Original paper

Archives of Psychiatry Research 2023;59:225-240
DOI:10.20471/dec.2023.59.02.06
Received September 01, 2022, accepted after revision October 23, 2022

Prevalence and Correlates of Extrapyramidal Side Effects Among Patients with Schizophrenia Spectrum Disorders on Typical and Atypical Antipsychotics

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Abstract - Background: Antipsychotic medication for the treatment of schizophrenia spectrum disorders are associated with adverse effects with extrapyramidal side effects constituting one of the most notable effects associated with poor medication adherence and poor quality of life. Aims: The study aims to compare the prevalence of extrapyramidal side effects (EPSE), among patients with schizophrenia spectrum disorders on typical and atypical antipsychotic medications. The secondary aim is to determine the association of extra-pyramidal side effects with socio-clinical variables. Methodology: A cross-sectional hospital-based study with systematic random sampling recruitment of 340 participants and 303 completed the study. Variables with significant association on chi square analysis were subjected to logistic regression analysis. Results: The overall prevalence of extrapyramidal side effects among patients with schizophrenia spectrum disorder on antipsychotic medication was 42.6 %. The prevalence of tardive dyskinesia, parkinsonism and akathisia were 7.9 %, 38.6 and 3.6 %, respectively. The prevalence of extra-pyramidal side effects due to use of typical, atypical and combination drug was 44.4 %, 51.2 % and 34.5 %, respectively with haloperidol (59.4 %) and risperidone (71.4 %) having the greatest effect. Being elderly was associated with tardive dyskinesia, duration of treatment, severity of illness and type of illness with parkinsonism and severity of illness with akathisia. Conclusion: The findings of this study support the high prevalence of extrapyramidal side effects from either using typical and atypical antipsychotic medications. Therefore, Clinicians should discuss on these side effects and proffer possible solutions with their patients prior to commencement of antipsychotic medications in order to promote medication adherence.

Keywords: akathisia, drug-induced; antipsychotic agents; drug-related side effects and adverse reactions; tardive dyskinesia; schizophrenia

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Introduction

The use of antipsychotic medications (APM) has improved the treatment outcome of psychotic disorders, especially disorders that run chronic course like the schizophrenia spectrum disorders. Side effects of anti-

psychotics have been shown to mitigate compliance and adherence to their use thereby leading to the "revolving door syndrome" in such disorders. One of the side effects of serious concerns is extrapyramidal side effects. Schizophrenia spectrum disorders is a psychotic disorder characterized by hallucinations, delusions, cognitive impairment and disturbances in behaviour, with onset usually in late adolescence or early adulthood and continuing throughout life, thereby requiring long term treatment [1,2]. It consists of positive and negative symptoms. Positive symptoms are associated with increased activity of D2 receptors in the mesolimbic dopaminergic pathway and are characterized by hallucinations, delusions and abnormal behaviour while negative symptoms represent deficits in normal functions such as blunted affect, asocial behaviour and diminished motivation and it result from decreased activity in the mesocortical dopaminergic pathway with D1 receptor dominating [3,4]. Antipsychotic medications are a group of drugs that are effective in alleviating the psychotic symptoms of schizophrenia; they act by blocking dopamine D_2-receptors in the central nervous system (CNS) [5]. They are broadly classified into typical (first generation, traditional or conventional) and atypical (second generation or novel) antipsychotics. Typical antipsychotic medications or first-generation antipsychotics are effective in alleviating positive symptom of the schizophrenia but are limited by lack of efficacy against negative and cognitive symptoms as well as a disabling extrapyramidal side effect [6]. Atypical antipsychotics or second-generation antipsychotics potentially antagonize the 5HT2 receptor and block the D2 receptor less potently than typical antipsychotics. The development of these atypical antipsychotics such as clozapine, risperidone, olanzapine, quetiapine in 1990's yielded a better outcome in treatment of schizophrenia by reducing the extrapyramidal symptom but was also limited by serious metabolic side effects [7].

All APMs act by blockage of postsynaptic dopaminergic receptors (D_1 - D_5) in the CNS [8]. Both antipsychotic efficacy and extra-pyramidal side effects are mediated by antagonism of dopamine (D2) receptors and studies with positron emission tomography have demonstrated the distinctive degree of D2 receptor blockage associated with antipsychotic efficacy (D2 receptor antagonism of 60-70 %) and extra-pyramidal side effect (D2 receptor antagonism of 75-80 %) [9]. EPSE results from an imbalance between the inhibitory (dopaminergic neuron) and the excitatory (cholinergic neuron) in the striatum with dopamine blockade causing a relative cholinergic excess [8]. The use of second-generation antipsychotics clozapine is associated with a lower risk of extrapyramidal side effects when compared to first generation antipsychotics probably due to their relatively lower D_2 - receptor occupancy, higher 5 - HT_2 - receptor occupancy and limbic selectivity [10].

Extrapyramidal side effects are movement disorders characterized by involuntary movement, alteration of muscle tone, postural disturbance and intolerable desire to be moving continually that commonly occur with the use of antipsychotic medications. Antipsychotics induced extra pyramidal symptoms can be classified based on time relation with antipsychotic use and onset of extra-pyramidal symptoms into; acute (e.g., acute dystonia, pseudoparkinsonism, akathisia and neuroleptic malignant syndrome) and late (tardive syndrome). Acute extrapyramidal symptoms develop within hours or weeks after initiating or increasing doses of antipsychotics. Tardive dyskinesia and tardive dystonia are delayed onset syndrome [11]. Dystonia is an unpleasant and painful experience that occur as a result of intermittent or sustained muscle spasm that manifest in the form of stiff jaw, oculogyric crisis, torticollis, tongue protrusion, opisthotonus, dysarthria, dysphagia laryngeal and pharyngeal spasms. It may occur in 10 % to 25 % of patients receiving typical and atypical antipsychotics with about 50 % of cases occurring within the first 2 days and 90 % in the first 4 days of antipsychotic usage [12]. Younger adults and children are more commonly af-

fected. Other risk factors include high dose of antipsychotics, duration of use, male gender, mental retardation, positive family history of dystonia, previous dystonic reaction, cocaine and alcohol abuse [12]. The pathophysiology of acute dystonic reaction is still unknown. One theory posits that dystonia is the manifestation of an acute compensatory response to nigrostriatal D_2-receptor blockage by antipsychotics. The acute administration of antipsychotics provokes increased dopamine synthesis and release from nigrostriatal neurons and postsynaptic receptor upregulation [13]. As blood concentrations of the antipsychotics decline hours to days after a dose, a state of dopaminergic excess develops and hyperkinesis or dystonia results [13].

Akathisia is the sensations of restlessness and an irresistible urge to move. Mesocortical D_2-receptor blockade by APM and imbalance between the noradrenergic and the dopaminergic system have been implicated to cause Neuroleptic Induced Akathisia [14]. The prevalence of akathisia varies from 9 to 32 % among extra pyramidal side effects with no significant differences in rate using either typical or atypical antipsychotics [14]. Akathisia may persist for the duration of antipsychotic therapy and usually ceases after the discontinuation of antipsychotics. Neuroleptic induced Parkinsonism is characterized by the triad of bradykinesia, muscle rigidity and tremor. It is caused by D_2-receptor blockade greater than 80 % in the nigrostriatal pathway [15]. Symptoms usually manifest within 4 days from initiation of treatment, however there are variability in the time of onset of symptoms from commencement of antipsychotic medications usually ranging from few days to few months and it usually reverses with drug discontinuation [16]. It is observed in 11 % and 43 % of patients on atypical and typical antipsychotics respectively [17].

Tardive dyskinesia is manifested by involuntary choreoathetoid movements of the orofacial region, extremities, trunk and respiratory muscles. The movements are more pronounced with excitement, disappear during sleep and patient can temporarily succeed in decreasing the intensity of the involuntary movement for a short period of time when they wish to do so, while some patients are either unaware or are not bothered by the involuntary movements [18]. It develops after months or years of continuous use of antipsychotics [18]. Tardive dyskinesia can also persist after the discontinuation of antipsychotics or may even be irreversible. Prevalence of tardive dyskinesia ranges between 18 - 46 % [18]. Risk factors for tardive dyskinesia include the elderly, female, patients with brain damage, dementia, mood disorders, increased duration of antipsychotic therapy, and use of anticholinergic drugs, antiparkinsonian drugs and previous occurrence of extra pyramidal symptoms [19]. Tardive dyskinesia is a state of dopaminergic supersensitivity and cholinergic underactivity in the basal ganglia hypothesized to be caused by hypersensitivity of dopamine in the nigro-striatal pathway from chronic blockage by APM [20].

Antipsychotic induced extra-pyramidal side effect is estimated to occur in 19 % and 42 % of schizophrenic patients taking atypical and typical antipsychotic medications, respectively [21]. The point prevalence of EPSE in schizophrenic patients ranges between 29 - 74 % [21,22]. The differences in the point prevalence may be due to the differences in the researchers' definition of EPSE, instrument used and study population. Extrapyramidal symptoms were previously considered as indexes of antipsychotic action, but they are now considered as harmful adverse effects that jeopardizes the therapeutic benefit [23]. Extrapyramidal side effects adversely impact antipsychotic efficacy by masking the beneficial effect of antipsychotic medications on the negative, cognitive and depressive symptoms [24]. It is associated with increased burden of care, morbidity, drug noncompliance, relapse rate and stigmatization, thereby adversely impacting on the level of functioning and quality of life [23,25-26]. Akathisia is associated with premature treatment termination, exacerbation of psychotic symptoms increased suicidality and noncompli-

ance [27]. There is a dearth of knowledge on antipsychotic induced adverse effects in many developing countries including Nigeria. Data on the prevalence and impact of common adverse effects of antipsychotics like extra-pyramidal side effects are scarce with the available ones being no longer current and carried out in the southwestern part of the country [28]. This cross-sectional study therefore, hopes to generate data on the pattern of extra-pyramidal side effects among patients with schizophrenic spectrum disorder on antipsychotic medications (typical and atypical) in north-eastern Nigeria, a distinct part of the country.

Subjects and Methods

The study was conducted among patients with schizophrenia spectrum disorders in a tertiary health care centre at the outpatient clinic of Federal Neuropsychiatric Hospital Maiduguri which is located along Baga Road. It is a referral centre for the mentally ill in north eastern region of Nigeria and receives patients from the following states in Nigeria: Borno, Yobe, Adamawa, Gombe, Taraba and Bauchi and from the neighbouring countries of Chad, Niger and Cameroun. The hospital provides community and specialist services to patients as well as training facilities for postgraduate residency training, medical students and nurses. The study was conducted for duration of four months. Inclusion criteria were; patients aged between 18 - 65 years, have been on stable antipsychotic medication for at least one month and patients with ICD-10 diagnosis of schizophrenia, schizoaffective disorders and delusional disorders. Exclusion criteria were; comorbid psychoactive substance use disorder and all patients suffering from neurological conditions, thyroid or pituitary gland disease or seizure disorder.

Sampling procedure

A cumulative total of 340 schizophrenic patients were recruited into the study using a systematic sampling technique. The procedure of systematic random sampling technique employed in this study involved the identification of the estimate of the target population (2,700, from the records department) and dividing it by the sample size of the study (340). This yielded a sampling fraction (interval) of 8. The first unit was selected using a random number table (the 5th patient on the list). As such, the 13th, 21th, 29th and so forth were recruited.

Study Instruments

Questionnaires were used to collect data on the variables by the investigators. The first part of the questionnaire asked for the socio-demographic data of the patient (age, gender, education, occupation and marital status) and clinical data (drugs taken, the dose and length of therapy). Data were collected using the following instruments; Abnormal Involuntary Movement Scale (AIMS), Simpson and Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS) for assessment of extrapyramidal side effects; Positive And Negative Symptom Scale (PANSS) for assessment of presence or severity of psychopathology, Medication Adherence Rating Scale (MARS) for the assessment of level of adherence to medication. All patients were interviewed with all the instruments. The interview was carried out with each patient separately in a private room to ensure confidentiality.

Barnes Akathisia Rating Scale (BARS)

BARS is a 4-item anchored scale, the first three items assess objective and subjective characteristics of akathisia on a scale from 0 to 3 [29]. The fourth item, termed the global item, is measured on a scale of 0 to 5, with higher scores indicative of more severe akathisia [29]. The interrater reliability Cohen's kappa values have been as high as 0.738 in objective items, 0.827 in subjective awareness items, 0.901 in subjective distress and 0.955 in global clinical assessment [29,30]. It is the most widely used scale for akathisia. Akathisia was considered to be present at each time point according to the following operational criteria suggested by Schooler and Kane, when participants scored 2 or more on the global akathisia item of the BARS [30].

Simpson and Angus Scale (SAS)

SAS is a 10-item scale with 6 of its item measuring rigidity, one item measuring bradykinesia and three items measuring glabella tap, tremor and salivation. It is used for assessing Parkinsonian side effects, each rated on a 5-point scale from 0 to 4, with higher scores indicative of more severe symptoms [31]. The total score ranges from 0 to 40 and Parkinsonism is considered present according to the operational criteria suggested by schooler and Kane, when participants had a total score of 3 or more on the SAS [30]. It is a valid and reliable instrument with an interrater correlation coefficient of 0.87.

Abnormal Involuntary Movement Scale (AIMS)

AIMS is a 12-item anchored scale that provides a comprehensive rating of abnormal involuntary move-

ments in various body sites [32]. Items 1 – 7 assesses specific involuntary movements in 3 body regions: orofacial movement rated on 4 separate items; extremity movements on two separate items; and trunk movements on one item. Three separate items 8 - 10 deal with global severity, as judged by the examiner and the patients' awareness of the movements and associated distress. Two items 11 and 12 are "yes" or "no" items concerning problems with teeth and/or dentures to avoid false positive rating of dyskinesia. Each item is scored on a 5-point scale from 0 to 4, with higher scores indicative of more severe abnormal movements. Tardive dyskinesia is considered present according to the operational criteria suggested by schooler and Kane, when participants had one score of 3 or two scores of 2 on AIMS items 1 - 7 covering observed movements [30]. The scale takes about 15 minutes to complete. It is the most widely used scale with interrater reliability ranging from 0.66 to 0.82 for individual body area items, test-retest reliability ranging from 0.12 to 0.75 and the correlation for overall severity was 0.75 [33].

Positive and Negative Syndrome Scale (PANSS)

Is a 30-item interval scale with response options ranging from 1 - 7 with 7 positive symptoms item, 7 negative symptoms, and 16 general psychopathology items, each rated on a 7 - point symptom severity scale, ranking from 1 (absent) to 7 (extremely severe) [34]. The minimum and maximum total score ranges between 30 and 210. It takes about 45 minutes to administer. The positive, negative and general psychopathology scale have been found by coefficient alpha and test-retest reliability testing to be internally consistent and highly reliable (Cronbach's alpha ranged from 0.70 to 0.85 and inter-rater reliability was 0.82) with good construct, discriminate, convergent and predictive validity. PANSS is also used for monitoring treatment response and is sensitive to symptom change [34]. Patients were categorized based on operational criteria suggested by Leucht and associates into normal score (30 - 57), mildly ill (58 - 74), moderately ill (75 - 94), markedly ill (95 - 115) and severely ill (116 and above) which was used in the current study [35].

Medication Adherence Rating Scale (MARS)

MARS was created by Thompson and associates, for the assessment of medication adherence among psychiatric patients [36]. It is a 10 - item questionnaire answered with a "yes" or "no" response with scores ranging from a minimum of 0: low medication adherence to a maximum of 10: high medication adherence. A response consistent with nonadherence is coded as 0 and a response consistent with adherence is coded as 1. Patients are compliant if they respond "no" (no = 1, yes = 0) to questions 1 - 6 and 9 - 10 and "yes" (yes = 1, no = 0) to questions 7 - 8. It was first validated among schizophrenic patients with an internal consistency reliability of $\alpha = 0.75$ [36,37]. The authors categorized patients into three levels of medication adherence; high (8 - 10), moderate (4 - 7) and low adherers (< 4) which was adopted in this study [36].

Statistical Methods

Data was analysed using Statistical Package for Social science (SPSS) version 18. The mean and standard deviation was calculated for continuous variables. Frequencies and percentages were used to calculate categorical variables (prevalence rate of EPSE). Associations between the categorical independent variables and the dependent variables (EPSE) were analysed using a Chi square test or Fischer's exact test where appropriate and significant level was taken at $p < 0.05$ for all statistical analysis. Significant associations between dependent and independent variables were subjected to logistic regression analysis to determine the independent predictors of EPSE. All p-values reported in the study are two-tailed.

Ethical Clearance

Ethical Clearance was obtained from the Ethics Review Committee of Federal Neuropsychiatric Hospital Maiduguri. Potential participants were informed on the study protocol with only those who have consented enrolled in the study. For confidentiality only codes were used as identity.

Results

Three hundred and forty participants were recruited for this study. Out of this sample, 19 participants refused to give written informed consent and 18 failed to fulfil the inclusion criteria. Therefore, 303 (89.1 %) participants completed the study.

Sociodemographic characteristics of the participants

The study population comprised of 158 (52.1 %) males and 145 (47.9 %) females. Their ages ranged from 18 to 65 years, with a mean

Table 1. Sociodemographic characteristics of the participants

Variable	(n = 303) Frequency	Percentage (%)
Age distribution		
18-24	33	10.9
25-34	112	37.0
35-44	78	25.7
45-54	48	15.8
55-64	32	10.6
Mean +SD 37.29 (± 11.63)	M = 36.12 (± 4.4)	F = 38.59 (± 4.8)
Range 18-65 years		
Sex		
Male	158	52.1
Female	145	47.9
Religion		
Islam	288	95.0
Christianity	15	5.0
Marital status		
Single	110	36.3
Married	134	44.2
Divorced	40	13.2
Widowed	12	4.0
Separated	7	2.3
Educational status		
None	87	28.7
Primary school	22	7.3
Secondary school	48	15.8
Tertiary	49	16.2
Quranic/Islamic	97	32.0
Employment status		
Employed	229	75.6
Unemployed	74	24.4
Ethnicity		
Kanuri	165	54.5
Hausa	44	14.5
Fulani	16	5.3
Others	78	25.7

age of 37.29 (± 11.63) years. Majority of the participants were within the ages of 25 - 34 and 35 - 44 years (62.7 %). One hundred and thirty-four (44.2 %) were married, 54.5 % were Kanuri by tribe and 60.7 % had no western education. About a quarter (24.4 %) were unemployed and about half of the participants were elementary workers (Table 1).

Clinical characteristics of the participants

The clinical characteristics of the participants are shown in Table 2. The duration of

Table 2. Clinical characteristics of the participants

Variables	Frequency (n=303)	Percentage (%)
Type of medication		
Typical antipsychotics	178	58.7
Atypical antipsychotics	41	13.5
Combination of drugs	84	27.7
Specific drug types		
Haloperidol	62	20.5
Trifluoperazine	119	39.3
Chlorpromazine	53	17.5
Olanzapine	50	16.5
Risperidone	8	2.6
Clozapine	11	3.6
Type of diagnosis		
Schizophrenia	209	69.0
Schizoaffective disorder	87	28.7
Delusional disorder	7	2.3

	Total	Males	Females
Duration of treatment (years)	Mean ± SD (5.8 ± 4.6)	5.84 (4.4)	5.83 (4.8)
< 1 year		32	10.6
1 - 5 years		130	42.9
6 - 10 years		78	25.7
> 10 years		63	20.8

treatment in years ranged from 2 months to 20 years, with a mean of 5.84 (± 4.58) years. More than half of the participants were on typical antipsychotics alone 58.7 % (n = 178) and 13.5 % (n = 41) were on atypical antipsychotics alone. Combination of antipsychotic with other drugs (antipsychotic and mood stabilizer or antipsychotics and antidepressant) constituted 27.7 % (n = 87) (Table 2). The commonest typical antipsychotic used was Trifluoperazine (n = 119) and the commonest atypical drug used was Olanzapine (n = 50).

Prevalence of Extrapyramidal Side Effects

The overall prevalence of extrapyramidal side effects among patients with schizophrenia spectrum disorder on antipsychotic medication was 42.6 %.

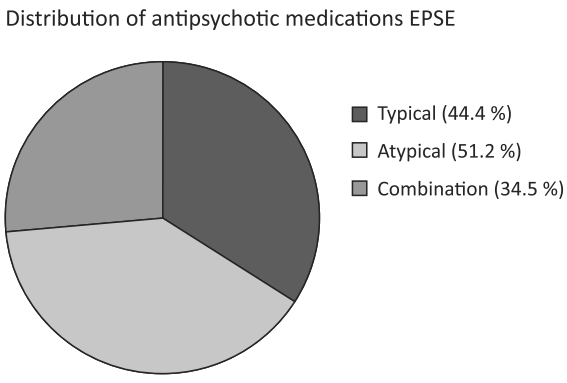

Figure 1. Prevalence of extrapyramidal side effects

Table 3. Sociodemographic and clinical characteristic of patients with Tardive dyskinesia (n = 24)

Variable	NITD Present (n)	%	NITD absent (n)	%	Total (n)	%	Chi square	p-value
Age in years**								
18 - 24	1	3	32	97	33	100	11.41	0.022*
25 - 34	3	2.7	109	97.3	112	100		
35 - 44	8	10.3	70	89.7	78	100		
45 - 54	7	14.6	41	85.4	48	100		
55 - 65	5	15.6	27	84.4	32	100		
Total	24	7.9	279	92.1	303	100		
Sex								
Male	16	10.1	142	89.9	158	100	2.203	0.201
Female	8	5.5	137	94.5	145	100		
Total	24	7.9	279	92.1	303	100		
Occupation**								
Professionals	0	0.00	22	100	22	100	13.15	0.011*
Technician	2	33.3	4	66.7	6	100		
Service and sales	2	6.5	29	93.5	31	100		
Skilled agricultural	5	20.8	19	79.2	24	100		
Unemployed	15	6.8	205	93.2	220	100		
Total	24	7.9	279	92.1	303	100		
Type of medication								
Typical	16	9.0	162	91.0	178	100	3.484	0.175
Atypical	5	12.2	36	87.8	41	100		
Combination	3	3.6	81	96.4	84	100		
Total	24	7.9	279	92.1	303	100		
Duration of treatment in years**								
< 1	1	3.1	31	96.9	32	100	1.180	0.758
1 - 5	11	8.5	119	91.5	130	100		
6 - 10	7	9.0	71	91.0	78	100		
> 10	5	7.9	58	92.1	63	100		
Total	24	7.9	279	92.1	303	100		
Type of illness**								
schizophrenia	20	9.6	189	90.4	209	100	3.554	0.169
schizoaffective	3	3.4	84	96.6	87	100		
delusional disorder	1	14.3	6	85.7	7	100		
Total	24	7.9	279	92.1	303	100		
Severity of illness**								
Normal (30 - 57)	9	6.1	138	93.9	147	100	4.756	0.313
Mildly ill (58 - 74)	8	7.6	97	92.4	105	100		
Moderately ill (75 - 94)	4	11.1	32	88.9	36	100		
Markedly ill (95 - 115)	3	21.4	11	78.6	14	100		
Severely ill (≥ 116)	0	0.0	1	100	1	100		
Total	24	7.9	279	92.1	303	100		
Medication adherence								
High	11	8.5	119	91.5	130	100	0.334	0.846
Medium	10	7.0	132	93.0	142	100		
Low	2	9.7	28	90.3	31	100		
Total	24	7.9	279	92.1	303	100		

NITD – neuroleptic-induced tardive dyskinesia; ** fishers exact test; *statistically significant

Table 4. Sociodemographic and clinical characteristic of patients with Parkinsonism (n = 117)

Variable	NIP Present (n)	%	NIP absent (n)	%	Total (n)	%	Chi square	p-value
Age in years								
18 - 24	16	48.5	32	51.5	33	100	2.479	0.648
25 - 34	39	34.8	109	65.2	112	100		
35 - 44	29	37.2	70	62.8	78	100		
45 - 54	19	39.6	41	60.4	48	100		
55 - 65	14	38.6	27	61.4	32	100		
Total	117	38.6	186	61.4	303			
Sex **								
Male	67	42.4	91	57.6	158	100	2.002	0.194
Female	50	34.5	95	65.5	145	100		
Total	117	38.6	186	61.4	303	100		
Occupation**								
Professionals	8	36.4	14	63.6	22	100	4.354	0.360
Technician	2	33.3	4	66.7	6	100		
Service and sales	12	38.7	19	61.3	31	100		
Skilled agricultural	14	58.3	10	41.7	24	100		
Unemployed	81	36.8	139	63.2	220	100		
Total	117	38.6	279	61.4	303	100		
Type of medication								
Typical	72	40.4	106	59.6	178	100		
Atypical	19	46.3	22	53.7	41	100	3.366	0.186
Combination	26	31.0	58	69.0	84	100		
Total	117	38.6	186	61.4	303	100		
Duration of treatment in years								
< 1	18	56.2	14	43.8	32	100	19.961	0.000*
1 - 5	58	44.6	72	55.4	130	100		
6 - 10	31	39.7	47	60.3	78	100		
> 10	10	15.9	53	84.1	63	100		
Total	117	38.6	186	61.4	303	100		
Type of illness**								
schizophrenia	90	43.1	119	56.9	209	100	6.289	0.043*
schizoaffective	26	29.9	61	70.1	87	100		
delusional disorder	1	14.3	6	85.7	7	100		
Total	117	38.6	186	61.4	303	100		
Severity of illness**								
Normal (30 - 57)	41	27.9	106	72.1	147	100	26.156	0.000*
Mildly ill (58 - 74)	42	40.0	63	60.0	105	100		
Moderately ill (75 - 94)	24	66.7	12	33.3	36	100		
Markedly ill (95 - 115)	10	74.1	4	28.6	14	100		
Severely ill (≥ 116)	0	0.0	1	100	1	100		
Total	117	38.6	186	61.4	303	100		
Medication adherence								
High	48	36.9	82	63.1	130	100	0.342	0.843
Medium	56	39.4	86	60.6	142	100		
Low	13	41.9	18	58.1	31	100		
Total	117	38.6	186	61.4	303	100		

NIP – neuroleptic-induced parkinsonism; ** fishers exact test; * statistically significant

Table 5. Sociodemographic and clinical characteristic of patients with Akathisia (n = 11)

Variable	NIA Present (n)	%	NIA absent (n)	%	Total (n)	%	Chi square	p-value
Age in years**								
18 - 24	1	3.0	32	97.0	33	100	2.703	0.609
25 - 34	2	1.8	110	98.2	112	100		
35 - 44	3	3.8	75	96.2	78	100		
45 - 54	3	6.2	45	93.8	48	100		
55 - 65	2	3.6	30	96.4	32	100		
Total	11	3.6	292	96.4	303	100		
Sex **								
Male	4	2.5	154	97.5	58	100	1.139	0.363
Female	7	4.8	138	95.2	145	100		
Total	11	3.6	292	96.4	303	100		
Occupation**								
Professionals	0	0.0	14	100	22	100	16.878	0.002*
Technician	2	33.3	4	66.7	6	100		
Service and sales	1	3.2	19	96.8	31	100		
Skilled agricultural	0	0.0	10	100	24	100		
Unemployed	8	3.6	139	96.4	220	100		
Total	11	3.6	292	96.4	303	100		
Type of medication								
Typical	5	2.8	173	97.2	178	100	1.804	0.406
Atypical	1	2.4	40	97.6	41	100		
Combination	5	6.0	79	94.0	84	100		
Total	11	3.6	292	96.4	303	100		
Duration of treatment in years								
< 1	0	0.0	32	100	32	100	2.818	0.421
1 - 5	6	4.6	124	95.4	130	100		
6 - 10	4	5.1	74	94.9	78	100		
.> 10	1	1.6	62	98.4	63	100		
Total	11	3.6	292	96.4	303	100		
Type of illness								
schizophrenia	7	3.3	202	96.7	209	100	0.544	0.762
schizoaffective	4	4.6	83	95.4	87	100		
delusional disorder	0	0.0	7	100	7	100		
Total	11	3.6	292	96.4	303	100		
Severity of illness**								
Normal (30 - 57)	2	1.4	145	98.6	147	100	20.396	0.000*
Mildly ill (58 - 74)	3	2.9	102	97.1	105	100		
Moderately ill (75 - 94)	6	16.7	30	83.3	36	100		
Markedly ill (95 - 115)	0	0.0	14	100	14	100		
Severely ill (≥ 116)	0	0.0	1	100	1	100		
Total	11	3.6	292	96.4	303	100		
Medication adherence**								
High	3	2.3	127	97.7	130	100	1.350	0.509
Medium	7	4.9	135	95.1	142	100		
Low	1	3.2	30	96.8	31	100		
Total	11	3.6	186	96.4	303	100		

NIA – neuroleptic-induced akathisia; ** fishers exact test; *statistically significant

The prevalence of tardive dyskinesia, parkinsonism and akathisia were 7.9 %, 38.6 and 3.6 %, respectively (Table 3, 4 and 5 respectively). The prevalence of extrapyramidal side effects due to use of typical, atypical and combination drug was 44.4 %, 51.2 % and 34.5 %, respectively (Figure 1).

Socio-demographic and clinical characteristics of patients with EPSE

Table 3 showed a statically significant relationship between tardive dyskinesia with age ($\chi^2 = 11.41$ ϱ = 0.022), and occupational status ($\chi^2 = 13.15$ ϱ = 0.011), for the socio-demographic variables with frequency of tardive dyskinesia increasing with increasing age and technicians having the highest frequency of tardive dyskinesia while none of the clinical variables were found to be significantly associated with tardive dyskinesia.

Table 4 showed that none of the socio-demographic variables were significantly associated with parkinsonism and the clinical variables associated with parkinsonism were; duration of treatment in years ($\chi^2 = 19.961$ ϱ = 0.000), type of illness ($\chi^2 = 6.289$, p = 0.043) and severity of illness ($\chi^2 = 26.156$, p = 0.000) with shorter duration of illness of less than one-year (56.2 %), diagnosis of schizophrenia (43.1 %) and markedly ill (74.1 %) patients having a higher frequency of parkinsonism. Occupational status (technician; $\chi^2 = 16.878$, p = 0.022) and severity of illness (moderately ill; $\chi^2 = 20.396$, p = 0.000) were the only socio-demographic and clinical correlates that were found to be significantly associated with akathisia at bivariate analysis (Table 5).

Logistic regression analysis showed that the independent predictors of EPSE were; increasing age for tardive dyskinesia (Ɓ = 1.773 ϱ= 0.002); duration of treatment (Ɓ = 0.609 ϱ = 0.001), type of illness (Ɓ = 0.531 ϱ = 0.015), and severity of illness (Ɓ = 1.759 ϱ = 0.000) for parkinsonism and severity of illness (Ɓ = 2.062 ϱ = 0.017) for akathisia (Table 6).

Table 6. Table showing logistic regression of predictors for EPSE (n = 303)

Variables	Exp (B)	p value
Tardive dyskinesia		
Age	1.773	0.002*
Occupation	1.100	0.603
Parkinsonism		
Duration of treatment	0.609	0.001*
Type of illness	0.531	0.015*
Severity of illness	1.759	0.000*
Akathisia		
Occupation	0.504	0.844
Severity of illness	2.062	0.017*

*statistically significant

Discussion

The aim of this study was to evaluate the pattern of extra-pyramidal side effects among outpatients with schizophrenia spectrum disorders and to examine its relationship with socio-demographic and clinical variables. The subjects were outpatients with a diagnosis of schizophrenia spectrum disorder who had been stabilized on antipsychotic medication for more than 2 months and who visited the hospital regularly.

The prevalence of any extrapyramidal side effects in this study was 42.6 % (n = 129). The prevalence of tardive dyskinesia, parkinsonism and akathisia were 7.9 %, 38.6 % and 3.6 % respectively. The findings of this study are consistent with those of Ojagbemi and associates, Ali and associates and Misdrahi and associates, [19,38-39]. The prevalence of EPSE reported is similar to a previous study in southwest and northwest Nigeria of 46 % [28]. The prevalence of tardive dyskinesia in this study was lower than that in southwestern Nigeria of 18 % [28]. The lower finding in this study may be due to the differences in the mean age of the study population (38 years vs. 45 years) and the mean duration of treatment in years. The prevalence of tardive dyskinesia at 7.9 % is also within the reported range of 3-62 % with a mean of 24 % [18-20]. The wide range

of prevalence figures reported for tardive dyskinesia may be attributed to differences in patient characteristics (i.e., presence of risk factors), and methodological discrepancies such as differences in case definition, criteria and sensitivity of the case finding procedure [24,37-40]. In South Africa a prevalence of 28 % was reported [41]. Parksepp and associates, reported a prevalence of 32.3 % in Europe; Kahn and associates, reported a prevalence of 11% in USA and Miller and associates, reported a similar rate of 8.3% to 11.8% in a secondary analysis of CATIE Schizophrenia Trial [40-43].

The prevalence of Parkinsonism in this study at 38.6 % is within the reported range of 11-43 % [21-22]. However, it is higher than that reported in southwestern Nigeria [28]. The differences might be due to differences in the number of participants on antipsychotic medication (303 vs 77) and mean duration of illness (5.8 vs 12 years). Studies have shown that the frequency of Parkinsonism reduces with increasing treatment duration [19]. The prevalence of akathisia at 3.6 % in this study is lower than what has been observed in previous literature of between 9-32 %, [13,14]. In southern Nigeria, a prevalence of 15 % was observed [28]. The complicatedness in assessing akathisia might have been intensified by the difficulty among schizophrenic patients in expressing their subjective experiences of a medication.

As with previous literature, this study found age (being elderly) to be significantly associated with tardive dyskinesia which has also been reported in southwestern Nigeria [28,44]. In this study tardive dyskinesia was seen in 15.6 % of participants within the age group 55 - 65 years compared to 3 % in those that were aged 18 - 25 years while Parkinsonism was commoner among the younger age group of 18-24 years accounting for 48.5 % compared to 38.6 % in the other age groups. Unlike in previous literatures, this study did not find any relationship between gender and tardive dyskinesia. In bivariate analysis, tardive dyskinesia and akathisia were found to be significantly associated with occupational status. Tardive dyskinesia and akathisia were overrepresented among technicians and skilled agricultural workers. However, the associations ceased to exist at the multivariate level. The study could not explain why technicians were more at risk, however a plausible explanation could be exposure to common occupational risk factor such as manganese among welders, electricians, and typists (manganese superoxide dismutase has been implicated in the pathophysiology of EPSE) [45].

In this study, clinical variables that tended to be associated with EPSE included duration of treatment, severity of illness and type of illness ($p < 0.05$). This study did not find any relationship between type of APM and EPSE. Contrary to the present result, Kahn RS, in an open randomized control trial of EUFEST (European first episode schizophrenia trial) reported that there was a significant difference in the prevalence of EPSE between typical and atypical antipsychotic medications [42]. He reported that low-dose haloperidol (1 – 4 mg/day) was associated with most EPS. The findings of this study are in keeping to a large trial (CATIE & CUtLASS) which have found virtually no significant differences in EPSE between these two classes of drugs [46,47]. These trials reported that the typical antipsychotics had a trend towards better outcome, lower in cost and a tendency towards better choice and they concluded that the differences could be accounted by the use of high potency antipsychotics (haloperidol) in a relatively large dose as a comparator to atypical antipsychotics. The mediating effect of anticholinergic medication may resolve some of the treatment emergent EPSE which may explain the reason for the failure to find excess rate of EPSE among patients on typical antipsychotic medication [48]. Peluso and associates, through a secondary analysis of CATIE schizophrenia trial and CUtLASS reported that there was no significant difference between treatment groups in terms of tardive dyskinesia, akathisia & parkinsonism and recommended that judicious prescription of adjunctive anticholin-

ergic agents to manage EPS when prescribing first generation antipsychotics can result in an EPS profile equivalent to second-generation drug treatment [48]. In this study about 42.9 % of the subjects had adjunctive anticholinergic medication and significantly more subjects receiving typical antipsychotic medication had anticholinergic medications added 65.7 % (117 of 178) compared to 2.4 % (1 of 41) subjects receiving atypical antipsychotics. The modest dose regimen together with the adjunctive use of anticholinergic may explain the relatively similar EPSE profile between typical and atypical antipsychotic medications. This study could not specify whether the anticholinergics were used prophylactically to prevent or to relieve EPSE. However, clinicians may more likely prescribe anticholinergics prophylactically as an adjunct to typical antipsychotics in anticipation of EPS. Many other studies have not found significant differences between atypicals and typicals in terms of greater risk for EPS, discontinuation rates (due to side effect) or symptom control [49-51].

A nonstatistical significant relationship of akathisia and tardive dyskinesia rate increasing as duration of treatment increases was observed. Conversely, the frequency of parkinsonism reduced with longer duration of treatment. It was seen in more than half of the population treated for less than one year compared to 1 in 6 of subjects treated for greater than 10 years with the differences being highly statistically significant both at the bivariate and multivariate level (X^2 = 19.961, p = 0.000; F = 15.425, p = 0.000) respectively. The findings are in line with previous literature [19,38-39]. A previous study in Nigeria demonstrated that tardive dyskinesia was associated with longer duration of treatment [28]. Miller and associates, reported that tardive dyskinesia was associated with increasing age, higher psychopathology, parkinsonism, akathisia and longer duration of treatment [43]. This study did not find any significant relationship between type of illness and tardive dyskinesia or akathisia but Parkinsonism was significantly ($\chi 2$ = 6.289, p = 0.043; F = 4.025, p = 0.046) overrepresented among patients with schizophrenia compared to schizoaffective disorder or delusional disorder. This finding may suggest that patients with schizophrenia are more prone to develop Parkinsonism but the present study cannot explain why.

Significant association was observed between PANSS score with Parkinsonism and akathisia. Parkinsonism was present among 71.4 % of the markedly ill group compared to 27.9 % of subjects with normal score (X^2 = 26.156, p - 0.000; F = 16.634, p = 0.000) while akathisia was present among 16.7 % of the moderately ill group compared to 1.4 % of subjects with normal score (X^2 = 20.395, p = 0.000; F = 5.943, p = 0.015). Although tardive dyskinesia was present in 21.4 % of the markedly ill group compared to 6.1 % of subjects with normal scores, the differences were found not to be statistically significant. The association of EPSE with severity of illness among patients with schizophrenia spectrum disorder may signify that the illness by itself may be a predisposing factor to the development of EPSE [19,20]. Ajagbemi and associates, reported an association of spontaneous parkinsonism in drug naive patients with schizophrenia and negative symptoms on PANSS and supported that the illness may be a contributory factor for EPSE [38]. This study did not find any significant relationship between tardive dyskinesia, parkinsonism, akathisia and level of medication adherence. This is in keeping with previous literature in Nigeria, and in the western countries [51-54].

Some of the limitations of this study were its cross-sectional nature and the fact that it was conducted in just one setting (Maiduguri), thereby limiting the generalization of its findings to patients with schizophrenia attending other outpatient clinic settings in Nigeria. The absence of control group and baseline data before treatment with antipsychotics is another limitation of this study. Therefore, there was no distinction between drug-induced or other causative factors. However, the strength of this study is that in addition to its large sample size, it assessed not only extrapyramidal side

effects but also examined other possible associated factors such as type of antipsychotic medication, medication adherence and severity of illness which were not included in previous studies done in Nigeria.

Keeping in mind the limitations of the study, it appears that atypical antipsychotic medications are not better than typical antipsychotic medications in terms of extra-pyramidal side effects, therefore, trying to use typical antipsychotics in monotherapy in lower doses and in conjunction with anticholinergic medication or atypical antipsychotics, whenever necessary, would be of great benefit to the patient in terms of extra-pyramidal side effects. Based on the cross-sectional and uncontrolled nature of this study, causal inference could not be definitely ascertained. Therefore, it is recommended that prospective case-controlled studies be carried out in this relevant topic with the aim of establishing inference.

Within the limitations of the study, the findings add to the evidence that many atypical antipsychotic medications are not better than their typical antipsychotic medication counterparts in terms of extra-pyramidal side effects. Clinicians should routinely discuss these side effects and its potential solutions with their patients prior to commencement of antipsychotic medication in order to optimize compliance and efficacy of the medications.

Acknowledgements

None.

Conflict of interest

None to declare.

Funding Sources

None.

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