



Pattern of Medications Causing Adverse Drug Reactions and the Predisposing Risk Factors Among Medical In-Patients in Clinical Practice: A Prospective Study

Peter Ehizokhale Akhiden¹, Olumuyiwa John Fasipe², Ambrose Ohumagho Isah³, Omagbemi Sampson Owhin¹, Oluseyi Ademola Adejumo⁴

¹Department of Internal Medicine, Irrua Specialist Teaching Hospital, Irrua, ³Department of Internal Medicine, University of Benin Teaching Hospital, Benin City, Edo State, ²Department of Pharmacology and Therapeutics, University of Medical Sciences, ⁴Department of Internal Medicine, Kidney Care Centre, University of Medical Sciences, Ondo City, Ondo State, Nigeria

Background: Pharmacological interventions sometimes carry inherent significant risks which include adverse drug reactions (ADRs), drug interactions (DIs) and other consequences of inappropriate medication use. An adverse drug reaction (ADR) is defined in this study as a response to a drug which is noxious and unintended that occurs at doses normally used in man for therapeutic purposes. Despite the extensive study and attention given to ADRs, they still represent a clinically significant problem and burden with high incidence and prevalence. **Aim:** The main aim of this study was to evaluate and highlight the pattern of medications most frequently involved in ADRs and the predisposing risk factors among adult medical in-patients in clinical practice setting with the goal of preventing them and improving their treatment outcome. **Methods:** The patients admitted into the adult medical wards of a Nigerian University Teaching Hospital over a 9-month period from December 2013 to August 2014 were prospectively recruited for the study and followed up till discharge. **Results:** Five hundred and seven (507) patients were evaluated during the study, out of which 269 (53.1%) of them were males and 238 (46.9%) were females. The mean age of the study population was 48.9 ± 17.8 years (median of 46 years). The drugs most frequently involved in ADRs were insulin in 14 (27.5%) patients, Non-steroidal Anti-inflammatory drugs in 10 (19.6%) patients, antihypertensives in 8 (15.7%) patients, antimalarials in 5 (9.8%) patients, herbal medications in 4 (7.8%) patients and antibacterials in 3 (5.9%) patients. Furthermore, four (4) fatal ADRs were observed during the study; in which herbal medications caused two (2) deaths, sulfadoxine/pyrimethamine combination (maloxine[®]) caused one (1) death, and Iron dextran caused one (1) death. The most frequently affected body systems by ADRs were the central nervous system and the gastrointestinal system corresponding to the Antidiabetic drug-insulin use causing neuroglycopenic symptoms and Non-steroidal Anti-inflammatory drugs (NSAIDs) use causing NSAID-induced gastroenteritis/GIT bleeding, respectively. The elderly age group (≥ 65 years), presence of polypharmacy (taking more than 5 different pharmacologically active medications by a particular patient at the same time) and the presence of multiple comorbidities in a particular patient are clinically proven and significant risk factors found to be associated with and predisposed adult medical in-patients to ADRs in this study. **Conclusion:** The negative health burden and consequences of ADRs with the predisposing risk factors were significantly high among these adult medical in-patients. In this study, ADRs increase patients morbidity, mortality and length (duration) of hospitalization. Insulin and NSAIDs caused the highest number of ADRs which indicate that adequate caution, proper care and continuous monitoring must be implemented during the course of treating patients with these drugs in order to optimize their clinical efficacy and prevent the occurrence of ADRs in them.

Key words: Adult medical in-patients, insulin, non-steroidal anti-inflammatory drugs, pattern of medications causing adverse drug reactions, predisposing risk factors to adverse drug reactions

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Received: March 17, 2018; Revised: August 21, 2018;
Accepted: October 10, 2018

Corresponding Author: Dr. Peter Ehizokhale Akhiden, Department of Internal Medicine, Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria. Tel: +2348037048831. E-mail: ehiden@ yahoo.co.uk

How to cite this article: Akhiden PE, Fasipe OJ, Isah AO, Owhin OS, Adejumo OA. Pattern of medications causing adverse drug reactions and the predisposing risk factors among medical in-patients in clinical practice: A prospective study. J Med Sci 2019;39:18-27.

INTRODUCTION

An adverse drug reaction (ADR) is an injury caused by taking a medication.¹ ADRs may occur following a single dose or prolonged administration of a drug or result from the combination of two or more drugs. The meaning of this expression differs from the meaning of "side effect", as this last expression might also imply that the effects can be beneficial.² The study of ADRs is the concern of the field known as pharmacovigilance and pharmacosurveillance. An adverse drug event (ADE) refers to any injury occurring at the time a drug is used, whether or not it is identified as a cause of the injury.¹ An ADR is a special type of ADE in which a causative relationship can be shown or established. Medications are essentially important in the clinical practice of patient care by well-trained healthcare professionals. Patient management often requires the use of medications. The use of medicines for patient care is considered to be a major component of patient management in health care settings.¹⁻³ Pharmacological interventions sometimes carry inherent significant risks which include adverse drug reactions (ADRs), drug interactions (DIs) and other consequences of inappropriate medication use.⁴⁻⁷ An adverse drug reaction (ADR) is defined in this study as a response to a drug which is noxious and unintended that occurs at doses normally used in man for therapeutic purposes.⁸⁻¹⁰ ADRs have been known to cause significant morbidity and mortality for centuries being as old as medicine itself.¹¹⁻¹⁴

ADRs may be classified by nature of predictability, cause, severity and location.

Based on predictability classification, an ADR can be regarded as a predictable ADR if the mechanism of occurrence is known. But is an unpredictable ADR when its mechanism of occurrence is unknown and cannot be delineated or established.

Based on cause classification, ADRs can be categorised as Type A (Augmented ADRs), Type B (Bizarre or Idiosyncratic ADRs), Type C (Chronic or Continuous use ADRs), Type D (Delayed-onset ADRs), Type E (End of use or Discontinuation of use or Sudden withdrawal effect ADRs) and Type F (Failure of treatment ADRs). Type A reactions which occur as a result of augmented pharmacologic effects (that is, dose dependent and predictable in nature) constitute approximately 80% of adverse drug reactions (ADRs). The Type A ADRs occur due to the excessive consequence of the drug's primary pharmacological effect (e.g. bleeding when using the anticoagulant warfarin) or a low therapeutic index of the drug (e.g. nausea from digoxin), and they are therefore predictable. They are dose-related and usually mild, although they may be serious or even fatal (such as intracranial bleeding from warfarin). Such reactions are usually due to inappropriate dosage, especially when drug elimination is impaired. The term "side effects" is often

applied to minor type A reactions.³ Type B reactions are bizarre or idiosyncratic ADRs whose mechanisms of occurrence are unknown and cannot be delineated or established. Types A and B were proposed in the 1970s,⁴ and the other types were proposed subsequently when the first two proved insufficient to classify ADRs.⁵

Furthermore, based on severity classification, Adverse drug reactions (ADRs) were classified as mild (laboratory abnormality or symptoms not requiring treatment), moderate (laboratory abnormality or symptoms requiring treatment / admission to hospital or resulting in non-permanent disability), severe (laboratory abnormality or symptoms that were life threatening or resulted in permanent disability), and fatal (any ADR that resulted in patient's death regardless and irrespective of the initial severity grading assessment).^{13,14} The United States (US) Food and Drug Administration defines a serious adverse event as one when the patient outcome is one of the following:⁶

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability- significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- Congenital anomaly
- Requires intervention to prevent permanent impairment or damage.

Severity is a point on an arbitrary scale of intensity of the adverse event in question. The terms "severe" and "serious" when applied to adverse events are technically very different. They are easily confused but can not be used interchangeably, requiring care in their usage. A headache is severe, if it causes intense pain. There are scales like "visual analog scale" that help clinicians assess the severity. On the other hand, a headache is not usually serious (but may be in case of subarachnoid haemorrhage, subdural bleed, even a migraine may temporally fit criteria), unless it also satisfies the criteria for seriousness listed above.

Based on location classification, adverse drug reactions (ADRs) or adverse drug effects may be a local ADR when it is limited to a certain part or location in the body. But can be regarded as a systemic/generalise ADR, when a medication has caused adverse drug effects throughout the whole body or systemic circulation. For instance, some ocular antihypertensive drugs cause systemic effects of hypotension,⁷ although they are administered locally as eye drops, since a fraction escapes into the systemic circulation.

ADR causality assessment is used to determine the likelihood that a drug caused a particular suspected ADR. There

are a number of different methods used to judge causation, including the Naranjo algorithm, the Venulet algorithm and the WHO causality term assessment criteria. Each have pros and cons associated with their use and most require some level of expert judgement to apply.¹⁷ An ADR should not be labeled as 'certain' unless the ADR abates with a challenge-dechallenge-rechallenge protocol (stopping and starting the agent in question). The chronology of the onset of the suspected ADR is important, as another substance or factor may be implicated as a cause; co-prescribed medications and underlying psychiatric conditions may be factors in the ADR.² Assigning causality to a specific agent often proves difficult, unless the event is found during a clinical study or large databases are used. Both methods have difficulties and can be fraught with error. Even in clinical studies some ADRs may be missed as large numbers of test individuals are required to find out that adverse drug reaction. Psychiatric ADRs are often missed as they are grouped together in the questionnaires used to assess the population.^{18,19} Despite the extensive study and attention given to ADRs, they still represent a clinically significant problem and burden with high incidence and prevalence.¹⁵⁻¹⁸ In the United States (US) for example, pharmaceutical treatment result sometimes in adverse drug events either due to inherent ADRs or from inappropriate medicine use or medication errors. These were noted in over 1.2 million hospital stays or about 3.1% of all hospital stays in the US in 2004.¹⁹⁻²¹ The incidence of serious and fatal adverse drug reactions in United States (US) hospitals was noted to be extremely high at 6.7% and 0.32% respectively, making these reactions ranked between the fourth and sixth leading causes of death.²²⁻²⁴

In the United Kingdom (UK), the incidence of ADRs among admitted patients was found to be 6.5% and admissions related to ADRs cost the National Health Scheme (NHS) up to £ 466 million annually or 0.62% of annual health budget.²⁵⁻²⁸ Furthermore, at a particular time in the UK, the equivalent of up to seven 800 bed space hospitals was occupied by patients with ADRs, which amounting to about 4% of hospital bed capacity in the UK. The duration of hospital stay was also increased by ADRs. The foregoing underscores the importance of the economic burden posed by ADRs.²⁹⁻³² A study by the Agency for Healthcare Research and Quality (AHRQ) found that in 2011, sedatives and hypnotics were a leading source for adverse drug events (ADEs) seen in the hospital setting. Approximately 2.8% of all ADEs present on admission and 4.4% of ADEs that originated during a hospital stay were caused by a sedative or hypnotic drug.²⁰ A second study by AHRQ found that in 2011, the most common specifically identified causes of adverse drug events (ADEs) that originated during hospital stays in the United States (US) were steroids, antibiotics, opiates/narcotics, and anticoagulants. Patients treated in urban teaching hospitals had

Table 1: Age and sex distribution of medical in-patients evaluated for adverse drug reactions in a Nigerian Teaching Hospital from December 2013 to August 2014

Age (years)	Sex		Total (%)
	Male (%)	Female (%)	
Mean age	48.3±17.9	49.5±17.7	48.9±17.8
Median	45	46	46
Range	17-89	19-87	17-89
<45	129 (25.4)	107 (21.1)	236 (46.5)
45-64	75 (14.8)	71 (14.0)	146 (28.8)
>64	65 (12.8)	60 (11.8)	125 (24.7)
Total	269 (53.1)	238 (46.9)	507 (100)

Table 2: Individual medicines causing adverse drug reactions among in-patients in a Nigerian Teaching Hospital from December 2013 to August 2014

Drug class	Frequency (%)	Individual agents (frequency)
Insulin	14 (27.5)	Soluble insulin (10), mixed human insulin (3), and isophane/zinc insulin (1)
Nonsteroidal anti-inflammatory drugs	10 (19.6)	Ibuprofen (7), diclofenac potassium (2) Piroxicam (1)
Antihypertensives	8 (15.7)	Amiloride/hydrochlorothiazide (3), amlodipine (2), lisinopril (2), and hydrochlorothiazide (1)
Antimalarials	5 (9.8)	Artemether/Lumefantrine (2), Sulphadoxine/Pyrimethamine (2)* Artesunate/Mefloquin (1)
Herbal medicines	4 (7.8)	Unknown constituents (4)*
Antibacterials	3 (5.9)	Amoxicillin (1), ampicillin/cloxacillin (1) metronidazole (1)
Corticosteroids	2 (3.9)	Dexamethasone (2)
Immune sera	2 (3.9)	Anti-tetanus serum (2)
Others	3 (5.9)	Cinnarizine (1), iron dextran (1)* Promethazine (1)
Total	51 (100.0)	

*Medicines causing fatal ADRs. ADRs=Adverse drug reactions

higher rates of ADEs involving antibiotics and opiates/narcotics compared to those treated in urban nonteaching hospitals. Those treated in private, nonprofit hospitals had higher rates of most ADE causes compared to patients treated in public or private, for-profit hospitals.²¹ In the United States (US), females had a higher rate of ADEs involving opiates and narcotics than males in 2011, while male patients had a higher rate of anticoagulant ADEs. Nearly 8 in 1,000 adults aged 65 years or older experienced one of the four most common ADEs (steroids, antibiotics, opiates/narcotics, and anticoagulants) during hospitalization.²¹ A study

showed that 48% of patients had an adverse drug reaction to at least one drug, and pharmacist involvement helps to pick up adverse drug reactions.²² In 2012 McKinsey & Co. concluded that the cost of the 35 million preventable adverse drug events would be as high as US \$115 billion.²³ Many countries have official bodies that monitor drug safety and reactions. On an international level, the World Health Organization (WHO) runs the Uppsala Monitoring Centre (UMC), and the European Union runs the European Medicines Agency (EMA). In the United States, the Food and Drug Administration (FDA) is responsible for monitoring post-marketing studies. In Canada, the Marketed Health Products Directorate of Health Canada is responsible for the surveillance of marketed health products. In Australia, the Therapeutic Goods Administration (TGA) conducts postmarket monitoring of therapeutic products. In the UK the Yellow Card Scheme was established in 1963. While in Nigeria, the National Agency for Food Drug Administration and Control (NAFDAC) monitor such similar health related safety activities concerning food and drug products. NAFDAC also set up pharmacovigilance and pharmacosurveillance medium for reporting adverse drug events (ADEs) such as adverse drug reactions (ADRs) and drug interactions (DIs) that occur within the nation, but this reporting medium is currently inefficient nationally and some how being underutilized by Nigerians including the healthcare providers and healthcare professionals themselves. In developing countries including Nigeria, there is minimal information on the in-hospital incidence of ADRs and the culprit medications.³³⁻³⁵ This information is useful for health planning, management, budgeting, policy formulation and development of treatment protocols to enable appropriate and optimal patient care.³⁶⁻³⁸

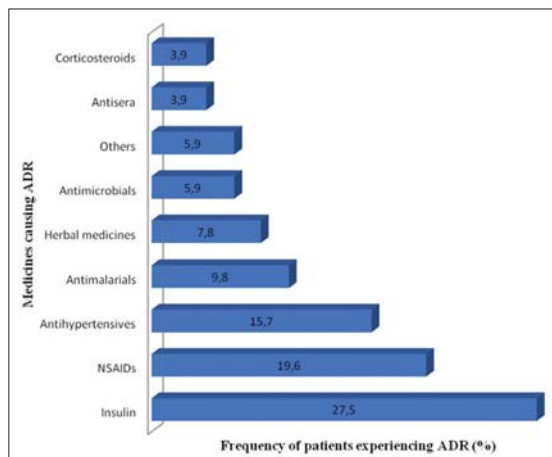


Figure 1: Medications causing adverse drug reactions among medical inpatients in a Nigerian Teaching Hospital from December 2013 to August 2014. The four fatal adverse drug reactions were observed during the study; in which, herbal medications caused two deaths, sulfadoxine/pyrimethamine combination (Maloxine®) caused one death, and Iron dextran caused one death. Details of the drug causing adverse drug reactions are shown in Table 2

This study was designed to evaluate and highlight the pattern of medications most frequently involved in ADRs and the predisposing risk factors among adult medical in-patients at the University of Benin Teaching Hospital (UBTH), Benin City, Edo State, Nigeria.

METHODS

This was a descriptive, prospective study with serial entry points for the patients admitted into the internal medicine wards of UBTH, Benin City, Edo State, South-South Nigeria, over a 9-month period from December 2013 to August 2014. They were all adult medical patients whose ages were above 17 years

Table 3: Duration of hospital stay (days) by different categories of in-patients in a Nigerian Teaching Hospital from December 2013 to August 2014

Patient category	Mean duration of stay±SD (days)	Median duration of stay (days)
All patients	11.9±11.3	9
Male	10.9±10.2	7
Female	12.9±12.3	10
Young (<45 years)	11.3±9.3	9
Middle aged (45-64 years)	11.7±9.7	10
Elderly (>64 years)	13.0±15.7	8
No ADR	11.6±11.0	8
Admitted solely due to ADR (ADR-out)	6.1±3.7	7
ADR occurring during admission (ADR-in)	18.3±14.8	15

SD=Standard deviation; ADR=Adverse drug reactions; ADR-out=Patients admitted solely because of ADRs; ADR-in=Patients that developed ADRs during admission

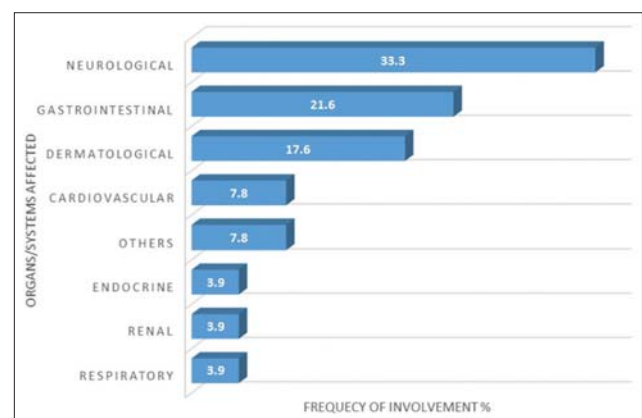


Figure 2: Organ/system affected by adverse drug reactions among medical inpatients in a Nigerian Teaching Hospital from December 2013 to August 2014

and were fulfilling the inclusion criteria for recruitment, evaluation, and followed up. Medications prescribed for the admitted patients were supplied by the hospital pharmacy or, however, they may occasionally be required to purchase some medications from retail outlets outside the hospital when these drugs are not available in hospital pharmacy. Patients are generally admitted through the accident and emergency unit where they are reviewed by various cadres of medical doctors until they are transferred to the wards under unit consultants. Some patients are admitted directly from the outpatient clinics into the wards, while a few may be transferred in from other nonmedical wards. The patients are then reviewed daily in the various units and managed until discharge.

The inclusion criteria for evaluation were all the patients admitted to the medical wards after commencing the study provided they granted their informed consents to participate in the study.

The exclusion criteria were as follows:

1. Patients already on admission before commencing the study
2. Patients admitted from other wards after initial management for nonmedical condition(s)
3. Patients diagnosed and subsequently managed for nonmedical condition(s) after initial medical diagnosis and management
4. Patients who did not grant their informed consents to participate in the study.

Data information about all the recruited patients was obtained and entered into a data collection form modified from the WHO-International Network of Rational Use of Drugs prescribing indicator form.³ Patients were evaluated with respect to medications used on days 0 (admission day), 1, 3, 7, 10, 14, 21, and weekly thereafter until the day of discharge or death. An encounter was regarded as a patient studied on admission on such specified days. An initial sociodemographic data stating age, sex, religion, and occupation among others were obtained at admission. Thereafter, the records of all prescribed medications, including the dates, route, doses, and frequencies, were all noted for these inpatients during admission. The reviews and changes made in patients' medications between the days of evaluation were also noted to enable the estimation of number of drugs taken during admission.

Information concerning ADR occurrence and its nature was sought from attending physicians, patients, their relatives, and nursing staff. Charts and case notes were screened for records of ADRs. Clinical evaluation and assessment of laboratory results were also carried out. Repeated admission of the same patient was regarded as two separate admissions when separated by an interval of at least 1 month, otherwise,

Table 4: Causality rating of adverse drug reactions observed among medical inpatients in a Nigerian Teaching Hospital using the World Health Organization and the Naranjo algorithms from December 2013 to August 2014

WHO rating	Naranjo algorithm
Certain 10 (19.6%)	Definite 9 (17.6%)
Probable 17 (33.3%)	Probable 19 (37.3%)
Possible 24 (47.1%)	Possible 23 (45.1%)
Unlikely 0 (0%)	Doubtful 0 (0%)
Conditional 0 (0%)	-
Unclassifiable 0 (0%)	-

WHO=World Health Organization

Table 5: Assessment of some known risk factors for adverse drug reactions among medical inpatients in a Nigerian Teaching Hospital from December 2013 to August 2014

Risk factor	ADR absent frequency (%)	ADR present frequency (%)	χ^2	<i>P</i>
Gender				
Male	244 (48.1)	25 (5.0)	0.371	0.542
Female	212 (41.8)	26 (5.1)		
Age (years)				
<65	352 (69.4)	29 (5.8)	10.152	0.001
≥65	104 (20.5)	22 (4.4)		
Number of medications				
1-5	64 (12.6)	3 (0.6)	11.891	0.018
6-10	274 (54.0)	18 (3.6)		
11-15	90 (17.8)	6 (1.2)		
16-20	24 (4.7)	2 (0.4)		
21-25	4 (0.8)	4 (0.8)		
Number of comorbidities				
1	91 (17.9)	4 (0.8)	21.962	<0.001
2	163 (32.1)	6 (1.2)		
3	145 (28.6)	9 (1.8)		
4	45 (8.9)	7 (1.3)		
≥5	12 (2.4)	7 (1.3)		

ADR=Adverse drug reactions

such admission was considered as a single admission and the interval excluded from the duration of hospital stay.¹⁶

The definition of ADRs used in the study was that of the WHO: "any noxious and unintended response to a drug that occurs at doses used in humans for the prophylaxis, diagnosis, or therapy of disease."³ ADRs were classified as mild (laboratory abnormality or symptoms not requiring treatment), moderate

Table 6: Incidence, prevalence, case fatality rate, and overall mortality rate for adverse drug reactions among medical inpatients in a Nigerian Teaching Hospital from December 2013 to August 2014

ADR parameter	Value
ADR-out	18 (3.6%)
ADR-in (incidence)	33 (6.5%)
Total ADR (prevalence)	51 (10.1%)
ADR case fatality rate	7.8% (4/51)
ADR overall mortality rate	0.8% (4/507)

ADRs=Adverse drug reactions; ADR-out=Patients admitted solely because of adverse drug reactions; ADR-in=Patients that developed adverse drug reactions during admission

(laboratory abnormality or symptoms requiring treatment / admission to hospital or resulting in non-permanent disability), severe (laboratory abnormality or symptoms that were life threatening or resulted in permanent disability), and fatal (any ADR that resulted in patient's death regardless and irrespective of the initial severity grading assessment).^{13,14} Causality of ADR was assessed using the WHO causality criteria¹⁵ as well as the Naranjo algorithm,¹⁶ while the ADRs were classified according to the severity grading assessment and the system/organ class.¹¹

Data collected was encoded and analyzed using the Statistical Package for Social Sciences (SPSS) version 17 (released 2008; SPSS Incorporations, Chicago, IL, USA). Results were expressed as the mean $\pm$ standard deviation or using frequency and percentage values where necessary. The *t*-test and Chi-square were used to compare means and proportions, respectively. The level of statistical significance was set at $P < 0.05$.

Ethical clearance was obtained from the UBTH Ethical Research Committee before commencing this study. The Ethical Clearance/Protocol Research Number issued for the study was ADM/E.22 A/VOL. VII/104. In addition, verbal informed consent was obtained from each of the patients whose medical records were used, while the medical records for those who did not grant their informed consent were excluded from the study. Consent was sought from patient's relative where the patient had an impaired level of consciousness. Participants' confidentiality were respected and maintained by ensuring that no unauthorized person had access to the information on the data information sheets, that no information can be traced to the subjects (as the coding system was used for the data information sheets instead of writing the patients' names on them) and no unauthorized use of information was made.

RESULTS

A total of 507 admitted patients were evaluated during this study. Regarding sex distribution, 269 (53.1%) were

male while 238 (46.9%) were female. The mean age for all patients was 48.9 ± 17.8 years (Median of 46 years; Range of 17 years–89 years). Although the mean age for females (49.5 ± 17.7 years) was older than that of the males (48.3 ± 17.9 years), the difference was not statistically significant ($t = -0.771$, $df = 505$, $P = 0.44$). Table 1 showed the age and sex distribution of the patients. Table 1 revealed that those patients under 45 years of age were the most predominant with a frequency of 236 (46.5%) patients, followed by those within the age group of 45–64 years with a frequency of 146 (28.8%) patients. While the elderly age groups (65 years and above) constitute 125 (24.7%) of the admitted patients.

Table 2 showed the details of the medications causing ADRs. The drugs causing the most frequent ADRs were insulin in 14 (27.5%), nonsteroidal anti-inflammatory drugs (NSAIDs) in 10 (19.6%), antihypertensives in 8 (15.7%), and antimalarials in 5 (9.8%). In addition, herbal medications and antibacterials caused ADRs in 4 (7.8%) and 3 (5.9%) of patients, respectively. The other medications involved in ADRs are shown in Table 2. Furthermore, four fatal ADRs were observed during the study, in which, herbal medications caused two deaths, sulfadoxine/pyrimethamine combination (Maloxine®) caused one death, and iron dextran caused one death.

Table 3 showed the summary for the duration of hospital stay by different categories of patients. The mean duration of stay by all patients was 11.9 ± 11.3 days (median of 9 days). Females had a mean duration stay of 12.9 ± 12.3 days (median of 10 days) and stayed significantly longer than males who stayed a mean duration of 10.9 ± 10.2 days with a median of 7 days. ($t = -1.985$, $df = 505$, $P = 0.048$). The young age group (that is those <45 years old), stayed a mean duration of 11.3 ± 9.3 days (median of 9 days), while the middle-age group had a mean duration stay of 11.7 ± 9.7 days (median of 10 days). While the elderly age group (65 years and above) had a mean duration stay of 13.0 ± 15.7 (median of 8 days) appeared to have stayed longer than patients below 65 years of age (that is, the young and middle age groups). However, this was not found to be statistically significant ($t = -1.299$, $df = 505$, $P = 0.195$).

Patients admitted solely because of ADRs (ADR-out) had a significantly shorter duration of stay with a mean duration stay of 6.1 ± 3.7 days (median duration stay of 7 days) when compared to those without ADRs whose mean duration of stay was 11.6 ± 11.0 days (median duration stay of 8 days), and this was found to be statistically significant ($t = 2.110$, $df = 472$, $P = 0.035$). Those patients who developed ADRs during admission (ADR-in) had a mean duration of stay of 18.3 ± 14.8 days (median of 15 days). This was significantly

longer than the duration of stay for patients without ADRs ($t = -3.398$, $df = 487$, $P = 0.001$) and also significantly longer than the duration for those who were admitted solely because of ADRs ($t = 3.432$, $df = 49$, $P = 0.001$).

Figure 1 showed the frequency distribution pattern for patients experiencing ADRs versus their precipitant culprit drugs. Insulin caused ADRs in most number of patients 14 (27.5%). NSAIDs, was next in frequency of causation in 10 (19.6%), followed by antihypertensives in 8 (15.7%). Antimalarials, herbal medicines, and antibacterials caused ADRs in 5 (9.8%), 4 (7.8%), and 3 (5.9%) of patients, respectively. The other medications involved in ADRs are shown in Figure 1.

The systems/organs involved in ADRs are shown in Figure 2. The most frequently involved body system was the central nervous system (neurological) in 169 (33.3%) patients. This was followed by the gastrointestinal system in 110 (21.6%) patients, the skin (dermatological) in 89 (17.6%) patients, and cardiovascular system in 40 (7.8%) patients. The endocrine, respiratory, and renal systems were equally affected in 20 (3.9%) patients each. In this study, it was observed that ADRs often affected multiple body systems in a patient.

The causality rating for the observed ADRs was assessed using both the WHO causality assessment rating criteria and the Naranjo algorithm as shown in Table 4. Using the WHO causality assessment rating, certain cases were 10 (19.6%), probable cases were 17 (33.3%), and possible cases were 24 (47.1%). Using the Naranjo algorithm, definite cases were 9 (17.6%), probable cases were 19 (37.3%), and possible cases were 23 (45.1%).

An evaluation of some known risk factors for ADRs considered gender, age, number of medications used, and number of comorbidities. Gender was not found to be a statistically significant risk factor for ADRs in this study (Chi-square = 0.371, $P = 0.542$). Age was found to be a statistically significant risk factor as the elderly age group (age ≥ 65 years) was more at risk compared to those patients < 65 years ($\chi^2 = 10.152$, $P = 0.001$). Number of medications used was also a significant risk factor for developing ADRs ($\chi^2 = 13.174$, $P = 0.018$). Number of comorbidities was also found to be strongly associated with ADRs ($\chi^2 = 21.962$, $P < 0.001$). This was summarized in Table 5. The association of ADRs with patients age group or number of medications being used by the patients or number of individual patients co-morbidities was estimated by excluding patients who were admitted for ADR (that means, patients who developed ADRs prior to admission [ADR-out]).

ADRs were classified as mild (laboratory abnormality or symptoms not requiring treatment), moderate (laboratory abnormality or symptoms requiring treatment/admission to

hospital or resulting in non-permanent disability), severe (laboratory abnormality or symptoms that were life threatening or resulted in permanent disability), and fatal (any ADR that resulted in patient's death regardless and irrespective of the initial severity grading assessment).^{13,14} Most ADRs were mild and moderate in 21 (41.2%) cases and 24 (47.1%) cases, respectively. Severe ADRs occurred in 2 (3.9%) cases, while 4 (7.8%) cases were fatal ADRs.

Table 6 showed that the number of patients admitted solely because of ADRs (ADR-out) was 18, which accounts for 3.6% of admissions, while those that experienced ADRs during admission (ADR-in) were 33 (6.5%) patients. The total number of patients who had ADRs was 51, giving an ADR prevalence of 10.1% and incidence of 6.5%. The case fatality rate for ADRs was 7.8% (4/51), while the ADR-related mortality rate was 0.8% (4/507).

DISCUSSION

This study was designed to evaluate and highlight the pattern of medications most frequently involved in ADRs and the predisposing risk factors among adult medical inpatients in a Nigerian Tertiary Healthcare clinical practice setting, with the goal of preventing them and improving their treatment outcome. The most commonly affected system by ADRs was the central nervous system, probably because two out of the first three topmost implicated classes of medications causing ADRs manifest with symptoms referable to the central nervous system. For example, insulin leads to impair consciousness due to hypoglycemia, while antihypertensives manifest mainly with postural dizziness and headache due to postural hypotension and increased intracranial pressure, respectively. The next most common system involved was the gastrointestinal system, and this may be related to the fact that NSAIDs which constituted the second most common class of medications involved in ADRs usually manifest with problems referable to the gastrointestinal system. In fact, the systems largely affected followed the pattern of medications causing ADRs. Fattinger et al. found the gastrointestinal and the hematological systems as the first and second most commonly affected, respectively, among in-patients in their study. The pattern of morbidity and thus medication used differ in both settings, therefore, the pattern of ADRs will be different.

Mild and moderate ADR cases were far more frequent (41.2% and 47.1%, respectively) when compared to severe and fatal ADR cases. This pattern is similar to the findings in other studies.^{13,14} Furthermore, the elderly age group (≥ 65 years), presence of polypharmacy (taking more than 5 different pharmacologically active medications by a particular patient at the same time) and the presence of multiple comorbidities

in a particular patient are clinically proven and significant risk factors found to be associated with and predisposed adult medical in-patients to ADRs in this study, as this finding was quite similar to the patterns observed in other studies done somewhere else.^{6,11,17,18} ADRs occurring during admission (incidence) was observed in 6.5% of admitted patients, while 3.6% of the patients were admitted due to an ADR. The prevalence of 10.1% was similar to the ADR prevalence obtained in some European studies ranging from 6.6% to 11%.^{6,11,17} A meta-analysis in the United States by Lazarou *et al.* obtained an incidence of 6.7% for serious ADR among in-patients. The incidence and prevalence values observed, in this study, thus appear to be consistent with values in previous studies done in Switzerland, France, and the UK.^{9,11,17}

The ADR-related mortality rate of 0.8% was somewhat between values obtained in the UK study (0.15%) and to that obtained in a Swiss study (1.4%). The lower rate observed in the UK study can be attributed to the fact that the study looked at ADRs causing admissions only. The Swiss study not only showed a higher mortality but also looked at both ADRs causing admission and those occurring during admission.^{6,11}

Patients experiencing ADR during hospitalization (ADR-in) stayed significantly longer than those without ADR (median stay of 15 days vs. 8 days, respectively). ADRs have been found to prolong the duration of hospital stay in several studies.⁶⁻⁹ The median length of stay obtained for patients with ADR-in and those without ADR (15 days and 8 days, respectively) is similar to results obtained in an in-patient study by Davies *et al.* (14.5 days and 8 days, respectively). Patients admitted solely because of ADRs (ADR-out) had a statistically significant shorter duration of hospital stay (median of 7 days) than those patients without ADR that stayed a median duration of 8 days and also much shorter than those patients that developed ADR during hospitalization (median duration of 15 days). The finding of shorter duration of hospital stay for patients with ADR causing admission (occurring outside the hospital) compared to those without ADR and those with ADR occurring during admission has been noted in a French study. This shorter duration of hospital stay is related to the fact that there is a shorter diagnostic time for ADRs, in effect, a shorter time was spent looking for the cause of morbidity since this was obvious from initial clinical evaluation especially as most of the ADRs were mild (41.2%) or moderate (47.1%). Furthermore, their clinical management was essentially observational care and measures such as stopping or adjusting drug dosage.¹⁷ However, a few of the patients required more intense treatment with the prolonged stay.

Gender was not found to be a statistically significant risk factor associated with ADR in this study. This finding here differs from what has been observed in other several

studies.^{6,11,17,18} The association of gender and ADRs, such as other aspects of ADRs, is not well characterized among Nigerians and may differ. Some other known risk factors for ADR, however, were found to be significantly associated with ADRs in this study. These were age (elderly), number of prescribed medications (polypharmacy), and number of comorbidities.

The two methods used to ascertain causality rating for ADRs caused by a suspected drug, the WHO causality rating assessment criteria, and Naranjo algorithms, showed similar causality ratings, which strengthen the ascribed causality rating. The limitation and strength of this study were that it considered only consented adult medical in-patients; while unconsented adult medical inpatients, pediatric unit patients, and adult surgical unit patients were completely excluded from the study. Finally, all the observed results are completely and exclusively applicable to only adult medical inpatients in clinical practice setting.

CONCLUSION

The negative health burden and consequences of ADRs with the predisposing risk factors were significantly high among these adult medical in-patients. In this study, ADRs increase patients morbidity, mortality and length (duration) of hospitalization. Insulin and NSAIDs caused the highest number of ADRs which indicate that adequate caution, proper care and continuous monitoring must be implemented during the course of treating patients with these drugs in order to optimize their clinical efficacy and prevent the occurrence of ADRs in them. The elderly age group (≥ 65 years), presence of polypharmacy (taking more than 5 different pharmacologically active medications by a particular patient at the same time) and the presence of multiple comorbidities in a particular patient are clinically proven and significant risk factors found to be associated with and predisposed adult medical in-patients to ADRs in this study.

This information is useful for healthcare planning, management, budgeting, policy formulation and development of treatment protocols to enable appropriate and optimal patient care.

Acknowledgment

The authors of this research work want to especially acknowledge and thank the Almighty God for granting us wisdom and understanding to prepare this research work for publication.

Financial support and sponsorship

Nil.

Conflicts of interest

There is no conflict of interest.

REFERENCES

1. Mohamed YH, Mandira D, Fatema M. Drug Utilization and antibiotic use in the primary health care centers in Sharjah. *East Mediterr Health J* 1997;3:444-51.
2. Elixhauser A, Owens P. Adverse Drug Events in U.S. Hospitals. Healthcare Cost and Utilization Panel Statistical Report; April, 2007. Available from: <http://www.hcup-us.ahrq.gov>. [Last accessed on 2015 Jul 19].
3. NAFDAC. Safety of Medicines in Nigeria – A Guide for Detecting and Reporting Adverse Drug Reactions. NAFDAC/NPC/NIG; 2004. p. 1.
4. Beard K, Lee A. Introduction to Adverse Drug Reactions. *Adverse Drug Reactions*. 2nd ed. London: Pharmaceutical Press; 2006. p. 1-3.
5. Pirmohamed M, Park BK. Adverse drug reactions: Back to the future. *Br J Clin Pharmacol* 2003;55:486-92.
6. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, *et al*. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18 820 patients. *BMJ* 2004;329:15-9.
7. Davies EC, Green CF, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: A pilot study. *J Clin Pharm Ther* 2006;31:335-41.
8. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M, *et al*. Adverse drug reactions in hospital in-patients: A prospective analysis of 3695 patient-episodes. *PLoS One* 2009;4:e4439.
9. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. *JAMA* 1998;279:1200-5.
10. Brvar M, Fokter N, Bunc M, Mozina M. The frequency of adverse drug reaction related admissions according to method of detection, admission urgency and medical department specialty. *BMC Clin Pharmacol* 2009;9:8.
11. Fattinger K, Roos M, Vergères P, Holenstein C, Kind B, Masche U, *et al*. Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine. *Br J Clin Pharmacol* 2000;49:158-67.
12. WHO. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision – ICD-10. World Health Organization; 2007. Available from: <http://www.iacr.com.fr/icd10flyer.pdf>. [Last accessed on 2015 Apr 10].
13. Zed PJ, Abu-Laban RB, Balen RM, Loewen PS, Hohl CM, Brubacher JR, *et al*. Incidence, severity and preventability of medication-related visits to the emergency department: A prospective study. *CMAJ* 2008;178:1563-9.
14. Oshikoya KA, Njokanma OF, Chukwura HA, Ojo IO. Adverse drug reactions in Nigerian children. *Paediatr Perinat Drug Ther* 2007;8:81-8.
15. Causality Assessment Algorithms and Scales; 2005. Available from: <http://www.pharmacovigilance.co.in/causalityassessment.html>. [Last accessed on 2015 Apr 20].
16. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45.
17. Moore N, Lecomte D, Noblet C, Mabilille M. Frequency and cost of serious adverse drug reactions in a department of general medicine. *Br J Clin Pharmacol* 1998;45:301-8.
18. Rademaker M. Do women have more adverse drug reactions? *Am J Clin Dermatol* 2001;2:349-51.
19. Arulmani R, Rajendran SD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. *Br J Clin Pharmacol* 2008;65:210-6.
20. Shah RB, Gajjar BM, Desai SV. Drug utilization pattern among geriatric patients assessed with the anatomical therapeutic chemical classification/defined daily dose system in a rural tertiary care hospital. *Int J Nutr Pharmacol Neurol Dis* 2012;2:258-65.
21. Jimoh AO, Omar I, Adebisi IM, Sani Z, Bello A. Review of morbidity profile and drug prescribing patterns of a university clinic in North-Western Nigeria. *Int J Med Sci* 2014;1:107-15.
22. Fadare JO, Agboola SM, Opeke OA, Alabi RA. Prescription pattern and prevalence of potentially inappropriate medications among elderly patients in a Nigerian rural tertiary hospital. *Ther Clin Risk Manag* 2013;9:115-20.
23. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American geriatrics society updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2012;60:616-31.
24. Maio V, Del Canale S, Abouzaid S; GAP Investigators. Using explicit criteria to evaluate the quality of prescribing in elderly Italian outpatients: A cohort study. *J Clin Pharm Ther* 2010;35:219-29.
25. Liu GG, Christensen DB. The continuing challenge of inappropriate prescribing in the elderly: An update of the evidence. *J Am Pharm Assoc (Wash)* 2002;42:847-57.
26. Harugeri A, Joseph J, Parthasarathi G, Ramesh M, Guido S. Potentially inappropriate medication use in elderly patients: A study of prevalence and predictors in two teaching hospitals. *J Postgrad Med* 2010;56:186-91.
27. Chang CB, Yang SY, Lai HY, Wu RS, Liu HC, Hsu HY, *et al*. Using published criteria to develop a list of potentially inappropriate medications for elderly

- patients in Taiwan. *Pharmacoepidemiol Drug Saf* 2012;21:1269-79.
28. Adebayo ET, Hussain NA. Pattern of prescription drug use in Nigerian army hospitals. *Ann Afr Med* 2010;9:152-8.
29. Federal Ministry of Health. National Policy on Malaria Diagnosis and Treatment. National Malaria Control Programme. Abuja, Nigeria: Federal Ministry of Health; March, 2010.
30. Zaveri HG, Mansuri SM, Patel VJ. Use of potentially inappropriate medicines in elderly: A prospective study in medicine out-patient department of a tertiary care teaching hospital. *Indian J Pharmacol* 2010;42:95-8.
31. Guaraldo L, Cano FG, Damasceno GS, Rozenfeld S. Inappropriate medication use among the elderly: A systematic review of administrative databases. *BMC Geriatr* 2011;11:79.
32. Olanrewaju TO, Aderibigbe A, Busari OA, Sanya EO. Antihypertensive drug utilization and conformity to guidelines in a sub-Saharan African hypertensive population. *Int J Clin Pharmacol Ther* 2010;48:68-75.
33. Brattwall M, Turan I, Jakobsson J. Musculoskeletal pain: Prescription of NSAID and weak opioid by primary health care physicians in Sweden 2004-2008 – A retrospective patient record review. *J Pain Res* 2010;3:131-5.
34. Public Alert on Safety of Drugs Marketed/Manufactured in Nigeria and Other Countries. Abuja: National Agency for Food and Drug Administration and Control; 2011. Available from: http://www.nafdac.gov.ng/index.php/consumers/recalls-alerts/jmedsci_32_18R3recalls-a-safety-alerts/148-public-alert-on-safety-of-drugs-marketed-manufactured-in-nigeria-and-other-countries. [Last accessed on 2012 Sep 11].
35. Tamuno I, Fadare JO. Drug prescription pattern in a Nigerian tertiary hospital. *Trop J Pharm Res* 2012;11:146-52.
36. Isah AO, Ross-Degnan D, Quick J, Laing R, Mabadeje AF. The Development of Standard Values for the WHO Drug Use Prescribing Indicators. INRUD Nigeria/DAP/WHO. Available from: http://www.archives.who.int/icium/icium1997/posters/1a2_txt.html. [Last accessed on 2017 Aug 18].
37. World Health Organization. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision – ICD-10. World Health Organization; 2007. Available from: <http://www.iacr.com.fr/icd10flyer.pdf>. [Last accessed on 2017 Sep 10].
38. WHO Collaborating Center for Drug Statistics Methodology. Guidelines for Anatomical Therapeutic Classification Classification and Defined Daily Dose Assignment, 2016. World Health Organisation; 2017.