POTENTIAL DRUG-DRUG INTERACTIONS AMONG PATIENTS WITH TYPE 2 DIABETES AND HYPERTENSION IN KISII TEACHING AND REFERRAL HOSPITAL, KENYA

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DEDICATION

I dedicate this work to my dear wife, Naomi Bosibori, and my daughters, Tatiana and Letisha, for making it possible, my late father William Otachi and my late mum Renchina Nyanganyi.

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LIST OF ABBREVIATIONS AND ACRONYMS

ADR	Adverse Drug Reaction
ACE	Angiotensin Converting Enzyme
ADE	Adverse Drug Event
AIDS	Acquired Immunodeficiency Syndrome
CNS	Central Nervous System
CYP	Cytochrome P450
DDI	Drug-Drug Interactions
DNA	Deoxyribonucleic Acid
DSM IV	Diagnostic and Statistical Manual of Mental Disorders IV
EMA	European Medicines Agency
GFJ	Grapefruit juice
HIV	Human Immunodeficiency Virus
IDF	International diabetes Federation
KNH	Kenyatta National Hospital
MAOIs	Mono Amine Oxidize Inhibitors
pDDI	Potential Drug Drug Interactions
PLWH	People Living with HIV/AIDS
SSRI's	Selective Serotonin Reuptake Inhibitor
T2DM	Type 2 diabetes mellitus
TCA	Tricyclic Antidepressant
UNAIDS	United Nations Acquired Immunodeficiency Syndrome
UoN	University of Nairobi
WHO	World Health Organization

OPERATIONAL DEFINATIONS

Potential drug-drug interaction: This is a pharmacological or clinical response that is likely to occur after the administration of a drug combination different from anticipated and likely to cause unwanted out comes which are severe.

Adverse drug reaction: A response to a drug which is harmful and unintended, and which occurs at normal doses used in human being for diagnosis, therapy or prophylaxis of disease, or for modification of a physiological function.

Social demographic factors: These are characteristics of a population based on aspects such as age, sex, level of education and employment status.

Major drug interaction: These are drug interactions, which are life threatening and/or require medical intervention to minimize or prevent serious adverse effects.

ABSTRACT

Introduction

Hypertension in diabetics represents an important health problem as the combination of these ailments is common, and can carry significant morbidity and mortality rates. The prevalence of hypertension in diabetic people is probably 1.5–2 times higher than in the general population. Patients with Type 2 diabetes and hypertension routinely receive a combination of several drugs to treat both of these chronic conditions, and as such, the possibility of drug interactions is high. There are no local studies on prevalence of potential drug-drug interactions among patients receiving both hypoglycemic and antihypertensives and thus the need to carry out the study.

Objective

To assess the selection, combination and possible drug-drug interactions of pharmacological agents used in the management of outpatients with both hypertension and diabetes at Kisii Teaching and Referral Hospital.

Methods

A hospital-based cross-sectional study design was used. The study comprised two quantitative cross-sectional studies were conducted. In the first study, medical records data for 168 patients from outpatient department were sampled using modified systematic random sampling technique. All prescriptions of drugs were checked for compliance with treatment guidelines and for any drug-drug interaction using Medscape Interaction Checker. A survey on awareness of drug–drug interaction among prescribers and dispensers was carried out on a sample size of 30, by questionnaire-guided interviews. Descriptive statistics was used to summarize variables. Statistical analyses were done using the statistical software Epi info 7 and Stata version 10.

Results

Swelling of limbs (7.8%) was the common co-morbidity. About 76% of the prescriptions conformed to International Diabetes Federation and World Health Organization hypertension treatment guidelines. Using Medscape Interaction Checker, 96% prescriptions had least one drug-drug interaction. Overall 672 drug-drug interactions were detected, with an average of 4

interactions per prescription. Thirty four (5%) of the potential interactions were classified as major interactions, while most of the potential drug-drug interactions (334, 50%) were moderate.

The most common major interaction was losartan and enalapril followed by enalapril and pregabalin. The common moderate drug-drug interactions were insulin and enalapril, metformin and ciprofloxacin, and glibenclamide and enalapril.

Fifty four percent of the drug-drug interactions were pharmacodynamic, while the rest (31%) were pharmacokinetic in nature. Most of the potential major (13 of 26) and moderate (97 of 333) interactions involved a combination of antihypertensive and other drugs. Polypharmacy, use of sulfonylurea, use of metforminand patient weight were positively associated with the number of drug-drug interactions. Polypharmacy had the greatest influence on drug-drug interactions accounting 31.3%. average number of drus per prescription was 5.

There were 43% of the respondents that could cite the various guidelines that are used for management of diabetes and hypertension. Most of the respondents (67%) could not identify specific interactions when presented with commonly prescribed drug combinations involving hypoglycemics and antihypertensives.

Conclusion

The prevalence of potential drug-drug interactions was high. There is a knowledge gap among health workers regarding drug-drug interactions. All prescriptions should be analyzed for drug-drug interactions and this should be done by prescribers and dispensers.

CHAPTER ONE:

1.0 INTRODUCTION

1.1 BACKGROUND

Hypertension causes 4.5% of the current worldwide disease burden in both developing and developed countries (1). When hypertensive patients are also diagnosed with diabetes, numerous medications may possibly be considered as an appropriate therapy. So many medications can be overwhelming and it is necessary that due diligence is taken in their selection and combination (2).

There are many concerns that arise due to polypharmacy which include prescribing errors, the cost of medication, possible adverse effects and unwanted drug-drug interactions. An adverse drug interaction occurs when the effects and /or kinetics of one drug are altered by co-administration of a second drug. Drug interactions can be modified by disease factors and genetic (2).

It is estimated that up to 58% of patients are worried that they will be prescribed drugs that will have a negative impact on their health due to interactions (2). These worries are not unfounded given that some drugs like terfenadine , mifefradil and cisapride have been withdrawn from the market due to drug-drug interactions, such as *torsades de pointes* (2).

The accurate incidence of interactions is unknown because of poor reporting and documentation of these interactions and most do not result in major injury to patients or do not necessitate admission to health facilities (4). According to the World Health Organization, minimizing or preventing the possibility of interactions ought to be the goal of quality of care since interactions can cause considerable morbidity and mortality (3). A study by Cruciol-Souza and Thomson (2006) found that at least 1 drug-drug interaction was present in 887 prescriptions (4).

Healthcare providers ought to take responsibility for the harmless prescribing of medications bearing in mind both possible adverse reactions as well as drug interactions. It is acknowledged that having diabetes and hypertension at the same time can be challenging in patient management. Polypharmacy cannot be avoided in managing these patients but care needs to be

exercised to avoid drug-drug interactions that can be clinically fatal to the patients. The healthcare workers should therefore have knowledge of drug interactions in order to make informed choices when prescribing drug combinations to deal with patients with diabetes and hypertension.

A number of factors can influence how patients with diabetes and hypertension are managed with regard to prescribing and dispensing. These include prescriber and dispenser , patient, industry and disease-related factors. This study will assess the selection, combination and likely drug-drug interactions of pharmacological drugs used for the management of outpatients with both hypertension and diabetes at Kisii Teaching and Referral Hospital.

1.2 PROBLEM STATEMENT

Drug-drug interactions are a major problem in health facilities the world over. The prevalence of interactions is estimated to be between 1- 22% (37). Underlying risk factors for drug-drug interactions include polypharmacy and co morbid conditions.

High blood pressure in patients with diabetes presents a major health problem because of increased risk of polypharmacy. Polypharmacy leads to prescribing drugs that may have drug interactions. The interactions can lead to life threatening situations, hospitalization, increased burden to patients, and adjusted quality of life. A considerable number of the drug-drug interactions can be avoided if health workers involved in patient care have the right information. Kisii Teaching and referral Hospital serves patients from various regions that visit the facility for various ailments including diabetes and hypertension which are among the conditions on the rise, thus availability of data for the study.

1.3 RESEARCH QUESTIONS

1. Are Diabetes Federation and World Health Organization guidelines adhered to in selection and combination of antihypertensive and hypoglycemic agents?

2. What is the prevalence of potential drug-drug interactions among diabetic-hypertensive patients in Kisii Teaching and referral Hospital?

3. Are health workers aware of the drug-drug interactions that are likely to occur in patients who are having diabetes and hypertension?

1.4 OBJECTIVES OF THE STUDY

1.4.1 Main Objective

To assess the selection, combination and potential drug-drug interactions of pharmacological agents used in the management of outpatients with both hypertension and diabetes at Kisii Teaching and Referral Hospital.

1.4.2 Specific Objectives

i) To compare the selection and combination of antihypertensive and hypoglycemic agents in hypertensive-diabetic patients with those recommended by International Diabetes Federation and World Health Organization guidelines on management of hypertension.

ii) To determine the prevalence and types of potential drug-drug interactions between co-administered antihypertensive and hypoglycemic agents.

iii) To assess the knowledge of health workers on drug-drug interactions in patients taking antihypertensives and hypoglycemics.

1.5 STUDY JUSTIFICATION

There are no local studies on prevalence of potential drug-drug interactions among patients receiving both hypoglycemic and antihypertensives and thus the need to carry out the study. The findings of this study will highlight the need to include drug interaction checking software in the dispensing and prescribing settings.

CHAPTER TWO:

2.0 LITERATURE REVIEW

2.1 DRUG-DRUG INTERACTIONS

A drug-drug interaction (DDIs) is defined as the pharmacological or clinical reaction to the administration of a drug regimen different from that predictable from the known effects of the two agents when given separately. Drug interactions can result to making a drug less effective, increased action and unintended side effects. Drug interactions are divided into three categories namely: drug-drug interaction, drug-food/beverage interactions and drug-disease interactions.

Medscape Interaction Checker has been used to check drug interactions in a clinical study by Kothari and Ganguly (2014). It was found at that 71.5% prescriptions were identified having at least one drug –drug interaction. Several other studies have also reported the successful use of Medscape Interaction Checker for determination of potential drug-drug interactions. Another study by Oshikoya (2013) on clinically significant interactions between antiretroviral and co-administered drugs for HIV-infected children found out a total of 280 patients were at risk of 596 potential drug-drug interactions (6). Another study by Siwa (2015) on assessment of drug-drug interactions in hypertensive patients at a super-specialty hospital found out that among the 227 patients, 48 of them developed 53 clinically significant DDIs (7).

2.1.1 Classes of Drug Interactions

There are two key classes of interactions namely: pharmacodynamic and pharmacokinetic interactions. Pharmacodynamic interactions involve, additive, synergism and antagonism (8). In pharmacokinetic interactions one agent affects the circulating levels of another drug by altering absorption, distribution, metabolism and excretion (9). To ascertain if a drug is a substrate, an inhibitor or inducer *in vitro* studies of the drug have to be performed (10). Many drugs undergo transformation by CYP 450 system, due to this CYP 450 has become a vital determinant in the occurrence of potential drug-drug interactions (11).

2.1.2 Significance of Drug Interactions

There are many recognized interactions, several of which are minor or of no clinical significance. For example combination of atorvastatin and fluoxetine which does not result to any interaction (12). However, there are many potentially significant interactions for example combination of itraconazole and atorvastatin. Itraconazole increases the level of atorvastatin by affecting hepatic intestinal enzyme CYP3A4 metabolism. Combination of phenytoin and diltiazem, leads to phenytoin decreasing the effect of diltiazem, when these drugs are combined close monitoring should be done. The importance of a drug interaction can also differ between individuals depending on gender, disease condition and age. It is necessary to consider drug interactions when starting drug therapy, changing a dose, altering the route of administration or stopping a therapy (13).

A drug interaction can be useful, fetal or have no considerable effect. Combining angiotensin converting enzyme (ACE) inhibitor and calcium channel blocker leads to increased additive blood pressure-lowering effect (11). An example of harmful pharmacodynamic drug interaction is when a drug that induces sleep is taken after consumption of alcohol and this results to exaggerated central nervous system (CNS) depression (13).

2.1.3 Clinically Significant Drug Interactions

Several studies have been undertaken on clinically relevant drug-drug interactions. Representative studies are highlighted.

A study by Jomo (2014) on mentally ill patients on antipsychotics had potential drug- drug interactions which were both pharmacodynamic and pharmacokinetic. For example combination of fluphenazine and chlorpromazine led to potentially serious drug-drug interaction which was the increase in QTC interval. This causes the heart muscle to take longer than normal to recharge between beats (14).

A study by Guantai (1998), found out that chloroquine had drug interactions, which interfered with ion conductance processes at the neuromuscular junction (NMJ). For example combining chloroquine and gallamine brought about induction of ion at the neuromuscular junction and a combination of chloroquine and physostigmine brought about antagonistic effect in the neuromuscular junction.(15)

A study by Mccance-Katz (2010) on drug-drug interactions of clinical significance among the opioids when (methadone and buprenorphine) found potential life-threatening drug interactions between buprenorphine and benzodiazepines. This was due to pharmacodynamic interaction resulting in fatal respiratory depression (16).

A study by Dumbreck (2015) noted 32 potentially serious drug-disease interactions involving drugs recommended in National Institute of Health and Care Excellence (NICE) clinical guidelines for type 2 diabetes (17).

2.2. DRUG INTERACTIONS INVOLVING ANTIHYPERTENSIVE DRUGS.

2.2.1 Non-steroidal Anti-inflammatory Drugs and Antihypertensive Drugs

Drug-drug interactions can occur when blood pressure lowering agents are combined with nonsteroidal anti-inflammatory drugs (NSAIDs). For example combination of NSAIDs, alcohol and some blood pressure lowering drugs have resulted to drug-drug interactions according to reports (18).

NSAIDs, for example ibuprofen when combined with blood pressure agents, diminish the outcome expected is decreased hypotensive effect of drugs, this effect takes place after 5 days of treatment with both drugs (18)

A study done by Fournier (2012) on drug interactions between antihypertensive drugs and NSAIDs found that, in one-fourth of the cases, the drug-drug interaction between NSAIDs and antihypertensive drugs explained the reported a acute renal failure which is a serious drug side effect (19)

2.2.2 Antipsychotic and Antihypertensive Drugs.

A study done by Markowitz et al. (1995) found that hypertension is widespread in patients with psychiatric illness. Considerable numbers of patients are given concomitant therapy with antihypertensives and antipsychotics (20). Many antipsychotics obstruct the antihypertensive efficacy of guanethidine and related drugs. A major drug interactions like "epi-reversal" (hypotensive response) can occur when epinephrine is administered intravenously to a patient taking chlorpromazine (20).

2.2.3 Antihypertensives and Cough/Cold Medications and Interaction of MAOI Antidepressants Interactions

Cough and cold medicines also have decongestants that can influence blood pressure in two ways. Decongestants may create blood pressure and heart rate increase and may prevent high blood pressure drugs from functioning properly. Cough and cold medications might also contain NSAIDs that cause fluid retention and diminish kidney function. This might cause blood pressure to rise even with the concomitant use of antihypertensives (21).

Mono amine oxidase inhibitor (MAOI) antidepressants such as phenelzine and tranylcypromine, can interact with hydralazine, methyldopa, reserpine and guanethidine can result in blood pressure increase. On the other hand, beta-blockers can be more effective when combined with MAOI antidepressants leading to greater than anticipated drop in blood pressure and postural hypotension (22).

2.2.4 Drug-food Interactions Involving Antihypertensive Drugs.

Among the citrus fruits that are have been known historically to interact with high blood pressure agents is grapefruit juice; majority of these interactions are by pharmacokinetic mechanism through enhancing metabolism (23). Caution should be exercised against consumption of grapefruit juice while on antihypertensives, antilipidemics and immunosuppressants. This is due to these drugs being substrates of CYP 450 3A and grapefruit juice is capable of reducing the activity of CYP450 3A by 47% (27). Combination of nifedipine and grapefruit juice leads to

increased levels of nifedipine because of the enzyme inhibitory effects on metabolism of furacoumarin in grapefruit juice (24).

The clinical importance of drug interactions involving grapefruit juice and anticoagulant, antihypertensive and antidepressant drugs is well known (25). Numerous theoretical interactions between antidiabetic agents and other foods have been reported (26). Green tea is known to contain caffeine. Some antihypertensive drugs such as metoprolol and propranolol interact with caffeine and this result in increase in blood pressure this applies also when green tea is used together with MAOI which are used to treat depression (27).

2.3 DRUG INTERACTIONS INVOLVING HYPOGLYCEMIC DRUGS

Fungal infection and bacterial infections cause variation of blood glucose levels occur. Because of limited dietary intake due to illness, blood glucose tends to be minimal. The unstable glucose levels can be also due to drug-drug interactions the fact that diabetic patients are generally treated with multiple drugs, and are therefore at an increased threat of harmful drug-drug interactions. Several potentially life-threatening drug-drug interactions include combination of insulin and pioglitazone which results in of fluid retention and heart failure. Oral hypoglycemic agents together with mono amine oxidase inhibitor antidepressants causing a drop in blood sugar (28).

Some interactions of moderate clinical significance include thiazide diuretics and furosemide that cause hyperglycemia, which antagonize the effects of hypoglycemic agents. Calcium channel blockers, for example nifedipine, can also cause hyperglycemia and beta blockers are capable of masking signs and symptoms of hypoglycemia (29).

Fluoroquinolones are commonly regarded as safe antimicrobial agents with fairly few drug interactions. Although infrequent, both hypoglycemia and hyperglycemia (dysglycemia) appear to occur with all the fluoroquinolones (30). It is well known that antiretroviral therapy/HAART is linked with an increase in prevalence of insulin resistance, glucose intolerance and diabetes. The manifestation of these glucose imbalances and diabetic conditions presents a pharmacological challenge because of the possible pharmacokinetic interactions link with antidiabetic drugs and antiretroviral drugs (31).

A study by Gossell-Williams (2013) on potential impairment of hypoglycemic control associated with drug interactions found out that a total of 37 combinations of drugs were identified to potentiate hypoglycemia (32).

In a study by Bachmakov et al (2013) on interaction of hypoglycemic drugs with liver mediated transporters, established that metformin uptake were extensively inhibited by repaglinide (33).

Tables 1 shows some medications that can raise blood glucose and antagonize the effects of hypoglycemic agents, though the clinical impact of some of the effects is unknown. Table 2 shows drugs that may lower blood glucose, thereby exaggerating the effects of hypoglycemic agents. Potential interactions can occur between sulfonylureas and medications that cause change of liver enzymes. Examples of drugs that can induce metabolism are Phenytoin, phenobartitone and ritabutin. Examples of drugs that can inhibit metabolism are allopurinol, erythromycin, cimetidine and chloramphenicol. Appendix 5 lists common diabetes, hypertension, and lipid drug interactions.

Table 1: Some drugs that can cause hyperglycemia

Drug	**Probable mechanism**
Lomidine	Adrenergic action
Clozapine	Impairs insulin secretion
Corticosteroids	Oppose insulin action
Diuretics(thiazides)	Oppose insulin action
Niconitic acid	Oppose insulin action
Nifedipine	Delays insulin action
Oral contraceptive hormones	Oppose insulin action
Phenytoin	Blocks insulin secretion
Phenothiazines	Not known
Sugar containing Syrups	Increased glucose intake

Table 2: Some drugs that may cause hypoglycemia

Drug	**Suggested mechanism**
ACE inhibitors	Increase insulin action
Alcohol	Inhibits hepatic glucose production and release
Fibrates	Not known
Monoamine inhibitors	Not known
Quinine (7 Quinidine)	Increases insulin secretion
Salicylates (large dose)	Not known

Adapted from Australian Prescriber Vol.24 2001 (33).

2.4: DIABETES AND HYPERTENSION TREATMENT GUIDELINES

According to the WHO high blood pressure guidelines, ACE-inhibitors should be given priority when starting patients on drugs especially in diabetic nephropathy. Angiotensin receptor blockers (ARBs) can be used for the start for people who cannot tolerate ACE-inhibitors. Diuretics or calcium channel blockers (CCBs) can be used as first supplement drug to ACE inhibitors and Angiotensin II receptor blockers (ARBs) if patients fail to attain target blood pressure (34).

Beta blockers ought to be used in people with coronary heart disease. Alpha blockers should be considered in elderly patients as a supplement drug mostly in men with prostate enlargement (41) according to WHO high blood pressure guidelines.

According to International Diabetes Federation (IDF) guidelines, monotherapy with hypoglycemics should be given precedence as the first choice. Metformin ought to be used with care in elderly patients with, liver disease and severe respiratory conditions. When oral combination fails, insulin should be added to the treatment regimen. The guidelines caution against using two drugs from the same class (35).

2.5 DRUG INTERACTIONS BETWEEN ANTIHYPERTENSIVE AND HYPOGLYCEMIC DRUGS

Many interactions between blood glucose lowering drugs and some classes of high blood pressure lowering drugs do take place, majority of interactions are of moderate clinical significance. When these combinations are administered close monitoring of blood glucose levels is recommended (3).

A study by Thamer (1993) on the correlation between high blood pressure drug use and low glucose levels, it was noted that of low blood sugar was 5.5 times more prevalent in insulin as opposed to sulfonylurea users and was not influenced by use of angiotensin-converting enzyme (ACE) inhibitors overall. Though, use of the ACE inhibitor enalapril was linked with an increased risk of low blood glucose (36). Angiotensin converting enzyme inhibitors are known to increase insulin sensitivity though this claim has a poor quality of evidence (37). Another study by Parameshappa (2010) on drug-drug interactions between propranolol and glipizide, found increased risk of hypoglycemia (38).

When acarbose and miglitol are combined with digoxin or propranolol, they reduce the absorption of both digoxin and propranolol and when digoxin is combined with metformin, metformin renal clearance is delayed by digoxin (39).

CHAPTER THREE:

3.0 METHODS

3.1 Study Site

The study was carried out at Kisii Teaching and Referral Hospital (KTRH). KTRH was built in 1916 by colonial government to treat soldiers. It has extended over time and operated as a District hospital until 2007 when it was upgraded to a level 5 hospital. It is currently a regional referral hospital. The hospital has a catchment of three million people and a staff establishment of 500 workers and 13 specialists. It has inpatient bed capacity of 454 and outpatient special clinic attendance of an average of 505 patients per month.

3.2 Study Design

The study consisted of two hospitals based cross-sectional studies. The first study was a survey of patient files and the second was a health care worker survey.

3.3 RETROSPECTIVE SURVEY OF DRUG-DRUG INTERACTIONS IN DIABETIC-HYPERTENSIVE PATIENTS

3.3.1 Study Population

The study population was all adult patients having diabetes and hypertension, on medication and attended the outpatient clinic at Kisii Teaching and Referral Hospital between June to December 2015.

3.3.2 Eligibility Criteria

The study participants were included if they were aged between 18- 90 years, of either gender, suffered from both Type 2 diabetes and hypertension, on at least one antihypertensive drug and one hypoglycemic agent and who attended outpatient clinic at Kisii Teaching and Referral

Hospital during the period of the study June and December 2015. Patients who did not meet the inclusion criteria and those with incomplete records were excluded.

3.3.3 Sample Size Considerations

The sample size was computed based on the estimated prevalence of drug-drug interactions of 11 % from the previous studies (40). Being retrospective study, the sample size was estimated using Fischer's formula for sample size determination (41). The following formula was used

$N=Z^2 P (1-P)/d^2$

Where:

N is the total sample required for the study

Z is the standard normal deviation corresponding to 95 % confidence level (Z = 1.96).

P is the prevalence of drug-drug interactions which is estimated to be 11 % (29)

d is the level of the confidence (set at 5%).

When the above formula was applied, a sample size of 150 patient files was required. This figure was inflated by 10% in anticipation of files with missing data and other unforeseen anomalies. For this study, a total of sampled patient files were 168.

3.3.4 Sampling Technique

A list of patient having both diabetes and hypertension who attended the outpatient special clinic between June and December 2015 was prepared, and this constituted the sampling frame of 1006 study participants. A systematic random sampling technique was applied, whereby the total number of eligible subjects was divided by the target sample size to obtain the sampling interval which was 6. Sampling then involved randomly drawing every 6th file and assigning a different and unique study code against the patient number. The code was counterchecked (against the outpatient number) every time the researcher picked the file for data extraction to ensure that no files were repeatedly picked during the review.

3.3.5 Data Collection

The sampled patient medical files and prescriptions were retrieved and information extracted using the Data Collection Form (Appendix 3). The data collection tool was also designed to collect information on the following patient characteristics: gender, age weight, residence, level of education and marital status. Information on the following clinical characteristics was obtained: diagnosis, pre-existing liver disease and chronic kidney disease. The documented medication history and known allergies were also recorded. The Data Collection Form was pretested at KNH by taking information from about 5 patients from to assess the suitability of the form. Medscape Interaction Checker (www.medscape.org), an online software, was used to identify the presence and nature of interactions (42). The software gives various interactions between two drugs when keyed in; it also gives the types of interaction (pharmacodynamic or pharmacokinetic interaction) that may occur as well as the necessary alert if the type of interaction is fatal or if close monitoring is needed when certain drugs are combined.

In addition the medication history was critically evaluated to determine the proportion of patients who were managed in accordance with the World Health Organization/International Society of Hypertension and International Diabetes Federation Management guidelines.

3.3.6 Case Definition

The WHO definition for polypharmacy was used. It was defined as ‘‘the administration of many drugs at the same time’’. The potential drug-drug interactions for each were classified as described in Table 3.

Table 3: Classification of drug-drug interactions (42)

Type of interaction	Characteristic
Based on severity	
Major	The interaction is life threatening, need medical intervention to minimize or prevent adverse effects
Moderate	Might result in an exacerbation of the patient's state or require an adjustment in therapy
Minor	Would have some degree of clinical effects which need monitoring
None	No interaction
Based on the mechanism of the interaction	
Pharmacokinetic	Absorption, distribution, metabolism and elimination
Pharmacodynamic	Synergistic, antagonism and additivity

3.4 SURVEY OF HEATH CARE WORKERS KNOWLEDGE OF DRUG-DRUG INTERACTIONS

3.4.1 Study population for the health care workers survey

The study population was all prescribers (medical and clinical officers) and dispensers (pharmacists and pharmaceutical technologists) working in outpatient special clinic and the Pharmacy at Kisii Teaching and Referral Hospital.

3.4.2 Inclusion Criteria and Exclusion Criteria

The respondents were included in the interviews if they were: prescribers and dispensers who were working at the outpatient special clinic between January to March 2016 and who gave informed consent. Those who declined to participate in the study were excluded.

3.4.3 Sample Size Determination, Sampling Technique and Participant Recruitment

The sampling unit was prescriber and dispenser. There were 67 prescribers and dispensers in outpatient special clinic at Kisii Teaching and Referral Hospital. Thirty respondents were purposively sampled and interviewed, with at least five respondents from each cadre. A sample size of 30 is considered sufficient as these was nearly half the health care work force in the unit.

Participants were recruited at noon at the end of the clinic so as to avoid interrupting the normal work flow. They were recruited in the clerking rooms. Written consent was obtained after explaining the objective of the study to the potential respondents. Appendix 3 has the informed consent form. They were informed that it is voluntary to participate in the study and they may pull out from the study at any time with no necessarily giving a ground for withdrawal.

3.4.4 Data collection Procedures and Instruments.

A pre-tested questionnaire was used to collect data from prescribers and dispensing staff. Data that was collected using a questionnaire appendix 4 which was designed to collect the following information on health care workers included: demographics and number of years of practice. In addition the questionnaire had 10 closed ended questions in which health care workers were tested on their knowledge of polypharmacy, sources of information on drug interactions and treatment guidelines, mechanisms and identification of selected drug-drug interactions Informed written consent was obtained before administering the questionnaire. The responses were evaluated for correctness and a score was assigned. They were encouraged to ask any questions that would to enable them understand the nature of the study.

3.4.5 Quality Assurance and Data Management

Participant's privacy was maintained by not recording their name or clinic number in the data collection forms. Every study participant was allocated unique identifier which was used throughout the study. Any document linking the patient's name, file number and data collection number was kept by the principal investigator under lock and key. Reviewing of patient files and data abstraction was carried out within the records department. All raw data was filed and kept under lock and key by the principal investigator. The data log identifying each participant by name was kept confidential and was accessible only to the principle investigator. Abstracted data

was entered into Epi Info7 databases. The data were cleaned and any changes made to the original copy of the data were recorded.

3.4.6 Variables

The dependent variable was the number of drug-drug interactions per patient. The covariates were: gender, age, weight, residence, level of education and marital status, diagnosis, pre-existing liver disease, and chronic kidney disease and medications.

3.5 STATISTICAL ANALYSIS

Continuous variables were summarized as means and standard deviation of the means. Categorical variables were summarized as counts and percentages. Student's *t*, $\chi 2$ (Chi-square) and Fisher's exact tests were performed for inferential analysis as appropriate. To identify the risk factors for the number of drug-drug interactions per patient linear regression analysis with robust estimation was conducted. To control for confounding and to identify the most important risk factors for the outcome model building by manual forward step wise approach was done. The level of significance was set at 0.05 or less. All statistical analyses were done using the statistical software Epi info 7 and Stata Version 10.

3.6 ETHICAL CONSIDERATIONS

Ethical approval was obtained from Kenyatta National Hospital and The University of Nairobi Ethical Research Committee (KNH/UON-ERC) - Ref. No P674/10/2015 (Appendix 9). The in-charge of Kisii Teaching and Referral hospital gave consent for the principal investigator to access patient files. Informed consent was sought from the anticipated participants in the qualitative arm, prior to data collection. Patient confidentiality was maintained by using a different and unique study code against the patient admission numbers documented in a list of the codes and inpatient numbers were accessed by the principal investigator alone. Participants were informed that they were free to leave the study at any time without having to give any reason. Any withdrawal from study would not lead to any consequences. The health workers who agreed to participate were not given any monetary compensation to take part in the in the survey**.**

3.7 DISSEMINATION PLAN

The research findings were shared with medical scholars in the University of Nairobi on 7th November 2016, through Ministry of Health Department of Curative and Rehabilitative Services aiming at influencing policies and treatment guidelines development, Pharmacy and Poisons Board Department of Pharmacovigilance unit and Kisii Teaching and Referral Hospital aiming at improving prescribing patterns among clinicians hence influencing patient treatment outcome. The findings were published in an open access peer reviewed journal.

CHAPTER FOUR:

4.0 RESULTS

4.1 CROSS-SECTIONAL STUDY TO IDENTIFY DRUG-DRUG INTERACTIONS

4.1.1 Demographic Characteristics of Outpatient Sample

The following are the results for outpatient data for both 168 study participants. Most of the participants were aged between 50 and 70 years (43.4%), female (64.2%), living in rural areas (67.92%) and the level of education was missing (Table 4).

Table 4 Demographic Characteristics

Demographics	Frequency (f)	Percentage (%)
Age		
20 – 30	4	2.4%
31 - 40	8	4.8%
41 - 50	32	19.0%
51 - 60	61	36.3%
61 - 70	41	24.4%
71 - 80	20	11.9%
81 - 90	2	1.2%
Gender		
Male	64	38.1%
Female	104	61.9%
Residence		
Urban	60	35.7%
Rural	108	64.3%
Level of education		
Primary	1	0.6%
Secondary	4	2.4%
Tertiary	3	1.8%
University	3	1.8%
Missing	157	93.5%

4.1.2 ATTENDANT CLINICAL CONDITIONS AND COMORBIDITIES

The most common attendant clinical conditions and co-morbidities among the outpatients were, swelling of limbs (7.8%), urinary tract conditions (6.0%), upper/lower respiratory infections (5.4%), gastrointestinal conditions (6.0%), and eye conditions (3.6%) Table 5.

Table 5: Attendant Clinical Conditions and Co-morbidities

COMORBIDITIES	**Frequency**	**Percent**
Swelling and pain of limbs	13	7.7
None reported	80	47.6
Urinary tract conditions	10	6.0
Gastrointestinal conditions	10	6.0`
Upper/lower respiratory infection	9	5.4
Eye problems	6	3.6
Brucellosis and malaria	6	3.6
Diabetic wound	6	3.6
Numbness	5	3.0
Skin conditions and body itches	4	2.4
Mental problems	3	1.8
Body pains and other aches	5	3.0
Cardiovascular conditions	2	1.2
HIV and associated symptoms	4	2.4
Others	10	6.0
TOTAL	**168**	**100.00%**

4.1.3 DRUGS PRESCRIBED

The most common drugs prescribed to outpatients were hypoglycemics (49%), which included metformin, glibenclamide and insulin. Aside from that, 26% of the drugs prescribed were antihypertensives which included carvedilol, enalapril, losartan and nifedipine. Additionally, 13% of the drugs prescribed to the participants were antibiotics which included amoxicillin, flucloxacillin, ceftriaxone, cotrimoxazole; and 12 % were analgesics which included tramadol,

diclofenac, meloxicam aspirin and paracetamol. The classes of drugs are presented in the pie chart in Figure 1.

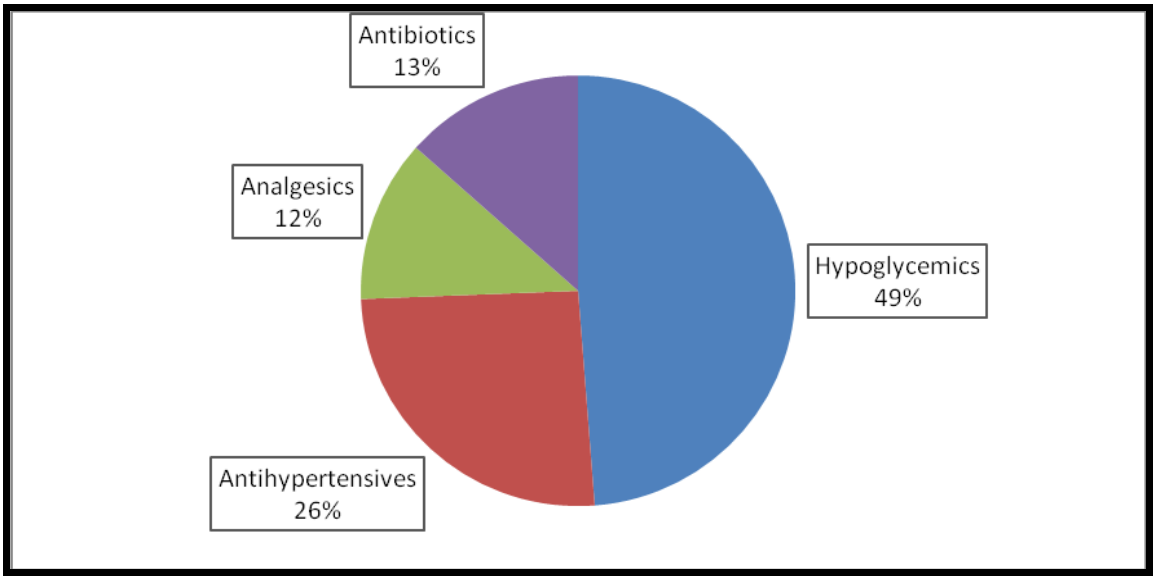

Figure 1: Distribution of Drug Classes Prescribed to the Study Participants

4.1.4 PREVALENCE OF POLYPHARMACY

From the histogram (Figure 2) the mode was 5, meaning that 215 (23.5%) of the patients had 5 drugs per prescription. The lowest number of drugs in a prescription was 3 (3.6%). The WHO cut-off value for polypharmacy is 4 to 5 drugs. Cumulatively, 60.3% of the patients had 4-6 drugs per prescription. Those with over 7 drugs per prescription were 36.1% which was a fairly large number. The highest number of drugs per prescription was 11, which represented 11 out of the 168 participants (1.2%). Therefore the frequency of polypharmacy was high.

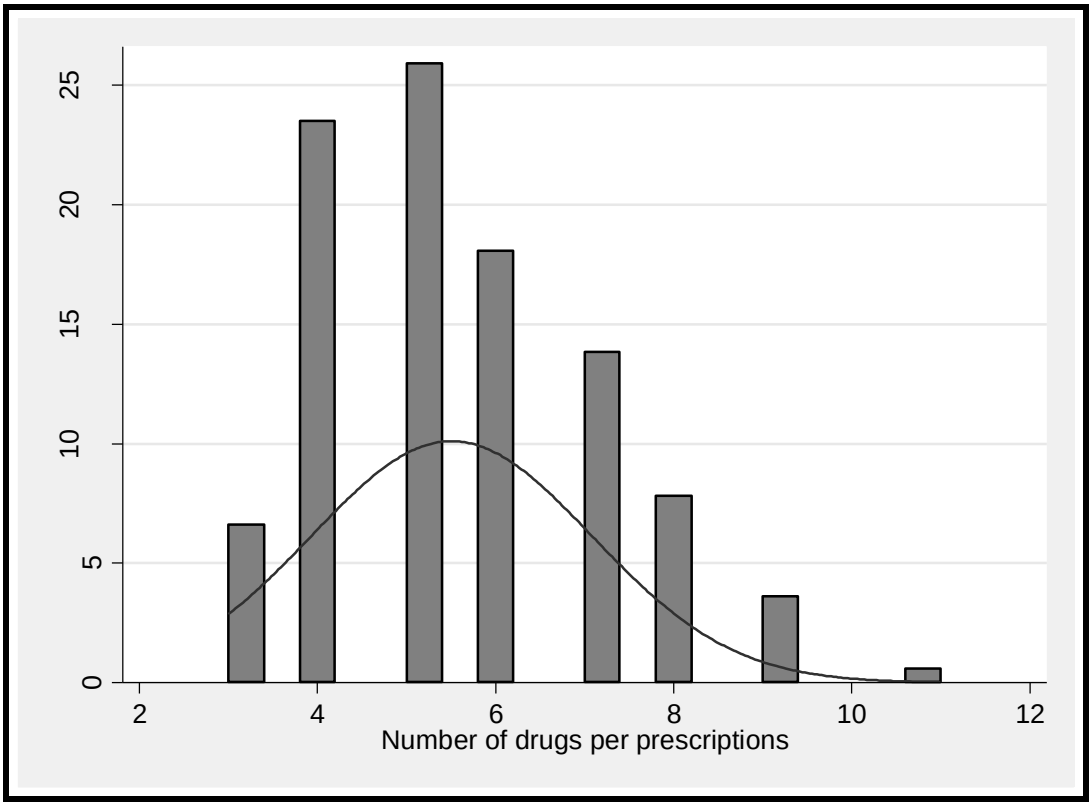

Figure 2: Number of Drugs per Prescription

The most commonly prescribed hypoglycemic and antihypertensive drug combinations were: glibenclamide and enalapril; followed by insulin and enalapril; and captopril and glibenclamide respectively. The prescribed hypoglycemic and hypertensive combinations are summarized in Table 6.

Table 6: Commonly Prescribed Hypoglycemic and Antihypertensive Drugs

Drug combination	**Frequency**	**Percentage**
Glibenclamide + Enalapril	53	61
Insulin + Enalapril	14	16
Captopril + Glibenclamide	11	13
Enalapril + Insulin	7	8
Metformin + Nifedipine	3	2
Total	88	100

4.5 PRESCRIBING ACCORDING TO THE GUIDELINES RECOMENDATIONS

Analysis of the antihypertensive and anti-diabetic drugs prescribed to the outpatients showed that 76% of the prescriptions conformed to IDF and WHO hypertension medication guidelines (see Section 2.4). Deviations from the stipulated guidelines were observed in 40 (24%) of the prescriptions. All the observed deviations involved anti-hypertensive. All hypoglycemic drugs were prescribed according to the International Diabetes Federation (IDF) guidelines.

Majority of the deviations observed involved the prescription of calcium channel blockers without a thiazide diuretic as recommended in the WHO hypertension guidelines. In some instances a thiazide diuretic was prescribed without inclusion of any other hypertensive drug. The guidelines recommend that thiazide diuretics be used as add-on therapy to the first-choice ACE inhibitors and ARBs. Carvedilol (a β-blocker) was prescribed to a female patient without inclusion of any other hypertensive drug; β-blockers should be considered for combination therapy, and only in patients with tachycardia or coronary heart disease. The distribution of the deviations is shown in Table 7.

Table 7: Summary of Observed Deviations from Guidelines

Observation	**Frequency**	**Percent**	**Guideline recommendation**
Thiazide not included	38	22.6	Antihypertensives especially calcium channel blockers should be prescribed along with a thiazide diuretic.
Thiazide only	1	0.6	Thiazide should be prescribed along with other antihypertensives
Carvedilol only	1	0.6	Should be prescribed as part of combination therapy, and only in patients with tachycardia or coronary heart disease.
Total	40	23.8	

4.6 POTENTIAL DRUG INTERACTIONS IN OUTPATIENT PRESCRIPTIONS

4.6.1 Number of Drug –Drug Interactions

A total of 672 potential drug-drug interactions were identified from the 168 outpatient prescriptions. Ninety six percent of the prescriptions had at least one drug-drug interaction. The average number of interaction was 4. Thirty percent of prescriptions had more than two interactions. Most of the prescriptions had less than six interactions. Figure 3 show the distribution.

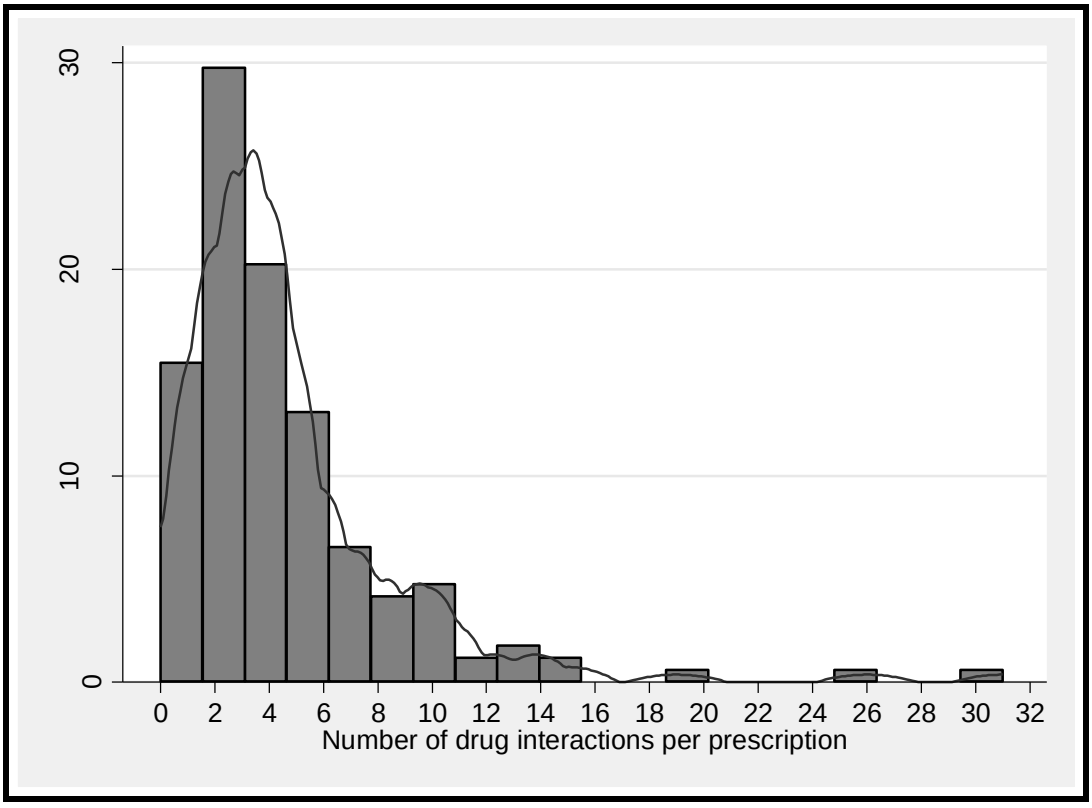

Figure 3: Number of Interactions per Prescriptions for Outpatients

Two prescriptions (1.2%) had only major interactions, 36 (22.2%) had only moderate interactions and 28 (17.3%) had only minor interaction. Three (1.9%) of the prescriptions had at least one major and one moderate interaction. Majority of prescriptions (49.3%) had at least one and one minor interaction. The distribution of categories of interactions is depicted in Table 8.

Table 8: Distribution of Interaction per Prescription

Type of interaction	Number of prescriptions	Percentage
Major	2	1.2%
Moderate	36	22.2%
Minor	28	17.3%
Major and moderate	3	1.9%
Major and minor	3	1.9%
Moderate and minor	80	49.3%
Major, moderate and minor	10	6.2%
Totals	162	100

4.6.2 Categories of Drug-Drug Interactions

The potential drug-drug interactions were classified as either major, moderate, or minor depending on the severity of the outcome of the reaction. Thirty four (5%) of the identified potential interactions were classified as major interactions, while most of the potential drug-drug interactions (334, 50%) and 46% were minor. The most common drug combination that could result in major interaction was losartan and enalapril followed by enalapril and pregabalin. Losartan and enalapril increase the toxicity of each other by pharmacodynamic synergism which can result in dual blockade of renin-angiotensin system that increases the risk of hypotension, hyperkalemia and renal impairment. Combination of enalapril and pregabalin results in the two drugs additively increasing the toxicity of each other, thereby elevating the risk of developing angioedema of the face, mouth and neck. Angioedema may result in respiratory compromise. These major interactions are catalogued in Table 9.

Table 9: List of Major Drug-Drug Interactions in Prescriptions of Patients with Diabetes and Hypertension in Kisii Hospital

Drugs combination	Frequency	%	Mechanismof interaction	Outcome of interaction
Enalapril and losartan	10	29.4	Pharmacodynamic synergism	Increase risk of hypotension, hyperkalemia and renal impairment
Enalapril and pregabalin	9	26.5	Pharmacodynamic additive	Risk of angioedema of face, mouth and neck. Angioedema may result in respiratory compromise
Atenolol and carvedilol	5	14.7	Pharmacodynamic additive	-Increase of serum potassium
Furosemide and gentamicin	4	11.8	Pharmacodynamic synergism	Increased risk of ototoxicity and nephrotoxicity
Captopril and pregabalin	2	5.9	Pharmacodynamic additive	Risk of angioedema of face, mouth and neck. Angioedema may result in respiratory compromise
Nifedipine and erythromycin	2	5.9	Pharmacokinetic metabolism	Increase level of erythromycin by affecting CYP3A4
Carbamazepine and hydrochlorthiazide	1	2.9	Pharmacodynamic synergism	Increase risk of systemic hyponatremia
Coartem and morphine	1	2.9	Pharmacokinetic metabolism	Increase level of morphine by affecting hepatic enzyme CYP2D6.
Total	34	5.1		

As mentioned, most of the identified potential interactions were classified as moderate interactions. Examples of drug combinations that were observed and could result in moderate drug-drug interactions were: insulin and enalapril; metformin and ciprofloxacin; and glibenclamide and enalapril. Co-administration of insulin and enalapril results in a moderate interaction whereby enalapril increases the effects of insulin by pharmacodynamic synergism. Combination of metformin and ciprofloxacin results to moderate interaction whereby ciprofloxacin increases effects of metformin by pharmacodynamic synergism. The most common moderate drug combination was glibenclamide and enalapril. The moderate drug combinations that were observed and could result in moderate drug-drug interactions are presented in Appendix 6.

4.6.3 Mechanisms of Drug –Drug Interactions

The potential interactions were categorized as pharmacodynamic (362, 54%), pharmacokinetic (210, 31%) and unspecified (100, 15%). All three pharmacodynamic mode of drug interactions were observed – synergism (158, 44%); additive (22, 6%) and antagonism (182, 50%). The average number of pharmacodynamic interactions was 2.2 interactions per prescription. Combination of hydrochlorothiazide and metformin was the most common antagonistic drug combination. This combination leads to hydrochlorothiazide decreasing effects of metformin by pharmacodynamic antagonism. The co-administration of captopril and glibenclamide results to pharmacodynamic synergism, where captopril increases the effects of glibenclamide which should be monitored closely. Combination of enalapril and pregabalin results in the two drugs additively increasing toxicity of each other and this was the most common additive drug combination. The distribution of different subcategories of pharmacodynamic interaction is shown Appendix 7.

All four pharmacokinetic mechanisms of drug interactions were observed; absorption (61,29%); distribution (21,10%); metabolism (42,20%) and elimination (86,41%). The average number of pharmacokinetic interactions was 1.3 interactions per prescription. Prescribing nifedipine and metformin leads to nifedipine increasing levels of metformin by enhancing absorption and this was the most common drug interaction at the level of absorption as shown in Appendix 5. The most common drug interaction at the level of elimination was the combination of metformin and hydrochlorothiazide where by hydrochlorothiazide increases levels of metformin by basic (cationic) drug competition for renal clearance.

Other pharmacokinetic interactions observed included the co-administration of nifedipine and amitriptyline, whereby nifedipine could increase the level of amitriptyline by affecting hepatic/intestinal enzyme CYP3A4 metabolism; a similar interaction applies to combination of pioglitazone and nifedipine. Combination of atorvastatin and amitriptyline leads to atorvastatin increasing the effect of amitriptyline by P-glycoprotein efflux transporter inhibition. The distribution of different subcategories of pharmacokinetic interactions is shown Appendix 8

4.6.4 Drug –Drug interactions by Drug Class

Most of the potential major interactions (13 of 26) involved combination of antihypertensive and other drugs. Moderate drug-drug interactions involved by combination of antihypertensives and other drugs (126 of 333) followed by combination of hypoglycemic and other drugs (97 of 333). Combination of hypoglycemic and antihypertensives (231 of 313) caused most of the minor drug-drug interactions. These are summarized in Table 10.

Table 10: Drug interactions by drug class

Drug class combination	**Type of Interaction**					
	Major	**%**	**Moderate**	**%**	**Minor**	**%**
Interaction between two hypoglycemic agent	1	(3.8%)	5	1.5%	2	0.6%
Interaction between hypoglycemic and Antihypertensives agent	2	7.7%	73	21.9%	231	73.8%
Interaction between two antihypertensive agents	7	26.9%	32	9.6%	2	0.6%
Interaction between hypoglycemic and other agents	3	11.5%	97	29.1%	56	17.8%
Interaction between antihypertensive and other agents	13	50%	126	37.8%	22	7.0%
Total		26	-	333	-	313

4.7. Regression Analysis to Identify Determinants of the Number of Drug Interaction per Patient

Table 11: Regression Analysis of the Determinants of Drug Interactions per Patients

	BIVARIABLE ANALYSIS		MULTIVARIABLE ANALYSIS	
Covariates	**Crude β-coefficient (95% CI)**	**P-value**	**Adjusted β-coefficient (95% CI)**	**P-value**
Gender	0.261	0.694	—	—
Age	0.004 (-0.047- 0.054)	0.887	—	—
Polypharmacy	1.607 (1.007 - 2.208)	0.000	1.740 (1.166 - 2.314)	0.000
Sulfonylurea	1.974 (0.534- 3.414)	0.008	11.393(3.699- 19.087)	0.004
Weight	0.044 (0.002- 0.086	0.038	11.393 (3.699- 19.087)	0.002
Metformin	2.935 (1.747- 4.122)	0.000	1.786307 (0.222- 3.351)	0.002
Insulin	-1.776 (-3.678- 0.125)	0.067	—	—
ACE-inhibitor	-0.509 (-1.908 0.890)	0.473	—	—
Nifedipine	0.332 (-1.038- 1.702)	0.633	—	—
Antibiotics	0.109 (-2.031- 2.248)	0.920	—	—

On bi-variable analysis, the 4 variables that were positively associated with the number of drug-drug interactions per patient were polypharmacy, use of sulfonylurea, patient weight and use of metformin. Of these variables, polypharmacy had the greatest influence and on its own accounted for 31.3% of the variance in the number of drug-drug interactions. These variables remained significant on multivariable analysis.

All these variables were used for model building and they remained significantly associated with the number of drug-drug interactions even after adjusting for confounding. The only two variables that were negatively associated with the number of drug-drug interactions per patient were use of insulin and ACE inhibitors, but these findings were not statistically significant. Use

of insulin reduced the number of drug-drug interactions experienced per patient by about 1.8. -1.776 (-3.678- 0.124).

4.7.1 Statistical Interaction between use of Sulfonylurea and body Weight

On model building, there was statistical interaction between body weight and use of sulfonylurea. To explain the interaction the study sample was stratified according to body weight. Patients with a body weight of above 85kg were considered as being considered. Patients on sulfonylurea had more drug-drug interactions per patient of about 5.2-5.7 per patient Table 12. There was no statistically significant difference in the number of drug-drug interactions in the weight categories for patients on sulfonylurea (p =0.778). For patients who were not on sulfonylurea, those who were heavier had more drug-drug interactions by about 2 units. This difference was large and was significant (0.004).

Table 12: Stratified data Analysis Number of Drug-Drug Interactions across Weight Category and use of Sulfonylurea

On a sulfonylurea	Weight less than 85kgs	5.263 ± 3.867	0.718
	Weight above 85kgs	5.740 ± 4.959	
Not on a sulfonylurea	Weight less than 85kgs	2.429 ± 1.989	
	Above 85kgs	4.5 ± 5.081	**0.004**

4.2 PART TWO: SURVEY OF HEALTH WORKERS' KNOWLEDGE OF DRUG INTERACTIONS

4.2.1 Demographic Characteristics of Health Care Workers

Thirty respondents were purposively sampled to assess knowledge of drug-drug interactions. Most of the respondents were male (67%) with majority of them being pharmacists and medical officer interns (27% for each cadre). Table 13 depicts the demographic characteristics of the respondents.

Table 13: Demographic Characteristics of Health Care Workers

Sex	**n**	**Percent**
Male	20	67
Female	10	33
Current job title		
Pharmacist	6	20
Pharmacist intern	2	7.0
Medical officer intern	8	27
Clinical officer intern	7	23
Medical officer	4	13
Pharmaceutical technologist	3	10
Total	30	100

4.2.2 Awareness of Guidelines for Managing Type 2 Diabetes and Hypertension

There were 43% of the respondents that could cite the various guidelines that are used for management of diabetes and hypertension. The guidelines cited by the respondents included the National Guidelines on Diabetes, the Kenyan Guidelines for the Management of Diabetes provided by the Ministry of Health, the Kenya Diabetes Strategy document, and the Kenya Treatment Guidelines that includes treatments for other chronic conditions.

4.4.3 Respondents Awareness of Specific Drug-Drug Interactions of Frequently Prescribed Drugs

Most of the respondents could not identify specific interactions when presented with commonly prescribed drug combinations involving hypoglycemics and antihypertensives. The few that presented their responses on the effect of the combinations stated that the interactions led to increased metabolism, end organ compromise, synergistic effects, and antagonism as some of the correct responses for the selected drug combinations.

Awareness of respondents on selected drug-drug interactions commonly prescribed drugs is shown in Table 14.

Table 14: Awareness of Drug-Drug Interactions

Type of drug combination	Percent aware of the interaction
Nifedipine and insulin	9 (30%)
Propranolol and glibenclamide	10 (33%)
Phenytoin and insulin	10 (33%)
Digoxin and metformin	11 (36.67%)

Respondents cited drug interaction booklets, school notes, practical sessions, Medscape Interaction Checker and drug indexes as their sources of information on drug-drug interactions.

4.4.4: Opinion of Respondents Regarding Polypharmacy

The average number of drugs per prescription was five indicating a high prevalence of polypharmacy. However, despite the fact that health care workers acknowledged that polypharmacy leads to negative consequences, the respondents felt that in some circumstances polypharmacy could not be avoided, with some of the informants stating that it is a "*necessary evil*" and critical in ensuring patients have the "*right combination of medications for their condition"*

The general response from the respondents was that drug-drug interactions are distinctly different from different from adverse reactions. Some respondents cited that drug-drug interactions involve ''*how one drug affects the other*'' while adverse reactions involves ''*the effects on the patient''*. The knowledge on adverse drug reactions and drug-drug interactions was further exemplified by other respondents who affirmed that adverse reactions involved ''*the unwanted effects of drug''* while the drug-drug interactions refers to ''*the pharmacological reactions that result from the usage of multiple drugs*''. However, some respondents termed adverse drug reactions as "*the unwanted effects that occur because of the concurrent use of drugs*".

4.4.5: Mechanisms of Drug-Drug Interactions

The mechanisms of drug-drug were not clear to the majority of the respondents. These respondents either stated that they were not sure, leaving the question unanswered or gave incorrect interactions answers. However, the few respondents listed synergism, increased metabolism, end organ compromise, antagonism, glycogenesis, antihypertensive action, and masking of warning signs as some of the mechanisms of drug-drug interactions.

From the above responses it was noted that the respondents were not adequately conversant with the various guidelines that are used in the management of Type 2 diabetes and hypertension. Most of the respondents affirmed that polypharmacy is a problem and could lead to adverse reactions and drug-drug interactions, but also that in many cases it could not be avoided. Most of the respondents were not aware of selected drug-drug interactions involving antihypertensives and diabetics, though most respondents could differentiate between adverse drug reaction and drug-drug interaction.

CHAPTER 5: DISCUSSION

5.1: DISCUSSION

With an increase in patients having diabetes and hypertension and who are taking several medications concurrently clinical monitoring of drug-drug interaction is required. This study set out to establish if WHO/International Society on management of Hypertension (ISH) and International Diabetes Federation (IDF) guidelines are followed among prescribers in managing patients having Type 2 diabetes and hypertension. The study also sought to find out the knowledge of health providers on drug-drug interactions.

In regard to prescribing according to the guidelines it was found from the study 76% of the prescriptions were prescribed according to the WHO/ISH and International Diabetes Federation (IDF) guidelines. Comparable findings were reported in a study on adherence to guidelines by Oude Wesselink (2015) which found adherence to guidelines to be to be at 70% (43). However, a study by Fürthaue and Johannar (2013) on adherence found 70% non-adherence to guidelines (44).

Almost 96% of prescriptions presented with at least one drug-drug interaction. This is comparable to a study by Bacic (2010) which found 90.6% prescriptions had clinically significant potential interactions (45). Another study by Ganguly (2014), identified 71.5% prescriptions had at least one drug-drug interaction (46). Meiners and Bergsten (2001) reported 32% of pediatric prescriptions had drug-drug interactions (47). The differences in the prevalence of drug-drug interactions might be due to differences in the study participants and study settings in various studies.

The average number of interactions per prescription was 4.1. This was comparable to other previous studies, such as a study by Rodrigues (2015) which found an average potential drug-drug interactions of 5 interactions per prescription (48). In this population polypharmacy was high average of 5 drugs per prescription because patients had diabetes and hypertension as co-morbidities. This is comparable to a study by Salwe (2016) found polypharmacy among elderly

patients to be 5 drugs per prescription (49). Early initiation of insulin may reduce the incidence of polypharmacy because it reduces the need to use oral hypoglycemic.

The interaction can be explained by the fact patients on sulfonylurea are more likely to have drug-drug interactions than other patients because they are notorious for pharmacodynamic and pharmacokinetic interactions. Patients who are overweight are more likely to be using more medications and this explains why when used with sulfonylurea the number of drug-drug interactions increased.

The prevalence of potential major drug-drug interactions was found to be 4% in this study, which is comparable to reports in previous studies. For example, a study by Pergolizzi (2014) found the prevalence of potential major interactions was 5.7% (50) and another study by Cruciol-Souza (2006) found a prevalence of 3.7% (51). Even one major drug-drug interactions is dangerous to the patient.

In this study, a potentially major pharmacokinetic drug-drug interaction in patients on combination of nifedipine and erythromycin were observed. Nifedipine increases levels of erythromycin by affecting CYP3A4 metabolism. This could be attributed to the fact that these drugs are metabolized by cytochrome P450 enzyme system (52). The combination of enalapril and losartan could lead to a major pharmacodynamic synergism as the combination increases risk of hypotension, hyperkalemia and renal impairment (42). Similar drug combinations caused major interactions in a study by Ganguly (2014). The knowledge of substrates, inhibitors and inducers of CYP isoenzyme may assist prescribers to anticipate and avoid certain drug combinations that may interact and improve rational prescribing practices (53). Most prescriptions had both moderate and minor interactions.

Most of the identified potential interactions were classified as moderate in nature. The prevalence of potential moderate drug-drug interactions was 50%, and this is comparable to previous studies. A study by Almeida (2007) found the prevalence of potential moderate drug-drug interactions was 57% (54). Another study by Dai (2016) found potential moderate drug-drug interactions to be 57% (55). Most of the potential moderate drug-drug interaction involved the combination of glibenclamide and enalapril, and captopril and glibenclamide. This is due to

the fact that these are the recommended first line choices for the management of Type 2 diabetes and hypertension.

Most of the healthcare providers (67%) could not cite specific implications of combining commonly prescribed hypoglycemic and antihypertensive agents and most were not aware of specific guidelines for the management of Type 2 diabetes and hypertension; none of the respondents named the WHO or IDF guidelines. This is comparable to a systematic review by Marieke (2012) which found lack of knowledge of the national or international guidelines and recommendations for TB treatment (56). Respondents' opinion on polypharmacy was that it could not be avoided in many cases due to co-morbid conditions of patients which forces the service providers to prescribe multiple drugs. Information on drug-drug interactions was obtained from various sources which were cited by the respondents. A similar study by Malone DC (2008) also found printed material and personal digital assistants as the possible sources of potential drug-drug interactions (57). There was lack of knowledge on the mechanism of drug-drug interactions majority of the respondents could not report the pharmacodynamic and pharmacokinetic as the mechanisms of drug-drug interactions. A comparable study by Kamuhabwa (2013) found 84.6% of health workers had poor knowledge on basic information required before dispensing (58).

Drug-drug interactions should be suspected whenever more than one drug is prescribed. In our study setting screening of drug-drug interactions does not take place. All prescriptions should be analyzed for drug-drug interactions and this should be done by prescribers and dispensers. The results obtained from the study shows that the prevalence of potential drug-drug interactions was high among outpatients with Type 2 diabetes and hypertension at Kisii teaching and referral Hospital.

5.2 STUDY LIMITATIONS

There are a limited number of previous studies done on the same subject in Kenya for comparison; most of the comparable studies in Kenya were on HIV, tuberculosis and malaria.

Being a retrospective study, getting all required data from the medical records was a challenge due to poor record keeping. This was handled by inflating the sample size by 10%. Many of the

health workers were unwilling to take part in the interviews to assess knowledge on potential drug-drug interactions. This could likely have led to selection bias (non-participation bias).

CHAPTER SIX: CONCLUSION AND RECOMMENDATION

6.1 CONCLUSION

There was high prevalence of drug-drug interactions among patients with Type 2diabetes and hypertension at Kisii Teaching and Referral Hospital and knowledge gap among health care workers regarding drug-drug interactions.

6.2 RECOMMENDATION

Based on the study findings, it is recommended that drug interaction software for detection of potential drug-drug interactions should be installed at prescribing and dispensing areas. Frequent consultation between prescribing physicians and all health care providers should be enhanced for early detection of drug-drug interactions. Continuous medical education of healthcare workers on drug-drug interactions should be initiated and done continuously. Development of specific guidelines for the management of hypertension and Type 2 diabetes, due to lack of such guidelines dedicated to handling these co-morbid conditions. Future prospective cohort study with a larger sample size from different institutions may be necessary in order to provide more evidence.

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APPENDICES

APPENDIX 1: PRESCRIPTION DATE EXTRACTION FORM

Patient's unique number…… Age ……..Weight …….

Gender: 1) Male ☐ Residence 1) Urban ☐ Date of Administration……

2) Female ☐ 2) Rural ☐ Date of Discharge ……

a) Level of Education	*b) Marital Status*	*c) Occupation*	*d) Diagnosis*
i. None ☐ ii. Primary ☐ iii. Secondary ☐ iv. Tertiary ☐ v. University ☐ vi. Unknown ☐	i. Single ☐ ii. Married ☐ iii. Separated ☐ iv. Divorced ☐ v. Widowed ☐ vi. Cohabiting ☐ vii. Other Specify…… ☐ …… ☐	i. Farmer ☐ ii. Business/ Self Employment ☐ iii. Formal Employment ☐ iv. Unemployed ☐	i. Type 2 Diabetes ii. Hypertension iii. Other Specify…… …….. ……

e) Other Chronic Conditions	F) Drugs Prescribed (prescription one)	g) Drug prescription two (in cases where a prescriptions is charged)

i. …….. ii. …….. iii. …… iv. …….. v. …….. vi. …….. H. Adverse Outcomes …… …… …….. ……	☐ …… ☐ …….. ii. …….. iii. …… ☐ …… iv. …….. v. …….. vi. …….. vii. ……..	i. …….. ii. …….. iii. …… iv. …….. v. …….. vi. …….. vii. …….. Reason for Change Available ☐ Yes ☐ No

Drugs prescribed by ☐ Mo ☐ Co Intern ☐ Mo Intern Nurse Mo Specialist Co

1) Drugs prescribed accordi☐o the guidelines

☐ Yes ☐ No

APPENDIX 2: DRUG-DRUG INTERACTION DATA EXTRACTION FORM
Drugs from appendix one above are entered into the drug interaction checker, the findings are entered into appendix two below.

Patient's unique number…….

A) Type of drug interaction	**B) Mechanism of interaction**	
	Pharmacodynamic interaction	Pharmacokinetic interaction
Major ☐ Moderate ☐ Minor ☐ None ☐	Synergism ☐ Additive ☐ Antagonism ☐	Absorption ☐ Distribution ☐ Metabolism ☐ Elimination ☐

APPENDIX 3: PARTICIPANT INFORMATION AND CONSENT FORM

You are being invited to participate in a survey assessing awareness of potential drug-drug interactions in Kisii Teaching and Referral Hospital. Before you decide whether to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and feel free to ask for more information, especially if there is anything that you do not understand. We would like to stress that you do not have to accept this invitation and should only agree to take part if you want to.

Thank you for reading this:

Title of the study: Potential drug-drug interactions in patients with type 2 diabetes and hypertension

Institution: Department of Pharmacology and Pharmacognosy , School of Pharmacy, University of Nairobi, P.O BOX 30197-00400,Nairobi

Investigator: Dr Eric Otachi Ogamba P.O BOX 30197-00400 Nairobi: Tel:0720118456

Supervisors: Dr Eric M. Guantai, Dr George Osanjo and Prof. G. Muriuki ;Department of Pharmacology and Pharmacognosy

Ethical Approval: Kenyatta National Hospital/University of Nairobi Ethics and Research Committee, P.O BOX 20723-00100, Nairobi Tel: 2726300/2716450 Ext. 44102

Permission is requested from you to enroll in this medical research study. You should understand the following general principles which apply to all participants in a medical research:

1) Your agreement to participate in this study is voluntary.
2) You may withdraw from the study at any time without necessarily giving a reason for you withdrawal.
3) After you have read the explanation please feel free to ask any questions that will enable you to understand clearly the nature of the study.

Purpose of the study: The purpose of the study is to assess potential drug-drug interactions in patients with type 2 diabetes and hypertension in the Hospital.

Procedure to be followed: With your permission, I will administer a questionnaire to you or leave you with the questionnaire to fill. All information obtained will be handled with confidentiality. It will take 10-15 minutes to administer the questionnaire.

Risks: There will be no risks involved in this study.

Benefits: There will be no direct benefits to you but findings of this study will be useful in improving management of patients with hypertension and type 2 diabetes in Kisii Teaching and Referral Hospital.

Confidentiality: Utmost confidentiality will be ensured. Your name will not be mentioned or used during data handling or in any resulting publications. Study numbers/codes will be used instead.

Contacts: Please feel free to contact me, my academic department or the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee for any clarifications or concerns. Use the contacts provided above.

I now request you to sign the consent form below.

CONSENT FORM

I confirm that I have read and understood the information given above for the study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. I understand that my participation is voluntary and I am free to withdraw at any time without giving any reason, without my rights being affected. I agree to take part in the above study.

Name……Signature……Date……..

Witnessed by:

Name…….Signature…….Date…….

(Investigator)

APPENDIX 4: QUESTIONNAIRE TO PRESCRIBERS AND DISPENSERS

Data Collector_____

Date Collected_____Questinnaire Number_____

A) ELIGIBILITY CHECK LIST

1. Has the prescriber or dispenser signed the consent form? { } Yes { }No

2. Is the prescriber or Dispenser currently working at Kisii Teaching and Referral Hospital?

{ } Yes { }No

NOTE

a) The two eligibility criteria above MUST be answered YES before the Questionnaire is administered.

b) All questionnaires are completed ANONYMOUSLY. We would appreciate if you answer all the questions and answer as honest as possible.

B) PRESCRIBER OR DISPENSER DEMOGRAPHIC QUESTIONS

Please (√) the best answer for each question. Kindly choose only one answer per question.

1.What is your gender ? { }Male { }Female

2.how old are you?

[ ] Under 25 years [ ] 31 -35 years [ ] 41- 45 years

[ ] 26- 30 years [ ] 36- 40 years [ ] Over 45 years

3. What is your highest level of education?

[ ] Diploma [ ] Bachelors Degree

[ ] Higher Diploma [ ] Post –graduate Degree

4. What is your current job title/designation/cadre ?

[ ] Clinical Officer Intern [ ] Medical Officer

[ ] Registered Clinical Officer [ ] Medical Specialist/ Consultant

[ ] Medical officer Intern [ ] Pharmacist

[ ] Pharmaceutical technologist [ ] Others (Specify)…….....

5. How long have you been workin as aprescriber or Dispenser ?(years of practice)?

[ ] Under 1 year [ ] 6- 9 years

[ ] 1- 5 years [ ] Over 10 years

C) **AWARENESS OF DRUG- DRUG INTERACTIONS**

1.What do you understand by the term polypharmacy?

……
……

2. What is your opinion of Polypharmacy in patients with diabetes and hypertension?

……
……

3.Are drug-drug interaction and adverse drug reaction same?

……
……

4.List some of likely outcomes of drug-drug interactions?

……
……

5.What are some of the mechanisms of drug-drug interaction of hypoglycemic and antihypertensives you know?

……
……

6.Where do you find information on potential drug-drug interactions from?

……
……

7. What are some of the guidelines you know that are used in managing diabetic and hypertensives?

……
……

8. What is a drug information center?

……
……

9. Do you think drug information centers are important in hospitals?

……
……

APPENDIX 5: COMMON DIABETES, HYPERTENSION, AND LIPID DRUG INTERACTIONS.

Medication	**Drug-drug interactions**	**Drug-nutrient interactions**	**Drug- disease interactions**
HMG-CoA reductase inhibitors(statins)	Lovastatin,simvastatin,atorvastatin:3A4 Fluvastatin:CYP2C9 Pravachol: sulfated, but still cases of rhabdomylysis reported	Lovastatin; food increases absorption lovastatin extended- release; food decreases absorption	Watch for myopathy and rhabdomyolysis
Fibric acids	Gemfibrozil: inhibitor of 3A42C8,increase ezetimibe levels fenofibrate ;3A4,less risk of interaction	None	Do not use if active cholecystitis
Sulfonylureas	Inhibitors/inducers CYP2C9	Alcohol first generation sulfonylureas may cause flushing reaction, if severe nausea/vomiting	Metabolized liver/kidney caution if dysfunction ADR: loss of efficacy or hypoglycemia
Metformin	Cimetidine may compete with metformin for renal elimination, with	vitamin B12depletion;periodic monitoring if at risk	Lactic acidosis: renal insufficiency and hypoxic states(congestive heart failure, surgery, shock, or

TZDs Glucosidase inhibitors	any increase levels of metiformin Strong inducers/inhibitors of cyp2c8 clinical effect of interaction: unknown May decrease digoxin absorption ;may increase effect effect of warfarin ; Action: space administration	none none	liver disease, including alcohol intake)ADR: hospitalization/death Fluid rentention ADR: Peripheral eodema , heart failure, pulmonary edema ALT≥3×upper normal limit: do not start therapy; stop if taking none
Exenatide	May slow absorption of medications:caution if rapid absortion needed(e.g acetaminophen pain meds)	none	Renal insufficiency: potential for increased nausea/vomiting gastroparesis:may worsen symptoms
HYPERTENSION			
Diuretics	NSAIDS and phenytoin may reduce effectiveness of loop diuretics thiazides may affect lithium levels	Thiazide and loop diuretics may cause hypokalemia.potassium sparing diuretics may cause hyperkalemia	Caution in hyperuricemia or gout; may exacerbate attack may exacerbate lupus may worsen or cause severe photosensitivity reactions

Adopted from Pharmacy Update by Curtis Triplitt, PharmD, CDE

APPENDIX 6: DRUG COMBINATIONS WITH MODERATE DRUG-DRUG INTERACTIONS

Drug combination	Frequency
aceclofenac carvedilol	2
aceclofenac glibenclamide	4
aceclofenac hydrochlorothiazide	2
aceclofenac nebivolol	4
aceclofenac predinisone	1
amlodipine nifedipine	1
amoxicillin hydrochlorothiazide	1
aspirin atenolol	2
aspirin captopril	2
aspirin enalapril	6
aspirin furosemide	1
aspirin glibenclamide	1
aspirin hydrochlorothiazide	5
aspirin losartan	2
aspirin meloxicam	1
asprin hydrochlorthiazide	1
asprin losaratn	2
atenolol digoxin	1
atenolol hydrochlorothiazide	2
atenolol losartan	3
atenolol nifedipine	1
atorvastatin amitriptyline	2
atorvastatin nifedipine	1
atorvastatin triamscilone	1
benzhexol chlorpromazine	1
betamethasone ciprofloxacin	1
bezhexol chloropromazine	1
butabital omeprazole	1
captopril aspirin	2
captopril furosemide	3
captopril glibenclamide	9
carvedilol digoxin	1
carvedilol furosemide	1
chloropromazine enalapril	1
ciprofloxacin carvedilol	1
ciprofloxacin glibenclamide	1
ciprofloxacin insulin	3
ciprofloxacin meloxicam	1
ciprofloxacin metform	5
clotrimazole pessaris	1
coartem atorvastatin	1
coartem ciprofloxacin	1
coartem nifedipine	1
diclofenac ciprofloxa	1
diclofenac enalapril	3
diclofenac glibenclamide	3
digoxin metformin	1
doxycycline cefuroxime	1
enalapri aspirin	1
enalapril glibenclamide	1
enalapril aspirin	3
enalapril diclofenac	3
enalapril furosemide	3
enalapril glibenclami	44
enalapril insulin	18
enalapril meloxicam	9
esomeprazole glibenclamide	5
flucloxacillin diclofenac	2
flucloxacillin hydrochlorothiazide	2
flucloxacillin ibuprofen	2
flucloxacillin meloxicam	1
flucloxacin hydrochlorothiazide	1
fluconazole losartan	1
furosemide asprin	1
furosemide captopril	2

furosemide enalapril	2
furosemide hydrochlorothiazide	2
furosemide losartan	1
glibenclamide aceclofenac	4
glibenclamide aspirin	3
glibenclamide captopril	1
glibenclamide ciprofloxacin	4
glibenclamide diclofenac	1
glibenclamide ibuprofen	1
glibenclamide insulin	2
glibenclamide ketorolac	1
glibenclamide levofloxacin	2
glibenclamide meloxicam	2
glibenclamide norfloxacin	1
glibenclamide propranalol	1
hydrochlorothiazide amoxicillin	1
hydrochlorothiazide aspirin	1
hydrochlorothiazide diclofenac	1
hydrochlorothiazide flucloxacillin	1
hydrochlorothiazide furosemide	3
hydrochlorothiazide glibenclamide	2
hydrochlorothiazide insulin	1
hydrochlorothiazide ketorolac	1
hydrochlorothiazide meloxicam	1
hydrochlorothiazide metformin	4
hydrochlorothiazide metoprolol	1
hydrochlorothiazide nifedipine	1
hydralazine metoprolol	1
ibuprofen glibenclamide	2

ibuprofen hydrochlorothiazide	4
ibuprofen losartan	1
insulin metformin	1
ketorolac flucloxacillin	1
lamivudine nevirapine	1
lamivudine zidovudine	1
levofloxacin insulin	1
levofloxacin meloxica	1
levofloxacin metformi	2
losartan aspirin	1
losartan atenolol	1
losartan furosemide	1
losartan hydrochlorothiazide	6
losartan ibuprofen	2
losartan metoprolol	2
losartan spironolactone	1
losartan trimethoprim	1
meloxicam enalapril	4
meloxicam flucloxacillin	1
meloxicam glibenclamide	8
meloxicam hydrochlorothiazide	2
metformin ciprofloxacin	1
metformin furosemide	2
metformin hydrochlorothiazide	2
metformin insulin	2
metronidazole losartan	1
metronidazole sulfame	1
nebivolol furosemide	1
nebivolol losartan	1
nebivolol nifedipine	3
nevirapine nifedipine	1
nifedipine amitriptyline	1
nifedipine atorvastatin	4
nifedipine dexamethasone	2
nifedipine erythromycin	1
nifedipine gentamycin	1

nifedipine hydrocortisone	1
nifedipine metoprolol	1
nifedipine predinisolone	2
nifedipine propranalol	2
nifedipine theophilline	1
nifedipine tobramycin	1
norfloxacin metformin	1
ofloxacin insulin	1
omeprazole cefuroxime	1
omeprazole losartan	1
pioglitazone ciprofloxacin	1
predinisolone nifedipine	1
predinisolone theophilline	1

propranolol diclofenac	1
spirolactone enalapril	1
spirolactone furosemide	1
sprinolactone digoxin	1
sprinolactone furosemide	1
sulfamethoxazole losartan	1
sulphamethoxazole glibenclamide	1
tramadol amitriptyline	1
triamcinolone aspirin	1
trimethoprim enalapril	1
Total	**334**

APPENDIX 7: DISTRIBUTION OF PHARMACODYNAMIC INTERACTION SUBCATEGORIES

Drug combination	Synergism	Additive	Antagonism	Total
aceclofenac carvedilol	0	0	1	1
aceclofenac glibenclamide	2	0	0	2
aceclofenac hydrochlrothiazide	1	0	1	2
aceclofenac nebivolol	2	0	0	2
amitriptylline metformin	1	1	1	3
amoxicillin hydrochlorothiazide	1	0	0	1
aspirin captopril	0	0	2	2
aspirin enalapril	3	0	0	3
aspirin glibenclamide	1	1	1	3
aspirin hydrochlorothiazide	2	0	2	4
aspirin losartan	1	0	0	1
aspirin meloxicam	0	0	2	2
asprin hydrochlorothiazide	0	0	1	1
asprin losartan	0	0	1	1
asprin losartan	1	0	0	1
atenolol carvedilol	0	0	1	1
atenolol hydrochlorothiazide	1	0	1	2
atenolol losartan	1	0	0	1
atenolol nifedipine	1	0	0	1

atorvastatin amitriptylline	0	0	2	2
benzhexol chloropromazine	1	0	0	1
benzhexol chloropromazine	1	0	0	1
butabital omeprazole	1	0	0	1
captopril furosemide	2	0	1	3
captopril glibenclamide	1	0	0	1
captopril pregabalin	1	0	0	1
carbamazepine hydrochlorothiazide	1	0	0	1
carvedilol furosemide	1	0	0	1
ciprofloxacin insulin	0	1	1	2
ciprofloxacin meloxicam	0	0	2	2
ciprofloxacin metformin	1	0	2	3
clotrimazole pessaris	0	0	1	1
coartem nifedipine	0	0	1	1
dexamethasone metform	0	0	1	1
dexamethatsone glibenclamide	0	0	1	1
diclofenac ciprofloxa	1	0	0	1
diclofenac enalapril	1	0	0	1
diclofenac glibenclamide	0	0	1	1
enalapri aspirin	0	0	1	1
enalapri glibenclamid	0	0	1	1
enalapril aceclofenac	0	0	1	1
enalapril aspirin	1	0	1	2
enalapril diclofenac	0	1	0	1
enalapril furosemide	2	0	1	3
enalapril gli glibencamide	1	0	0	1
enalapril glibenclami	4	0	10	14
enalapril insulin	3	0	5	8
enalapril meloxicam	1	0	4	5
enalapril pregabalin	1	0	0	1
esomeprzole glibenclamide	2	0	0	2
flucloxacillin diclofenac	0	0	1	1
flucloxacillin ibuprofen	0	0	1	1
flucloxacillin meloxicam	1	0	0	1
flucloxacin hydrochlorothiazide	0	0	1	1
fluconazole losartan	1	0	0	1
fluconazole sulfamethoxazole	0	0	1	1
furosemide asprin	1	0	0	1
furosemide captopril	0	0	1	1
furosemide enalapril	0	0	2	2

furosemide hydrochlorothiazide	0	0	1	1
furosemide metformin	1	0	0	1
glibenclamide aceclofenac	2	0	0	2
glibenclamide captopril	0	0	1	1
glibenclamide ciprofloxacin	1	0	0	1
glibenclamide enalapril	0	0	6	6
glibenclamide enalapr il	1	0	0	1
glibenclamide hydrochlorothiazide	8	1	4	13
glibenclamide ibuprofen	0	0	1	1
glibenclamide insulin	0	0	1	1
glibenclamide levofloxacin	1	0	0	1
glibenclamide meloxicam	1	0	0	1
glibenclamide propranalol	0	0	1	1
hydrochlorothiazide amoxicillin	1	0	0	1
hydrochlorothiazide aspirin	1	0	1	2
hydrochlorothiazide diclofenac	1	0	0	1
hydrochlorothiazide folic acid	1	0	0	1
hydrochlorothiazide furosemide	1	1	1	3
hydrochlorothiazide glibenclamide	10	0	5	15
hydrochlorothiazide insulin	3	2	1	6
hydrochlorothiazide meloxicam	1	0	1	2
hydrochlorothiazide metformin	0	1	0	1
hydrochlorothiazide metformin	13	5	13	31
hydrochlorothiazide metoprolol	0	0	1	1
hydrochlorothiazide sulfamethoxazole	1	0	0	1
hydrochlorothiazide triamcilone	0	0	1	1
hydrochlorothiazide metoprolol	0	0	1	1
hydrocortisone hydrochlorothiazide	1	0	0	1
ibuprofen hydrochlorothiazide	2	0	2	4
ibuprofen losartan	2	0	0	2
ibuprofen sulfamethoxazole	0	1	0	1
imipramine nifedipine	0	0	1	1
insulin enalapril	0	0	1	1
insulin hydrochlorothiazide	1	0	0	1
lamivudine nevirapine	0	0	1	1
lamivudine zidovudine	1	0	0	1
levofloxacin insulin	1	0	0	1
losartan enalapril	3	0	1	4
losartan furosemide	1	0	0	1
losartan hydrochlorothiazide	0	0	2	2

losartan ibuprofen	0	0	1	1
losartan metoprolol	1	0	0	1
losartan spironolactone	0	0	1	1
losartan trimethoprim	0	0	1	1
losartan enalapril	1	0	0	1
losratn ibuprofen	0	0	1	1
meloxicam enalapril	1	0	1	2
meloxicam glibenclamide	0	0	5	5
meloxicam hydrothiazide	1	0	0	1
metformin furosemide	2	1	1	4
metformin hydrochlorothiazide	13	2	17	32
metformin hydrocortisone	1	0	0	1
metformin insulin	2	0	1	3
metformin metformin	0	0	1	1
metformin nifedipine	4	0	3	7
metformin trimethoprim	0	0	1	1
metfromin hydrochlorothiazide	1	0	1	2
metronidazole nifedipine	0	1	0	1
nebivolol nifedipine	2	0	0	2
nevirapine nifedipine	1	0	0	1
nifedipine amitriptyline	1	0	0	1
nifedipine amitriptyline	1	0	0	1
nifedipine amlodipine	1	0	0	1
nifedipine atorvastatin	1	1	2	4
nifedipine erythromycin	0	0	1	1
nifedipine griseofulvin	0	0	1	1
nifedipine hydrocortisone	1	0	0	1
nifedipine metformin	10	2	13	25
nifedipine metformin	1	0	0	1
nifedipine metfromin	0	0	1	1
nifedipine pioglitazone	0	0	1	1
nifedipine predinisolone	0	0	1	1
nifedipine theophilline	0	0	1	1
norfloxacin metformin	1	0	0	1
ofloaxcin hydrochlorothiazide	1	0	0	1
omeprazole glibenclamide	0	0	3	3
pioglitazone ciprofloxacin	0	0	1	1
pioglitazone hydrochlorothiazide	3	0	1	4
pioglitazone nifedipine	1	0	0	1

predinisolone metformin	0	0	1	1
predinisolone nifedip	0	0	1	1
pregabalin analapril	1	0	0	1
pregabalin enalapril	1	0	3	4
sprinolactone digoxin	0	0	1	1
sprinolactone furosem	0	0	1	1
sulfamethoxazole losartan	1	0	0	1
sulfamethoxazole metformin	0	0	1	1
tramadol amitriptyline	0	0	1	1
trimethoprim enalapril	0	0	1	1
Total	**163**	**22**	**177**	**362**

APPENDIX 8: DISTRIBUTION OF PHARMACOKINETIC INTERACTION SUBCATEGORIES

Drug combination	**A**	**D**	**M**	**E**	**Total**
aceclofenac hydrochlorothiazide	0	0	0	1	1
acetaminophen acetazolamide	0	0	1	0	1
amoxicillin hydrochlorothiazide	0	0	0	1	1
aspirin glibenclamide	1	1	0	0	2
aspirin hydrochlorothiazide	0	0	0	3	3
aspirin meloxicam	0	0	0	1	1
asprin hydrochlorothiazide	0	0	0	1	1
asprin losartan	0	0	0	1	1
atorvastatin amitriptyline	0	3	0	0	3
atorvastatin nifedipine	0	0	1	0	1
atorvastatin triamscilone	0	1	0	0	1
butabital omeprazole	0	0	1	0	1
carvedilol digoxin	0	0	0	1	1
cefixime aspirin	0	0	0	1	1
ciprofloxacin carvedilol	0	0	1	0	1
clotrimazole pessaris	0	0	1	0	1
coartem atorvastatin	0	0	1	0	1
coartem nifedipine	0	0	1	0	1
digoxin metformin	0	0	1	0	1
diltazem metformin	0	0	0	1	1
enalapril meloxicam	0	0	0	2	2

esomeprazole glibenclamide	2	1	0	0	3
esomeprzole glibenclamide	1	0	0	0	1
felodipine nifedipine	0	0	1	0	1
flucloxacillin diclofenac	0	1	0	1	2
flucloxacillin hydrochlorothiazide	0	0	0	2	2
flucloxacillin ibuprofen	0	1	0	1	2
flucloxacillin meloxicam	0	1	0	0	1
flucloxacin hydrochlorothiazide	0	0	0	1	1
fluconazole losartan	0	0	1	0	1
furosemide hydrochlorothiazide	1	1	0	0	2
glibenclamide hydrochlorothiazide	1	0	0	0	1
glibenclamide omeprazole	0	0	1	0	1
hydrochlorothiazide amoxicillin	0	0	0	1	1
hydrochlorothiazide aspirin	0	0	0	2	2
hydrochlorothiazide flucloxacillin	0	0	0	1	1
hydrochlorothiazide folic acid	0	0	0	1	1
hydrochlorothiazide furosemide	1	1	0	0	2
hydrochlorothiazide meloxicam	0	0	0	1	1
hydrochlorothiazide metformiin	0	0	0	1	1
hydrochlorothiazide metformin	1	0	0	21	22
metformin enalapril	0	0	0	1	1
nifedipine metformin	1	0	0	0	1
hydrochlorothiazide sulfamethoxazole	0	0	0	1	1
ibuprofen hydrochlorothiazide	0	1	0	3	4
ibuprofen sulfamethox	0	0	1	0	1
imipramine nifedipine	0	0	1	0	1
ketorolac flucloxacillin	0	1	0	0	1
levofloxacin meloxicam	0	0	0	1	1
levofloxacin metformi	0	0	1	0	1
losartan ibuprofen	1	0	0	0	1
losartan metoprolol	0	1	0	0	1
losartan sulfamethoxazole	0	0	1	0	1
magnesium hydroxide hydrochlorothiazide	0	0	0	1	1
meloxicam flucloxacillin	0	0	0	1	1
meloxicam hydrochlorothiazide	0	0	0	1	1
metformin hydrochlorothiazide	0	0	0	20	20
metformin nifedipine	10	0	0	0	10
metformin trimethoprim	0	0	0	1	1
metronidazole losartan	0	0	1	0	1
metronidazole nifedipine	0	0	1	0	1

metronidazole sulfamethoxazole	0	0	1	0	1
nevirapine nifedipine	0	0	1	0	1
nifedipine amitriptyline	1	0	0	0	1
nifedipine amitriptyline	0	1	0	1	2
nifedipine amlodipine	0	0	1	0	1
nifedipine atorvastatin	3	0	2	0	5
nifedipine coartem	0	0	2	0	2
nifedipine dexamethasone	0	1	1	0	2
nifedipine erythromycin	0	0	1	0	1
nifedipine erythromycin	0	0	1	0	1
nifedipine gentamycin	0	1	0	0	1
nifedipine griseofulvin	0	0	1	0	1
nifedipine hydrocortisone	0	0	1	0	1
nifedipine metformin	34	0	0	1	35
nifedipine metformin	1	0	0	0	1
nifedipine metformin	1	0	0	0	1
nifedipine pioglitazo	0	0	2	0	2
nifedipine predinisol	0	0	3	0	3
nifedipine propranalol	0	0	0	1	1
nifedipine theophilline	0	0	1	0	1
nifedipine tobramycin	0	1	0	0	1
ofloaxcin hydrochlorothiazide	0	0	0	1	1
omeprazole cefurxime	1	0	0	0	1
omeprazole glibenclam	0	0	3	1	4
omeprazole losartan	0	0	1	0	1
pioglitazone nifedipi	0	0	2	0	2
predinisolone nifedip	0	1	0	0	1
predinisolone theophi	0	0	1	0	1
sprinolactone digoxin	0	1	0	0	1
sulfamethoxazole losartan	0	0	0	1	1
sulfamethoxazole metformin	0	0	0	1	1
sulphamethoxazole glibenclamide	0	1	0	0	1
triamcinolone aspirin	0	0	0	1	1
trimethoprim enalapri	0	0	0	1	1
trimethoprim hydrochlorothiazide	0	0	0	1	1
Total	**61**	**21**	**42**	**86**	**210**

KEY: A-Absorption D-Distribution M-Metabolism E-Elimination

APPENDIX 9: KNH-UoN ERC ETHICAL APPROVAL FOR THE STUDY

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KENYATTA NATIONAL HOSPITAL APPROVED 04 FEB 2016 KNH/UoN-ERC P.O. Box 20723-00202 NRB.

Ref: KNH-ERC/A/43

4th February, 2016

Otachi Eric Ogamba
Reg. No. U51/74520/2014
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Eric,

Revised research proposal: Potential Drug- Drug Interactions among Patients with Type 2 Diabetes and Hypertension in Kisii Teaching and Referral Hospital (P674/10/2015)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and **approved** your above proposal. The approval period is from 4th February 2016 – 3rd February 2017.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Chair, KNH-UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chair, Dept of Pharmacology and Pharmacognosy, UoN
Supervisors: Dr. Eric Guantai, Dr. George O. Osanjo, Prof. G. Muriuki