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Original Article

Comparative Study of Extrapyramidal Side Effects, Sexual Dysfunctions and Hyperprolactinaemia Using Typical and Atypical Antipsychotic Medications Among Patients with Schizophrenia in Maiduguri.

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Abstract

Background: Extra-pyramidal side effects, sexual dysfunctions and hyperprolactinaemia are major side effects with the use of antipsychotic medications that impede treatment adherence leading to relapse, increased cost of care and rehospitalization among patients with schizophrenia on antipsychotic medications. The study aims to compare the prevalence of extra-pyramidal side effects (EPSE), sexual dysfunctions (SD) and hyperprolactinaemia (HPRL) among patients with schizophrenia spectrum disorders on typical and atypical antipsychotic medications. The secondary aim is to determine if any associations exist between extra-pyramidal side effects, sexual dysfunctions and hyperprolactinaemia.

Methodology: A cross-sectional hospital-based survey involving 209 patients with schizophrenia were interviewed with structured instruments for the assessment of sexual dysfunction, EPSE and the estimation of serum prolactin was done using Enzyme-linked Immunosorbent Assay. Frequencies and Chi-square analysis were used to compare differences in EPSE, SD & HPRL.

Result: The study revealed non-statistically significant differences as a group between typical and atypical antipsychotic medication in terms of extra-pyramidal side effects, sexual dysfunction and hyperprolactinaemia. However, a significant association was observed when individual drugs were compared with haloperidol causing the highest frequency of hyperprolactinaemia (χ^2 = 14.9, P = 0.011). A significant relationship between sexual dysfunction and hyperprolactinaemia, sexual dysfunction and extra-pyramidal side effects as well as extra-pyramidal and hyperprolactinaemia was found when individual items for sexual functionin were used.

Conclusion: The significant relationships between sexual dysfunction only in the domains of sexual desire and arousal with hyperprolactinaemia and extrapyramidal side effects as well as hyperprolactinaemia with extrapyramidal side effects point to a common anti-dopaminergic activity of antipsychotics via different pathways. Prospective studies among a larger sample of patients with schizophrenia are needed to unfold these relationships.

Keywords: Schizophrenia, Sexual Dysfunction, Extra-Pyramidal Side Effects, Hyperprolactinaemia, Typical Antipsychotics, Atypical Antipsychotics.

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Introduction

Schizophrenia is a spectrum of disorders with a lifetime prevalence of about 1% in the general population.[1] It is characterized by disturbance in perception, cognition, emotion and behavior, with onset usually in late adolescence or early adulthood and continues throughout life, thereby requiring long-term treatment. 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.[2] They are broadly classified into typical (first generation, traditional or conventional) and atypical (second generation or novel) antipsychotics.[3] Shortly after the introduction of chlorpromazine in the 1950s, it became evident that these agents are associated with disabling motor side effects.[4] Two of the most notable side effects of antipsychotic medications are extra-pyramidal and endocrine side effects. Both extra-pyramidal and endocrine side effects of antipsychotic drugs are mediated by dopamine D_2-receptor blockage via different pathways.[5] The same classes of antipsychotics that induce extra-pyramidal side effects also cause hyperprolactinaemia and sexual dysfunction. So, there appears to be a relationship between extra-pyramidal side effects, sexual dysfunction and hyperprolactinaemia but the mechanism is poorly explored.[6] Previous studies have found an association between typical antipsychotics (especially the high potency agents) and extra-pyramidal side effects, hyperprolactinaemia and sexual dysfunction while the atypical antipsychotics are associated with a reduced capacity for extrapyramidal side effects, hyperprolactinaemia and sexual dysfunction. However, non-industry funded large controlled trials [7-8] and meta-analyses [9-10] have shown no significant difference (with the exception of clozapine) between the two groups of antipsychotics in terms of their efficacy and side effects profile. The choice of high-potency typical antipsychotic medication at a higher dosage as a comparator to atypical antipsychotics may account for the excess rates of antipsychotic side effects in most industry-funded trials. Antipsychotic induced extra-pyramidal side effects and sexual dysfunction are major side effects that restrict the usefulness of these agents in the management of schizophrenia leading to poor drug compliance, relapse of psychotic symptoms and poor quality of life. [8-10]

Antipsychotic medication side effects have scarcely been researched in Nigeria. Data on the prevalence and impact of common adverse effects of antipsychotics like extra-pyramidal side effects and sexual dysfunction are either lacking or no longer current. The available ones are insufficient and cannot be generalized to the whole population. In a cross-sectional study done about two decades ago, [11] estimated the prevalence of extra-pyramidal side effects in the southwestern and northwestern parts of Nigeria using typical antipsychotic medications only. Another cross-sectional study by Oyekanmi et al,[12] in Nigeria on sexual dysfunction was conducted in the southwestern part of Nigeria and may not be generalized to the northern parts of the country. There are no studies on the correlation between sexual dysfunction and prolactin levels in Nigeria. This cross-sectional study, therefore, hopes to generate data on the pattern of extra-pyramidal side effects, sexual dysfunction and serum prolactin levels among patients with schizophrenic spectrum disorder on antipsychotic medications (typical and atypical).

Methodology

Study setting and study design

The study was conducted at the outpatient department of Federal Neuro-psychiatric Hospital Maiduguri. With a 90% response rate, 209 participants completed the cross-sectional survey. Patients with schizophrenia diagnosed using the International Classification of Disease Tenth Revision (ICD-10) criteria, within the age ranges of 18-65 years and who have been stable for at least 3 months, who have given informed consent were included in the study while participants with co-morbid substance use, neurologic or medical illness, pregnant or nursing mothers and endocrine disorders such as diabetes mellitus thyroid and pituitary gland disease were excluded from the study.

Study instruments

The participants were interviewed using the socio-demographic questionnaire designed by the authors to evaluate for socio-clinical variables such as age, gender, ethnicity, education, employment, and marital status as well as the type of antipsychotic medications used, dosage of the drug, duration of illness and duration of treatment. For the assessment of EPSE, the Abnormal Involuntary Movement Scale (AIMS), Simpson and Angus Scale (SAS), and Barnes Akathisia Rating Scale (BARS) was used to assess for tardive dyskinesia, Parkinsonism and akathisia respectively and the Arizona Sexual Experience Scale (ASEX) was used for the assessment of sexual dysfunction. Blood samples were collected from 8 a.m. before having their breakfast for the estimation of serum prolactin level by enzyme-linked immunosorbent assay technique.

The Abnormal Involuntary Movement Scale (AIMS)

The AIMS is a 12-item anchored scale. [13] Items 1–7 assess 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 patient's awareness of the movements and associated distress. Two items 11 and 12 are "yes" or "no" items concerning problems with teeth and/or dentures because such problems can lead to a false positive rating of dyskinesia. Each item is scored on a 5-point scale from 0 to 4, with instructions to rate the highest severity observed with higher scores indicative of more severe abnormal movements. Tardive dyskinesia was considered to be present at each time point according to the operational criteria suggested by Schooler and Kane, [14] when participants had one score of 3 or two scores of 2 on AIMS items 1–7 covering observed movements. The scale takes about 15 minutes to complete and it is by far the most widely used scale for rating Tardive dyskinesia. The interrater reliability has been demonstrated by Smith et al,[15] which ranged from 0.66 to 0.82 for individual body area items, test-retest reliability ranged from 0.12 to 0.75 and the correlation for overall severity was 0.75.[15]

Simpson and Angus Scale (SAS)

SAS contains ten items for assessing Parkinsonian and related extra-pyramidal side effects each rated on a 5-point scale from 0 to 4, with higher scores indicative of more severe symptoms.[16] Six of the items measure rigidity (arm dropping, shoulder shaking, elbow rigidity, leg pendulousness and neck rigidity). There is a single item of gait, which is the only measure for bradykinesia and the other 3 items measure glabella tap, tremor and salivation. The mean score is obtained by the average of the scores. A mean score of 0.3 was cited as the upper limit for patients without Neuroleptic Induced Parkinsonism (NIP) or related extra-pyramidal symptoms. Parkinsonism was considered to be present at each time point according to the operational criteria suggested by Schooler and Kane, [14] when participants had a total score of 3 or more on the SAS. The interrater correlation coefficient for two raters was 0.87, with a range between 0.71 and 0.96, except for the salivation item, where it was between 0.16 and 1.0 [16] SAS is the most widely used in clinical and research settings,[7-8, 17] for parkinsonian–like side effects.

Barnes Akathisia Rating Scale (BARS)

BARS is a four-item anchored scale,[18] The first three items assess objective and subjective characteristics of akathisia on a scale from 0 to 3. The fourth item termed the global item, is measured on a scale of 0 to 5, with higher scores indicative of more severe akathisia. 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.[18-19] 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, [14] when participants scored 2 or more on the global akathisia item of the BARS.

Arizona Sexual Experience Scale (ASEX)

The ASEX,[20] is a 5-item self-report inventory that evaluates the sexual functioning of patients taking psychotropic drugs. Each question represents 1 domain, i.e., drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm. Response is rated on a 6-point Likert scale (agree, disagree). The ASEX is interpreted on the basis of a total score and/or assessment of scores on individual items. A total score ≥ 19, a score ≥ 5 on any 1 item, or a score ≥ 4 on any 3 items are considered to be indicators of sexual dysfunction. Higher ASEX scores reflect greater severity of sexual dysfunction. The scale takes about 5 minutes to complete. It is the most widely used rating scale and it is applied to both sexually active and sexually inactive patients. The ASEX has excellent internal consistency test-retest reliability and favorable convergent and discriminant validity.[20-21]

Serum Prolactin Assessment

Morning venous blood samples were centrifuged in a glass tube, the plasma was stored in a plastic tube at -80^0C and prolactin was assayed using the Enzyme Immunoassay Test Kit [Microparticle enzyme immunoassay (MEIA)] for the quantitative determination of prolactin concentration in the serum. The Prolactin hormone (PRL) AccuBind^{TM} ELISA Test kit was used to quantitatively measure prolactin in the serum of patients with schizophrenia spectrum disorder. It is a rapid, sensitive and reliable assay for the measurement of prolactin. PRL AccuBind^{TM} ELISA test is based on the principle of a solid-phase enzyme-linked immunosorbent assay.[22] The test sample is allowed to react simultaneously with the antibodies, resulting in the prolactin molecules being sandwiched between the solid phase and enzyme-linked antibodies. The normal ranges of values are 1.2-19.5 and 1.8-18.5 in adult females and males respectively.

Statistical analysis

Statistical analysis of the data was carried out after it was entered into the Statistical Package for Social Sciences software (SPSS Version 18). Comparison of sociodemographic variables and the frequency of EPSE, SD & HPRL across the study groups were done using the Chi-square test, with Fischer's exact wherever the cell counts were <5. Spearman's rank correlation analysis was utilized in exploring the relationship of EPSE, sexual dysfunction and hyperprolactinaemia.

Result

Socio-demographic and clinical characteristics of the participants

The socio-demographic and clinical characteristics of the participants on typical and atypical antipsychotic medications were compared using a chi-square test as shown in Table 1 below. No significant difference was noted in comparison of the socio-demographic characteristics of patients with schizophrenia spectrum disorders on typical and atypical antipsychotic medication except for the educational status where patients on atypicals were almost three times more likely to obtain tertiary education (31.8% vs. 10.9%; χ^2 = 14.84, p= 0.005), marital status, with the divorced 2 times commoner among patients on typical antipsychotics (χ^2 = 9.466, p = 0.005). and the employment status where 73.9 % of patients on typical antipsychotics were employed compared to 56.8% of patients on atypical (χ^2 = 4.880, p= 0.027). For the clinical characteristics, statistically significant differences were observed with the use of adjunctive benzhexol where patients on typical antipsychotics were almost thirty times more likely to have benzhexol added to their medication (χ^2 = 53.39, p = 0.000) while 66.1% of patients on typical antipsychotics are on two drug regime compared with 22.7% of those on atypical antipsychotics (χ^2 = 27.61, p= 0.000).

Comparison of side effects (extrapyramidal side effects, sexual dysfunction and hyperprolactinaemia) among patients on typical and atypical antipsychotic medications

The frequency of antipsychotic medication side effects is shown in Table 2 which demonstrates that there are no statistically significant differences in the prevalence of EPSE, SD & HPRL among patients on typical and atypical antipsychotic medication even though sexual dysfunction and hyperprolactinaemia were more frequently observed among patients on typical antipsychotics while EPSE was more frequent among patients on atypical antipsychotics.

Table 1: Socio-clinical characteristics of patients with schizophrenia spectrum disorders on typical and atypical antipsychotic medications

Variable	Typical (n=165) Freq.	%	Atypical (n=44) Freq.	%	Total (n=209)		χ^2	P value
Age								
18-24yrs	17	10.3%	3	6.80%	20	9.60		
25-34yrs	52	31.5%	18	40.9%	70	33.5	1.876	0.759
35-44yrs	43	26.1%	10	22.7%	53	25.4		
45-54yrs	33	20.0%	7	15.9%	40	19.1		
55-65yrs	20	12.1%	6	13.6%	26	12.4		
Gender								
Male	92	55.8%	25	56.8%	117	56.0	0.016	0.900
Female	73	44.2%	19	43.2%	92	44.0		
Education								
None	59	35.8%	9	20.5%	68	32.5		
Primary	14	8.5%	3	6.8%	17	8.1	14.84	0.005*
Secondary	16	9.7%	7	15.9%	23	11.0		
Tertiary	18	10.9%	14	31.8%	32	15.3		
Quranic	58	35.2%	11	25.0%	69	33.0		
Occupation								
Employed	43	26.1%	19	43.2%	62	29.7	4.880	0.027*
Unemployed	122	73.9%	25	56.8%	147	70.3		
Marital status	59	35.8%	21	47.7%	80	38.3	9.466	0.005*
Single	76	46.1%	14	31.8%	90	43.1		
Married	23	13.9%	4	6.8%	26	12.4		
Divorced	4	2.4%	4	9.1%	8	3.8		
Widowed	3	1.8%	2	4.5%	5	2.4		
Separated								
Ethnicity								
Kanuri	89	53.9%	24	54.5%	113	54.1		
Hausa	35	21.2%	6	13.6%	41	19.6	3.644	0.456
Babur	10	6.1%	5	11.4%	15	7.2		
Shuwa	13	7.9%	2	4.5%	15	7.2		

Others	18	10.9%	7	15.9%	25	12.0		
Religion								
Islam	155	93.9%	40	90.9%	195	93.3	0.510	0.475
Christianity	10	6.1%	4	9.1%	14	6.7		
Duration of illness								
<1 year	18	10.9%	3	6.8%	21	10.0		
1-5 years	73	44.2%	20	45.5%	93	44.5	0.880	0.830
5-10 years	43	26.1%	11	25.0%	54	25.8		
>10 years	31	18.8%	10	22.7%	41	19.6		
No of Drugs								
One	52	31.5%	33	75.0%	85	40.7		
Two	109	66.1%	10	22.7%	119	28.7	27.61	0.000*
Three and more	4	2.4%	1	2.3%	5	2.4		
Benzhexol addition								
Yes	106	64 .2%	1	2.3%	107	51.2	53.39	0.000*
No	59	35.8%	43	97.7%	102	48.8		

Table 2: Antipsychotic medication side effects (EPSE, SD, HPRL) among patients on typical and atypical antipsychotic medications

Variable	**Typical (n= 165)**		**Atypical (n=44)**		χ^2	**p-value**
	n	**%**	**Freq.**	**%**		
EPSE						
NITD (+)	14	8.5%	6	13.6%	1.065	0.302
NIP (+)	67	40.6%	23	52.3%	1.928	0.165
NIA (+)	5	3.0%	2	4.5%	0.246	0.620
SD (+)	62	37.6%	12	27.3%	1.671	0.204
HPRL	77	46.6%	15	34.8%	5.012	0.053

NITD (Neuroleptic induced tardive dyskinesia), **NIP** (Neuroleptic induced parkinsonism), **NIA** (Neuroleptic induced akathisia), **SD** (Sexual dysfunction), **HPRL** (Hyperprolactinaemia).

Comparison of drug specific frequency of extra-pyramidal side effects, sexual dysfunction and hyperprolactinaemia

As shown in Table 3, there were no statistically significant differences in the rate of specific antipsychotic side effects except for hyperprolactinaemia (χ^2 = 14.9, P = 0.011) with haloperidol having the highest frequency of hyperprolactinaemia. Tardive dyskinesia was more frequently observed among patients on clozapine (37.5%), parkinsonism in the risperidone group (100%) and akathisia in the clozapine group (12.5%). The highest frequency of sexual dysfunction was seen among patients on haloperidol (47.6%), followed by risperidone (40.0%) and the lowest among the clozapine group

(12.5%). In general patients on typical antipsychotics had a higher rate for sexual dysfunction compared with those on atypical antipsychotics with the exception of risperidone. The highest frequency of hyperprolactinaemia was observed among patients on haloperidol (57.1%), and none among the clozapine group (0.00%) with the differences being statistically significant ($\chi^2 = 14.9$, $P = 0.011$).

Table 3: Drug specific frequency of EPSE, SD & HPRL

Variables	Haloperidol (n = 42) Freq. %	Trifluoperazine (n = 84) Freq. %	Chlorpromazine (n = 39) Freq. %	Olanzepine (n = 31) Freq. %	Risperidone (n = 5) Freq. %	Clozapine (n = 8) Freq. %	χ^2 p-value
EPSE							
NITD (+)	5	6	3 7.7%	3	0	3	8.74
	11.9%	7.1%	16	9.7%	0.0%	37.5%	0.120
NIP (+)	19	32	41.0%	13	5	5	8.86
NIA (+)	45.2%	38.1%	1	41.0%	100%	62.5%	0.115
	2	2	2.6%	1	0	1	2.82
	4.8%	2.4%		3.2%	0.0%	12.5%	0.728
SD (+)	20	32	10	9	2	1	7.06
	47.6%	38.1%	25.6%	29.0%	40.0%	12.5%	
							0.216
HPRL	24	45	16	9	2	0	14.9
	57.1%	53.6%	41.0%	29.0%	40.0%	0.00%	0.011*

NITD (Neuroleptic induced tardive dyskinesia), **NIP** (Neuroleptic induced parkinsonism), **NIA** (Neuroleptic induced akathisia), **SD** (Sexual dysfunction), **HPRL** (Hyperprolactinaemia).

Correlation between extrapyramidal side effects, sexual dysfunction and hyperprolactinaemia

The relationship between the three was explored using Spearman's correlation analysis as shown in table 4 and 5. Extra-pyramidal side effects (as a group) significantly positively correlated with hyperprolactinaemia but not with sexual dysfunction (total ASEX score). However, using individual item scores of ASEX, extra-pyramidal side effects significantly positively correlated with ASEX 1 (how strong is your sex drive; rs=0.130, p-value 0.023) and ASEX 2 (how are you sexually aroused; rs=0.116, p-value 0.044). Amongst the EPSE group, Parkinsonism was found to be significantly correlated to sexual desire disorder (rs=0134, p-value 0.019). A statistically significant correlation was also found between individual items of ASEX and hyperprolactinaemia on ASEX 1 (p=0.001), ASEX 2 (p=0.008) and ASEX 5 (p=0.045). (Tables 4 and 5).

Table 4: Correlation of EPSE group, sexual dysfunction and hyperprolactinaemia

	EPSE GROUP		HPRL		SD	
	rs	**P-value**	**rs**	**P-value**	**rs**	**P-value**
EPSE	-	-	0.140	0.015*	0.087	0.132
SD	0.087	0.132	0.067	0.243	-	-
HPRL	0.140	0.015*	-	-	0.067	0.243

*Correlation is significant at the 0.05 level (2-tailed). SD (Sexual dysfunction), HPRL (Hyperprolactinaemia), EPSE (extrapyramidal side effect)

Table 5: Correlation of individual items of ASEX with EPSE group, SD & HPRL

Spearman's rho	**EPSE group p-value**	**TD p-value**	**NIP p-value**	**NIA p-value**	**HPRL p-value**
Sexual drive	0.023*	0.247	0.019*	0.158	0.001*
Sexual arousal	0.044*	0.857	0.080	0.103	0.008*
Erection/lubrication	0.319	0.262	0.232	0.698	0.201
Reaching orgasm	0.283	0.372	0.094	0. 223	0.448
Satisfying orgasm	0.568	0.450	0.316	0.224	0.045*

*Correlation is significant at the 0.05 level (2-tailed). SD (Sexual dysfunction), HPRL (Hyperprolactinaemia), **TD (**Tardive dyskinesia), **NIP** (Neuroleptic induced parkinsonism), **NIA** (Neuroleptic induced akathisia).

Discussion

This study found no significant difference in the rates of extrapyramidal side effects, sexual dysfunction and hyperprolactinaemia among patients placed on typical and atypical antipsychotic medications. This finding has replicated the findings of previous studies.[7-9, 23] Sexual dysfunction was found to be slightly higher among patients on typical antipsychotic medications 37.6% compared with 27.3% of the atypical antipsychotics. Contrary to the findings of this study, Saad et al., [24] in Egypt reported that 61.25% of their respondent had sexual dysfunction, and the atypical antipsychotics caused more sexual dysfunction (70%) compared with typical antipsychotics (52.25%) with the differences being statistically significant. They also reported that sexual dysfunction was highest among the risperidone group, followed by olanzepine and least among the haloperidol group with the differences being statistically significant. Nunes et al.,[23] also reported that antipsychotic medications were associated with sexual dysfunction and the second-generation APM were more prone to induce sexual dysfunction. The differences in the rates of sexual dysfunction could be explained by the differences in the sample characteristics, study design, study instrument, drug dosage, and duration of treatment. In this study, almost half of the patients on typical APM were on concomitant anticholinergics and some of the typical APM used have intrinsic anticholinergic properties which are also associated with sexual dysfunction.

Previous studies, however, have reported that the prevalence of sexual dysfunction among patients treated with first-generation antipsychotics or with risperidone is higher compared to second-generation antipsychotics,[25-27] however, other studies have not confirmed these findings.[28-30] In line with our study Malik et al., [31] reported a non-statistically significant difference in the rate of sexual dysfunction among patients on typical and atypical antipsychotic medications in a large multicenter randomized European First Episode Schizophrenia Trial (EUFEST) study.

Our study also showed that the use of haloperidol and risperidone was associated with more sexual dysfunction (47.6%) and (40.0%) while clozapine was least likely to cause sexual dysfunction (12.5%). Nebhinani et al., [32] in India using ASEX reported that 20%, 43% and 16% of patients on trifluoperazine, risperidone and olanzepine respectively had sexual dysfunction. Another comparative study by Kumar and Sinha, [33] also reported that risperidone and haloperidol were more frequently associated with sexual dysfunction with sexual desire disorder as the most prevalent form of sexual dysfunction. Furthermore, Baggely's [34] review study revealed that the relative effect of antipsychotics on sexual dysfunction can be as follows: risperidone> typical> olanzapine> clozapine> quetiapine> aripiprazole.

With regards to EPSE, this study did not find a significant difference between typical and atypical antipsychotic medication. Those on atypical antipsychotics even had a higher rate of EPSE compared with the typical antipsychotics. This is contrary to some literature which finds typical APM to be associated with more EPSE compared to atypical APM. [35-37] Contrary to the present result, Kahn RS,[35] 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 APM. He reported that low-dose haloperidol (1–4 mg/day) was associated with most EPSE. The findings of this study are similar to two clinical trials (CATIE & CUtLASS)[7-8] conducted by non-industry-funded independent investigators which have found virtually no substantial differences in EPSE between these two classes of drugs. The Cost Utility of the Latest Antipsychotics in Schizophrenia Study 1 (CUtLASS-1) was a pragmatic randomized controlled trial (RCT) that tested the hypothesis that the clinical and cost-effectiveness of second-generation antipsychotics would be superior in individuals whose antipsychotic treatment was being changed owing to inadequate response or side-effects. They reported that the first-generation drugs were associated with a trend towards better outcomes and lower costs, and second-generation drugs were not superior, even on measures of patient preference. One possible explanation for the relative lack of distinction between drug classes seen in CUtLASS-1 is that the second-generation antipsychotics were not associated with the expected relief from Extrapyramidal symptoms. In the USA, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study demonstrated, similarly, that there was no significant difference between second-generation antipsychotics when compared with perphenazine in terms of the emergence of EPS. It has been suggested in the analysis of CATIE and CUtLASS that the differences between first- and second-generation drugs in early studies could have resulted from the use of haloperidol often in relatively high doses as the comparator. [38-39] Furthermore, the doses of several second-generation antipsychotics used in clinical practice are higher than those used in the studies sponsored by their manufacturers.

The mediating effect of anticholinergic medication may resolve some of the treatment emergent EPS which may explain the reason for the failure to find excess rate of EPSE among patients on typical antipsychotic medication.[40] Peluso et al., [40] 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 anticholinergic agents to manage EPSE when prescribing first-generation antipsychotics can result in an EPSE profile equivalent to second-generation drug treatment. In this study about 51.2% of the subjects had adjunctive anticholinergic medication and significantly more subjects receiving typical APM

had anticholinergic medications added 64.2% (106 of 165) compared to 2.3% (1 of 44) subjects receiving atypical APM. Even though this study could not explain whether the anticholinergics were used prophylactically to prevent or to relieve EPSE, clinicians prescribing a first-generation drug may have expected the development of EPSE and would have been more likely to prescribe an anticholinergic drug as an adjunct in anticipation of or in response to EPSE. The modest dose regimen together with the adjunctive use of anticholinergic may explain the relatively similar EPSE prolife between the typical and atypical APMs.

In line with the present study, Crossley et al.,[41] also reported that there were no significant differences between atypicals and typicals in discontinuation rates (due to side effects) or symptom control. Another study in agreement with this study is a large meta-analysis of randomized controlled trials involving 2320 patients, which found no greater risk of EPSE between first- and second-generation antipsychotics, other than clozapine.[36] Another randomized trial of a secondary analysis of CATIE Schizophrenia Trial showed that there was no difference in terms of EPSE between typical and atypical APM.[38] Similarly, a more recent naturalistic 4-year cohort study of 352 adult and elderly patients (age range: 18–78 years, mean: 42 years) with schizophrenia, schizoaffective disorder, and affective disorders suggested that there is no significant difference between Tardive dyskinesia rates in patients receiving SGAs (5.9%) or FGAs (5.6%).[42]

Though not statistically significant, Hyperprolactinaemia was found to be more prevalent among patients placed on typical antipsychotic medications (46.6%) compared to 34.8% among patients on atypical antipsychotics in this study. This finding has similarly been reported in literatures, [43-44] and supports the findings that typical APM is associated with more DA-2 antagonism than atypical APM. Veronika,[45] reported in her study that hyperprolactinaemia is directly related to the DA-2 antagonist potency of antipsychotics, and not to the classification of antipsychotics as 'typical 'versus 'atypical'. In this study haloperidol caused most of the hyperprolactinaemia (57.1%), followed by trifluoperazine (53.6%), seen in 40% in the risperidone group and 29% in the olanzepine group (9.1%) (χ^2 14.9, p 0.011). Montgomery et al.,[46] reported that except for risperidone, the typical antipsychotic medications were more associated with hyperprolactinaemia. Also, Kinon et al.,[47] reported that among women and men, risperidone was associated with more hyperprolactinaemia (88%) compared to 47.6% for those on conventional antipsychotics and they concluded that patients treated with conventional antipsychotics or risperidone had more hyperprolactinaemia compared with other antipsychotic medications.

As both extrapyramidal side effects and prolactin elevation are related to the amount of D2 occupancy,[38, 41] the study tried to explore whether extrapyramidal side effects were associated with higher levels of prolactin. The association of prolactin level and EPSE was tested using Spearman's rank correlation test. The prolactin values showed a positive correlation with EPSE as a group (TD, NIA, NIP); (rs=0.140 p-0.015) and an examination of the possible association between prolactin level and the individual types of EPSE revealed that only Parkinsonism was associated with hyperprolactinaemia (rs=0.145, p-0.011). In line with this study, Esel et al.,[48] demonstrated a significant positive correlation between prolactin values and the severity of EPSE. On the other hand, Volavka et al., [49] and Kondo et al., [50] found no relationship between prolactin level and EPSE. As it has been hypothesized that a drug's receptor profile is largely responsible for its specific side effect profile, both hyperprolactinaemia and EPSE have been hypothesized to be associated with increased D2 antagonism which may partly explain their synergistic relationship.[5] Furthermore, the common practice of prescribing more than one psychotropic medication with its complexity of most antipsychotic medications exerting their effects not only on the dopaminergic receptors but also the muscarinic, serotonergic, adrenergic and histaminergic receptors may be responsible for these relationships. Therefore, an improved understanding of these relationships could help clinicians for a better understanding of the mechanisms of antipsychotic side effects.

The study also explored the possible association of sexual dysfunction and hyperprolactinaemia and found no significant correlation between the two using the ASEX total score (rs=0.067, P-value 0.243), however, a significant correlation was found on the domains of sexual desire (p =0.001), sexual arousal (p= 0.008) and satisfactory orgasm (p= 0.045) on the individual item score of ASEX with hyperprolactinaemia. The reason why our study did not find an association of hyperprolactinaemia with total ASEX score but only with sexual desire, arousal and satisfactory orgasm, may partly be explained by the affectation of the reward system from sustained dopamine blockage thereby reducing the motivation to engage in sexual activity and the ability to experience pleasure, while loss of sexual gratification after a sexual act could result from high prolactin level. Therefore, our finding of the relationship of hyperprolactinaemia with not all components of the ASEX as well as the total ASEX score suggest that sexual dysfunction is not only a direct consequence of hyperprolactinaemia from dopamine antagonism but other factors including serotonergic, adrenergic and anticholinergic mechanisms, and extra-pyramidal side effects also play a role. [28-30, 51-52]

Knegtring et al., [25] compared prolactin rising and prolactin sparing antipsychotics for sexual dysfunction with an objective to study if the sexual side effects of prolactin rising antipsychotics were reducible to serum prolactin and concluded that 40% of emerging sexual side effects in schizophrenia were attributable to the prolactin rising properties of antipsychotics indicating that other factors contribute to the emergence of sexual dysfunction. Conversely, sexual dysfunction is also found in patients with normal serum prolactin values.[53-54] and the fact that clozapine, having no sustained influence on prolactin levels is associated with sexual problems indirectly supports the proposition that prolactin levels are not the only or major reason behind antipsychotic-induced sexual problems.[55] Moreover, many patients with elevated prolactin levels (even with PRL levels > 100 ng/ml) may be without the symptoms of HPRL.[56-57] Furthermore, The Cost Utility of the Latest Antipsychotics in Schizophrenia Study data suggest that sexual side effects are likely secondary to multifactorial causes rather than simply PRL levels alone.[58] Other factors including the disease itself, psychosocial and genetic factors, comorbid diseases, the use of co-medication with known effects on sexual performance, as well as other pharmacological actions of AP drugs, are equally important.[59-60] Extra-pyramidal symptoms may reduce mobility and sexual functioning.[61-62]

A potential association between sexual functioning and EPSE was also explored. The study found that EPSE as a group (TD, NIP, NIA) did not significantly correlate with the ASEX total score, however, it correlated significantly with items 1 (sexual desire) and 2 (sexual arousal) of the individual ASEX score. Among the EPSE group, only Parkinsonism was positively correlated with sexual dysfunction in the domains of sexual desire. Therefore, the association of EPSE only on the domains of sexual desire and arousal in this study may suggest that the reduced dopamine activity from the use of antipsychotic medication results in decreased libido and the immobility from EPSE may be responsible for sexual dysfunction seen among these patients. In line with these findings Liu Serfert et al.,[6] found an association of impairment of sexual function with involuntary movement of the lower body, impaired balance, excessive salivation, akinesia, and akathisia in males and impairment of sexual function with involuntary movement of facial expression muscles and impaired balance in female patients.

The study has some limitations. The cross-sectional design prevents causal inferences from being made. The relationship between drug dosage and antipsychotic side effects was also not explored. The strengths of the study are numerous; large sample size, use of standardized study instruments, comparison of six different types of antipsychotic medications with extra-pyramidal side effects, sexual dysfunction and hyperprolactinaemia.

Conclusion

This study found no significant difference between typical and atypical antipsychotic medications in terms of extrapyramidal side effects, sexual dysfunction and hyperprolactinaemia. The study demonstrated a positive correlation between sexual dysfunction and hyperprolactinaemia, extrapyramidal side effect and hyperprolactinaemia, and sexual dysfunction and extrapyramidal side effect. Based on the findings of this study, we recommend that before the commencement of any antipsychotic medication assessment of serum prolactin level, sexual dysfunction and extrapyramidal side effects done and be routinely repeated in order to manage such side effects and place patients accordingly on medications with the least potentiality of inducing hyperprolactinaemia, sexual dysfunction or extra-pyramidal side effect.

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