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# Magnitude, Nature, and Risk Factors of Adverse Drug Reactions Associated with First Generation Antipsychotics in Outpatients with Schizophrenia: A Cross-Sectional Study

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**Background:** ADRs to antipsychotics are amongst the major challenges in the treatment of patients with psychotic disorders. The extent of patient-reported ADRs assessed in many studies using standardized scales is found to be inconsistent. However, there is a paucity of such research in Eritrea. The aim of the study is therefore to determine the magnitude, nature, and the possible risk factors associated with ADRs of the first generation antipsychotics in outpatients with schizophrenia at Saint Mary Neuro-Psychiatric National Referral Hospital in Asmara, Eritrea, using the LUNSERS self-rating scale.

**Methods:** A cross-sectional, descriptive and analytical study design utilizing a quantitative approach was employed. Data were collected from patients' self-administered questionnaires, interviews, and medical records. The collected variables were analyzed using SPSS 22.0 with descriptive statistics, correlation, t-tests, ANOVA, and multiple regression. Statistical significance was tested at  $P$ -value<0.05.

**Results:** In this study, 93.8% of the research participants experienced at least one ADR. LUNSERS total mean score of the relevant items was 28.01 (SD=18.46) with 24.7% of the study participants scoring medium-to-high. The prevalence of the categories of ADRs was psychic (91.3%), autonomic (78.1%), extra-pyramidal (76.9%), miscellaneous (66.5%), hormonal (58.3%), anti-cholinergic (44.2%), and allergic reactions (44.2%). At multivariate level, factors significantly and positively associated with total ADR score were smoking ( $P=0.028$ ) and being at secondary educational level ( $P=0.015$ ).

**Conclusion:** There was high prevalence of ADRs with moderate-to-high overall ADR scores in a significant number of patients. The most frequently reported ADRs were psychic, autonomic, extra-pyramidal, hormonal, and miscellaneous. Smoking and secondary level of education were found to be the main determinants of ADRs.

**Keywords:** schizophrenia, first generation antipsychotics, adverse drug reactions, LUNSERS, risk factors

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## Lay Summary

Adverse effects of antipsychotics are amongst the major challenges in the treatment of patients with psychotic disorders. This study determined the magnitude, nature, and the possible risk factors associated with adverse effects of antipsychotics in outpatients with schizophrenia at Saint Mary Neuro-Psychiatric National Referral Hospital in Asmara, Eritrea using a standardized self-rating scale. In this study

almost all of the study participants experienced at least one adverse effect. One in four of the study participants scored medium-to-high adverse drug reaction scores, indicating a high severity. The occurrence of the adverse effects by category was higher for psychic, autonomic, extra-pyramidal, hormonal, and miscellaneous than for anti-cholinergic and allergic reactions. Smoking and having a secondary level of education were identified as associated factors for the higher adverse drug reaction score. In conclusion, the burden of severe adverse effects of antipsychotics among schizophrenic patients in St. Mary neuro-psychiatric national referral hospital was high. Close monitoring of patients is highly required as it can compromise their quality-of-life and treatment adherence.

## Introduction

Antipsychotics are the main class of drugs in the treatment of schizophrenia and other psychotic illnesses<sup>1–3</sup> and their use has resulted in decreased mortality<sup>4,5</sup> and improved patient's quality-of-life.<sup>6,7</sup> However, adverse drug reactions (ADRs) of these products are the major challenges in treating patients with psychotic disorders.<sup>8–11</sup>

Extrapyramidal symptoms, sedation, sexual-dysfunction, anticholinergic effects, weight gain, memory and concentration problems, cardiovascular, gastrointestinal, and metabolic adverse effects are the commonly reported ADRs of antipsychotics.<sup>1,12–17</sup> ADRs can occur at first dose, during prolonged administration of a drug and/or single or combination therapy of two or more drugs.<sup>15</sup> The extent and range of ADRs due to antipsychotics may depend on an individual's susceptibility differences, environmental factors, genetic variation,<sup>18–20</sup> and range of drugs used.<sup>16</sup>

Despite the introduction of second generation antipsychotics (SGAs) decades ago FGAs are still commonly used as first-line pharmacologic therapy in psychotic illnesses in low- and middle-income countries.<sup>1,21</sup> Similarly, in Eritrea only chlorpromazine, haloperidol thioridazine, and fluphenazine decanoate are included in the National List of Medicines (6th edition, 2015).

The limited choice of antipsychotics available in Eritrea adds more challenges to the treatment of patients with psychotic disorders beside the shortage of Psychiatrists and Physicians and inadequacy of laboratory setups in the National Referral Hospital. Assessing and monitoring of ADRs is therefore required in developing appropriate interventional strategies to manage, prevent, and minimize the risks of undesirable effects and thereby improve quality-of-life and adherence, avoid relapse, and

reduce treatment costs.<sup>22,23</sup> However, there is a paucity of research regarding the magnitude and nature of ADRs of antipsychotics in Eritrea. The aim of this study is therefore to determine the magnitude and nature of FGAs-related problems and identify possible risk factors in outpatients at Saint Mary Neuro-Psychiatric National Referral Hospital (SMNPNRH) in Asmara, Eritrea using the LUNSERS self-rating scale.

## Materials and Methods

### Study Design and Setting

A cross-sectional descriptive and analytical study design with a quantitative approach was used. It was conducted in outpatient departments of SMNPNRH, which is the only Neuro-Psychiatric Referral Hospital in Eritrea located in the capital Asmara.

### Source and Study Population

SMNPNRH serves clients referred from all over the country; thus, the source population is diverse. Patients aged 18 years and above who were on treatment of schizophrenia between August 28 and October 12, 2018 were included in the study. Those who had an established diagnosis of schizophrenia, with no major co-morbidities, having records of antipsychotic medications for at least 1 month prior to the commencement of the study, clinically stable and willing to participate in the study were included in the study. Those who had major co-morbidities, women who were pregnant or breast feeding, those who were clinically unstable, and patients taking other medications except those taken for management of ADRs were excluded from the study.

### Data Collection Tools

Liverpool University Neuroleptic Side-Effect Rating Scale (LUNSERS)<sup>24</sup> and patients' background characteristics data collection tool were used to collect the data. LUNSERS is a 41-item self-rating scale, which requires respondents to indicate how much they experienced each of the adverse effects listed in the last 1 month. In addition, ten "red herring" items, symptoms that do not directly relate to known antipsychotic ADRs, were also included to countercheck the accuracy of the self-reported ADRs by patients. The 41 ADRs are also grouped into seven pre-specified categories of ADRs; namely extra-pyramidal, anti-cholinergic, other autonomic, allergic, psychic, hormonal, and miscellaneous reactions.

## Psychometric Property of the Tools

LUNSERS<sup>24</sup> is found to be a validated and reliable tool in previous studies. In the current study Cronbach's alpha of the overall LUNSERS was found to be 0.887, indicating good reliability (internal consistency). Besides, even though the Cronbach's alpha coefficient of the sub-scales of LUNSERS in the original study was not reported, the Cronbach's alpha coefficient of the present study for the seven sub-scales was computed and ranged from 0.294 to 0.781. It is rare to obtain a Cronbach's alpha coefficient greater than 0.6 for scales/sub-scales having items less than 10. However, three subscales (psychic=0.781, Extrapyramidal=0.723, and allergic=0.646) were found to have a Cronbach's alpha coefficient greater than 0.6; evidencing satisfactory reliability. Practically, for scales with less items (items less than 10); Cronbach's alpha might not be decent and hence the mean inter-item correlation above 0.2 is accepted.<sup>25</sup> Mean inter-item correlation was computed and found to be acceptable (autonomic=0.598, miscellaneous=0.553, anticholinergic=0.683, hormonal=0.380), as suggested by Briggs and Cheek.<sup>25</sup> Moreover, pre-test was made on 30 participants to evaluate the data collection tool, feasibility, and to familiarize data collectors with the tools. Accordingly, necessary amendments were made on the questionnaire and data collection approach.

## Exposure and Outcome Definition and Measurement

In this study, patients were taking one or more FGAs, namely chlorpromazine tablet, fluphenazine decanoate intramuscular injection, and haloperidol tablet. Dose of antipsychotics was determined by the clinicians based on the patients' medical conditions. Antipsychotic dose was converted to chlorpromazine equivalents (mg/day) to allow for dose comparison across the different antipsychotics based on conversion factors obtained from the literature.<sup>26</sup> The conversion factors used were 13 mg/month fluphenazine decanoate depot and 2 mg/day haloperidol oral, each of them equivalent to 100 mg chlorpromazine oral. For patients taking more than one antipsychotic, the chlorpromazine-equivalent dose for each antipsychotic was added up to give a total dose. The primary outcome of this study was self-reported adverse drug reactions following use of antipsychotics.

## Patient Recruitment and Data Collection Approach

First, the targeted patients were identified with the help of clinicians in the outpatient departments of SMNPNRH

based on the checklist for inclusion criteria. For this purpose, the clinicians used the most recent medical diagnosis and other information detailed in the case notes. Each eligible patient was then transferred to the data collectors and after written informed consent was obtained, data collection was carried out in separate rooms. To ensure completeness of the questionnaires and appropriateness of data collection, the whole process was strictly followed by a supervisor. Data on ADRs were collected from patients using a self-administered questionnaire. Further, an interview and medical cards review was carried out to collect the socio-demographic and clinical data.

## Statistical Analysis

Data was entered into a computer using an entry program developed with CSPro version 7.0 software package. Verification, by double entering, was done to eliminate errors during data entry. The data was then exported to Statistical Package for Social Science version 22 (SPSS-22) for analysis. Mean inter-item correlation and Cronbach's alpha statistics were computed to determine the internal consistency of the LUNSERS scale with its sub-scales. Descriptive analyses of the demographic, clinical, and LUNSERS items were performed using frequency (percent) for categorical variables as well as mean (SD) and median (IQR) for continuous variables.

The prevalence of overall ADRs, subscales of ADRs, and of particular ADRs was determined by computing percentages of patients who scored one or more on the relevant LUNSERS items or subscales. Moreover, the mean of the total ADR score, LUNSERS sub-scale score, and individual ADRs of each client was also calculated by summing the values on all of the items. Normality of the LUNSERS score was assessed using Kolmogorov-Smirnov test before computing Pearson's correlation coefficient, running *t*-test, and analysis of variance (ANOVA). Correlation analysis of LUNSERS score and quantitative demographic and clinical variables was performed using Pearson's correlation coefficient. Furthermore, to compare the level of ADRs across various categories of demographic and clinical variables, *t*-test (with two categories), and ANOVA along with LSD post hoc (with more than two categories) were used.

In order to examine the effect of an explanatory variable on the LUNSERS score after adjusting other important explanatory variables (found to be significant at bivariate analysis using correlation, *t*-test, and ANOVA), hierarchical multiple regression was used. Before

modelling the regression, the basic assumptions (multicollinearity, linearity, and existence of relationship between the outcome and explanatory variables) were examined. After having the model, the assumptions of normality of residuals, homoscedasticity, and existence of multivariate outliers were examined. The maximum variance inflation factor (VIF) and tolerance values were 2.25 and 0.44 testifying to no multicollinearity. On the other hand, the existence of a relationship between the LUNSERS score and the explanatory variables was realized using the correlation coefficients, *t*-test, and ANOVA tests performed at bivariate analysis, while linearity was observed using scatter plots. After fitting the hierarchical multiple regression using a two-step approach, the residuals were normally distributed. Explanatory variables that were highly correlated ( $P < 0.01$ ) were considered at the first step, leaving the others to the second step. Moreover, the largest Cook's distance and Leverage values were 0.037 and 0.103, respectively, showing that there were no influential outliers in the model.

## Ethics Approval and Consent to Participate

Ethical clearance was obtained from the research ethics and protocol review committee of the Ministry of Health and Asmara College of Health Sciences. Written informed consent was obtained from the respondents. Besides, this study was conducted in accordance with the Declaration of Helsinki and all ethical and professional considerations were followed throughout the study to keep patient data strictly confidential.

## Operational Definitions

### Adverse Drug Reaction

A reaction which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function<sup>27</sup> and can be experienced and identified by patients independent of laboratory or clinical testing. This was determined by a score of one or more on the appropriate LUNSERS items.

### Counseling on ADRs

This is the status of whether patient counseling about ADRs is given by health professionals. Those patients who reported that they had been advised about adverse effects of their medication were considered as counselled.

## Insight into Illness

The information about insight into illness was collected from patients' clinical or medical records by the data collectors. In patients who believe that they have a mental illness, the unusual mental events (delusions and hallucinations) are pathological and they are in need for treatment, considered as having good insight. Those patients who do not recognize any one or more of the three factors stated above are considered as having impaired insight, which is once more categorized into partial insight (do not recognize one factor) and poor insight (do not recognize two or all factors).

## LUNSERS

Scale used for subjective reporting of antipsychotic ADRs.

## Red Herrings

Symptoms that do not directly relate to known antipsychotic ADRs which are included in the LUNSERS to determine the accuracy of the patient self-report.

## Schizophrenia

It is a mental illness characterized by a heterogeneous combination of symptoms which includes delusions, hallucinations, and cognitive deficits, which frequently follow a chronic illness and is associated with decline in social and occupational functioning.<sup>28</sup> The diagnosis is taken from the most recent detailed case notes.

## Total ADR Score

It is the degree of intensity of ADRs reported by patients using LUNSERS. The possible total score ranged from 0–164, with higher scores reflecting a greater number and perceived severity of ADRs.

## Results

A total of 251 eligible patients were asked to participate in the study. However, nine participants declined to provide consent. Thus, a total of 242 patients were enrolled in the study, making a response rate of 96.4%. Demographic and clinical characteristics of the study participants are summarized in [Table 1](#).

The schizophrenic patients were taking at least one FGA, with a mean duration of illness of 157.90 months (SD=112.44). The most commonly prescribed antipsychotic was Chlorpromazine oral tablet. In a few patients ( $n=14$ , 5.7%), concomitant drugs were used to treat ADRs. Concurrent use of two or more FGAs was common among the study participants (49.17%). The mean dose of



**Table 1** Demographic Characteristics of the Study Participants (n=242)

Characteristics		Frequency	Percent
Gender			
	Male	138	57
	Female	104	43
Religion			
	Christian	205	84.7
	Moslem	37	15.3
Education			
	Primary/no formal education	38	15.7
	Middle	54	22.3
	Secondary	113	46.7
	Higher	37	15.3
Employment			
	Employed	73	30.2
	Unemployed	169	69.8
Marital status			
	Single	110	45.5
	Married	98	40.5
	Divorced	20	8.3
	Separated	7	2.9
	Widowed	7	2.9
Residence			
	Asmara	162	66.9
	Outside Asmara	80	33.1
Smoking			
	Yes	48	19.8
	No	194	80.2
Alcohol			
	Yes	25	10.3
	No	217	89.7
Characteristics	Min, Max	Mean, SD	Median, IQR
Age (years)	18, 70	39.73, 11.22	39.00, 16.00
Weight (kg)	35, 100	61.47, 11.56	60.00, 17.00

**Abbreviations:** SD, standard deviation; IQR, inter quartile range; Min, minimum; Max, maximum; n, number of participants.

the antipsychotics in chlorpromazine equivalent was 244.64 (SD=147.61, range=48.08–792.31). As reported by clinicians in the outpatient department (OPD) and retrieved from medical records, the majority of the study

participants (53.3%) had good insight to their illness. About half (50.4%) of the study participants stated that they were counselled about the ADRs by the prescribers only and simply when ADRs occurred (Table 2).

## Magnitude and Nature of ADRs

In this study 93.8% of the study participants experienced at least one ADR. Excluding the red herrings, LUNSERS total mean score was 28.01 (SD=18.46) with a total ADR of 3309 and a mean of 13.6 (range=0–36) per patient. When the LUNSERS score is categorized, the majority of the study participants (75.6%) scored lower ADRs

**Table 2** Clinical Variables of the Study Participants (n=242)

Characteristics		Frequency	Percent
Antipsychotic medications <sup>a</sup>			
	Chlorpromazine oral tablet	167	69
	Haloperidol oral tablet	37	15.3
	Fluphenazine decanoate depot	164	67
Other medications used		14	5.7
	Promethazine	10	4.1
	Trihexyphenidyl	2	0.8
	Diazepam	2	0.8
Number of antipsychotics			
	Single	123	50.83
	Multiple	119	49.17
Counseling on ADRs			
	Yes	122	50.4
	No	120	49.6
Insight			
	Poor insight	53	21.9
	Partial insight	60	24.8
	Good insight	129	53.3
Characteristics	Min, Max	Mean, SD	Median, IQR
Duration of illness (months)	3, 651	157.90, 112.44	147, 75
Antipsychotic dose (mg/day, chlorpromazine equivalents)	48.08, 792.31	244.64, 147.61	196.15, 200

**Note:** <sup>a</sup>Participants can select more than one response.

**Abbreviations:** IQR, inter quartile range; SD, standard deviation; Min, minimum; Max, maximum; n, number of participant.

followed by medium (22.7%) and high scores (1.7%) (Table 3).

According to LUNSERS subscales (categories of ADRs), the prevalence of ADRs of antipsychotics were found to be 91.3% for psychic, 78.1% for autonomic, 76.9% for extra-pyramidal, 66.5% for miscellaneous, 58.3% for hormonal, 44.2% for anti-cholinergic, and 44.2% for allergic reactions (Table 4). Moreover, about two-fifths of the patients reported red herrings (44.2%), but most of them (86.4%) reported only one or two red herring items, with a score ranging from 1–18. The most frequently reported individual ADRs were tiredness (62.8%), tension (59.9%), depression (59.1%), restlessness (57.9%), difficulty getting to sleep (56.6%), difficulty staying awake during the day (55.8%), sleeping too much (55%), and feeling sick (53.3%) (Table 4). The detailed ADRs reported during the study are displayed in Table 4.

## Association of Socio-Demographic and Clinical Variables with ADRs

In order to assess the difference in the average score of ADRs among various categories of the demographic and clinical variables, bivariate analysis using independent sample *t*-test (variables with only two categories) and ANOVA (variables with more than two categories) were run. Independent sample *t*-test of the socio-demographic and clinical variables showed that males ( $M=31.04$ ,  $SD=18.72$ ) as compared to females ( $M=24$   $SD=17.39$ ) were found to have a higher LUNSERS score ( $P=0.003$ ). Patients who are smokers also ( $M=35.92$   $SD=18.57$ ) reported a higher LUNSERS score ( $P=0.001$ ) than the non-smokers ( $M=26.06$ ,  $SD=17.99$ ). Moreover, patients taking more than one antipsychotic ( $M=30.81$ ,  $SD=17.17$ ) as compared with those with a single antipsychotic ( $M=25.30$   $SD=19.31$ ) reported higher LUNSERS score ( $P=0.020$ ). The three other variables tested, namely alcohol consumption, ADRS-counseling, and employment,

however, did not show statistically significant differences in LUNSERS scores (Table 5).

A significant increase in LUNSERS score with educational attainment ( $P=0.004$ ) was observed on ANOVA, however, no significant difference was observed among the categories of insight ( $P=0.693$ ) (Table 6). The least significant difference (LSD) approach of post hoc analysis has revealed that those in secondary ( $MD=9.69$ ,  $P=0.005$ ) and higher ( $MD=9.25$ ,  $P=0.029$ ) levels of education had higher LUNSERS scores than those in Primary/no formal education (Table 7).

On the other hand, the link between LUNSERS scores and age, weight, dose, as well as duration of illness was assessed using Pearson's correlation. Shorter duration of illness ( $r=-0.140$ ,  $n=242$ ,  $P=0.030$ ) and higher antipsychotic dose ( $r=0.174$ ,  $n=242$ ,  $P=0.007$ ) correlated with statistically significant increase in LUNSERS score. However, age ( $P=0.382$ ) and weight ( $P=0.423$ ) were not significantly associated with an increase in LUNSERS score (Table 8).

Finally, multivariate analysis using hierarchical multiple regression after adjusting the variables that were significant at bivariate level was used. The hierarchical multiple regression (Table 9) indicated that educational level and smoking were significant predictors of LUNSERS score. The result revealed that smokers had a higher LUNSERS score (on the average by 7) than non-smokers. Similarly, the LUNSERS score among secondary level was more (on the average by 8.36) than those at primary/no formal education. All the remaining explanatory variables were not significant determinants of LUNSERS score, at multiple regression model. The fact that the standard errors did not change much at both steps reflect the stability of the model (Table 9). Moreover, examination of the adjusted *R*-square value showed that the addition of the two variables at step 2 did not improve the fit of the model.

## Discussion

### Magnitude and Nature of ADRs

This study found that the prevalence of first generation antipsychotics induced ADRs was comparable to the results of similar studies, which used LUNSERS to measure ADRs, from Australia<sup>29</sup> and Singapore<sup>8</sup> and is higher than the findings reported in another study from Australia.<sup>30</sup> These studies showed a relatively higher prevalence of ADRs in those with no or low usage of SGAs when compared to those with high

**Table 3** Categories of Total ADR Score in the Sample Population

Total ADR Score Category	Percent
Very high (101–164)	0
High (81–100)	1.65
Medium (41–80)	22.73
Low (0–40)	75.62

**Table 4** Prevalence, Total ADR Score and Nature of ADRs

Variables	Prevalence	Total ADR Score		
	n (%)	M (SD)	Actual Range	Expected Range
ADRs of antipsychotics	227 (93.8)	28.01 (18.46)	0–92	0–164
Psychic ADRs	221 (91.3)	11.00 (7.30)	0–33	0–40
Tiredness	152 (62.8)	1.36 (1.28)	0–4	0–4
Tension	145 (59.9)	1.2 (1.26)	0–4	0–4
Depression	143 (59.1)	1.13 (1.19)	0–4	0–4
Difficulty getting to sleep	137 (56.6)	1.2 (1.26)	0–4	0–4
Difficulty staying awake during the day	135 (55.8)	1.26 (1.37)	0–4	0–4
Sleeping too much	133 (55)	1.26 (1.36)	0–4	0–4
Difficulty in concentrating	118 (48.8)	1.07 (1.30)	0–4	0–4
Difficulty in remembering things	107 (44.2)	0.88 (1.16)	0–4	0–4
Increased dreaming	106 (43.8)	0.94 (1.27)	0–4	0–4
Lack of emotions	88 (36.4)	0.7 (1.10)	0–4	0–4
Autonomic ADRs	189 (78.1)	2.99 (2.76)	0–13	0–20
Feeling sick	129 (53.3)	1.01 (1.17)	0–4	0–4
Dizziness	106 (43.8)	0.84 (1.11)	0–4	0–4
Increased sweating	70 (28.9)	0.5 (0.92)	0–4	0–4
Palpitations	64 (26.4)	0.4 (0.77)	0–4	0–4
Diarrhea	35 (14.5)	0.24 (0.64)	0–4	0–4
Extrapyramidal ADRs	186 (76.9)	4.45 (4.52)	0–20	0–28
Restlessness	140 (57.9)	1.15 (1.20)	0–4	0–4
Muscle stiffness	90 (37.2)	0.74 (1.10)	0–4	0–4
Parts of body moving on their own	73 (30.2)	0.64 (1.12)	0–4	0–4
Shakiness	68 (28.1)	0.64 (1.12)	0–4	0–4
Slowing of movements	66 (27.3)	0.57 (1.01)	0–4	0–4
Muscle spasms	41 (16.9)	0.39 (0.98)	0–4	0–4
Over-wet or drooling mouth	41 (16.9)	0.33 (0.79)	0–4	0–4
Miscellaneous	161 (66.5)	2.21 (2.24)	0–10	0–16
Headaches	100 (41.3)	0.79 (1.10)	0–4	0–4
Putting on weight	80 (33.1)	0.69 (1.11)	0–4	0–4
Losing weight	55 (22.7)	0.45 (0.96)	0–4	0–4
Pins and needles	36 (14.9)	0.28 (0.74)	0–4	0–4
Hormonal ADRs	141 (58.3)	2.28 (2.60)	0–11	0–24
Reduced sex drive	87 (36)	0.79 (1.19)	0–4	0–4
Difficulty achieving climax	68 (28.1)	0.60 (1.09)	0–4	0–4
Increased sex drive	40 (16.5)	0.28 (0.74)	0–4	0–4
Period problems	34 (14)	0.32 (0.87)	0–4	0–4
Periods less frequent	26 (10.7)	0.23 (0.72)	0–4	0–4
Swollen or tender chest	9 (3.7)	0.07 (0.42)	0–4	0–4
Anticholinergic ADRs	107 (44.2)	3.42 (3.22)	0–13	0–20
Blurred vision	100 (41.3)	0.75 (1.06)	0–4	0–4
Passing a lot of water	99 (40.9)	0.94 (1.31)	0–4	0–4
Constipation	84 (34.7)	0.71 (1.11)	0–4	0–4
Dry mouth	78 (32.2)	0.6 (0.99)	0–4	0–4
Difficulty passing water	46 (19)	0.41 (0.94)	0–4	0–4
Allergic ADRs	107(44.2)	1.65 (2.61)	0–13	0–16
Sensitivity to sun (photosensitivity)	80 (33.1)	0.79 (1.24)	0–4	0–4

(Continued)



**Table 4** (Continued).

Variables	Prevalence	Total ADR Score		
	n (%)	M (SD)	Actual Range	Expected Range
Itchy skin	46 (19)	0.38 (0.92)	0–4	0–4
Rash	30 (12.4)	0.25 (0.75)	0–4	0–4
New or unusual skin marks	24 (9.9)	0.23 (0.76)	0–4	0–4
Red herrings	107 (44.2)	1.78 (3.04)	0–18	0–40

**Abbreviations:** M, mean; n, number; SD, standard deviation; %, percent.

SGAs usage. The prevalence and types of antipsychotics used in these studies are shown in Table 10. Total ADR score categories, which imply the total number and severity of ADRs, indicate that one quarter of the participants rated ADRs as medium-to-high level. This finding is lower than McCann et al's<sup>30</sup> result, which reported over 40%. The accumulated ADRs are likely to affect the patients' quality-of-life and their treatment adherence.

In this study, psychic, autonomic, extrapyramidal, and hormonal reactions were found to be highly prevalent, whilst anticholinergic and allergic reactions were

relatively less prevalent. Tiredness, tension, depression, restlessness, initial insomnia (difficulty falling asleep), and difficulty staying awake during the day, sleeping too much and feeling sick were the most prevalent individual ADRs in this study. Similar to this research, some other studies had found psychic and extrapyramidal ADRs to be most prevalent<sup>8,30,31</sup> and anticholinergic ADRs least prevalent.<sup>8</sup> Likewise, tiredness, memory problems, tension, depression, restlessness, and concentration problems were among the most prevalent ADRs of Day et al's<sup>31</sup> findings. However, inconsistent with the Day et al study,

**Table 5** Independent Sample t-Test of the Mean Score of ADRs Among Various Categories of the Demographic and Clinical Variables

Variables		M (SD)	MD	95% CI	P-value
Gender					
	Male	31.04 (18.72)	7.04	2.39–11.68	0.003
	Female	24.00 (17.39)			
Smoking status					
	Yes	35.92 (18.57)	9.86	4.12–15.60	0.001
	No	26.06 (17.99)			
Alcohol consumption					
	Yes	34.36 (16.85)	7.08	−0.56–14.72	0.069
	No	27.28 (18.53)			
ADRS-counseling					
	Yes	29.77 (2.16)	3.55	−1.11–8.20	0.135
	No	26.22 (16.45)			
Employment					
	Unemployed	27.49 (16.75)	2.59	−7.43–3.98	0.550
	Employed	29.22 (29.99)			
Number of antipsychotics					
	Single	25.30 (19.31)	−5.51	−10.15–0.88	0.020
	≥2	30.81 (17.17)			

**Abbreviations:** M, mean; MD, mean difference; CI, confidence interval.

**Table 6** ANOVA of the Mean Score of ADRs Among Various Categories of Educational Level

Variables		M (SD)	P-value	P-trend
Educational Level				
	Primary/no formal education	21.21 (13.33)	0.018	0.004
	Middle	25.07 (16.74)		
	Secondary	30.90 (20.72)		
	Higher	30.46 (16.00)		
Insight				
	Poor insight	26.15 (14.49)	0.693	-
	Partial insight	28.97 (14.56)		
	Good insight	28.33 (21.37)		

**Abbreviations:** M, mean; SD, standard deviation; PO, per Os; IM, intramuscular.

anticholinergic ADRs including dry mouth and blurred vision were less prevalent in this study, which could be attributed to the sparse prescription or availability of anticholinergic drugs in Eritrea. Since FGA are the only antipsychotics available currently in the Eritrean National List of Medicines, applying simple checklists and subjective rating scales such as LUNSERS, (ultra) brief symptom ratings PSRS (4-Item Positive Symptoms Rating Scale) and BNSA (Negative Symptom Assessment) for each medication visit may be useful tools in detecting and managing ADRs in a timely fashion and reducing their magnitude and impact on patients' quality-of-life and adherence to treatment. Maintaining the availability of anticholinergic preparations and their timely use will also be important in the prevention and management of extrapyramidal ADRs (Parkinson's).

Generally, the discrepancy in the magnitude and nature of ADRs of antipsychotics can be ascribed to the difference in the population susceptibilities, clinical practice, monitoring strategies, vigilance of health professionals to detect ADRs, management given to the identified ADRs, and availability of diagnostic resources. Moreover, the adequacy of doses and combinations of medications and availability of choices and selection of antipsychotics for the management of schizophrenia may influence outcomes of treatment.

## Association of Socio-Demographic and Clinical Variables with ADRs

In the current study, higher ADRs score was found in smokers when compared to non-smokers and in higher education attainments when compared to primary/no formal education. Closer monitoring of patients with co-morbid substance use disorders (smoking), taking appropriate measures to help raise awareness about problems related to the use of substances, introducing psychoeducational programs for patients and relevant others are some of the complementary service components that could help treatment outcomes. The correlation between higher education attainments with higher ADRs score documented in the current study may be attributed to greater awareness and recognition and articulation of medication ADRs and access to more information.

Inconsistent with the available research database, the current study found no significant association of antipsychotic ADRs with antipsychotic dose,<sup>8–32–34</sup> and antipsychotic polypharmacy.<sup>35–38</sup> Nevertheless, the average dose used in this study was low (245 mg/day) as the average antipsychotic dose recommended in maintenance therapy is a total CPZeq range of 300–600 mg<sup>39</sup> and doses of less than 400 mg/day are considered low.<sup>40</sup> This low dose used

**Table 7** Post Hoc LSD Analysis of the Mean Score of ADRs Among Various Categories of Educational Level

Variables	MD (95% CI)	P-value
Educational level		
Middle, primary/no formal education	3.86 (−3.72–11.45)	0.317
Secondary, primary/no formal education	9.69 (2.97–16.41)	0.005
Higher, primary/no formal education	9.25 (0.97–17.52)	0.029
Secondary, middle	5.83 (−0.99–11.76)	0.054
Higher, middle	5.38 (−2.26–13.03)	0.167
Higher, secondary	0.44 (−7.23–6.34)	0.898

**Abbreviations:** MD, mean difference; PO, per Os; IM, intramuscular.

**Table 8** Pearson's Correlation of Demographic as Well as Clinical Variables and ADR Score

Variables	r, n	P
Age	0.056, 242	0.382
Weight	0.052, 242	0.423
Duration of illness	-0.140, 242	0.030
Dose	0.174, 242	0.007

**Abbreviation:** r, Pearson's correlation coefficient.

in the majority of the study participants could be the reason for showing no difference in ADR scores rendering to the different doses used. However, this low dose used to treat the majority of the study sample and the occurrence of high magnitude of ADRs within such a dose range is remarkable and requires further investigation. Identifying evidence-based optimal use in prescribing antipsychotics and evaluating dose–response relationships on a regular basis and avoiding antipsychotic polypharmacy whenever possible can reduce the likelihood and magnitude of ADRs significantly.

Besides, the current study reported no significant ADRs score difference between males and females, which is consistent with a previous study<sup>30</sup> and inconsistent with another study which reported higher risk of antipsychotic ADRs in females.<sup>42</sup> Moreover, in the current

study, no statistical difference of ADR score with duration of illness, patient age, and body weight, insight into illness, ADRs counseling, and alcohol consumption status was observed. This was inconsistent with former studies with regard to patient age,<sup>43</sup> duration of illness,<sup>8,41</sup> and alcohol consumption status.<sup>34</sup>

Use of a validated and reliable scale to measure ADRs (LUNSERS) and the high response rate (96.4%) are some of the strengths of this study. The red herrings score of less than 20 which determined the accuracy of the patients' self-report of ADRs can also be considered as a strength. This study was not however without limitations. First, in some cases, it was challenging to differentiate if the adverse event was drug-related or a psychiatric symptom, which can lead to both exposure and outcome misclassification bias. Second, the results of this study are limited to stable schizophrenic patients, who are diagnosed for at least 1 month, having no other co-morbidities, taking no other concomitant drugs and those who attended OPD during the study period. This may exclude acutely and more severely ill patients, patients with severe ADRs, the early onset ADRs of antipsychotics and non-adherent patients who possibly did not come to the hospital regularly. Third, as ADRs were self-reported and not always objectively confirmed, this can introduce information bias which can underestimate or overestimate the prevalence of

**Table 9** Socio-Demographic and Clinical Predictors of LUNSERS Score Using Two-Step Hierarchical Multiple Regression Model

	Predictors	b (95% CI)	SE (B)	β	P-value
Step 1	Intercept	16.09 (9.54–22.64)	3.32		<0.001
	Gender <sup>a</sup>	2.94 (–2.16–8.04)	2.59	0.08	0.258
	Smoking <sup>b</sup>	7.78 (1.62–13.95)	3.13	0.17	0.014
	Education – Middle <sup>c</sup>	1.04 (–6.46–8.53)	3.80	0.02	0.785
	Education – Secondary <sup>d</sup>	7.67 (0.99–14.34)	3.39	0.21	0.025
	Education – Higher <sup>e</sup>	5.35 (–3.06–13.77)	4.27	0.11	0.211
	Antipsychotic dose	0.02 (0.00–0.03)	0.01	0.13	0.035
Step 2					
	Intercept	13.62 (6.43–20.81)	3.65		<0.001
	Gender <sup>a</sup>	2.69 (–2.41–7.79)	2.59	0.07	0.300
	Smoking <sup>b</sup>	7.00 (0.76–13.25)	3.17	0.15	0.028
	Education – Middle <sup>c</sup>	1.57 (–5.94–9.07)	3.81	0.04	0.681
	Education – Secondary <sup>d</sup>	8.36 (1.65–15.07)	3.41	0.23	0.015
	Education – Higher <sup>e</sup>	5.96 (–2.47–14.39)	4.28	0.12	0.165
	Antipsychotic dose	0.01 (–0.01–0.03)	0.01	0.09	0.269
	Number of Antipsychotics <sup>f</sup>	1.60 (–4.32–7.51)	3.00	0.04	0.569
	Duration of illness	0.02 (–0.00–0.04)	0.01	0.11	0.094

**Notes:** b (95% CI), unstandardized coefficient and the corresponding 95% CI; SE (B), standard error of the coefficient; β, standardized coefficient. R<sup>2</sup>=0.086 for step 1, Δ R<sup>2</sup>=0.011 for step 2. Dummy coding: <sup>a</sup>Coded female=0, male=1; <sup>b</sup>Coded no=0, yes=1; <sup>c</sup>Coded middle=1, otherwise=0; <sup>d</sup>Coded secondary=1, otherwise=0; <sup>e</sup>Coded higher=1, otherwise=0; <sup>f</sup>Coded 0=single, 1=multiple.

**Table 10** Prevalence of ADRs Reported Among Different Studies Using LUNERS and Types of Antipsychotics Used

Studies and Number of Study Respondents	ADRs Prevalence (%)	Antipsychotic Drugs Used		
		FGAs (%)	SGAs (%)	FGAs and SGAs Combined (%)
Current study (Eritrea), n=242	93.8	100	0	0
Australia, <sup>29</sup> n=100	100	60	40	0
Singapore, <sup>8</sup> n=96	89.6	25	70.8	4.2
Australia, <sup>30</sup> n=81	50	4.9	86.4	8.6

**Abbreviation:** n, number of study respondents.

ADRs. Fourth, as the study was cross-sectional, the causal association between the antipsychotics and ADRs could not be ascertained.

In conclusion, ADRs of anti-psychotics were found to be highly prevalent with moderate-to-high overall ADR scores in a significant number of patients. This warrants the introduction of risk minimization strategies including staff training on identification, management, and prevention of ADRs, revision of treatment guidelines and algorithms, improving the laboratory set-up to enable therapeutic and adverse event monitoring, and inclusion of SGAs in the National List of Medicines. Due to the inherent limitations of this research, further studies with better epidemiological designs are required to substantiate these findings.

## Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on request.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest for this work.

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