that might have negatively affected adherence.

Though, the prevalence of non-adherence reported in this study, falls within the range of most studies conducted earlier by Adewuya et al. (2009), Yang et al. (2012) and Kassis et al. (2014), the rate was below 66.9 and 74% reported in Egypt by Amr et al. (2013) and by Banerjee and Varma (2013) in India respectively. This discrepancy could be attributed to the methodological differences in the studies, such as the tools used for the assessment of adherence and the different cut-off values used for the definition of adherence and non-adherence.

The independent medication-related predictors of non-adherence found in this study were; the cost of the medications, drug combination(s), the dosing frequency and the side effect profile. In terms of the cost of the medications, the higher the cost of the medication per day, the higher the rate of non-adherence. In this case, subjects whose medications cost more than $1 per day were more than four times more likely to be non-adherent to their prescribed medications than those whose medication cost ≤ $1 per day. This finding might not be unconnected to the fact that over 70% of the study subjects had less than tertiary education which also translates to low socio-economic placement and very low if not non-existent earning. More so, North-Eastern Nigeria, the setting in which the study was conducted has one of the highest poverty rates in the country with over

70% of the inhabitants living below the $1 per day benchmark (National Bureau of Statistics, 2013; United Nations Development Programme, 2013). The poverty levels might have been further complicated by the 'Boko Haram' insurgency with its attendant socio-economic consequences. Thus, since adherence is determined to a large extent by one's income, it means non-adherence in a significant proportion of the subjects might be accounted for by these economic considerations. This finding is in tandem with that of Kane et al. (2013) that also reported the cost of medication as an important predictor of non-adherence.

Logistic regression analysis also showed that subjects who were on more than one drug (polytherapy) were over two times more likely to be non-adherent to their medications when compared to their counterparts who were on monotherapy. Similar outcomes have been documented in patients with HIV/AIDS who were on multiple antiretroviral medications and diabetics (Chesney, 2000; Hauber et al., 2013). The reasons that could be advanced for this include; the discomfort arising from the high 'pill burden' and the likelihood of more drug-induced side effects due to multiple drug combinations. There was a positive correlation between polypharmacy and side effects in this study. From the economic perspective, the cost is likely to be more for subjects on polytherapy than for those on monotherapy which might also contribute to non-adherence. Earlier study by Razzouk et al. (2015) in Brazil has shown the impact of antipsychotic polytherapy cost on the public health care system and thus advocated for rational monotherapy. A landmark study that has led some credence to this study finding is that of Baldessarini et al. (2008) that showed reduced levels of adherence among patients with bipolar disorder on polytherapy.

The dosing frequency was the strongest predictor of medication-related non-adherence in this study. Subjects on multiple daily dosing frequency (that is, greater than two times per day) were almost eight times more likely to be non-adherent when compared to those on lesser dosing frequency. Pfeiffer et al. (2008) have also reported inverse relationship between dosing frequency and medication adherence among patients on antipsychotics. The possible reasons for this outcome are: the tendency of forgetting to take the medications as prescribed when the dosing frequency is high, some of the medications side effects particularly sedation and cognitive impairment may hinder adherence in subjects with busy work schedules, and the discomfort associated with taking the medications severally on daily basis. The negative impact of multiple dosing frequency on adherence is not restricted to patients with mental illnesses alone, as Caldeira et al. (2014) demonstrated such effects among patients with cardiovascular diseases in a meta-analysis.

The final independent predictor of non-adherence among the subjects was the presence of side effects. Subjects who had one side effect or the other were almost seven times more likely to be non-adherent than those without side effects. Of those who were non-adherent, over 80% had at least one side effect. This is because the presence of side effects is associated with significant impairment in the quality of life of the subjects as well as it served as a hindrance to them in carrying out some of their activities of daily living. Secondly, based on this study interaction with some of the patients in our clinical setting, those who experienced incapacitating side effects (particularly EPSE), view it as punitive and therefore abhor psychiatric medications. This negative view of the side effect profile contributes significantly to non-adherence to psychotropic medications among some African patients. A study by DiBonaventura et al. (2012), on the impact of side effects on medication adherence among psychiatric patients revealed a similar outcome.

Limitations of the study

Based on the cross-sectional nature of this study, inferences cannot be made between non-adherence and some of the variables identified. Secondly, instruments such as the Barnes akathisia or the extrapyramidal symptoms scales should have been more valid measures of extrapyramidal side effects while serum prolactin assay would have been a more objective indicator of hyperprolactinaemia than the clinical symptoms.

CONCLUSION

Though, the predictors of non-adherence among psychiatric patients are multifactorial, the strongest determinants in this study were the cost of medications, polytherapy, multiple daily dosing frequency and the presence of side effects. From the clinicians' perspective, the authors are of the strong opinion that the last three factors are modifiable, and therefore recommend the following measures:

1) Adhering to guidelines that encourage rational pharmacotherapy based on monotherapy except where the use of multiple drugs becomes compelling.
2) Considering lower dosing frequency (preferably once daily dosing) in sub-Saharan African clinical settings.
3) Integrating questioning and examinations for symptoms of side effects and instituting early intervention where necessary in the study setting.

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Conflicts of interest

The authors declare no conflict of interest.

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