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PATTERN OF ADVERSE DRUG REACTIONS REPORTED AT ZONAL PHARMACOVIGILANCE CENTRE, ILORIN, NORTH-CENTRAL NIGERIA: A 15 YEAR REVIEW

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ABSTRACT

Background: Drugs have the potential to cause adverse drug reactions (ADRs). ADRs causes a great burden on healthcare system in terms of increasing morbidity and mortality with significant economic consequences. ADRs requires active monitoring and in sub-Saharan Africa, ADRs are either not reported or under reported which poses a great challenge. This study was conducted with the aim of understanding the pattern and occurrence of ADRs, the sociodemographic distribution, organ system affected, implicated drugs for the ADRs and clinical outcome.

Method: This study is a 15year retrospective study that analyzed the ADRs reported to Zonal Pharmacovigilance Center, Ilorin, North-central Nigeria. A total of 280 patients reported 301 adverse drug reactions between 2005 and 2020 to the ZPC and the ADRs reported were analyzed.

Results: The age group most commonly affected by ADRs was 31-40 years with affectation of both gender. The organ system mostly affected was the skin and patients presented with pruritus and skin rash. The most common suspected drug for the ADRs were antiretroviral drugs. Most of the ADRs were mild and most patients recovered fully.

Conclusions: ADRs were under-reported in this study. Most were mild in nature and affected patients recovered fully. It is important to understand the pattern and occurrence of ADRs for the safety of patients and to reduce its burden on healthcare system. This can be achieved by effective monitoring and sensitization of health care workers.

INTRODUCTION

Adverse drug reaction (ADR) is defined as a response to drug that is noxious and unintended occurring at doses normally used in humans for prophylaxis, diagnosis or treatment of a disease or for modification of physiological function¹⁻³. All drugs have the potential to cause adverse drug reaction. Adverse drug reactions (ADRs) are major cause of morbidity and mortality in patient care⁴. ADRs related hospital admission have consistently increased, and this has caused a great burden on the health care system with significant economic consequences. ADRs are commonly encountered in hospital setting where multiple drugs are prescribed and combined in the management of the patient⁵. The repeated occurrence of adverse drug reactions over the years has attracted lots of professional and public attention which increased the doubt on the effectiveness and quality of drug safety surveillance systems⁶. A group of scientists proposed that the assessment of adverse drug reaction is likely to be the most important aspect of drug treatment in medical practice. ADRs are responsible for around 4.9% of hospital admissions worldwide and in some cases, this figure can be as high as 41.3%. There is thus no doubt that drug safety is an important public health issue^{7,8}. Pharmacovigilance (PV) as defined by the WHO is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem². Spontaneous reporting

of suspected adverse drug reactions has long been the cornerstone of pharmacovigilance for the identification of early signals of problems related to drug safety and use of drugs worldwide^{1,2}. The practice of pharmacovigilance in sub-Saharan African countries has not been encouraging and some ADRs occur without being reported. Some health professionals including doctors and pharmacists have contributed significantly to successful pharmacovigilance through spontaneous reporting. This significant contribution by these professionals has encouraged the assessment of the benefit-risk ratio of some drugs, as well as contributed to signal detection of unsuspected and unusual ADRs previously undetected during the initial evaluation of a drug^{9,10}. Efforts should be intensified to give a wider coverage for this reporting particularly in sub-Saharan African region. Understanding the benefit and risk of drug therapy is necessary for an effective nationwide pharmacovigilance system¹¹. Adverse drug reaction monitoring plays a crucial role in meeting the challenges posed by the ever-increasing range and potency of drugs as it is a well-established fact that no drug is completely free of adverse effects. It has also been found to impact greatly on patient care in terms of morbidity and mortality, drug compliance and treatment outcome^{12,13}. These effects are enormous, and studies have shown that most adverse reaction in sub-Saharan Africa countries including Nigeria are either not reported or under reported^{14,15}. This study was designed to generate data on the socio-demographic pattern of ADRs, its

occurrence and reporting, organ system affected, the frequency, severity and outcome.

METHODS

The study was a retrospective analysis of all the ADRs reported at Zonal Pharmacovigilance Centre (ZPC) in University of Ilorin Teaching Hospital (UITH), Ilorin, North-central Nigeria. The ZPC is the adverse drug reactions monitoring center for the zone.

Study setting and Participants:

The Zonal pharmacovigilance (ZPC) center in UITH serves the North-central geo-political zone of the country. All ADRs reported to this ZPC between the year 2005 to year 2020 was reviewed and analyzed for socio-demographic profile of patients, organ system affected by ADRs, pattern and type of reactions, suspected/causative drugs, severity and outcome of the reactions and management of the ADRs.

According to the WHO definition, this study only included ADRs associated with a dose normally used in humans and reports associated with drug administered for ordinary prophylactic or therapeutic purposes. Reports related to drug abuse, suicide attempts and medication errors were excluded. Other inclusion criteria are: (a) an identifiable reporter (b) an identifiable patient (c) at least one suspected drug (d) at least one ADR.

Spontaneous reporting of ADRs is practiced in Nigeria using a standard structured yellow form as recommended by the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) in Sweden. All completed adverse drug reaction forms were submitted to ZPC for onward transmission to National Pharmacovigilance Center (NPC) for documentation and analysis. A filled yellow/adverse reaction form is known as the individual case study report (ICSR)

Data abstraction:

The ICSR of patients who experienced adverse drug reaction(s) from 2005 to 2020 was sourced from the ZPC in UITH, Ilorin and data mining was done to obtain the following information: Socio-demographic data of patients, batch and National Agency for Food Drug Administration and Control (NAFDAC) number identification for suspect drugs with ADRs, suspect drugs with ADRs (dosage form, specific indication for use, specific name, specific manufacturer), and ADR (specific type, duration, system organ classification, and outcome), reporter of ADR (institution and profession).

To reduce the possibility of duplication, each ADR filled form was individually compared based on the patient's age, sex, and residence. The reporter, date of onset of the reaction, outcome and other medications being used by the patients were also be compared.

Data management and analysis:

The data were analyzed with IBM SPSS statistics software, version 22. Descriptive statistics was used to summarize the demographic and clinical characteristics. Means and standard deviations was used for continuous variables. Frequencies and percentages were used for categorical variables. Chi-squared test was applied to compare categorical variables between groups. The significance level was set at $p < 0.05$. Patient records were anonymized and de-identified prior to analysis.

Ethical consideration:

Ethical approval was obtained from the Ethics and Research Committee of the University of Ilorin teaching hospital with approval number ERC PAN/2021/10/0204. Strict confidentiality was maintained about the particulars of the involved patients during and after the study.

RESULTS

A total of 301 ADRs were reported by 280 patients under the period being reviewed. Adverse drug reactions as seen in this study affected all age group and gender. The age group mostly affected was 31-40 years (n=112,

40%), followed by 21-30 years (n=56, 20%) and 41-50 years (n=56, 20%) which has equal frequency (table 1).

The gender distribution showed that females (n = 165, 58.9%) were more affected than males (n= 115, 41.1%) (table 1).

Table 1

Age and Sex distribution of adverse drug reactions over the study period (N =280)

Variable	Frequency	Percentage
Age group (years)		
0 – 10	19	6.7
11 – 20	18	6.4
21 – 30	56	20
31 – 40	112	40
41 – 50	56	20
61 – 70	19	6.7
Gender distribution		
Male	115	41.1
Female	165	58.9

Dermatologic adverse drug reactions like pruritus and skin rashes were the most reported ADR (n=122, 40.6%) and this was followed by adverse drug reactions affecting the central nervous system (CNS) like headache and dizziness (n=92, 30.6%). Other

organ system affected include the gastrointestinal tract (GIT) which was mainly nausea and vomiting (n=82, 27.1%) and cardiovascular system (n=5, 1.7%) as shown in figure 1 below.

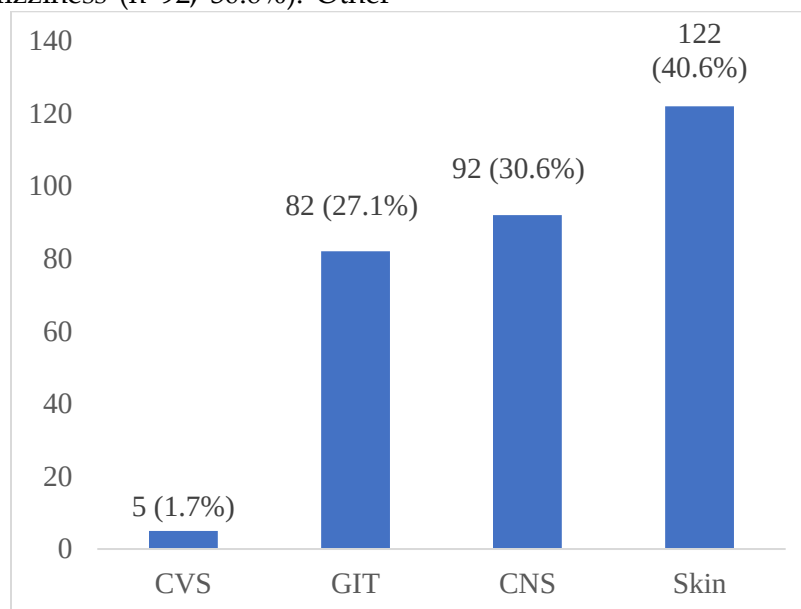


Figure 1: Organ-system affected by adverse drug reactions

Antiretroviral drugs were found to be the most commonly involved in reported ADRs (n=132, 45.2%). This is followed by antimicrobial agents which were mostly antibacterial drugs (n=71, 24.2%) and antimalarial drugs (n=58, 19.9%) as shown in table 2 below.

Table 2
Suspected drugs causing adverse drug reactions

Drugs	Frequency	Percentage
Antimalarial	58	19.9
Antimicrobial	71	24.2
Antiretroviral	132	45.2
Anti-Ulcer drugs	7	2.5
Antihypertensive	11	3.7
Analgesics	9	3.1
Others	4	1.2

The outcome of the adverse drug reactions showed that majority of the ADRs were mild in nature as most of the patient (n=236, 84.4%) recovered fully. About 10.8% of the reported ADRs was life threatening ADRs affecting 30 patients while fatality was 3.1% affecting 9 patients (table 3).

Table 3
Outcome of reported adverse drug reactions

Outcome	Frequency	Percentage
Recovered fully	236	84.4
Life threatening	30	10.8
Recovered with disability	5	1.7
Death	9	3.1

DISCUSSION

ADRs are major cause of morbidity and mortality in patient care and the occurrence has greatly impacted the outcome of patient care, drug compliance and casted a shadow on effectiveness of pharmacovigilance in health care settings⁴. It has been reported in some quarters that ADRs are generally under-reported^{14,15}. This study was done to analyze the ADRs reported to North-central Zonal pharmacovigilance center in Ilorin, Kwara state. It was a retrospective study that looked out for the pattern of ADRs, socio-demographic profile of affected patients, suspected or causative drugs, organ system

affected, severity and outcome of the adverse drug reactions.

A total of 280 patients reported 301 adverse drug reactions between 2005 and 2020 to the ZPC in Ilorin, North-central, Nigeria. This finding is different from the ones reported from developed countries. Vieira et al¹⁶ in a study on ADRs between 2008 and 2013 had about 1500 patients who reported nearly 2000 ADRs during the period of study. A similar finding was seen by Gulnihan et al¹⁷ in their study in Turkey between 2005 and 2014. Our finding showed that ADRs were still under reported in this part of the country.

Age is an important risk factor for the development of some medical conditions

including adverse drug reactions. The age group that was mostly affected by ADRs was between 31-40 years which was followed by 21-30 years and 41-50 years. Studies by Awodele et al^{18,19} reported the age group mostly affected by ADRs as 21-40 years. Some researchers also reported a slightly older age group (41-50 years) as the most affected^{20,21}. This age group of 41-50 years was the second most affected age group in this study. Lima et al²² reported the age group commonly affected by ADRs in their study as 18-65 years. This study may not be able to specifically point to while the age group mostly affected by ADRs varies but it may not be unrelated to the fact that common diseases being treated in different regions varies with the age of the populace. In other word, there are diseases that affects particular age group and ADRs caused by treatment of such disease affects only that age group being treated.

ADRs affects both male and female but a recent study by Watson et al²³ analyzed global report for half of a century and showed that females are generally more affected by ADRs. Study by Gor et al²⁴ showed equal affectation of male and female by adverse drug reaction. The pattern of gender distribution from this study showed that both male and female developed adverse drug reactions though there was female preponderance (58.9%) which was similar to what was commonly reported in the literature^{23,25-27}. There were few studies that reported male preponderance²⁸⁻³⁰.

The organ-system affected mostly by ADRs was the skin, dermatologic adverse drug reaction, (40.6%), and it was mostly mild, in form of pruritus and skin rash which subsided after the suspected drugs were stopped. Thirty patients (10.8%) had life threatening skin manifestation like Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TENS). These type of ADRs were severe in nature.

Saha et al³¹ reported 24.5% in their study for patients that developed overlap of SJS and TENS.

ADRs affecting the Central Nervous System (CNS) followed that of the skin. The central nervous system ADRs affected ninety-two patients (30.6%) and they presented mostly with headache and dizziness which subsided after the discontinuation of the suspected drugs. These findings on organ-system affected by ADRs were similar to findings in other studies^{32,33}.

It is a known fact that as the number of drugs used by a patient increases the more the likelihood of developing adverse drug reactions. The interaction between the different drugs being used can be at the level of absorption, distribution, metabolism or excretion. It should also be noted that drug-drug interactions could occur predisposing to development of ADRs. The suspected drugs causing the reported ADRs in this study include the antiretroviral drugs accounted for 45.2% of the ADRs. This finding also supported the fact that the age group mostly affected by ADRs in this study were the active age group which predisposes them to sexually transmitted diseases like HIV/AIDS. The commonly used antiretroviral drugs as found in this study include zidovudine, tenofovir, lamivudine and dolutegravir. Singh et al³⁴ in their study found that the drug commonly suspected to be causing ADRs were the antibiotics. In this study antibiotics accounted for 24.2% of ADRs reported over the study period, particularly antibacterial agents used in the treatment of bacterial infections. They are the second most important agent implicated in causing ADRs in this study.

The outcome of the reported ADRs was analyzed and majority of patients that had ADRs recovered fully (84.4%) as most of the ADRs were mild in nature. Some patient

recovered with disability (1.7%) and 10.8% developed life threatening ADRs. Nine cases (3.1%) were fatal and resulted in death of the affected patients. These findings were similar to the ones reported by Watson et al²³ and other researchers in their studies³⁵⁻³⁶

Limitation of the study

This study was conducted in the North-central zone of Nigeria as there are six zones in the country, data generated may not be representative of other zones of the country.

CONCLUSION

This study concluded that ADRs were under-reported. The age group mostly affected by ADRs in the North central region of Nigeria was between 31-40 years with affectation of both gender though we noticed a female preponderance. Dermatologic reactions like pruritus and itching were the most commonly reported ADRs and antiretroviral drugs like zidovudine and tenofovir were the most common drugs implicated in causing ADRs. Most of the reported ADRs were mild in nature as the affected patients recovered fully from the ADRs after stopping the suspected drugs though nine cases were fatal which led to the death of affected patients.

RECOMMENDATION

Similar study should be conducted in the other zones of the country to generate a nation-wide data that will be of importance to health-care policy and decision makers. There should be sensitization programs to increase awareness among all cadre of health-care professionals on the importance of active pharmacovigilance and reporting of ADRs through the appropriate channels in order to protect and safeguard the health of the nation.

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