REVIEW OF ADVERSE DRUG REACTION REPORTS AT KOMFO ANOKYE TEACHING HOSPITAL (KATH), KUMASI-GHANA.

By

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A Thesis submitted to the Department of Clinical and Social Pharmcy, Kwame Nkrumah University of Science and Technology in partial fulfillment of the requirements for the degree of

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THIS THESIS IS SUBMITTED TO THE DEPARTMENT OF CLINICAL AND SOCIAL PHARMACY, KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, KUMASI, GHANA.

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JANUARY 2015

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DEDICATION

With gratitude to God, I dedicate this work to my wife Juliana Addai Kumah and children (Kwame Osei-Poku, Amma Birago and Kwaku Owusu-Asante.)

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This study has been possible through the contribution of many people and I thank all such people. However, I would like to express my sincere and deepest gratitude to my Supervisor Mrs Opare Addo for her guidance and constructive Comments throughout the study. I also express special thanks to the Lecturers of the Department of Clinical and Social Pharmacy Faculty of Pharmacy and Pharmaceutical Sciences and to Mr Robert Incoom for the knowledge and experience they have imparted to me. Finally I wish to thank Dr Karthyrine Spagensberg (Head of Polyclinic, KATH) and Mr Kwaku Sarfo for inspiring me a lot to complete this work.

DECLARATION

I hereby declare that this submission is my own work toward the Msc degree and to the best of my knowledge; it contains no material which has previously been published by another person or material which has been accepted for the award of any other degree of the university. Where this work is indebted to the work of others, due acknowledgement has been made in the text.

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ABSTRACT

BACKGROUND

The Drug Information Unit of KATH since 2011 as part of its duties been collecting ADRs reported in the hospital and submits them to the Food and Drugs Authority. Reports received since then (2011) have not been scientifically evaluated to assess its usefulness to patient care in the hospital. The study sought to review ADRs reports collected by the Drug information unit over a period of two years. The objective was to ascertain the category of patients who experience ADRs from their medications, the type of ADRs experienced, the kind of medications that gave the ADR and the outcome of the ADR.

METHODS

A retrospective study was conducted. ADRs reports received from January 2012 to December 2013 were reviewed. A data collection tool was designed and used to extract information from all the completed Food and Drugs Authorithy Adverse Reaction Reporting Form. Micromedex, Martindale, and British National Formulary (September 2013) were used to verify whether the reported Adverse Reactions were known and documented in compendia. The data obtained was entered into SPSS version 19 and analysed.

RESULTS

One hundred and thirteen (113) ADR reports were reviewed, 76.1% (n=86) involved females and 23% (n=26) were males. Forty five point one percent (45.1%, n=51) of ADRs reported involved Middle age (40-59yrs) individuals, thirty two point seven percent (32.7%, n=37) involved the elderly (>/=60). ADRs reported involving young adults (20-39yrs) was 20.4% whilst reports involving adolescent (13-19yr) and child (0-12yrs) were 0.9% respectively.

CNS reaction was the most frequently reported reactions (35.5%, n=39) followed by Dermatological reaction (15.9%, n=18) and then Gastro-Intestinal tract (GIT) reactions (9.7%, n=11).

Antihypertensive medications, specifically Calcium Channel blockers gave most of the reactions. Headache was the highest reported ADR (38.6%, n=17). Nifedipine was the cause of 47.1% (n=8) of headache reported. Sixty seven point six percent (67.6%) recovered whist 13.9 % had not recovered as at the time the ADR was reported. The outcome for 18.5% of reported ADRs was not known. Ninety point three percent (90.3%, n=102) of the reported ADRs were already known and documented. Seven point one percent (7.1%, n=8) of the ADRs reported were not found to be documented in any of the reference sources used. Two point six percent (2.7 % n=3) of the reported ADRs involved treatment failure. Pharmacist reported 57.5% (n=65) of the ADRs whilst doctors reported 40.7% (n=46).

Conclusion

Middle age patients and females are more likely to experience ADRs with their medication. Over a third of the ADRs reported affected the central nervous system. ADRs were more common in antihypertensive medications, particularly Calcium

Channel blockers. Majority of patients who experienced ADRs recovered, and a greater percentage (90.3%) of reported ADRs were known and documented in the Compendia. The few ADRs found not documented in any of the reference sources used may be new reactions that post marketing surveillance is revealing.

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LISTS OF ABBREVIATIONS

ADR---------- Adverse Drug Reaction

ADRF---------- Adverse Drug Reaction reporting Form

CVS---------- Cardiovascular System

DEENT---------- Dental Eye Ear Nose and Throat

EENT---------- Eye Ear Nose and Throat

FDA----------Food and Drug Authorithy

GIT----------Gasrto-Intestinal Tract

GUT---------- Gastro Urinary Tract

INR---------- International Normalised Ratio

KATH---------- Komfo Anokye Teaching Hospital

NSAID---------- Non Steroidal anti-inflammatory Drug

SPSS----------Statistical Package for the Social Sciences

ACEI---------- Angiotensin Converting Enzyme Inhibitor

ARB---------- Angiotensin Receptor Blocker

CHAPTER ONE

1.0 INTRODUCTION

An Adverse drug reaction (ADR) has been defined as "any response to a drug which is noxious and unintended occurring at human doses for prophylaxis, diagnosis and therapy or for the modification of physiological functions " (Edwards and Aronson, 2000). Adverse drug reactions (ADRs) are an important public health problem and one of the leading causes of morbidity and mortality (Shepherd, Mohorn, Yacoub *et al*, 2012; Lazarou, Pomeran and Corey 1998). It has been estimated that approximately 5.3% of hospital admissions were associated with ADRs (Kongkaew, Noyce and Ashcroft, 2008).

In the United Kingdom it is estimated that about 250,000 people that are admitted to the hospital in a year are due to adverse drug reaction (Hitchen, 2006). Studies have also shown that Adverse Drug Reactions are responsible for 11.5 % of hospital admissions in Norway, 13% in France and 16% in UK. Six point seven (6.7 %) of hospitalized patients' suffer serious ADRs whereas 0.32% suffers fatal Adverse Drug Reactions. (Moore, Lecointre, Noblet, Mabille *et al*.1998). In the United States, adverse drug reactions range between 4th and 6th among the leading causes of death in the hospital (Rhoden, 2009). The reported overall cost of drug-related morbidity and mortality exceeded $177.4 billion in 2000 in the United States of America. Also hospital admissions accounted for nearly 70% ($121.5 billion) of total costs, followed by long-term-care admissions, which accounted for18% ($32.8 billion(Ernst and Grizzle, 2001)

ADRs can have important consequences for patients and have a major impact on public health. They are among the leading causes of death in many countries and may

account for more than 5% of hospital admissions (Rogers *et al*, 2009). The cost of ADR in 2004 was estimated to be £466m a year in the United Kingdom NHS (Pirmohamed *et al*, 2004).

In developing countries such as Ghana, there is limited information on both the prevalence and the cost of ADRs.

In a study in the United Kingdom in which reports from patients and healthcare professionals between 2005 and 2007 were evaluated, 47 new serious reactions which were not included in summaries of product characteristics were identified (Avery, Anderson and Bond *et al*., 2009). Assessing post-marketing adverse drug reaction reports is therefore very important since it helps in detecting less common, but sometimes very serious ADRs. It has been postulated that approximately 30-80% of ADRs are preventable (Lepaklin, 2002). These reactions can be prevented only when they become known. Frequent assessment of adverse drug reaction reports will broaden our knowledge about adverse drug reactions that cannot be overlooked in the use of drugs. Since it is possible to prevent many adverse drug reactions, conscious efforts should be made to avoid problem-prone drug and monitor diligently medicines with predictable toxicity. This can be done only when time is taken to analyse reports given about medicines patient have been using. This study therefore sought to review ADRs reports collected by the drug information unit of Komfo Anokye Teaching Hospital (KATH) over a period of two (2) years.

1.1 RATIONAL FOR THE STUDY

Komfo Anokye teaching hospital is a referral centre located in the middle belt of Ghana specifically, in Kumasi the capital of Ashanti region. It is a tertiary institution affiliated to the Kwame Nkrumah University of Science and Technology. The hospital

offers specialist services in oncology, psychiatry, paediatrics, obstetrics, gynaecology, internal medicine and others. KATH is a 1200 bed capacity hospital and receives referrals from hospitals in and around Kumasi as well as referrals from the middle and northern part of Ghana. Many of these patients usually come with co-morbidities and complications. Poly-pharmacy is therefore, a common practice in managing patients at the hospital. In caring for these patients KATH uses a wide range of medicines with different brands. With such a wider population of patients, with all the risk factors for adverse drug reactions, using these medicines, it is expected that some may experience adverse drug reactions (ADRs). Some of these ADRs may not have been detected during clinical trials but may now be showing up.

As part of its duties the Drug Information Unit (DIU) of KATH has been collecting ADRs reported and submitting them to the Food and Drugs Authority. ADRs reports received since 2011 have not been scientifically evaluated to assess its usefulness to patient care at the hospital. The study sought to review ADRs reports collected by DIU over a period of two years. Findings of the study may lead to the discovery of new ADRs that some medicines cause. Findings may also help the Drug and Therapeutic Committee in deciding on what drugs to approve for procurement. Results of the study may also guide prescribers in selecting appropriate drugs for patients so that cost of ADRs related morbidities will be reduced. Finally, findings may provide useful information to FDA to guide them in asking for changes in product labelling.

1.2 RESEARCH QUESTIONS

1. What category of patients experienced adverse drug reaction (ADR) from their medications?

2. What type of ADR do patients experienced?
3. What kind of medicine gave the ADR?
4. What was the outcome of the ADR?
5. Are reported adverse drug reactions included in the product labelling?

1.3 GENERAL OBJECTIVE

The objective of the study is to conduct an audit on adverse drug reactions reported to the Drug

Information Unit of Komfo Anokye Teaching Hospital

1.4 SPECIFIC OBJECTIVES

1. To determine what category of patients experienced ADRs from their medications.

2. To determine the type of ADRs patients experienced

3. To determine the kind of medicine that gave the ADRs

4. To determine the outcome of the ADRs

5. To investigate whether reported adverse drug reactions are included in the product labelling.

CHAPTER TWO

2.0 LITERATURE REVIEW

Introduction

Adverse drug reaction remains a major public health problem. In the year 2000 alone it was estimated that the United States spent $177.4 billion on ADRs (Erns and Grizzle, 2001). In 2014 ADRs still rank fourth to sixth on factors that cause death in the United States (Qing-ping, Xiao-dong and Feng *et al*, 2014). Such expenditure is not unique to the United States alone. Medical cost in Dutch hospitals have been estimated to be 355million euro per year for ADRs and out of this amount 161 million euro was spent on preventable ADRs in 2004 (Hoonhout, de Bruijne and Wagner *et al*, 2009). In 2007 it was estimated that the cost of ADR-related visit to the emergency department in Canada was $35.7 million (Wu, Bell and Wodchis (2012). In China, a study by Qing-ping, Xiao-dong and Feng *et al* (2014) in which they analysed all cases of ADRs that occurred during inpatient procedures at the First Affiliated Hospital of Bengbu Medical College from January 1, 2008 to December 31, 2012, showed that for that one hospital alone 2739 ADRs were reported within 5years and the amount spent on these ADRs amounted to Yen 817401.69 (Qing-ping, Xiao-dong and Feng *et al*, 2014).

ADRs are important Public health issue so reporting of ADRs is deemed to be very essential since many adverse drug reactions are not detected during clinical trials. By the time of licensing, the drug would have been used in about 5000 human subjects and this allows only the more common ADR to be detected whiles majority of the potential ADRs go unnoticed (WHO, 2002).

Oftentimes information about serious adverse reactions which are rare, usually arising from chronic use, drug-drug interactions and the use in children, the elderly or

pregnant women is not available as a result of ethical considerations in these vulnerable patient groups. (Hegde *et al*, 2005; Fassihi & Robertson, 1990). For example, Rofecoxib a cyclooxygenase 2–selective, nonsteroidal anti-inflammatory drug (NSAID) that was approved by FDA in May 1999 for the relief of the signs and symptoms of osteoarthritis, for the management of acute pain in adults, and for the treatment of menstrual symptoms, and was later approved for the relief of the signs and symptoms of rheumatoid arthritis in adults and children, was withdrawn after 5years of introduction to the market because of increased risk of cardiovascular events, including heart attack and stroke. Again it took many decades before the deleterious effect of aspirin on the gastrointestinal tract became apparent. Several years passed before association of phocomelia with thalidomide became obvious. Terfenadine had to be withdrawn in 1998 following its introduction in 1985 because it was realized that it causes fatal cardiac arrhythmia (WHO, 2002). Concomitant administration of 40mg esomeprazole to warfarin treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing reports showed that a few isolated cases of elevated INR of clinical significance were reported during concomitant treatment (Teichert *et al*., 2011). Due to this new finding, it was recommended that monitoring should be done when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives. Recently an alert from Food and Drug Authorithy (FDA), Ghana, indicated that Paracetamol that has been approved for use over many decades have a rare but serious skin reaction including Stevens-Johnson syndrome, Toxic Epidermal Necrolysis and Generalised Exanthemtous Pustulosis (FDA Ghana, 2013).

2.1 Category of Patients who Experience ADRs

A number of factors contribute to patients experiencing adverse drug reactions from their medications. Among these are age, sex, polypharmacy and, comorbidities.

2.1.1 Age

Patients who are 60 years and above have a higher risk of experiencing ADRs from their medications (Jimmy and Padma, 2006). In their analysis of patterns of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital Jimmy and Padma concluded that occurrence of ADRs among older and elderly adults was significantly higher than other age groups. Other studies such as one by Hajar (2003) on adverse drug reaction and risk factors in older outpatients indicated that older people are more than twice as susceptible to ADRs as younger people (Hajar, 2003). In a similar way Debellis et al (2003) concluded in their study that ADRs are common among older persons in ambulatory settings and usually can be prevented (Debellis, Field and Gurwitz et al, 2003). A study titled Monitoring of adverse drug reactions associated with antihypertensive medicines at a university teaching hospital in New Delhi observed that incidence for ADR was higher in patients more than 40 years of age (Khurshid, Aqil andAlamet al, 2012) and that most of adverse drug reactions experienced involved middle aged patients and female. Some reasons that explain why older people are more prone to ADRs are that as people grow they develop many health problems. This necessitates the use of several different drugs at the same time, both prescribed and over the counter drugs. With age the liver's ability to metabolize drugs reduces (Budnitz, Shehab and Kegleret al, 2007), the kidneys are also less able to excrete drugs into the urine (Jimmy and Padma, 2006). Thus, the reduced clearance of the drug leads to increased body concentration of the drug increasing the risk of adverse effects (Klotz, 2009). Older

adults have smaller amount of body water but with a large proportion of fat compared to young adults (Rademaker M., 2001). Due to the low body water and larger body fat, medicines that dissolves in water reaches higher concentration and those that dissolves in fat accumulates in the tissues and can result in increased drug activity with associated adverse effects (Jimmy and Padma, 2006). This explains the observation by Jimmy and Pandma that type A reactions, which usually are augmented pharmacological action of the drug, are common among the elderly adults.

2.1.2 Sex

Sex has a significant effect on ADRs. Women are believed to be more prone to ADRs from their medications (Muaed Jamal Alomar, 2014). There are several anatomical and physiological differences between males and females. For example women have lower bodyweight and organ size with more body fat than men (Muaed Jamal Alomar, 2014). The rate at which female metabolize some drugs may be different from that of males because for example, hepatic enzyme CYP3A4 which metabolises many drugs is more active in female than in male (El-Eraky and Thomas, 2003). Such differences affect the pharmacokinetics and pharmacodynamics of drugs. Mateti *et al* (2012) in a study where they evaluated the incidence of ADRs due to angiotensin-converting enzyme Inhibitors in a cardiology department observed that about 80% of those who experienced ADRs were female (Mateti, Nekkanti, Vilakkathala, *et al* 2012). El-Eraky and Thomas (2003) suggested in a study that when drugs that prolong cardiac repolarisation are given women are more prone than men to develop torsade de pointes ventricular tachycardia. A study done on angiotensin converting enzyme inhibitors and cough by Muaed *et al* (2014) in northern India observed that females experienced cough more than males (Muaed, Jamal and Alomar, 2014). Rodenburg *et al* (2012) in a study about the incidence of ADRs caused by cardiovascular

medications; showed a marked difference between females and males (54% vrs 46%). The risk of experiencing an ADR from cardiovascular drugs in females and males compared as follows; for low-ceiling diuretics females chances of experiencing an ADR was 4.02 times greater than males. For cardiotonic glycosides females had 2.38 times greater chance of experiencing ADR than males and for high-ceiling diuretics females had a risk of 2.10 times greater than males (Rodenburg *et al*., 2012). One consistent observation in health research works is that females report symptoms of physical illness more frequently than males (Muaed, Jamal and Alomar, 2014). Female's inability to cope with ADRs and their willingness to seek medical care may also explain why they report more ADRs than males (Lagos-Jansen 2008).

2.1.3 Co-morbidities

Multiple disease make a patient more vulnerable to ADRs (Muaed, Jamal and Aloar, 2014). Investigators who carried out a study on prevalence and assessment of factors contributing to adverse drug reactions in wards of a tertiary care hospital, India, found that the number of diagnosis is a significant predisposing factor for ADRs. They also found that each additional diagnosis increases the odds of experiencing ADR by 1.2 (Demissew, Wubeante and Pramil, 2013). In a study led by Khokan (2012), Canada, in which the researchers reviewed the records of more than 64,000 patients who were aged 65 years or older, they concluded that comorbidity from chronic diseases and severity of illness increased the likelihood of ADRs (Khokan *et al* 2012). Min Zhang, Holman and Price *et al* (2009) in their study co-morbidity and repeat admission to hospital for adverse drug reactions in older adults also concluded that co- morbidity, but not advancing age, predicts repeat admissions for ADRs in older adults (Min Zhang, Holman and Price *et al*, 2009). Additional diagnosis goes with increase in the number of drugs a patient may be using. There is therefore an increased chance of

drug disease interaction or drug-drug interaction that leads to ADRs (Muaed, Jamal and Aloar, 2014). For example a patient being treated for arthritis with NSAIDs will have his risk of experiencing ADR increased if he is diagnosed to have peptic ulcer (Daneshtalab *et al*., 2004). In the same way diabetic patients who develop renal failure may develop ADRs such as hypoglycaemia or lactic acidosis from medications like Glibenclamide and Metformin which until the renal failure have controlled their sugar well. This is because the kidney is unable to eliminate the drug at the required rate and hence the drug action is prolonged (Muaed, Jamal and Aloar, 2014). Some beta-blockers being used to manage heart disease or high blood pressure can also worsen asthma and in diabetic patients it may mask the symptoms of hypoglycaemia. Prednisolone, because of its ability to cause water retention may gradually worsen congestive heart failure. Careful monitoring is therefore mandatory if it becomes necessary to use prednisolone in such conditions (Boer et al., 2003). AIDS for instance have been noted to increase the risk of ADRs, it has been reported that the incidence of ADRs such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is higher among those patients with HIV/AIDs (Muaed, Jamal and Aloar , 2014)

2.1.4 Polypharmacy

Multiple drugs are said to contribute to the vulnerability of patients to ADRs. A study in Taiwan indicated that the risk of ADRs in older people increases steadily as the number of medications used increases (Lai, Lin and Liao *et al*, 2012). A study titled pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital reported that the most common factors predisposing reporters to ADRs are polypharmacy and old age (Jose and Rao, 2006). Many studies have shown that patients taking more medications suffer from ADRs (Camargo,

Ferreira and Heineck, 2006) and (Onder, Pedone and Landi, *et al*, A2002). Using the minimum effective number of drugs to manage a condition is very essential in reducing incidence of ADRs. It has been observed that each additional medication multiplies the risk of an ADR by 1.1 (Davies, Green and Taylor, 2009). A combination of certain drugs cause synergistic toxicity and the toxicity may be greater than the sum of the risk of toxicity of either dug used alone (Hubbard, O'Mahony and Woodhouse, 2013). A risk of a patient experiencing NSAID-induced peptic ulcer may increase by 10% among elderly (Hubbard,O'Mahony and Woodhouse, 2013). However, if the NSAID is used together with a corticosteroid, it has been shown that the risk of developing peptic ulcer is about 15 times greater than people who are not using any of these drugs (Hubbard, O'Mahony and Woodhouse, 2013).(Piper, Ray and Daugherty 1991). Likewise the risk of an elderly patient being admitted at the hospital for hemorrhagic peptic ulcer disease increases several folds when anticoagulants are used together with NSAIDs. The risk are lower when these drugs are used individually (Hubbard, O'Mahony and Woodhouse, 2013).

2.2 Type of ADRs

Adverse drug reactions (ADRs) come in various forms. They are classified as side effects and allergic/hypersensitivity. Side effect reactions are dose dependent and predictable and they account for 85% to 90% of all ADRs (Jennifer, Goldman and Amanda *et al*, 2013). Allergies do not depend on dose and cannot be predicted. It is assumed that the immune system plays a role in bringing about these reactions. They form about 10% to 15% of all ADRs. (Jennifer, Goldman and Amanda *et al*, 2013). Marc, Riedl and Adrian *et al* (2003) also classified ADRs into immunologic and nonimmunologic according to their etiologies. Immune reactions specifically mediated by IgE are described as allergic reactions. Adverse drug reactions that

results from immune-mediated response to a drug agent in a sensitized patient is referred to as Hypersensitivity. Non immunologic ADRs are usually predictable. These include augmented pharmacologic action, hepatotoxicity, drug-drug interactions, drug overdose, idiosyncratic and intolerance. ADRs are observed from their effect on body organ systems such as the central nervous system (CNS), dermatological system, gastro-intestinal system (GIT), heamatologic system, metabolic system and others.

In a study by Haile, Ayen and Tiwari (2013) in which they sought to find the prevalence of adverse drug reactions and the factors which contribute to their prevalence, they observed that out of the total adverse reactions experienced by patients involved in the study about 83% of the reactions were type A, which represents augmentation of the pharmacological action of a drug. The metabolic systems, which accounted for 49(24.6%) were most frequently affected by adverse drug reactions, followed by gastrointestinal, 45(22.6%); hematological, 28(14.1%) and cutaneous, 21(10.6%) systems (Haile, Ayen and Tiwari, 2013). Khurshid and Mohammed *et al* (2012) found in a study in which they monitored adverse drug reactions associated with antihypertensive medicines at a university teaching hospital in New Delhi, that adverse drug reactions associated with central nervous system were the most frequent followed by musculo-skeletal complaints and gastro-intestinal disorders. Marco and Jonathan *et al* had a similar result in their study of Adverse Drug Reactions to Antiretroviral Therapy in HIV-Infected Patients. They found CNS reaction to be most common followed by GIT and the dermatologic reactions (Marco, Jonathan and Sumaya *et al*, 2 014). Jose and Rao in a study of pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital observed that, organ system most affected by ADRs was the dermatological system

and skin rash was the most frequently reported reaction (Jose and Rao, 2006). Prasad *et al* (2011) also found in their study of adverse drug reactions due to antihypertensive drugs in a tertiary care teaching hospital, that Cardiovascular adverse drug reactions constituted the highest reported ADRs, followed by gastrointestinal and respiratory reactions (Prasad, Kumar and Rahu *et al*, 2011). In another study by Jha *et al* (2007), the researchers found skin reaction to be the leading ADRs reported followed by gastrointestinal reactions, then CNS. Rashes were the most common type of ADRs reported followed by vomiting and then dizziness. (Jha, Bajrachary and Namgyal, 2007)

2.3 Medicines that have the potential to cause ADRs

Antihypertensives

In a study in which they monitored adverse reactions suspected to have been caused by antihypertensive medicines in a university teaching hospital in New Delhi, Khurshid *et al* found that calcium channel blockers were the drugs most frequently associated with ADRs followed by diuretics and then by β-blockers. Among individual drugs, Amlodipine was found to be the commonest medicine associated with adverse drug reactions (Khurshid, Aqil and Alam *et al*, 2012). Similar observation was made by Aqil, Imam and Hussain (2006) in their study entitled A pharmacovigilance study for monitoring adverse drug reactions with antihypertensive agents. They found Calcium channel blockers to be leading in causing ADRs followed by beta-blockers, angiotensin-converting enzyme inhibitors and diuretics. Headache is reported to be central nervous system ADR most frequently reported when Nifedipine and Amlodipine are given to manage hypertension (Micomedex, 2014). In a double-blind study where Nifedipine and Amlodipine were compared in treating hypertension it was observed that similar number of patients experience the

same kind of adverse reaction with both medicines. However, Nifedipine gave a greater number of headaches whilst Amlodipine gave more edema than nifedipine (Lorimer, Anderson and Laher *et al,* 1994). In United States and foreign controlled studies with 461 patients, the incidence of dizziness with immediate-release nifedipine was reported to be 27% compared to 15% for placebo (Micromedex, 2014). Another study which was multicenter, placebo-controlled, clinical trials involving 496 patients, reported the incidence of dizziness with extended-release Nifedipine as 4%, compared to placebo at 2%. Nifedipine has also been noted to cause rash and asthenia with incidence rate of 3% and 4-12% respectively (Micromedex, 2014).

Incidence of cough with administration of Nifedipine has been reported to be 6%. In United States and foreign controlled studies with 461 patients, the reported incidence of dyspnea/cough/wheezing with immediate-release Nifedipine was 6% compared to 3% for placebo (Micromedex, 2014). In another study where 800 hypertensive patients, were put on either nifedipine or lisinopril in a parallel, double-blind trial, 3.1% of those on nifedipine reported cough and 8.5% of those on lisinopril reported cough (Micromedex, 2014). The incidence of cough with nifedipine did not change with length of therapy, and was not related to dose, gender, or patient age (Micromedex, 2014). Peripheral oedema is another common ADR caused by calcium channel blocker. In a study in which how well patients (60yrs) are able to cope with long term treatment of hypertension with Amlodipine was investigated, it was realized that Amlodipine had a high tendency to cause oedema (P.001). Among the 828 patients involved in the study oedema occurred in 19% of them (Gastone, Bruno and Achille *et al*, 2002)

Angiotensin converting enzyme inhibitors

Cough is a common ADR caused by ACE inhibitors. Angiotensin receptor blockers also have been noted to causes cough with an incidence rate of 10% (Micomedex, 2014).In two prospective, parallel, double-blind, randomized clinical trials, patients who experienced dry cough on Lisinopril, and cough resolution when switched to placebo were rechallenged with Losartan 50 mg, Lisinopril 20 mg, or Hydrochlorothiazide 25 mg. In trial 1 (89% Caucasian; 64% female), cough occurred in 17%, 69% and 25% of patients who received Losartan 50 mg, Lisinopril 20 mg, or Hydrochlorothiazide 25 mg respectively. In trial 2 (98% Caucasian; 51% female), cough occurred in 29%, 62%, and 35% in patients who received losartan 50 mg, Lisinopril 20 mg, or placebo, respectively (Micromedex, 2014). Patients on conventional antihypertensive plus Losartan reports of chest pain with incidence of 12 % (Micromedex, 2014).

ACEI have been reported as a common cause of Angioedema experienced by patients and that patients on ACEI are said to be at risk of developing angioedema. Over the past decade the incidence of life-threatening angioedema associated with ACEI has been increasing and this has been attributed to increased use of long acting ACEI (Sarkar and Dhileepan, 2005). A study that looked at the risk individual medicines that works on the renin-angiotensin-aldosterone system poses for angioedema concluded that ACEI have 3-fold higher risk for angiodema than beta blockers and the risk is lower with angiotensin receptor blocker than ACEIs (Toh, Reichman and Houstoun et al, 2012).

Other ADRs such as nausea, rash and hypotension has been associated with ACE inhibitors. Angiotensin Converting Enzyme Inhibitors (ACEI) has also been reported

of as drug that induces cough. The incidence of ACE inhibitor-induced cough has been reported to be in the range of 5 to 35% among patients treated with these agents (Dicpinigatis, 2006). Angiotensin Converting Enzyme (ACE) normally break down the inflammatory peptide bradykinin, if ACE are inhibited there is accumulation of bradykinin, these cause sensitization of airway sensory nerves and enhance the cough reflex (Zuraw and Christiansen, 2011). A study by Mas, Gassò, and Álvarez *et al*, (2011) confirmed that bradykinins are involved in ACEI causing cough. ACE inhibitors are also known to cause angioedema. As ACEI prevents breakdown of bradykininsthere is bradykinin levels. The Bradykinin acts on vascular endothelial cells and increase vascular permeability. Fluids are able to leak out of the vessels accumulating to form the oedema. Zuraw, and Christiansen, (2011), recommended that ACEI induced Angioedema should always be considered in any patient taking an ACE inhibitor who experiences angioedema.

Antdiabetics

Metformin has been associated with diarrhoea with incidence rate of 53.2% for (immediate release) 9.6%to 12.5% for (extended-release) (Micrmedex, 2014). Asthenia, dizziness and headache are ADRs reported when metformin was taken. Incidence rate is 9.2% for asthenia and 5.7% for headache. Severe hypoglycemia may occur in patients receiving sulfonylureas like Glibenclamide, particularly in the elderly, debilitated, malnourished, or patients with adrenal or pituitary insufficiency. Also patients with renal or hepatic insufficiency (Micromedex, 2014).

Antihistamine

Cetirizine is reported to cause Urticaria with pruritis and facial oedema. (Schroter *et al*, 2002;

Calista *et al*, 2001)(Micromedex, 2014)

NSAIDs

Headache has been reported in 1 to 10% of patients treated with diclofenac or other NSAIDs (Micomedex, 2014).In a multiple-dose studies, 12.5% of patients receiving diclofenac potassium therapy (n=345) compared with 17.1% of patients receiving placebo therapy (n=327) reported headache (Micromedex, 2014). Stroke, dizziness, asthenia and paraesthesia have been reported with the use of NSAIDs (Micromedex, 2014). The risk of developing upper gastro intestinal bleeding is very high with patients taken aspirin (Micromedex, 2014). Aspirin like other NSAIDs inhibits prostaglandin biosynthesis by the fundic mucosa of the stomach this impairs the protection that protaglindin provide to the mucosa resulting in mucosal damage. Such damage may include erosions and micro bleeding. Again Aspirin increases reflux of bile acids into the stomach and this also help the erosion of the gastric mucosa (Micromedex, 2014). Between 1% to 10% of patients taking Diclofenac potassium or other NSAID therapy are reported to experience rash (Micromedex, 2014). Other skin reactions such as Stevens-Johnson syndrome, Toxic epidermalnecrolysis and Exfoliative dermatitis have been reported with NSAIDs but rarely occur. It has also been reported that Tramadol causes pruritis with incidence rate between 3% to 11.9% (Micromedex, 2014). In a three 12-week, randomized, double-blind, placebo controlled studies (combined n=1763) Pruritus was reported in 4% (9/216), 5% (15/311), 3% (18/530) of patients receiving Tramadol extended-release tablets 100 mg, 200 mg, or 300 mg, respectively; compared with 1% (7/668) of patients receiving placebo (Micromedex, 2014). Another two 12-week placebo-controlled studies reported that pruritis experienced by patients taking Tramadol extended release tablet (100mg , 200mg, 300mg and 400mg) was 6.2% (25/403), 8.5% (34/400), 7.5%

(30/400), and 11.9% (24/202) respectively, compared with 1% (4/406) of patients receiving placebo (Micomedex , 2014).

CHAPTER THREE

3.0 METHODS

3.1 PROFILE OF STUDY AREA

The study was conducted at Komfo Anokye teaching hospital. KATH is a tertiary institution located in the middle belt of Ghana specifically, in Kumasi the capital of Ashanti region. It is a tertiary hospital affiliated to the Kwame Nkrumah University of Science and Technology. The hospital offers primary services as well as specialist services in oncology, psychiatry, paediatrics, obstetrics and gynaecology, internal medicine and others. KATH is a

1200 bed capacity hospital and receives referrals from hospitals in and around Kumasi as well as referrals from the middle and northern part of Ghana.

3.2 STUDY DESIGN

The study was retrospective, covering the period from January 2012 to December 2013. All reports (113) submitted to the Drug Information unit of Komfo Anokye Teaching Hospital within the study period was included in the study.

3.3 DATA COLLECTION METHOD

A data collection tool was designed and the researcher reviewed all ADR forms submitted to the drug information unit and extracted relevant data using the data collection tool. Micromedex, Martindale, and British National Formulary (September 2013) were used to verify whether the reported adverse reactions were known and documented in compendia.

3.4 DATA HANDLING AND ANALYSIS

The data captured was entered into Statistical Package for Social Sciences (SPSS) Version 19.0 database and examined, cleaned and analyzed. Various relevant tables and figures were created from the data to allow for easy analysis and interpretation. Categorical variables were presented as frequencies and proportions and in tables and figures. Median and interquartile range were used to present the age of the study participants as age was a continuous data with skewed distribution. Kruskal-Wallis and Pearson Chi-square Test were used to determine association between age and outcome of adverse drug reaction. Chi-squared test was also used to determine association between gender and type of ADR and gender and outcome of ADR. A p-value < 0.05 was used to assess the level of significance of the assumed hypotheses.

3.5 SAMPLING

All ADR collected from January 2011 to December 2013 were sampled for the study.

3.6 PRE TESTING

Reports received in January 2012 were used to pre-test the data collection tool designed. This helped in amending the data collection tool.

3.7 INCLUSION CRITERIA

All ADR forms submitted to the Drug Information Unit within the study period were reviewed

3.8 EXCLUSION CRITERIA

All ADR reports that were not complete were excluded

3.9 ETHICAL CONSIDERATIONS

Approval was sought from the management of KATH as well as the head of Drug Information Unit. Ethical clearance was also sought from the Committee on human research, publication and ethics, Kwame Nkrumah University of Science and Technology. To ensure confidentiality, initials were used for names of patients. Names of health professionals were not captured and names of manufacturing companies involved were coded. The Computer used for data entry was password protected so that unauthorized persons did not get access to the information.

3.9 LIMITATIONS

Most of the reports were from one directorate. If all directorates were reporting as it should be the picture may have been different.

CHAPTER FOUR

4.0 RESULTS AND ANALYSIS

ADR reports reviewed over the period of January 2012 to December 2013

Most of the ADRs reports (n=92) were collected in the year 2013, whilst 24 reports were collected in the year 2012

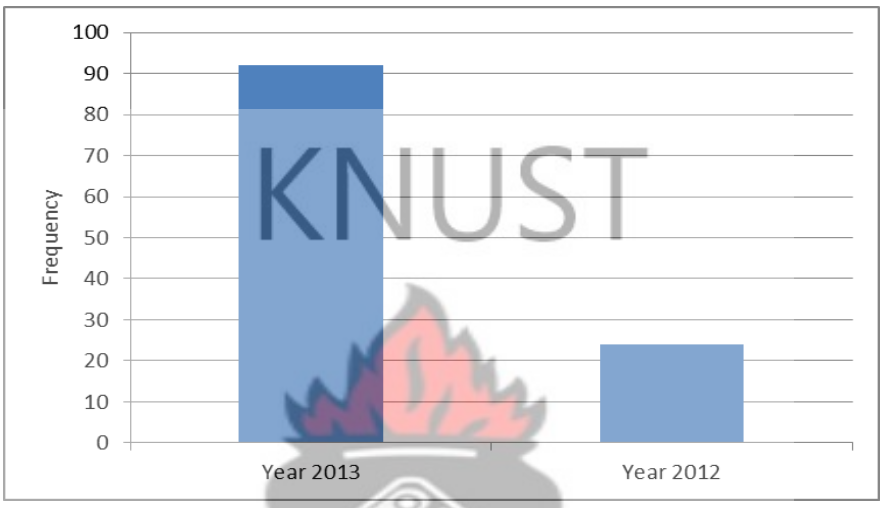

Fig 4.1 Distribution of ADRs reports over the two years period of the study.

The total number of reports submitted was 116. One hundred and thirteen (113) reports equivalent to 97.4% met the inclusion criteria. Three (3) reports were excluded because they either did not state the medicine that gave the reaction, the kind of reaction the patient experienced or the outcome of the reaction experienced. All the 113 were completely filled. Data was extracted from these forms. Each patient reported one ADR.

4.2 Category of patients who experienced ADRs from their medications.

The majority of patients (45.1%), (n=51) who reported experiencing ADRs were in the middle age group (40-59yrs). This was followed by the elderly with a percentage of 32.7% (n=37). Young adults then followed with a percentage of 20.4% (n=23) as shown in figure 4.1 below.

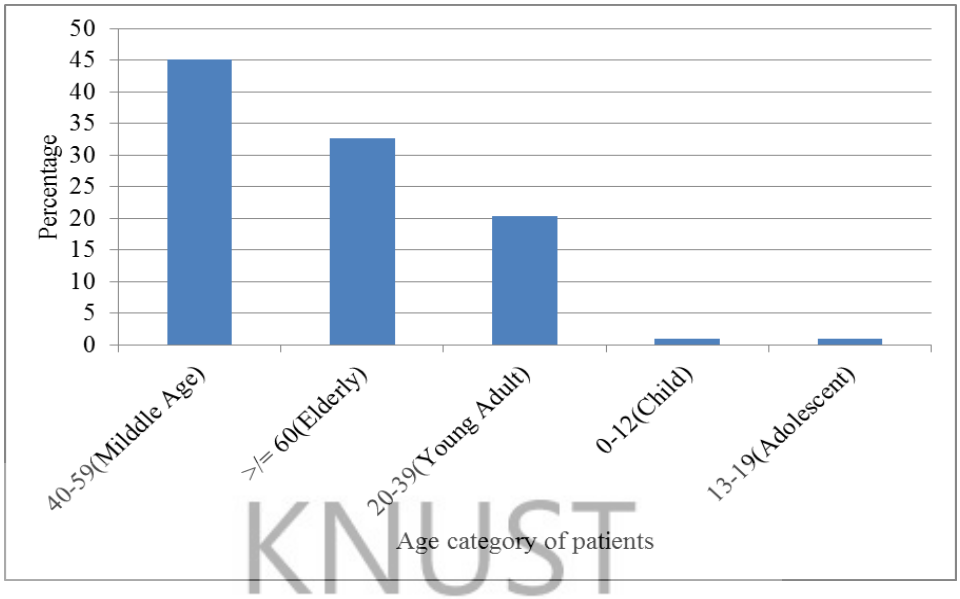

Figure 4.2: Age categories of patients reporting with ADRs

4.3 Sex distribution of patients reporting ADRs

Most of the patients (n=86) 76.1% in whom ADRs were reported were females and (n=26) 23% were male. This is shown in Figure 4.2 below.

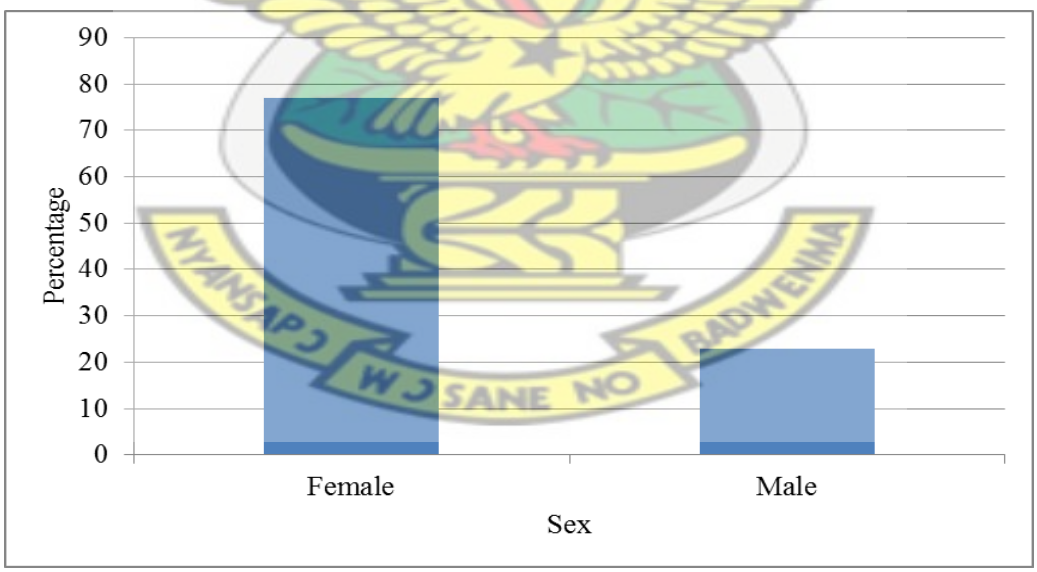

Figure 4.3: Sex distribution of Patients reporting with ADRs

4.2.0 Type of ADRs patients experienced

The organ systems and the type of ADRs that affected them are shown in the following figures.

4.2.1 Organ Systems affected by ADRs

The most affected organ system was the central nervous system (CNS) with a percentage of 35.5% (n=39). This was followed by Dermatological system (Skin) with a percentage of 15.9% (n=18). The Gastro-Intestinal tract was the third most affected organ system. It had a percentage of 9.7% (n=11). Cardiovascular reactions constituted 7.1% (n=8), whilst respiratory reactions constituted 6.2% (n=7). Eye Ear Nose and Throat (EENT) and Gastro Urinary Tract reactions had the same percentage occurrence of 3.5% each. (n=4). There were also treatment failures as indicated in the table 2. This constituted a percentage of 2.7 (n=3).

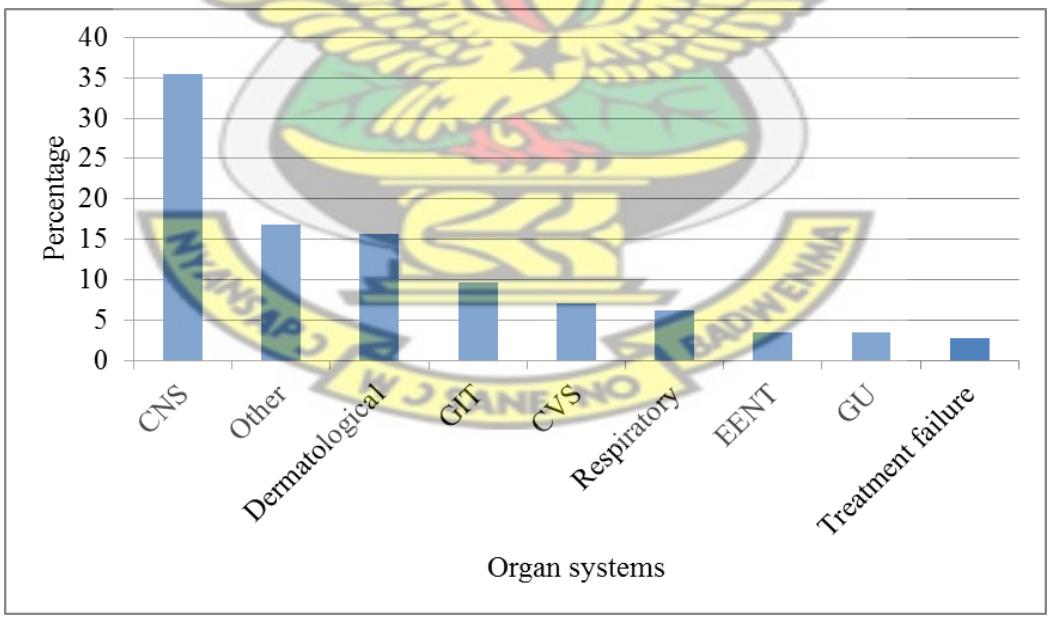

Fig 4.4: Organ systems affected by ADRs

4.2.2 ADRs affecting the CNS

Headache was the most frequently experienced reaction with a percentage of 17.7% (n=20), dizziness followed with a percentage of 7.1% (n=8). Asthenia was third with a percentage of 4.4% (n=5) Paraesthesia was fourth with a percentage of 3.5% (n=4) as shown in figure 4.4 below.

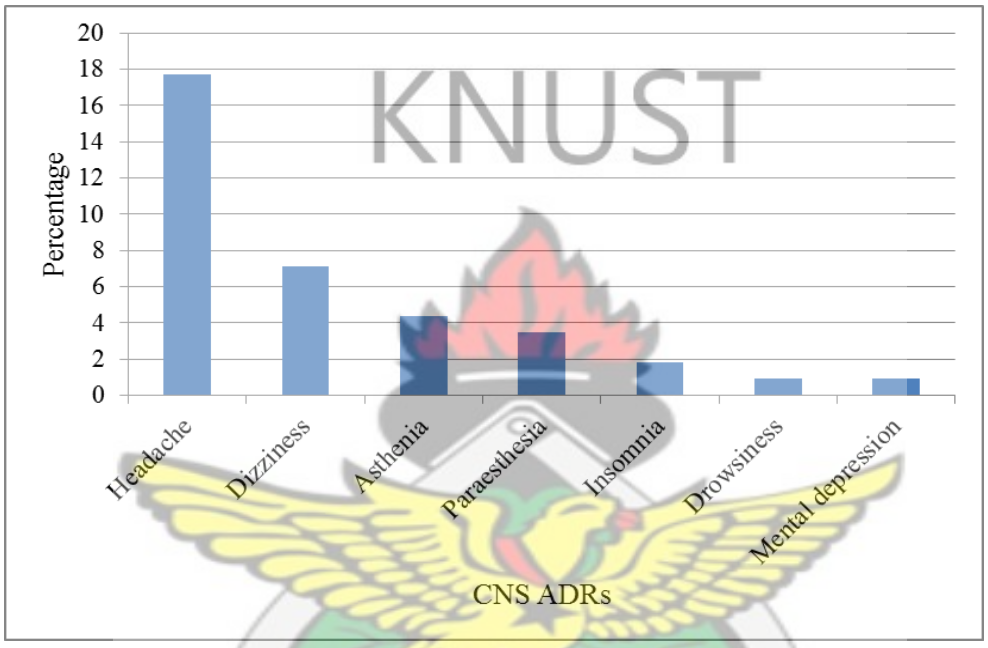

Fig 4.5: CNS related ADRs experienced by Patients

4.2.3 Dermatological reactions

Rash was the most frequently reported dermatological ADR (41.18%) (n=7) followed by Angiodema 35.29% (n=6) and then itching with a percentage of 17.65% (n=3) as shown in figure 4.5 below.

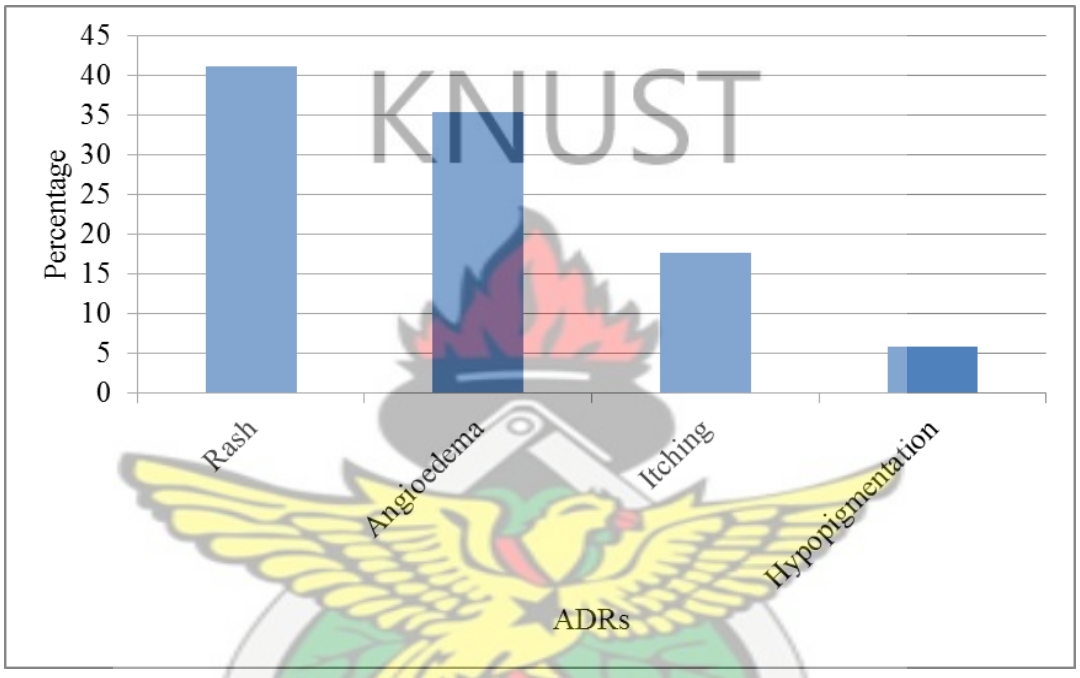

Fig 4.6: Dermatological ADRs experienced by Patients

4.2.4 Individual medicines contribution to rashes experienced

Tramadol gave most of the rash reported with a percentage of 28.6%, (n=2). All other five medicines gave the same percentage report of rash 14.3%, (n=1) as shown in figure 4.6 below.

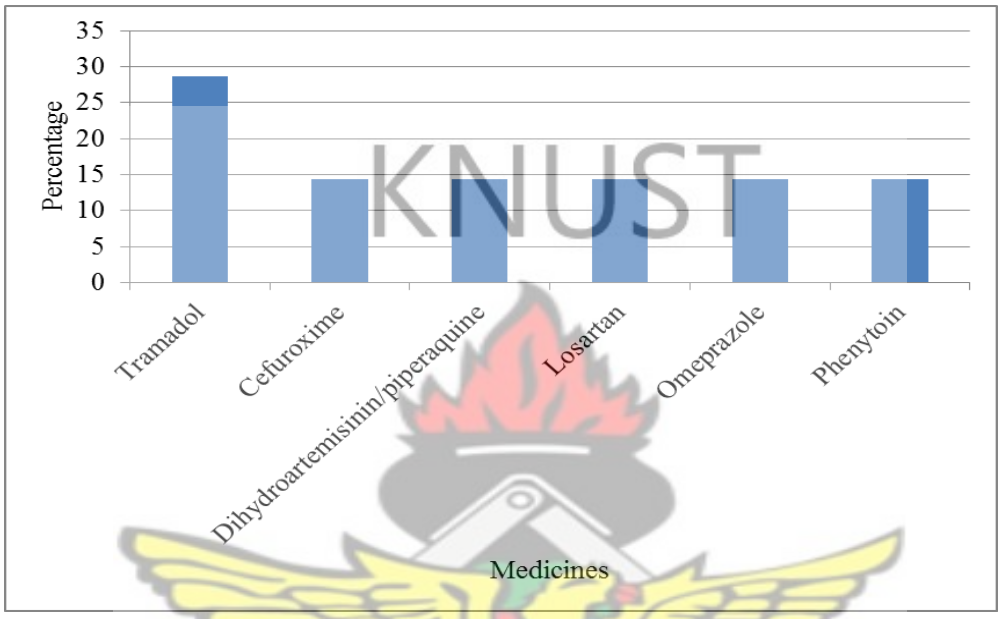

Fig 4.7: Individual medicine's contribution to rash reported as an ADR

4.2.5 Individual medicines contribution to angioedema experienced

Lisinopril gave most of the report of angioedema with a percentage of 66.7% (n=4). Calcium Carbonate and Artemether/Lumefantrine gave the same percentage report of 16.7% (n=1) each as shown in figure 4.7 below.

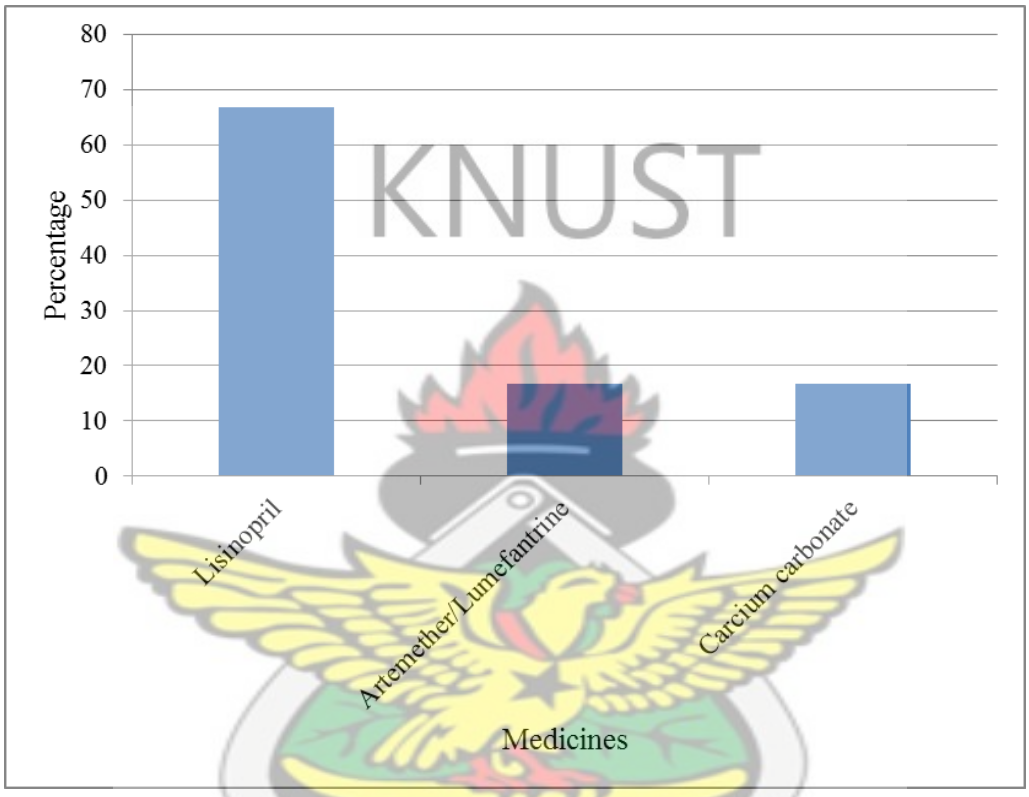

Fig 4.8: Individual medicine's contribution to Angioedema reported ADR.

4.2.6 Gastro-intestinal ADRs

The most common GIT ADR reported was diarrhoea with a percentage of 40% (n=4). Followed by abdominal pain 30% (n=3), constipation 20% (n=2) and vomiting 10% (n=1) as shown in figure 4.8 below.

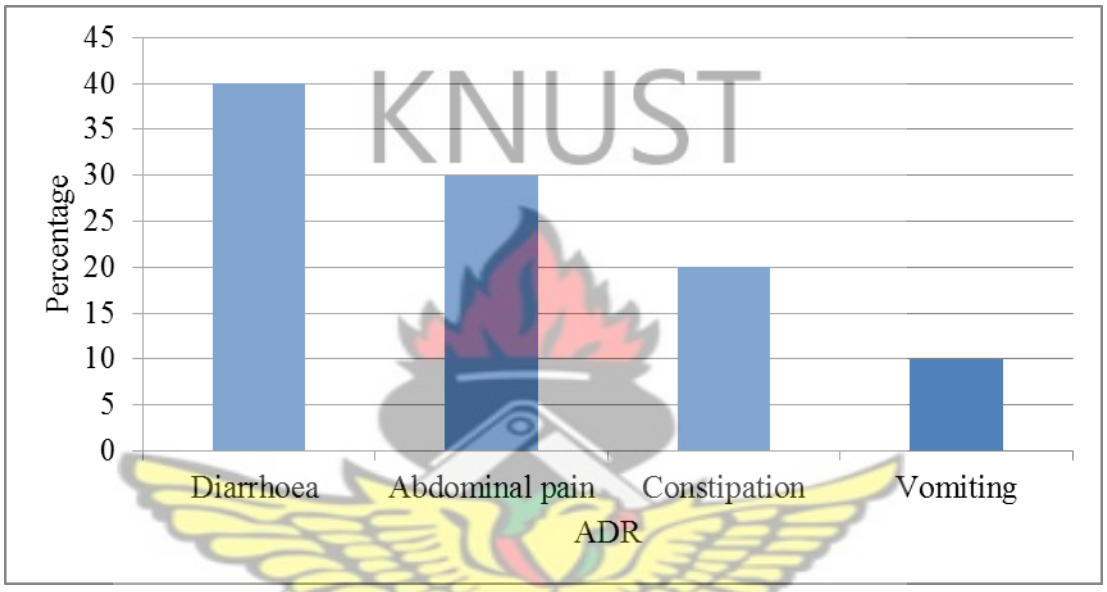

Fig 4.9: Gastro-Intestinal Tract ADRs experienced by Patients

4.3.0 Medicine that gave the ADRs

Antihypertensive medicines caused most of the ADRs reports with (n=64) and a percentage of 56.5% of reports submitted. This was followed by antibiotics and hypoglycaemics with occurrence of 7 reports constituting 6.2% each. Analgesic, anticonvulsant and diuretic each had six (6) reports constituting 5.3% each. Three (3) reports (2.7%) involved haematinics. Antimalaria, antidepressant and antibiotic/steroid had two (2) reports each constituting 1.8% each. Others had one (1) report each and together constituted 7.1%. These are shown in fig 4.9.

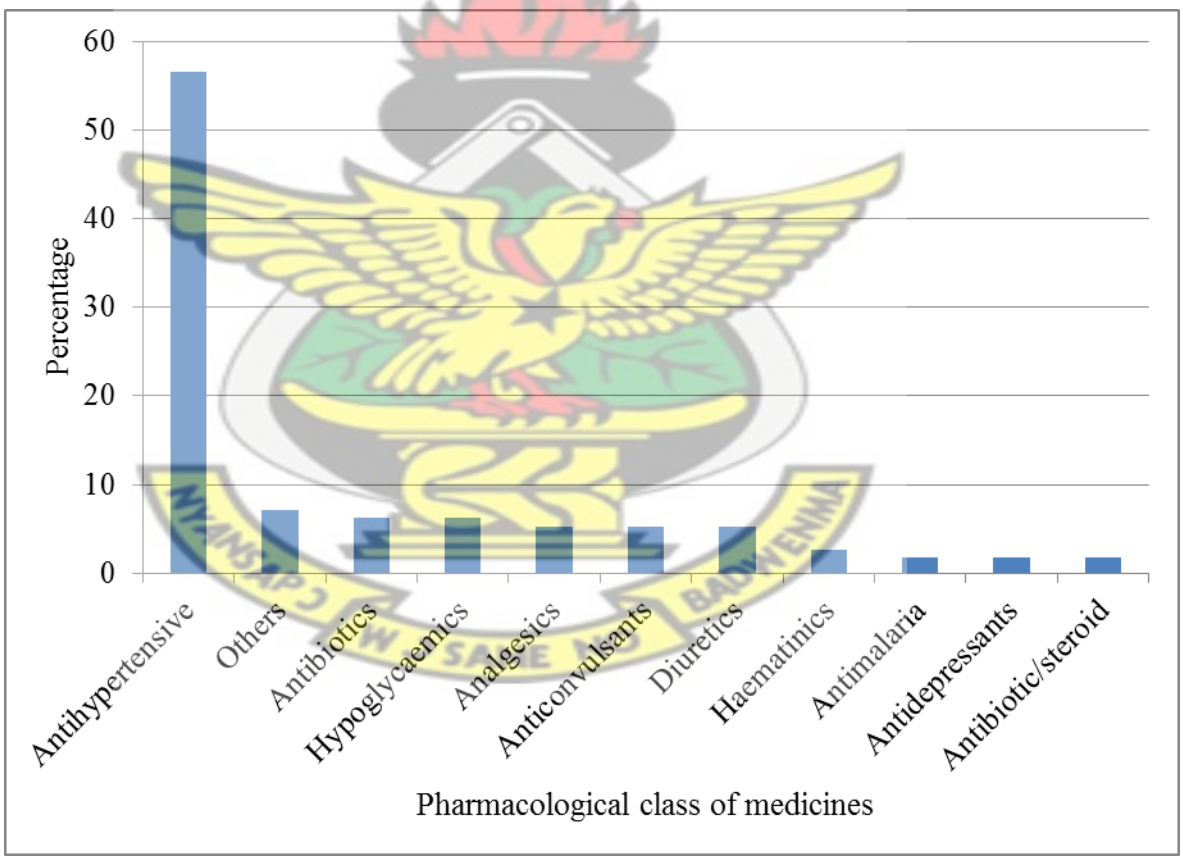

Fig 4.10: Pharmacological class of medicine suspected to have given ADRs

4.3.2 Sub classification of medicine that gave reported ADRs

Calcium channel blockers ranked first n=33 (29.2%) among the drugs suspected to have given ADRs. It was followed by Angiotensin converting Enzyme Inhibitor (ACEI) which had a frequency of seventeen (17) constituting 15%. Angiotesin Receptor Blockers followed with a frequency of ten (10) constituting 8.8%.opoids and Thiazolidine each had five (5) occurrences with a percentage of 4.4% whilst carboxamide, Biguanide and Centrally acting Antihypertensive each had four (4) occurrence constituting 3.5% each. Artemisinine based , Macrolide and Tricyclic Antidepressants each had two occurrence presenting 1.8%. There were others that had only one occurrence each and together represent 16.2% as shown in fig4.10

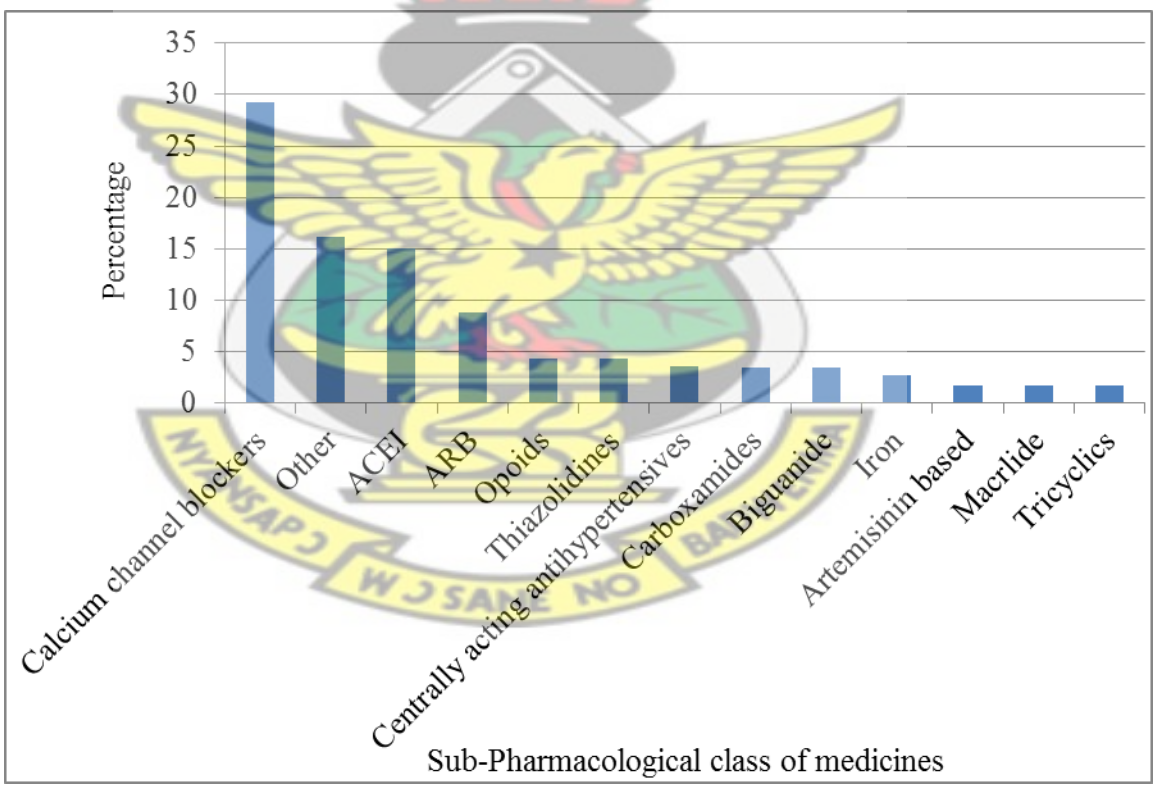

Fig 4.11: Sub-classification of Pharmacological class of drugs suspected to have caused ADRs experienced by Patients

4.3.3 ADRs caused by antihypertensives

Headache was the highest reported ADR n=17 (38.63) caused by antihypertensive.

With paraesthesia being the lowest reported ADR caused by antihypertensives n=2 (4.9%).

These are shown in figure 4.11 below.

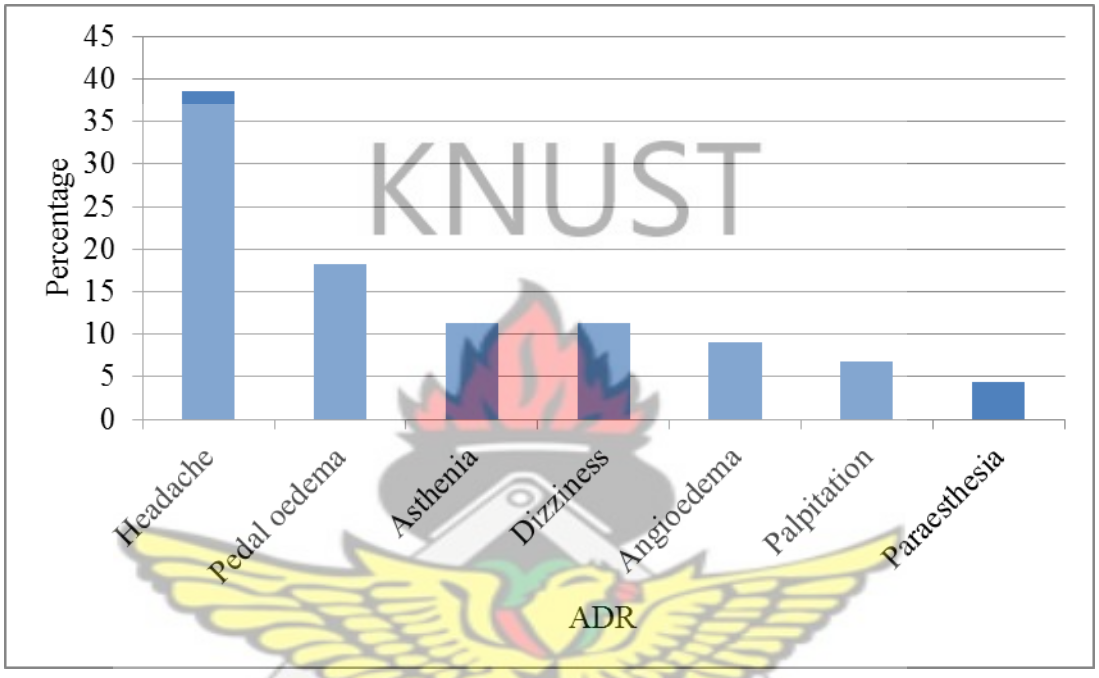

Fig 4.12: ADRs caused by Anti-hypertensives.

4.3.4 Headache Experienced With Antihypertensives

Nifedipine had the highest percentage report of headache n=8 (47.1%) followed by amlodipine n=5 (29.41%) and the bendrofluazide n=2 (11.76%). Lisinopril and losartan had the same percentage report of headache (n=1) with a percentage of 5.88% as shown in figure 4.12 below.

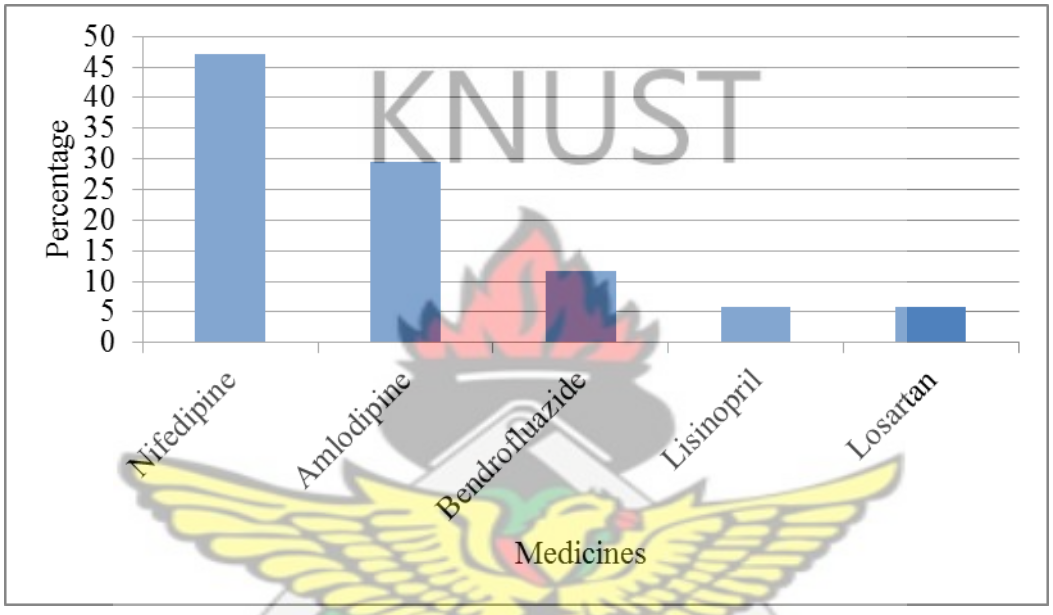

Fig4.13: Headache caused by individual Antihypertensives.

4.3.5 Pedal Oedema Caused by Individual Antihypertensives

Both Amlodipine and Nifedipine had same percentage report of pedal oedema 50% each (n=4).

This is shown in figure 4.13 below.

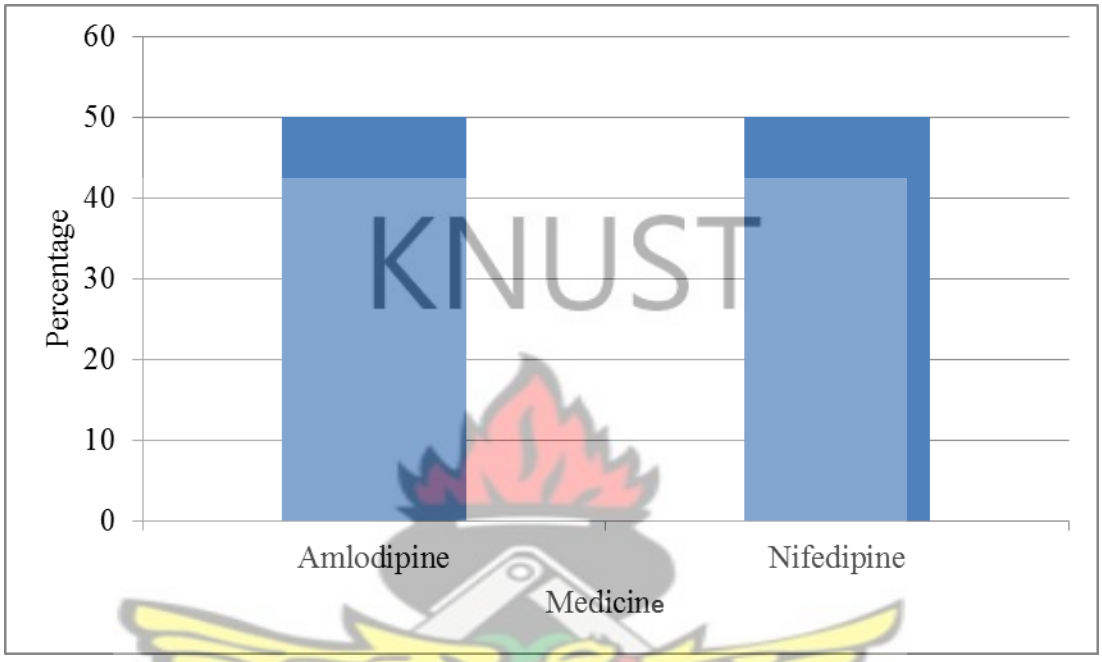

Fig 4.14: Pedal oedema caused by individual antihypertensives.

4.3.6 Diziness Caused by Individual Antihypertensives

Nifedipine and losartan both had the same percentage report of dizziness is 40% (n=2). followed by amlodipine with a percentage of 20 % (n=1). This is shown in figure 4.14.

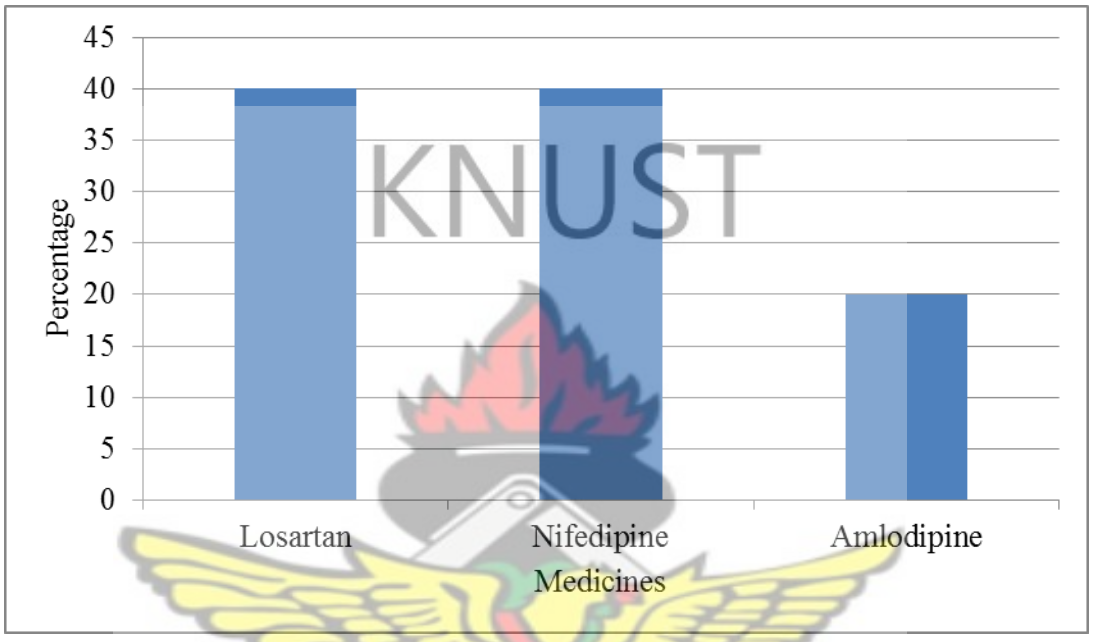

Fig 4.15: Diziness caused by individual Antihypertensives

4.3.7 Antihypertensives that gave cough as an ADR

Lisinopril gave 85.7% (n=6) of cough reported and Nifedipine 14.29% (n=1). This is shown in Fig4.15

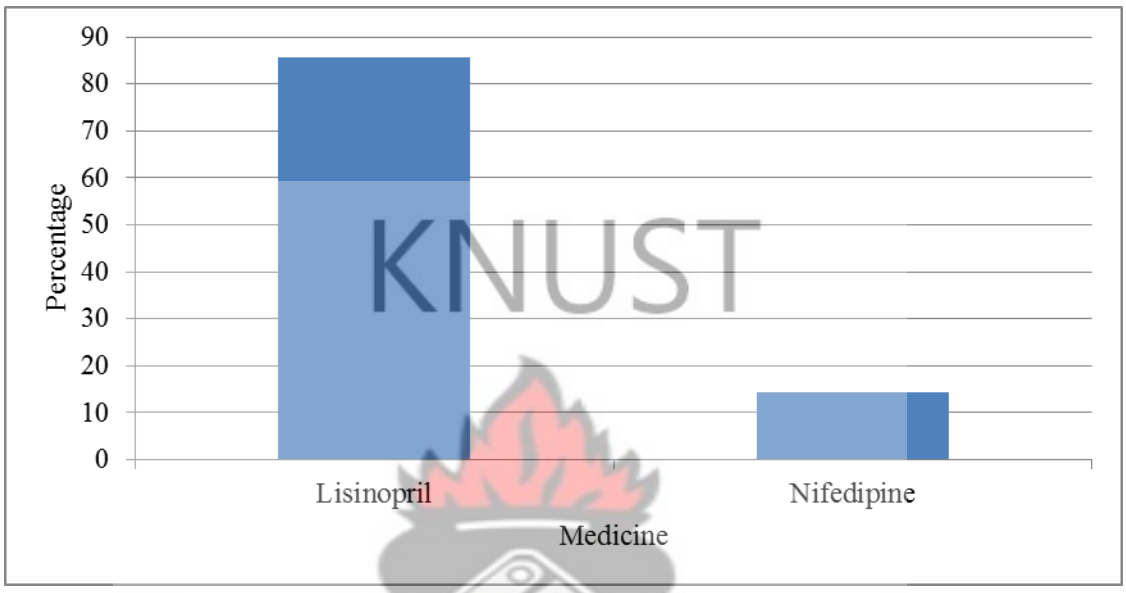

Fig 4.16: Cough caused by individual Antihypertensives

4.4.0 Outcome of ADR

A high number (n=76) representing 67.3 % recovered from the ADR followed by unknown to have recovered (n=20) representing 17.7%. Not yet recovered were (n=15) representing13.3%. and hospitalise (n=3) representing 2.7% this is shown in figure 4.16.

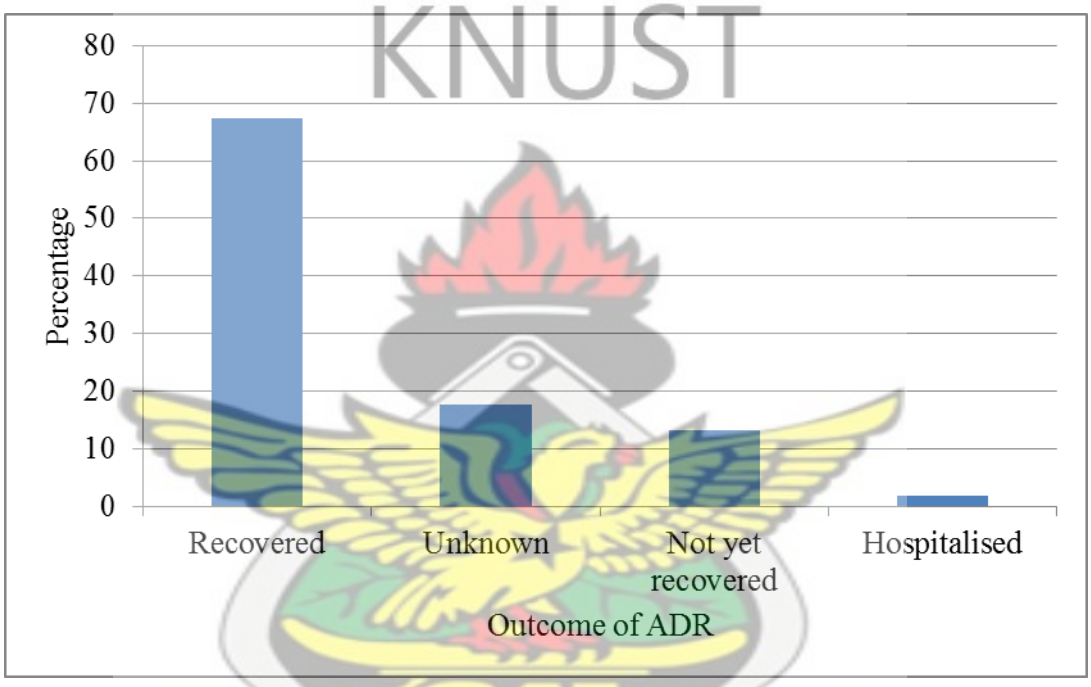

Fig 4.17: Outcome of ADRs experienced.

4.5.0 Inclusion of reported ADRS in compendia

Most of the ADRs (n=102) representing 90.3% were known and documented in compendia. Few 7.1% (n=8) were not documented in any of the reference sources used. The missing (n=3, 2.6%) represents treatment failure. These are shown in fig4.17.

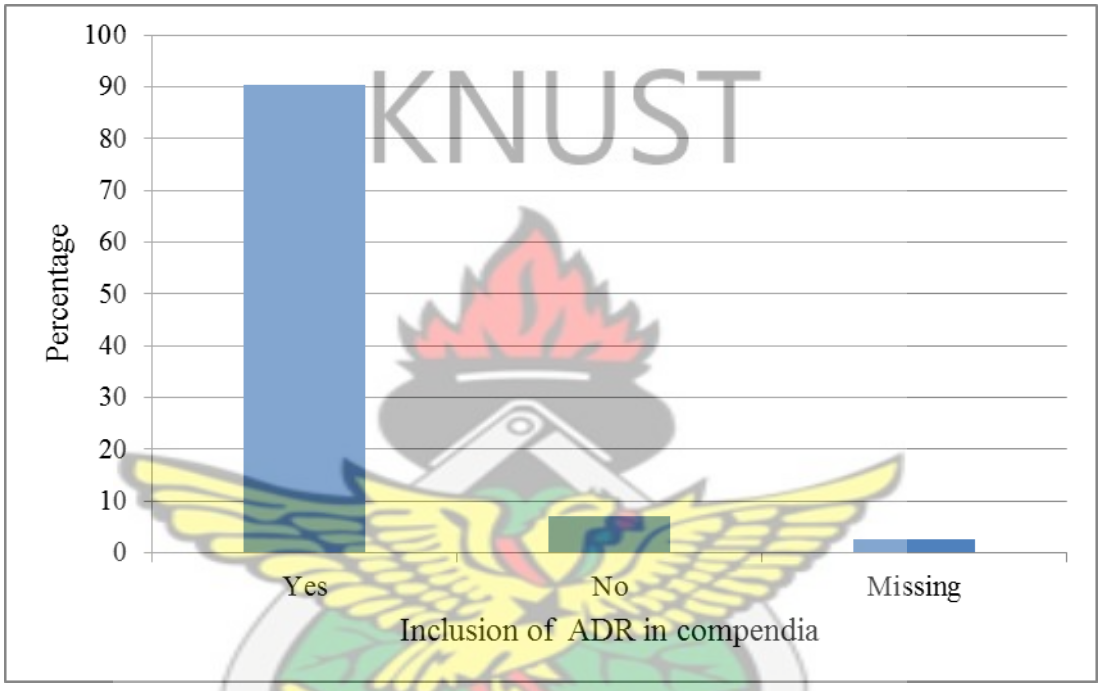

Fig 4.17: ADRs inclusion in compendia.

Table 4.1 ADRs not Documented

Drug	ADR Not Documented
Cetirizine	Galactorrhoea
Co-Amoksiclav	Paraesthesia
Lisinopril	Drowsiness
Calcium Carbonate	Angioedema
Nifedipine	Hypopigmentation
Metformin	Constipation
Bendrofluazide	Pedal oedema
Neopenetranfortemiconazole+metronidazole	Amenorrhea

A table showing ADRs not documented in reference sources used.

4.6.0 Profession of those who reported the ADRs

Most of the ADRs (n=65) representing 57.5% were reported by Pharmacists. This was followed by Doctors (n=46) representing 40.7%. Nurses and Pharmacy Technicians reported one ADR each representing 0.9% each as shown in fig.4.18

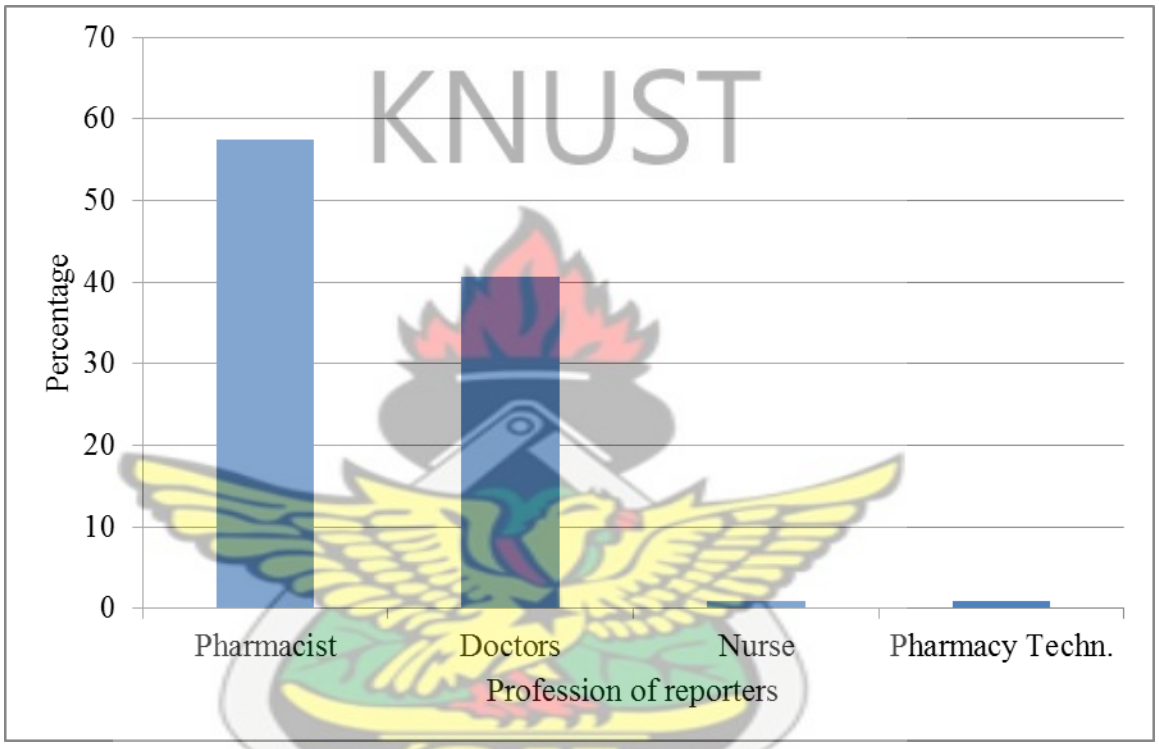

Fig4.18: ADRs reported by various Professions

4.7.0 Directorate/unit of ADR reporters

The Polyclinic directorate reported most of the ADRs (n=103) representing 90.2%. Followed by Drug Information (n=7) representing 6.1%. Anaesthesia, DEENT and Medicine reported one (1) ADR each which represent 0.9% each. These are shown in fig. 4.19 below.

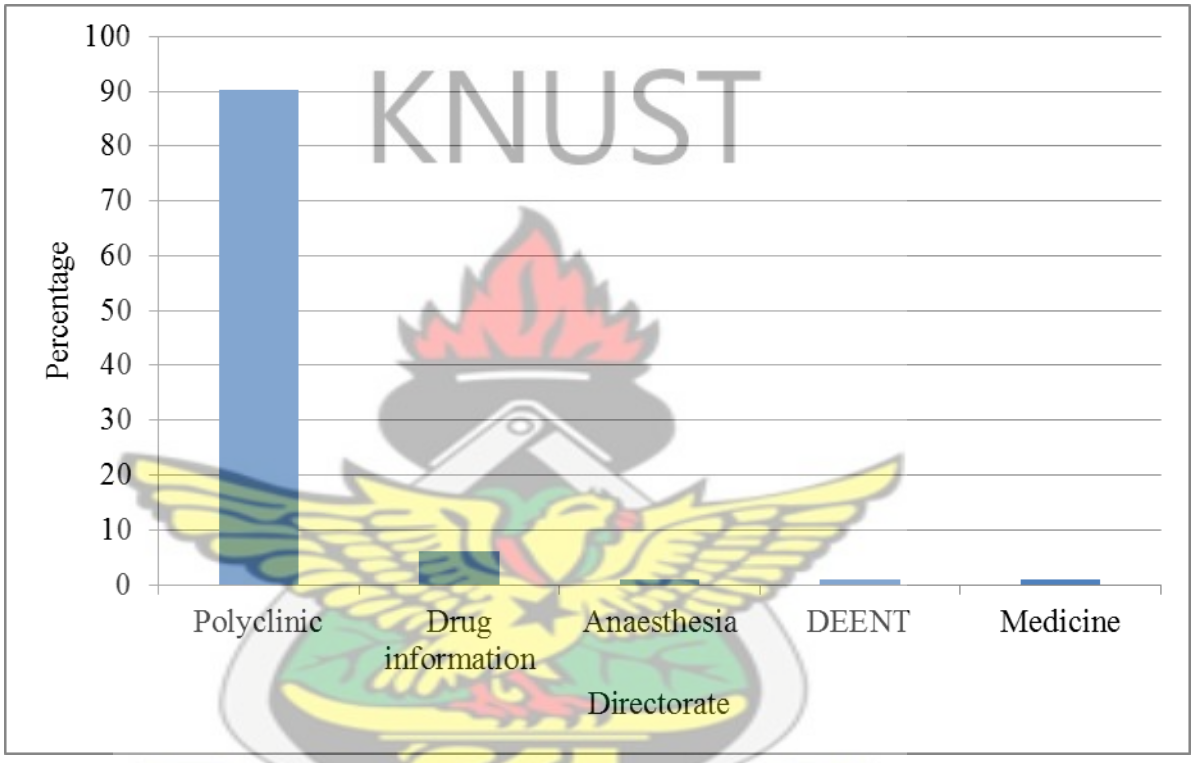

Fig 4.19: ADRs reports submitted by various Directorates.

4.8.0 Test of Hypothesis.

4.8.1 Research question 1:

Is there any association (relationships) between sex and outcome of adverse drug reaction?

Null Hypothesis (H_0): There is no association between sex and outcome of ADR in the population.

Alternative Hypothesis (H_1): There is association between sex and outcome of ADR in the population.

Pearson Chi-squared Test of association between sex and outcome of ADRs

Sex is categorical binary data made up of two independent groups whilst outcome of ADR is a

nominal categorical data made up of four independent groups.

Comparison of proportions between two categorical variables.

Table 4.2: Summary description of cross tabulation between sex and Outcome of adverse drug reaction.

			Outcome of Reaction				
			Recovered	Not yet recovered	Unknown	Hospitalised	Total
Sex	Male	Count	12	8	6	1	27
		% within Outcome of Reaction	17.1%	35.0%	30.0%	33.3%	23.2%
	Female	Count	58	13	14	2	86
		% within Outcome of Reaction	82.9%	65.0%	70.0%	66.7%	76.8%
Total		Count	70	20	20	3	113
		% within Outcome of Reaction	100.0%	100.0%	100.0%	100.0%	100.0 %

From the results of the cross tabulation, 17.1% of males and 82.9% of females patients recovered from the adverse drug reactions whiles 35% of males and 65% of females were not yet recovered from the adverse drug reactions they experienced. Also 1 male and 2 female were hospitalised whiles the outcome of adverse drug reaction for 30% of males and 70% of females were unknown. Also from the Pearson Chi-squared test result p=0.228, we failed to rejected the null hypothesis. Therefore there is no evidence of association between sex and outcome of adverse drug reaction. Hence in the wider population it could be that there are no relationships in the outcome of adverse drug reactions among sex.

4.8.2 Research question 2: Is there are any associations between outcome of ADR and age?

Null Hypothesis (H_0): The distribution of age in outcome of ADR groups (i.e. recovered, not yet recovered, unknown and hospitalized) is the same.

Alternative Hypothesis (H_1): The distribution of age in outcome of ADR groups (i.e. recovered, not yet recovered, unknown and hospitalized) is not the same.

Kruskal-Wallis Test of association between age and outcome of ADRs

Age is a continuous data but was not normally distributed (negative skewed distribution) in this study. The outcome of ADR experienced are made up of four independent groups (i.e. recovered, not yet recovered, unknown and hospitalized)

Assumptions

Though age is a continuous data it was not normally distributed therefore assumptions for the One way ANOVA t-test was not satisfied. Kruskal-Wallis test was therefore appropriate.

Table 4.3: Summary Statistic of Kruskal-Wallis Test

Variable	Recovered Median (IQR) N=67	Not yet recovered Median (IQR) N=20	Unknown Median (IQR) N=19	Hospitalized Median (IQR) N=2	p-value
Age	55.29 (40.0, 62.0)	62.35 (47.5, 63.5)	47.87 (38.0, 59.0)	12.50 (9.0, 39.0)	0.124

The results indicate that the recovered group have a median (IQR) age of 55.29 (40.0, 62.0) years compared with median (IQR) of 62.35 (47.5, 63.5), 47.87 (38.0, 59.0), and 12.5 (9.0, 39.0) years in the not yet recovered, unknown and hospitalized groups respectively. The difference in median age (-7.06 years) and p=0.124 indicate that there are no statistically significant distribution between outcome of ADR and age and that in the wider population patients age has no relationship with outcome of adverse drug reactions.

4.8.3 Research question 3: Is there are any associations between sex and type of ADR?

Null Hypothesis (H0): There is no association between sex and type of ADR in the population.

Alternative Hypothesis (H1): There is association between sex and type of ADR in the population.

Pearson Chi-squared Test of association between sex and type of ADR

Sex is categorical binary data made up of two independent groups whilst type of ADR is a nominal categorical data made up of eight independent groups.Comparison of proportions between two categorical variables

Table 4.4: Summary description of cross tabulation between sex and type of adverse drug reaction.

Sex			Type of ADR								
			CNS	CVS	Dermatological	EENT	Respiratory	GIT	GU	Others	Total
	Male	Count	6	2	2	1	2	4	4	4	25
		% within Nature of ADR	15.4%	25.0%	11.1%	25.0%	33.3%	36.4%	100.0%	21.1%	22.9%
	Female	Count	33	6	16	3	4	7	0	15	84
		% within Nature of ADR	84.6%	75.0%	88.9%	75.0%	66.7%	63.6%	.0%	78.9%	77.1%
Total		Count	39	8	18	4	6	11	4	19	109
		% within Nature of ADR	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

From the results of the cross tabulation, 15.4% of males and 84.6% of females patients experienced CNS adverse drug reactions. Also 11.1% of male and 88.9% of female experienced dermatological ADRs and 36.4% of males and 63.6% of females experienced GIT reactions. For cardiovascular (CVS) and EENT the same percentage of male and females experienced such reaction. The percentages were 25% male and 75% female. Again 33.3% of male and 66.7% of female suffered reactions relating to the respiratory system. All those who experienced Gastro Urinary Tract (GUT) reactions were male, no woman experienced GUT reactions.

Also from the Pearson Chi-squared test result p=0.014, we rejected the null hypothesis. Therefore there is evidence of association between sex and type of adverse drug reaction. Hence in the wider population it could be that there are relationships in the type of adverse drug reactions among sex.

CHAPTER FIVE

5.0 DISCUSSION

This study was conducted to assess the kind of patients who experienced ADRs with their medications, the type of reactions they experienced, what medications caused the ADRs and whether the ADRs experienced are known and documented. The study also looked at ADR reporting pattern among the directorates and healthcare professionals of the hospital, KATH.

Among the directorates, the Polyclinic directorate reported 90.2% of the ADRs. Professional groups that reported the ADRs included Pharmacist (57.5%), Doctors (40.7%), Nurses (0.9%) and Pharmacy Technicians (0.9%). This is not unusual although internationally, it is a reality that healthcare professional under-report ADRs (Peterson and Turner, 2003), it continues to be a responsibility of healthcare professionals to report ADRs they encounter. Pharmacist reported 57.5% of the ADRs reviewed as against 40.7% by doctors. This compares well with a report that in 2001 Canadian Pharmacist reported over 28% of total cases of ADRs as compared to physicians report of 25.5% cases.(Peterson and Turner, 2003).

5.1.0 Category of patients who experienced ADRs with their prescriptions

ADRs were experienced among all categories of age groups. However, the frequency of occurrence increased with age with the middle age patient (40-59yrs) being most affected (45.1%), followed by the elderly (>/= 60) with a percentage of 32.7%. This compares with observations made in other studies. Khurshid et al observed in their study in which they monitored adverse drug reactions suspected to be caused by antihypertensive medicines in a university teaching hospital in New Delhi that incidence of ADR was higher in patients more than 40 years of age (Khurshid, Aqil

and Alam *et al*, 2012). Prasad et al (2011) also observed that a high percentage of adverse drug reactions in their study involved middle aged patients. However, studies by Zopf, Rabe, Neubert, *et al* (2008) and Jimmy and Padma, (2006) also observed that patients who are 60 years and over are more prone to ADRs from their medications. Mateti *et al* in a study in which they evaluated the incidence of ADRs due to angiotensin-converting enzyme Inhibitors in cardiology department observed that about 56.66% of those who experienced ADRs were above 61years (Mateti, Nekkanti, Vilakkathala, *et al* 2012).

Older people are more prone to ADRs because as people grow they develop many health problems. This necessitates the use of different medications (either prescribed or over the counter) at the same time. The use of the different medications at the same time could lead to interactions that result in ADRs. With age the liver's ability to metabolize drugs reduces and (Budnitz, Shehab and Kegler *et al*, 2007) the kidneys ability to excrete drugs into the urine also reduces (Jimmy and Padma, 2006). Thus, medications metabolized or excreted by these organs will stay longer in the body of older people. The long stay of such medications in the body prolongs their pharmacological actions increasing the risk of adverse effects. (Klotz, 2009).Older adults are also known to have smaller amount of body water but with a large proportion of fat compared to young adults (Rademaker, 2001). A medication that dissolves in water reaches higher concentration and that which dissolves in fat accumulates in the tissues and result in increased pharmacological activity with associated adverse effects (Jimmy and Padma, 2006).This explains the observation that type A reactions, which are augmented pharmacological action of the drug, are common among older adults (Jimmy and Padma, 2006).

The study revealed that 76.1% of the reported ADRs were by females whilst 23.9% were by males. This confirms a belief that women are more prone to ADRs from their medications (Muaed Jamal Alomar, 2014). A study by Mateti et al on incidence of ADRs due to angiotensin-converting enzyme Inhibitors in cardiology department showed that about 80% of those who experienced ADRs were females (Mateti, Nekkanti, Vilakkathala,et al 2012). Another study on the incidence of ADRs caused by cardiovascular medications showed a marked difference between females and males (54% vrs 46%). Mohebbi ,Shalviri and Salarifar *et al* 2010). Patients and sex differences in cardiovascular drug-induced adverse reactions causing hospital admissions by Rodenburg and Stricker *et al* (2012) showed that women are more prone to ADRs than men. The Pearson chi test for association between sex and type of reaction gave a p-value of p=0.014. This indicates that there is a relationship between gender and type of ADR and therefore confirms possibility of the female gender being more susceptible to experiencing ADRs with their medication than men. Some reasons given for female reaction to medications more than men are that there are several anatomical and physiological differences between males and females. For example it is said that women have lower bodyweight and organ size with more body fat than men (Muaed, Jamal and Alomar, 2014). The female rate of metabolizing medications is different because for example, hepatic enzyme CYP3A4 is more active in females than males (El-Eraky and Thomas, 2003). Such differences affect the pharmacokinetics and Pharmacodynamics of drugs including drug absorption, distribution, metabolism and elimination. On the other hand the high reports by female may be due to the fact that, because of their inability to cope with distress caused by ADRs they experienced, more females than males sought medical care and reported their ADRs experiences (Lagos-Jansen 2008). This is not strange because

females reporting symptoms of physical illness more frequent than males is a consistent observation in health research works (Muaed, Jamal and Alomar, 2014).

5.2.0 Type of ADRs patients experienced

The three most affected organ/systems were Central Nervous system (35.5%), Dermatological (15.9%) and the Gastro Intestinal Tract (9.7%). Different observations have been made as to the pattern of ADRs most frequently experienced by patients. Jha et al (2007) and Jose and Rao, (2006) found the dermatologic system to be most affected by ADRs with skin rash being most frequently reported reaction. Prasad et al on the other hand found cardiovascular adverse drug reactions to be the highest reported reactions. Observation in this study was different from all the above. CNS reactions were most frequently reported with headache ranking highest followed by dizziness. This was followed by dermatologic reactions and then GIT reactions. The observation however, is consistent with report by Khurshid and Mohammed *et al* (2012) found in a study titled Monitoring of adverse drug reactions associated with antihypertensive medicines at a university teaching hospital in New Delhi. The study showed that ADRs affecting the central nervous system were the most frequent reported ADRs. Marco and Jonathan et al also reported that CNS reactions were most common reaction to anti-retroviral therapy (Marco, Jonathan and Sumaya et al, 2014), (Mohebbi , Shalviri and Salarifar et al 2010), (Arulmani, Rajendran and Suresh 2008). Rash was most frequently reported dermatological reaction. This is consistent with observation by Jha et al (2007). Jha et al found skin reactions to be the leading ADRs reported with rashes being the most common ADR reported. Jose and Rao, (2006) also made similar observation in their study titled Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. They found that the dermatological system was the organ system most

affected by reported ADRs and that skin rash was the most frequently reported reaction.

5.3 Medicines that gave the ADRs

In all 36 different medicines were involved in the reported ADRs. These included Analgesics, Antibiotics, Hypoglycaemics, antihypertensives, Opoids and others. Antihypertensive were the medications that gave the highest (56.5%) incidence of ADR. (Fig4.7). Among the anthypertensives, calcium channel blockers gave majority of the complains (29.2%) (Fig 4.8). This is consistent with the observation that Calcium channel blockers are antihypertensive that are often associated with adverse drug reactions (Khurshid, Aqil andAlamet al, 2012). Aqil, Imam and Hussain et al, (2006) in their study conducted to monitor adverse drug reactions caused by antihypertensive agents, found Calcium channel blockers to be leading in causing ADRs followed by beta-blockers, angiotensin-converting enzyme inhibitors and diuretics. Nifedipine gave most of headaches reported (47.1%), with varied contributions by various brands. It was followed by Amlodipine (29.41%) (Fig4.10). Headache is a central nervous system ADR that is most frequently reported when Nifedipine and Amlodipine are given to manage hypertension. In a multicenter, placebo-controlled, clinical trial with 496 patients involved, the incidence of headache with extended-release Nifedipine was reported as 19%, compared to placebo at 13%. In the same way in a summary of results from 1359 patients treated with Amlodipine, the incidence of headache was reported to be 7.3%. The occurrence of headache was not dependant on dose and was one of the most common reported side effects (Micrmedex , 2014) .

Another ADRs complained about CCBs include pedal oedema. Both Nifedipine and Amlodipine had the same occurrence of pedal oedema (Fig. 11). This is different from observation in a double-blind study where Nifedipine and Amlodipine were compared in treating hypertension.

It was observed in that study that similar numbers of patients experienced the same kind of adverse reaction with both medicines. However, Amlodipine gave more edema than Nifedipine. (Lorimer, Anderson and Laher *et al*, 1994).

Nifedipine gave more dizziness than Amlodipine. This is in line with other studies. A multicenter, placebo-controlled, clinical trials involving 496 patients, reported the incidence of dizziness with extended-release Nifedipine as 4%, compared to placebo at 2% and that of Amlodipine is reported to be 3.4% whilst incidence of dizziness experienced by patients taking Losartan is reported to be 3%. (Micromedex, 2014). This study, however, had a different observation. Incidence of dizziness by both Nifedipine and Losartan were the same.

Most of angioedema reported involved Lisinopril (Fig 4.7). This is not unusual, a study that looked at the risk individual medicines that works on the renin-angiotensin-aldosterone system poses for angioedema concluded that ACEI have 3-fold higher risk for angiodema than beta blockers and the risk is lower with angiotensin receptor blocker than ACEIs (Toh, Reichman and Houstoun et al, 2012). Again people of African descent are reported to have 5 times greater risk of developing angioedema on taken ACEIs (Kostis, Kim and Rusnak *et al*,2005). ACEI prevents breakdown of bradykinins and results in increased bradykinin levels. The Bradykinin acts on vascular endothelial cells and increase vascular permeability. Fluids are able to leak out of the vessels accumulating to form the oedema (Zuraw and Christiansen, 2011).

About 85.7% of cough reported was associated with Lisinopril (Fig 13). This is consistent with report that about 44% of those who use ACEI experiences dry cough (BasakRavi and Manavalan *et al* 2004). A double blind randomized clinical trial re-challenged people who had experience cough when taking Lisinopril with Losartan 50 mg, Lisinopril 20 mg and Hydrochlorothiazide 25 mg. Cough experienced by those on Losartan was 17%, those on Lisinopril 69% and those on Hydrochlorthiazide 25% (Micromedex, 2014). Association between cough and ACEI is so strong that American college of chest physicians' evidence-based clinical practice guidelines states that for patient with chronic cough, ACE inhibitors should be considered as the medication that is either wholly or partially causing the cough (Dicpinigaitis P V, 2006).

Angiotensin Converting Enzyme(ACE) normally break down the inflammatory peptide bradykinin, if ACE are inhibited there is accumulation of bradykinin, these then cause sensitization of airway sensory nerves and enhance the cough reflex (Pinargote, Paulette and Denisse Guillen et al, 2014). About 14.29% of cough reported was caused by Nifedipine. This is not unusual, in a parallel double blind trial of Nifedipine or Lisinopril in 800 hypertensive patients cough was spontaneously reported by3.1% of those on Nifedipine (Micromedex, 2014). Most of the ADRs observed were consistent with the pharmacological profile of the drugs involved, however, there were some few that were not. For example, Cetirizine causing excessive production of breast milk. Three reports of treatment failure involved Clindamycin, Ramipril and Bupivacine.

5.4 Outcome of the ADR

Out of the total number of ADRs reported, 67.6% recovered (Fig 14). This compares well with report of a study on Hospitalization due to adverse drug reactions and drug

interactions before and after HAART by Michelle et al. Michelle et al indicated that 65% of the patients had at least partial recovery as at when they were being discharged (Michelle, Kevin and Anne, 2000). Jose and Rao also reported in their study entitled Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital that 74.8% recovered from ADRs they experienced (Jose and Rao, 2006). Compared to the results obtained by Figueras *et al,* in a study entitled Spontaneous reporting of adverse drug reactions to non-steroidal anti-inflammatory drugs, a report from the Spanish system of Pharmacovigilance, patients unknown to have recovered from their ADRs is higher(18.5%) in this study as compared to 5.3%.reported by Figueras et al. (Figueras and Capellà et al, 1994). However, not yet recovered in this study (13.9%) compares well with (10%) reported by Figueras *et al*.

5.5 Inclusion of reported ADRs in compendia

A high percentage (90.3%) of the reported ADRs were known and documented in their respective drug profile. However 7.1% of the reported ADRs were not found to be documented in the reference sources used (Fig 15). These included cetirizine causing excess production of breast milk, Metformin causing constipation, Nifedipine causing hypopigmentation, Co-Amoksiclav causing paraesthesia, Lisinopril causing drowsiness, Calcium carbonate causing angiodema, Bendrofluazide causing pedal oedema and Neopenetranforte causing Amenorrhoea. The observation of 7.1% of the reported ADRs not found in reference sources used compares well with an observation in an evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme (Avery, Anderson and Bond et al, 2011). In this study patient's reports together with healthcare professional's reports identified 47 (10%) new serious reactions that had not previously been included in the products literature (

Avery, Anderson and Bond *et al*, 2011). (Hazell, Cornelius and Hannaford et *al*, 2013). These reported ADRs not known to be documented in respective drug profiles therefore, may be whistle blowers serving as signals to ADRs that had not been previously included in product literature.

6.0 CHAPTER SIX

Conclusion and recommendation

6.1 Conclusion

Middle age patients and females are more likely to experience ADRs with their medication. Over a third of the ADRs reported affected the central nervous system. ADRs were more common in antihypertensive medications, particularly Calcium Channel blockers. Majority of patients who experienced ADRs recovered, and a greater percentage (90.3%) of reported ADRs were known and documented in the Compendia. The few ADRs that were not found documented in any of the reference sources used may be new reactions that post marketing surveillance is bringing out.

6.2 Recommendations

1. ADR reporting should be strengthened in all directorates so that it will inform the procurement unit as to quality of drugs purchased to the hospital.

2. ADRs reports should be analysed every quarter and findings given to all prescribers to make them more vigilant of ADRs.

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APPENDX

DATA COLLECTION TOOL

A REVIEW OF ADVERSE DRUG REACTION REPORTS AT KOMFO ANOKYE TEACHING HOSPITAL (KATH), KUMASI-GHANA

1. Study identification Number (ID) Actual Age (yrs): ☐

2. Age category(yrs):
   1. 1-12 2.13-19 3.20-39 4.40-59 5. 60 and above

3. Gender: 1. male 2. Female

4. Description of the adverse drug reaction

5.What organ system was affected?

   1. CNS 2. CVS 3.Dermatological 4.EENT 5.Respiratory 6.GIT 7. GUT

   8. Treatment Failure

6. What CNS reaction did the patient experienced?

7. What Dermatological reaction did the patient experienced?

8. What GIT reaction did the patient experienced?

9. What CVS reaction did the patient experienced?

10. What was the outcome of the reaction?
    a. 1. Recovered 2. Not yet recovered 3. Unknown
    b. 4. Death 5. Disability 6. Hospitalised

11. Name of drug suspected to cause the adverse reaction?
……
12. Pharmacological class of the suspected drug
……..
13. What is the sub-Pharmacological classification of the suspected drug?

14. Indicate Brand Name or Manufacturer
……

15. Expiry date ……..

16. Is the ADR experienced by the patient known and documented in standard compendia?

c. 1. Yes 2. No

17. If yes, how is the ADR classified in the compendia?

d. 1. Common 2. Less common 3. Rare 4. Very rare

18. What was the indication for use of the drug? (Please state)

……..

……

19. What was the route of administration?

1. Oral 2. IV 3.IM 4.Topical 5. Others

20. Where was the drug obtained?

1. Hospital 2. Community Pharmacy

21. What other drugs were used together with the suspected drug? (Please list)

e. ……..

f. ……

g. ……

22. Were there any clinically significant drug-drug interactions?

1. Yes 2. No

23. If yes which drugs were involved? Please list)

……

……

24. What is the type of interaction involved?

1. Pharmacokinetic relating to Absorption 2. Pharmacokinetic relating to distribution

3. Pharmacokinetic relating to metabolism 4. Pharmacokinetic relating to excretion

5. Pharmacodynamic interaction

25. What is the profession of the reporter?

1. Doctor 2. Pharmacist 3.Nurse 4. Pharmacy Technologist 5.Others (Please state) …….

26. What is the directorate/department/unit of the reporter? (Please state)

……

27. What was the year of reporting? 1. 2011 2. 2012 3. 2013