# PREVALENCE AND MANAGEMENT OF POTENTIAL DRUG-DRUG INTERACTIONS AMONG CHRONIC LIVER DISEASE PATIENTS AT KENYATTA NATIONAL HOSPITAL

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## DECLARATION OF ORIGINALITY

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**Title of Work:** Prevalence and management of potential drug-drug interactions among chronic liver disease patients at Kenyatta National Hospital

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This is to certify that this research dissertation has been submitted for review with our approval as the University supervisors.

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## DEDICATION

I dedicate this dissertation to God for giving me the opportunity to reach this stage. I also dedicate it to my family for their moral, financial and spiritual support throughout my education life. Without them it could have been harder or impossible. I will as well dedicate this dissertation to my lecturers at the university of Nairobi, department of pharmaceutics and pharmacy practice, for their continuous support through course work and the commencing research. They have been of great help. Special dedication is to chronic liver disease patients and their healthcare providers for reference at KNH liver clinic.

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**ABBREVIATIONS AND ACRONYMS**

ADRs- Adverse Drug Reaction

CLD- Chronic liver disease

CMEs- Continuous Medical Education

DDIs- drug-drug interactions

HIV- Human Immunodeficiency Virus

HPV-human papilloma virus

KNH- Kenyatta National Hospital

KNH-UoN ERC-Kenyatta National Hospital-University of Nairobi Ethics Research Committee

pDDIs -potential drug-drug interactions

SBP- spontaneous bacterial peritonitis

TDF- tenofovir disoproxil fumarate

## OPERATIONAL DEFINITION OF TERMS

**Adverse drug reaction:** It is harmful and unintended response to a drug, and which occurs at normal doses used for therapy or prophylaxis of disease.

**Drug-drug interaction-** A DDI is defined as the clinical or pharmacological reaction to the administration of a multiple drug regimen that is different from the known effects of the two drugs when given separately**.**

**Major drug interaction:** these are life-threatening DDIs which require intervention to prevent or avoid them.

## ABSTRACT

**Background:** Drug-drug interactions in patients receiving multi-drug therapies are of great concern. Such interactions are important causes of adverse drug reactions that may lead to increased morbidity and mortality. The prevalence of drug-drug interactions varies with geographical regions and patient characteristics

**Study Objectives**: The main objective of the study was to assess the prevalence and management of potential drug-drug interactions among adult patients with chronic liver disease at Kenyatta National Hospital

**Study Design:** A cross-sectional study.

**Study Area:** Kenyatta National Hospital Liver Clinic.

**Study Population:** One hundred and thirty-seven (137) participants aged 18 years and above, with diagnosed chronic liver disease who met the study inclusion criteria.

**Methods:** Chronic liver disease patients were recruited while attending their liver clinic appointments. Participants were sampled through simple random sampling technique. Data was collected through interviews, using interviewer administered questionnaires. Some data on prescribed drugs was abstracted from patient files to compliment data obtained through the interviews. Once collected, data was entered into MS excel 2016. Bivariate and multivariate data analysis was carried out using STATA version 14.

**Results**: Majority of the respondents were male (63.5%). The mean age in years of the participants was 39.2 years. The total number of prescriptions evaluated for pDDIs was 67, giving a prevalence rate of 48.9%. The prevalence of participants with major DDIs in their prescriptions was 58.2%, moderate 37.3% and minor was 4.5%. Almost a half of the prescriptions that had pDDIs, 49.3% had only one pair of interacting drugs whereas a small proportion (4.5%) had six and above interacting pairs with 29.9% having two interaction pairs. The most commonly prescribed drugs among chronic liver disease patients were antibiotics (60.6%), followed by proton pump inhibitors (48.2%) then laxatives (29.9%). Independent predictors of pDDIs were total number of drugs per patient and having secondary level of education.

**Conclusion:** We were able to establish a moderate prevalence of pDDIs among chronic liver disease patients at KNH liver clinic which suggested average management of these patients.

**Recommendations**: The findings of this study should be shared with the respective prescribers to reduce the incidences of concomitant prescription of majorly and moderately interacting drugs.

# CHAPTER 1: INTRODUCTION

## 1.1 Background to the study

Chronic liver disease is defined as progressive deterioration or decline of liver functions over a period of six months or more. CLD starts with inflammation of the liver parenchyma. The process progresses to destruction and regeneration of liver parenchyma. This eventually leads to fibrosis and cirrhosis(1). The worldwide burden of CLD and cirrhosis is substantial. Liver disease accounts for about 2 million deaths per year globally, where 1 million are due to hepatocellular carcinoma and viral hepatitis and the remainder due to complications of cirrhosis.

Cirrhosis is ranked the 11th most common cause of death worldwide(2). There is a geographic variation in prevalence of chronic liver disease. In a study in the US, the prevalence of CLD was 3.9% in African Americans, 4.1% in whites, 3.9% in Native Hawaiians, 6.7% in Latinos, and 6.9% in Japanese(3).

Combination of drugs is a common practice and it's usually done to enhance the efficiency of drug treatment. However, selection of the optimal combination and optimal doses remains a matter of daily adjustments of the regimens(4). Therefore, in vivo studies to predict synergistic, additive and antagonistic responses to various drug combinations remains an area of considerable interest.

Drug-drug interactions in patients receiving multi-drug therapies are of great concern. Such DDIs are important causes of ADRs that may lead to increased morbidity and mortality. In a study that was done on prevalence of potential drug-drug interactions and its associated factors in a Brazilian teaching Hospital, the overall frequency of potential

DDI was 49.7% (5). In Ethiopia, a study was conducted on prevalence of pDDIs among internal medicine ward in University of Gondar Teaching Hospital where it was found out that 78% of all the participants had at least one or more potential DDI(6). There is one study that explored on DDIs among chronic liver disease patients and reported that at least one pDDI was found in 83.5% of patients(7). However, there was no a local study reporting on potential DDIs in CLD, thus this study by Culafic M et al was used to estimate sample size of the study.

**1.2 Problem statement**

Chronic liver diseases are one of the main causes of mortality locally and globally (8). Drug-drug interactions may occur in CLD patients on multi-drug regimens, thus increasing the risk of hospitalization and mortality. Studies done in Kenya on drug-drug interactions focused on hypertension and type 2 diabetes mellitus patients in Kisii Teaching and Referral Hospital (9) and Kenyatta National Hospital(10) and mentally ill patients at Mathari Mental Hospital(11).

The studies on CLD that have been done in Kenya have focused mainly on prevalence of specific subtypes of CLD such as non-alcoholic fatty liver disease at KNH and drug-induced hepatic injury (12). In addition, there were few published studies available on chronic liver disease in Kenyatta National Hospital, and the information may not be current(13)(14).

However, there was no a study done on pDDIs among CLD patients at KNH, the management of such drug-drug interactions and the outcomes. This study sought to assess

prescription patterns in CLD, the potential DDIs among chronic liver disease adult patients at KNH and the management of such DDIs.

### 1.3 Justification of the study

Studies on potential drug-drug interactions have been conducted in developed countries(15).

However, there was minimal literature available in developing countries including Kenya on the topic. Information on pDDIs and their management in chronic liver disease should be available in main referral hospitals like Kenyatta National Hospital so as to enlighten healthcare workers on rational prescribing in CLD. The information collected from this study will form a database on studies done on CLD at KNH.

### 1.4 Research questions

1. What are the prescription patterns among adult patients with CLD at KNH?
2. What is the prevalence and characteristics of potential drug-drug interactions among adult patients with CLD at KNH?
3. How are drug-drug interactions managed among adult patients with CLD at KNH?

## 1.5 Objectives

### 1.5.1 Broad objective

To assess the prevalence and management of potential drug-drug interactions among adult patients with CLD at KNH

### 1.5.2 Specific objectives

1. To assess prescription patterns among adult patients with CLD at KNH.
2. To determine the prevalence of potential drug-drug interactions and characterize the DDIs among adult patients with CLD at KNH.
3. To document the management of drug-drug interactions among adult patients with CLD at KNH.

## 1.6 Significance and anticipated output

This study will be beneficial to healthcare providers for future reference on pDDIs and their management among CLD patients. Thus, the study will also help chronic liver disease patients to receive optimal management. The study findings will be published and thus made available online for reference by future researchers.

### 1.7 Conceptual framework

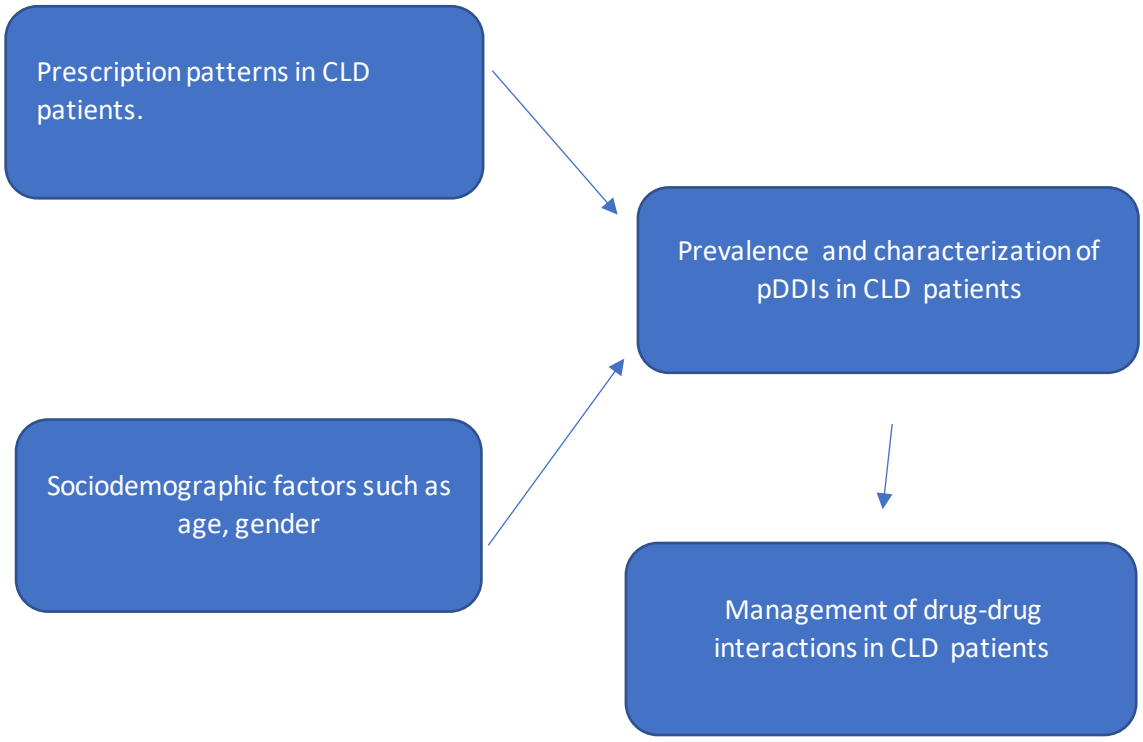


**Figure 1: Conceptual framework**

This study was anchored on three areas. These are; prescription patterns in chronic liver disease, prevalence and characteristics of pDDIs among chronic liver disease adult patients and management of DDIs among CLD adult patients.

The exposure was the prescription patterns while the outcome was the drug-drug interactions. The DDIs are dependent on the prescription patterns and sociodemographic factors of the patient. On the other hand, the management of DDIs is dependent on the specific drug-drug interaction.

## 1.8 Delimitations

The study was carried out at KNH liver clinic and only among chronic liver disease patients.

## 1.9 Limitations

The likely limitation to this study was incomplete records during data collection from the patient files. Incase such issue is encountered; the researcher did random sampling again to replace the participants whose files had missing data. This limitation may only affect the study on use of more time to sample and interview the participants but will not affect the results.

## CHAPTER TWO: LITERATURE REVIEW

### 2.1 Prescription patterns in chronic liver disease patients

In most CLD patients, medications are prescribed for prevention and management of complications of cirrhosis. According to a study carried out among 25 Spanish hospitals, the most prescribed diuretics were combination of spironolactone and furosemide(16).According to another study conducted in India, the most commonly prescribed class of antimicrobials was cephalosporin. Hepatic encephalopathy and variceal bleeding were managed using lactulose and propranolol respectively(17). Opioids is another class of drugs that is often prescribed among cirrhosis patient(18). Opioids are considered high risk in liver cirrhosis patients and thus should be avoided(19). In a study done on prescription patterns of NSAIDs and acetaminophen in patients with liver cirrhosis, NSAIDS were more frequently prescribed(20). However, this should be avoided. Statins are also used in cirrhotic patient to reduce risk of decompensation and death(21).

### 2.2 Drug-drug interactions

A drug-drug interaction is defined as the clinical or pharmacological reaction to the administration of a multiple drug regimen that is different from the known effects of the two drugs when given separately(9)**.** DDIs usually occur when one drug influences the effects of another drug when they are administered together. This may cause changes in the pharmacokinetic or pharmacodynamic parameters of the affected drug, eventually

leading to reduced efficacy, lack of efficacy, increased efficacy or a decrease or an increase in the number of adverse drug reactions(ADRs)(22).

The prevalence of drug-drug interactions varies geographically. A study was conducted in a Brazilian teaching hospital on the prevalence of potential DDIs and found that the overall prevalence of potential DDI was 49.7%. The prevalence of the potentially major DDI was 3.4%, where the most common interacting pair was digoxin-hydrochlorothiazide(5). In a retrospective study that was done in a general hospital in China on prevalence of pDDIs in outpatients, 30.29% of the prescriptions were identified with pDDIs(23). Some of the DDIs may contribute to hospital admission of the affected patients as reported by Dechanont *et al.*(24) In this study, the median DDI prevalence rate contributing to hospital admissions was 1.1%.

In Africa, several studies have been done on the prevalence of DDIs. In Ethiopia, a study was conducted on prevalence of pDDIs in University of Gondar Teaching Hospital where it was found out that 78% of all the participants had at least one or more potential DDI(6). In a research that was conducted in western Uganda on potential DDIs on in-patient medication prescriptions, the overall prevalence of pDDIs was approximately 23% (25). In another study in South Africa that was investigating the prevalence of pDDIs in primary healthcare clinics in the George subdistrict, it was found that 43.25% of the prescriptions had at least one potential DDI(26).

## 2.3 Classes of drug interactions

Drug interactions may occur at pharmacodynamic and pharmacokinetic levels. Pharmacodynamic DDIs refers to interaction where the drugs influence each other's effects directly. Pharmacodynamic interactions may be desired if synergistic effects are aimed at, such as in pain therapy or use of anti-infectives. However, they may also be undesired if they are antagonistic in nature. Pharmacokinetic drug interactions occur at the levels of absorption , elimination and metabolism(27). Drug interactions can also be classified as physicochemical interactions which occur due to incompatibility between chemical structure(28).

The severity of DDIs may be classified as major, moderate or minor interactions. Major DDIs are highly clinically significant and such drug combinations should be avoided since the risk of the DDIs outweighs the benefit. Moderate DDI have moderate clinical significance and should be avoided, but can only be used under special circumstances. Minor DDIs have minimal clinical significance. The prescriber should assess the risk, minimize it or consider an alternative drug and take steps to circumvent the interaction risk or institute a monitoring plan(29).

## 2.4 Burden of potential drug-drug interactions

DDIs are a global concern for patients on multiple drugs regimens. Several studies have been conducted on potential drug-drug interactions, both on general prevalence of pDDIs and on prevalence of pDDIs in specific categories of patients. A study that was done on overall prevalence of potential DDIs and its associated factors in a Brazilian teaching

Hospital revealed that the prevalence of DDIs was 49.7%(5). Another study that was conducted in Ethiopia on prevalence of potential drug–drug interactions showed that prevalence of pDDIs was 78% in that population (6). Another study on general prevalence of pDDIs was done in Uganda where the prevalence of pDDIs was 23%(25).

Studies of pDDIs on specific patient conditions have been done locally, such as in hypertensive and diabetic patients (10)(30)and mentally ill patients (11).However, no local study has reported on pDDIs in patients with CLD. Only one study was found on published literature reporting on prevalence of pDDIs (83.5%), published in European Journal of Hospital Pharmacy(7).

**2.5 Drug-drug interactions associated with the management of chronic liver disease**

Chronic liver disease management entails use of different pharmacological classes of drugs depending on the etiology and the complications involved. Management of CLD that is secondary to chronic viral hepatitis or schistosomes infestations involves treatment of the underlying cause, as well as the complications. CLD secondary to chronic hepatitis B infection is managed using antiviral agents such as tenofovir, peg-interferon alpha and entecavir(31). On the other hand, chronic hepatitis C infections associated with CLD are managed using Sofosbuvir, ribavirin and ledipasvir regimen. Persistent schistosomiasis infestation that leads to CLD is usually managed using praziquantel (32).

CLD secondary to Wilson's disease (WD) involves use of trientine or D-penicillamine and zinc and then use of other agents to manage complications that may arise (33). Primary Biliary Cholangitis (PBC), an autoimmune disease may also lead to chronic liver disease.

The first line therapy for PBC is Ursodeoxycholic acid (UDCA). UDCA may be used together with other agents such as antihistamines to calm the pruritus experienced by PBC patients(34). CLD associated with other autoimmune conditions is usually managed using corticosteroids and immunomodulators. Alcoholic liver disease (ALD) is usually managed through abstinence from alcohol intake and use of benzodiazepines to control the alcohol withdrawal syndrome, but other agents like clonidine, topiramate ,gabapentin, and baclofen can be used to avoid the potential side effects of benzodiazepines (35).

Complications in chronic liver disease include portal hypertension, ascites, gastrointestinal bleeding from esophageal, gastric or rectal varices, acute kidney injury, hepatopulmonary syndrome, hepatic encephalopathy, spontaneous bacterial peritonitis (SBP), hepatocellular carcinoma and coagulopathies. Anti-mineralocorticoid drugs such as spironolactone are the mainstay in the treatment of ascites. Acute gastrointestinal bleeding in patients with cirrhosis is managed using somatostatin/terlipressin and ceftriaxone, together with crystalloids as indicated in EASL practice guidelines for management of decompensated cirrhosis.

### 2.5.1 BDZS in alcohol withdrawal in ACLD

Traditional benzodiazepines can lead to fatal interactions when combined with agents with additive central nervous system depression effects such as phenothiazines, opioids, barbiturates, monoamine oxidase (MAO) inhibitors, antidepressants, alcohol and illicit drugs like heroin.

The elimination of some benzodiazepines such as alprazolam and diazepam are reduced by drugs that slow elimination of drugs in the liver such as fluoxetine, ketoconazole,

valproic acid, and cimetidine. The decreased elimination results in increased concentration of the BDZ in the blood and thus increased side effects. Absorption of benzodiazepines from the intestine may also be affected by concomitant administration with antacids. This interaction can be minimized by separating the administration of benzodiazepines and antacids by several hours(36).

### 2.5.2 Tenofovir df and lamivudine in chronic hepatitis b cirrhosis

Concomitant administration of tenofovir DF with aminoglycoside antibiotics such as gentamycin, amikacin and tobramycin may increase the risk of renal damage. Tenofovir DF also interacts with high dose of NSAIDs such as ibuprofen, diclofenac, ketoprofen and naproxen, leading to increased risk of nephrotoxicity. TDF has serious DDIs with adefovir, bacitracin, cabotegravir, cyclosporine, dabigatran, Lasmiditan, letermovir, nintedanib and such combinations should be avoided. With adefovir, both TDF and adefovir increases toxicity of each other through pharmacodynamic synergism, enhancing nephrotoxicity. Also, there is increased risk of nephrotoxicity and ototoxicity when TDF and bacitracin are used together(37).

Tenofovir DF also interacts with other antiviral agents, increasing risk of renal damage. Such antivirals include cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, atazanavir, lopinavir. However, these agents can be administered together, if need be, with close monitoring.

### 2.5.3 Sofosbuvir/ribavirin/ledipasvir in chronic hepatitis c infection with cirrhosis

Ledipasvir/sofosbuvir has serious DDIs when administered with colchicine, erdafitinib and topotecan, and it should never be used with carbamazepine, fosphenytoin, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St John's Wort and tipranavir.

Close monitoring should be done when it's administered with aluminum hydroxide /magnesium trisilicate, amiodarone, atorvastatin, calcium carbonate, cimetidine, sodium bicarbonate, dabigatran, digoxin, proton-pump inhibitors, famotidine, rosuvastatin, tenofovir DF and warfarin(38)**.**

### 2.5.4 Corticosteroids and immunomodulators in chronic autoimmune hepatitis e.g., prednisolone, methylprednisolone

Prednisolone has serious interactions with most vaccines such as anthrax vaccine, BCG vaccine live, diphtheria & tetanus toxoids/ acellular pertussis vaccine, inactivated vaccine, hepatitis A vaccine, inactivated hepatitis a/b vaccine, hepatitis a/typhoid vaccine, hepatitis b vaccine, HPV vaccine, influenza virus vaccine, measles (rubeola) vaccine, measles mumps and rubella vaccine, mumps, rubella and varicella vaccine, live meningococcal A C Y and W-135 polysaccharide vaccine, pneumococcal vaccine, travelers' diarrhea and cholera vaccine, typhoid vaccine , yellow fever vaccine, zoster vaccine live, rabies vaccine, rubella vaccine, Rota virus vaccine, small pox vaccine and tetanus toxoid.

Prednisolone also has serious interactions when administered with some drugs such as carbamazepine, cimetidine, clarithromycin, dihydroergotamine, ergotamine, erythromycin, ketoconazole, lovastatin**,** simvastatin, testosterone intranasal and

tofacitinib. Therefore, prednisolone should not be used together with these drugs and vaccines(39).

### 2.5.5 Lactulose and rifaximin in treatment of hepatic encephalopathy in chronic liver disease

Rifaximin has serious DDIs when administered together with BCG intravesical live and cholera vaccine. It (rifaximin) decreases effects of BCG intravesical live vaccine and cholera vaccine by pharmacodynamic antagonism. Close monitoring should be done when rifaximin is administered together with afatinib, amiodarone, azithromycin, carvedilol, clarithromycin, cyclosporine, darunavir, dipyridamole, erythromycin, itraconazole, ketoconazole, lopinavir, mefloquine, nifedipine, propranolol, quinidine, quinine, ritonavir, saquinavir, tacrolimus, tamoxifen, ulipristal, verapamil and warfarin(40). Lactulose has no serious DDIs but should be closely monitored when administered together with aluminum hydroxide, calcium carbonate, deflazacort, sodium bicarbonate and sodium citrate. Both lactulose and deflazacort decreases serum potassium. Aluminum hydroxide, calcium carbonate, sodium bicarbonate and sodium citrate decreases effects of lactulose through pharmacodynamic antagonism(41).

### 2.5.6 Pentoxifylline in severe alcoholic hepatitis

Pentoxifyline has no serious DDIs but has a minor DDI with theophylline. Pentoxifylline increases levels of theophylline by decreasing its metabolism when administered together. However, there should be close monitoring when pentoxifylline is administered together with amifostine, amiodarone, captopril, cimetidine, ciprofloxacin, duloxetine, fluoxetine, fluvoxamine, insulin aspart, nifedipine, ofloxacin, primaquine and warfarin(42).

### 2.5.7 Ursodeoxycholic acid in primary biliary cirrhosis

Ursodiol has no serious DDIs but should be monitored closely when administered together with aluminum hydroxide, calcium carbonate, ethinyl estradiol, sodium bicarbonate and sodium citrate. Concomitant administration of ursodiol with either aluminum hydroxide, ethinyl estradiol ,calcium carbonate, sodium bicarbonate, or sodium citrate decreases effects of ursodiol by pharmacodynamic antagonism, and thus should be used with caution(43).

## 2.6 Strategies to minimize unwanted DDIs in management of CLD patients

Potential DDIs must first be identified in order to identify patients at risk of harmful drug interactions. Strategies to minimize the risk of interactions include regulatory endeavors to improve labeling of new drugs on their metabolic profile as well as potentially hazardous DDIs. In this era is internet use, several software programs for detecting and managing drug-drug interactions can also be utilized by prescribers to minimize DDIs (44).

## 2.7 Research gap

Several studies had been done locally on pDDIs in patients with specific health conditions such as hypertension and diabetes (9),(10),HIV (45), mental illness s (11) among others. However, no local study had been done and published on pDDI in patients with chronic liver disease.

## CHAPTER THREE: METHODOLOGY

### 3.1 Study design:

A cross-sectional design was used to conduct the study. This design was used because it made it possible to assess prescription patterns in chronic liver disease, find out pDDIs among CLD patients and document the management of drug-drug interactions among CLD adult patients. The design was relatively quick, cheap and easy to conduct, and it's good for descriptive analyses.

### 3.2 Location of the study

The study was conducted at liver clinic of Kenyatta National Hospital (KNH). KNH is located in Nairobi County in Kenya. KNH is a referral university hospital with a bed capacity of about 2000 patients. The hospital serves a population of over 4 million people(46). It is among the public facilities in Kenya where patients can get comprehensive and specialized management of chronic conditions.

### 3.3 Target population and study population

Target population for the study was all chronic liver disease adult patients in KNH. Study population was those attending the liver clinic for follow up.

### 3.4 Inclusion criteria

Persons with the following characteristics were recruited into the study:

•Aged 18 or older

•patients with a documented diagnosis of CLD

•Enrolled for follow up at the KNH liver clinic.

•those who granted informed consent to participate in the study.

### 3.5 Exclusion criteria:

Psychologically challenged patients like the mentally ill, patients with Parkinson's disease and dementia. These patients may not have the capability to give credible information due to disorientation or inability to remember some details.

### 3.6 Sample size

Sample size was computed using Cochran formula (47).

There was one study that explored on drug-drug interactions among chronic liver disease patients and reported that at least one pDDI was found in 83.5% of patients(7). However, there was no a local study reporting on potential DDIs in CLD, thus this study by Culafic M et al was used to estimate sample size of the study.

Using the Cochran formula:

$$n = (pqz^2) / e^2$$

Where:

n is the desired sample size

p is the prevalence of DDIs from previous studies

e is the acceptable margin of error that is 5%

z is the standard deviation for a 95% confidence interval which is 1.96

q is the accepted level of precision that is 1-p.

Thus;

$$n = \{0.835 \text{ X } (1-0.835) \text{ X } 1.96^2 \} / 0.05^2$$

=212 participants

The population on follow up at the KNH liver clinic for CLD were less than 10000, thus sample size adjustment using the Cochran correction for a finite population was done (47)

$$n_1 = n_o /(1 + (n_o -1)/ N)$$

where $n_1$ is the corrected sample size

$n_0$ is the calculated sample size

N is the population sample size which is approximately 307 patients at KNH liver clinic.

$n_1 = 212/(1+211/307)$

$=125$

Adjusting for 10% attrition rate:

10% of 125 =12.5

Thus 125+12=137

=137 participants

**3.7 Sampling technique**

Participants were sampled by simple random sampling. This was achieved by use of a table of random numbers. The following steps were used:

Step 1: A list of all the CLD patients at KNH liver clinic was made.

Step 2: A sequential number was assigned to each CLD patient in the list.

Step 3: A table of random numbers was used to select the sample, using the sampling frame (population size) and the sample size from Step 3.

The sampled persons who met the eligibility criteria were informed by the researcher what the study entails. Printed informed consent form was availed for the persons who were willing to participate in the study, where they were required to sign against their names before participation in the study. Any sampled CLD patients who refused to give consent to participate in the study was excused without any victimization since participation was voluntary. Such persons were replaced to optimize on sample size. Replacement was done

by selecting the next random person from the sampling frame, using the table of random numbers.

### 3.8 Research instruments

An interviewer administered questionnaire and the respective patient file were used to collect data on social-demographics and prescription patterns. PDDIs were identified using Micromedex drug interactions checker.

Several softwares are used as tools for evaluation of potentially harmful DDIs. Micromedex® Drug-Reax was the most commonly used software for evaluation of these pDDIs in many studies. Some authors consider Micromedex® Drug-Reax to be the most reliable due to its high sensitivity. This software gives information on the mechanism of the DDI, clinical consequences of DDIs, onset and severity of the adverse outcome, and the level of evidence which supports the information. Other softwares that can be used to evaluate pDDIs are Lexi-Interact®, Drug Interaction Facts®, and Pharmavista®(48). In a comparative study for three brands of drug interaction softwares, Drug Interaction Checker (DIC), Lexi-Interact (LI) and Drug-Reax (DR) , DR displayed the highest sensitivity while DIC showed the lowest (49).

### 3.9 Pilot study

Pretesting of the interviewer administered questionnaires was done at the KNH liver clinic with some of the eligible CLD patients. The study was conducted by the principal investigator before the main study, once approval to conduct it was given by KNH-UoN

ERC. The pilot study had 10 participants. The 10 participants used in the pilot study were not a part of the sample size, and therefore, the data obtained from the pretesting was not be included in the project data. The participants of the pilot study were selected through simple random sampling of the eligible CLD patients who were attending liver clinic in two consecutive Thursdays (liver clinic appointment day).

### 3.10 Validity

Validity of the study was maintained by ensuring that the questionnaire was relevant with regard to the objectives of this study. The questions were arranged sequentially using clear, simple and concise language. The study site, KNH, gave a good representation of the general population since KNH receives referrals from all over Kenya and East Africa. In addition, the participants were chosen using simple random sampling of all patients with CLD at KNH. This ensured that the study sample was representative of the general population of patients with CLD, thus the study findings are generalizable to that population.

### 3.11 Reliability

Reliability means that the scores of an assessment instrument are stable and consistent. This refers to whether the instrument conveys the same results every time it's used on similar patients and similar setting. The data collection tools were pretested in the pilot study for reproducibility prior the actual study to note and adjust for any ambiguities in responses.

### 3.12 Data collection techniques

Data was collected through interviews, using interviewer administered questionnaires. The data that was collected using interviewer administered questionnaires is specifically sociodemographic information of the participants. Some data was abstracted from respective patient files to compliment data obtained through the interviews. The data that was collected from the files included the most recent prescription of the participant. Thus, the same data was not be collected by the two methods. Participants were selected through random sampling of the CLD patients on follow up at the KNH liver clinic. After the sampling, the selected persons were screened for eligibility to participate in the study using the eligibility screening form. The ones who met the eligibility criteria were informed by the researcher what the study entails, both verbally and in writing. Printed informed consent form was availed for the persons who were willing to participate in the study, where they were required to sign against their names before participation in the study. This was followed by an interview with the researcher, which was conducted through interviewer administered questionnaire. Interviews were done at the liver clinic on Thursdays every week during the liver clinic appointments of the CLD patients.

### 3.13 Data management

**a) Data entry**

After collection, data was entered in MS excel sheet within 24hrs. Data privacy and confidentiality was maintained by using codes to identify participants rather than using their names. Printed and filled questionnaires were stored by the interviewer under lock

and key with no access to unauthorized persons. Soft copy of the data was password protected. Collected and stored data was backed up daily and a copy of it stored away from the main storage. This ensured a copy was always available in case the primary data is tampered with or a laptop software fails or any other uncertainties.

**b) Data cleaning**

Cleaning and validation were be done once all the data has been entered, checked and corrected. Data cleaning was done using Microsoft Excel. Once any errors are detected, they were corrected so that the data can be analysed without losing its integrity and robustness. A clean dataset was stored in a computer hard disk ready for analysis. All the questionnaires were filed and stored in lockable drawers for confidentiality.

### 3.14 Data analysis.

**a) Descriptive analysis**

Descriptive statistics using proportions were be used to summarise categorical variables while measures of central tendency, such as mean and standard deviation were used to summarize for continuous variables. The prevalence and severity of pDDIs was estimated as a percentage with their 95% C.I. Prescribing patterns was estimated using proportions.

b) **Bivariate analyses.**

Associations between pDDIs, and participants characteristics (socio-demographics and other characteristics) were be conducted using logistic regression tests to inform multivariable analyses, and crude Odds Ratio (c.O.R) and 95% Confidence Interval (CI)

were be used to estimate the strength of crude association between independent and dependent variables.

**c) Multivariable analyses.**

The results of the bivariate analyses informed the multivariate analysis. All variables that were associated with the outcome variable (pDDIs) at P<0.2 were entered in the multivariate analysis using multivariate logistic regression models to estimate independent predictors/factors of the pDDIs. Adjusted odds ratio (a.O.R) and their 95% confidence intervals were reported. The threshold for statistical significance was set at $p < 0.05$, and all tests were two sided. All the analysis were conducted using the STATA version 14.

### 3.15 Ethical considerations

The study was carried out after approval from the KNH-UoN ERC. The process and purpose of the study was explained to eligible participants at the beginning of the study, both in writing and verbally. Study participation was voluntary and CLD patients who declined participation in the study were still be offered optimal care at the KNH liver clinic without any discrimination. All participants were required to give informed consent before being enrolled to the study. An informed consent form was typed and printed, with a space for names and signatures for all consenting participants. The findings of the study benefit the participants by ensuring they receive optimal management of CLD.

### 3.16 Dissemination

Once the study is completed, a copy of the study findings will be shared with KNH and University of Nairobi where it shall be publicized on the UoN-repository online. The research findings shall also be published with scientific journals to be available all over the world for future researchers. Furthermore, presentations will be done during scientific seminars for further dissemination of the study findings.

### 3.17 COVID 19 considerations

Protection of both the participants and interviewer against Covid-19 was optimized by provision of necessary personal protective equipment to both parties, maintaining recommended social distance during the interviews and maintaining a high level of hygiene in the interviewing area.

## CHAPTER FOUR: RESULTS

### 4.1 Response rate

The sample size for this study was 137 respondents. A total of 137 potential eligible participants were approached and out of this 5 refused to participate giving a response rate 96.35%.

### 4.2 Socio-demographic characteristics

Table 1 presents the socio-demographic characteristics of the respondents. A total of 137 CLD patients participated in the study. Majority of them were male (63.5%). The mean age in years of the participants was 39.2 $\pm$ 14.4 years. Most of the respondents were married/ever married (61.3%) and 62.8% of the participants had at least one comorbidity. A large proportion (70.8%) had no history of smoking whereas 42.3% ingested alcohol.

**Table 1: Baseline socio-demographic characteristics**

| Variable | Frequency (N=137) (percentage) | Variable | Frequency (N=137) (percentage) |
|---|---|---|---|
| Gender | | Education level | |
| Male | 87(63.5) | No Formal Education | 16(11.7%) |
| Female | 50(36.5%) | Primary | 61(44.5%) |
| Age in years (Mean±SD) | 39.2(SD+ 14.4) | Secondary | 39(28.5%) |
| Marital status | | College/University | 21(15.3%) |
| Single/Never married | 53(38.7%) | Time in years Since Diagnosis of CLD(Mean±SD) | 2.4 (SD+ 2.0) |
| Married/Ever Married | 84(61.3%) | Number of comorbidities | |
| Occupation | | None | 49(35.8%) |
| Business / Self-Employment | 59(43.1%) | One | 86(62.8%) |
| Formal Employment | 24(17.5%) | Two | 2(1.5%) |
| Unemployed | 54(39.4%) | Type of Comorbidities (N=88) | |
| Smoking status | | Hypertension | 2(2.3%) |
| Current Smoker | 10(7.3%) | Heart Failure | 3(3.4%) |
| Previous Smoker | 30(21.9%) | Diabetes Mellitus | 4(4.5%) |
| Never Smoked | 97(70.8%) | Cancer | 6(6.8%) |
| Alcohol intake | | Others | 73(83%) |
| Currently Drinking | 27(19.7%) | | |
| Previous Drinker | 58(42.3%) | | |
| Never Drunk | 52(38%) | | |

### 4.3 Prescribing patterns

#### 4.3.1 Number of medications in a prescription

The mean of the number of drugs in the prescriptions was 4.7±1.9 drugs.

**Table 2: Number of medications in the prescription**

| Number of Medication in the Prescription | Frequency (N=137) | Percentage (%) |
|---|---|---|
| One | 2 | 1.5 |
| Two | 13 | 9.5 |
| Three | 28 | 20.4 |
| Four | 24 | 17.5 |
| Five | 25 | 18.2 |
| Six | 18 | 13.1 |
| Seven | 16 | 11.7 |
| Eight | 8 | 5.8 |
| Nine and above | 3 | 2.2 |

#### 4.3.2 Classes of prescribed drugs

The most commonly prescribed drugs among chronic liver disease patients were antibiotics (60.6%), followed by proton pump inhibitors (48.2%) then laxatives (29.9%). Omeprazole was the most prevalent proton-pump inhibitor (25.5%) followed by esomeprazole (18.2%). Pantoprazole, as well as lansoprazole, was prescribed to only one patient among the respondents.

Lactulose was the most prescribed laxative for patients with hepatic encephalopathy. About 22.6% of the prescriptions had diuretics, with spironolactone and furosemide being prescribed together in most instances. The prescribing patterns are presented in figure 3 below.

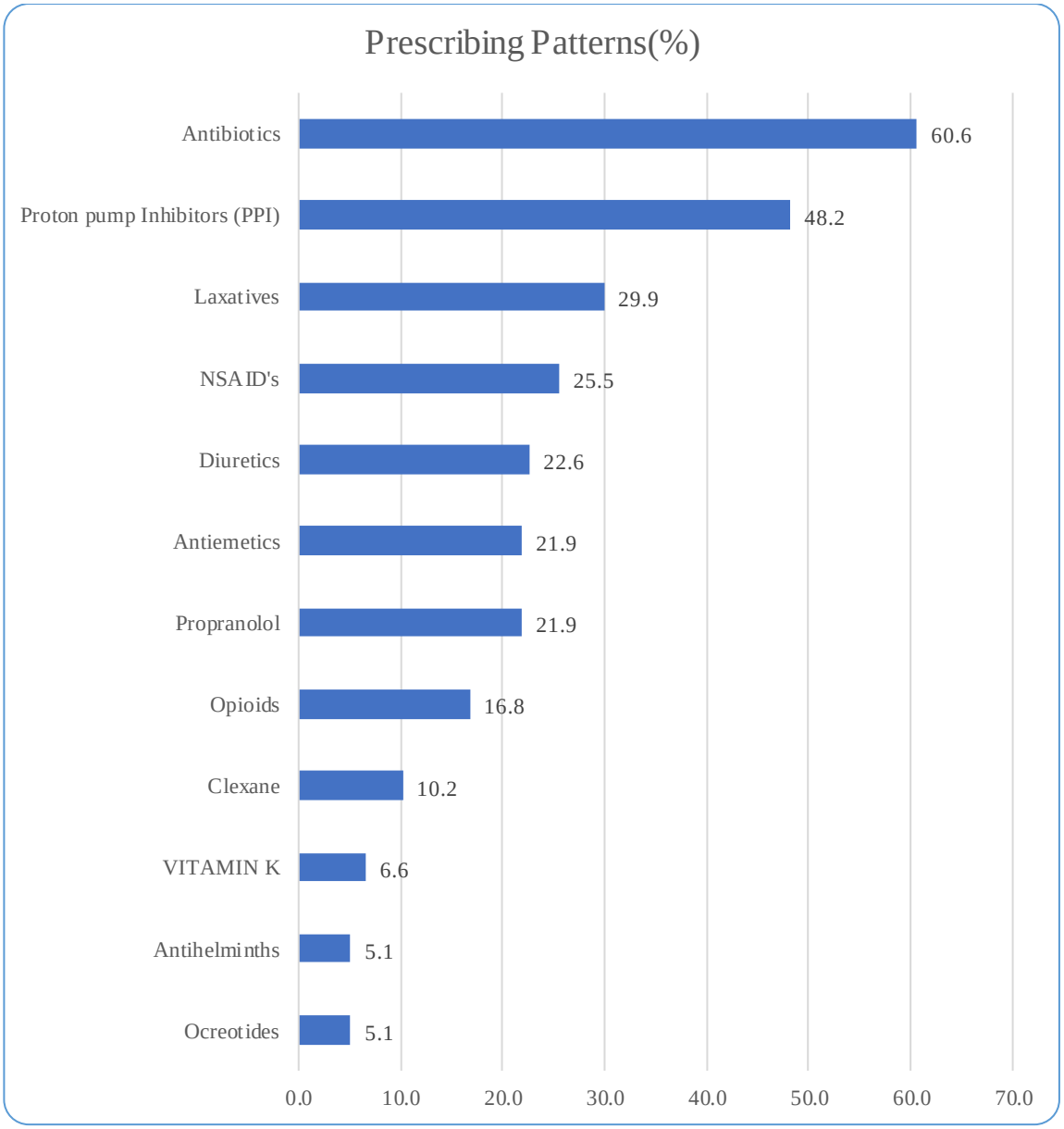


**Figure 2: Classes of prescribed drugs**

### 4.3.3 Types of antibiotics prescribed

The most frequently prescribed antibiotic was metronidazole (41.9%), followed by ceftriaxone (21%), then amoxicillin/clavulanic acid (10.5%) (Table 3).

**Table 3: Types of antibiotics prescribed**

| Antibiotics | Frequency | Percentage |
|---|---|---|
| Metronidazole | 44 | 41.9 |
| Ceftriaxone | 22 | 21.0 |
| Amoxicillin/clav | 11 | 10.5 |
| Ciprofloxacin | 6 | 5.7 |
| Cefuroxime | 4 | 3.8 |
| Rifaximin | 4 | 3.8 |
| Meropenem | 3 | 2.9 |
| Flucloxacillin | 2 | 1.9 |
| Ceftazidime | 2 | 1.9 |
| Fluconazole | 2 | 1.9 |
| Azithromycin | 1 | 1.0 |
| Itraconazole | 1 | 1.0 |
| Levofloxacin | 1 | 1.0 |
| Clindamycin | 1 | 1.0 |
| Co-trimoxazole | 1 | 1.0 |

NB: Not all prescriptions had antibiotics

### 4.4 Prevalence and characterization of pDDIs.

#### 4.4.1 Prevalence and characterization of pDDIs.

The total number of patients whose prescriptions had pDDIs were 67, giving a prevalence of 48.9% (Table 4). The prevalence of participants with major DDIs in their prescriptions was 58.2%, moderate 37.3% and minor was 4.5%.

**Note:** The data in table 4 differs from figure 3 because analysis for table 4 was done for severity of DDI in each individual patient (67 patients), picking only one DDI (the strongest) from his/her prescription; while analysis for figure 3 analysed all the DDIs (134) in all prescriptions.

**Table 4: Prevalence and characterization of potential drug-drug interaction**

| Variable | Category | Frequency | Percentage | 95% C.I | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Potential Drug-drug interaction (N=137) | No | 70 | 51.1 | 42.3 | 59.9 |
| | Yes | 67 | 48.9 | 40.1 | 57.7 |
| Severity of Potential Drug-Drug Interaction (N=67) | Minor | 3 | 4.5 | 0.0 | 10.4 |
| | Moderate | 25 | 37.3 | 25.4 | 49.3 |
| | Major | 39 | 58.2 | 46.3 | 70.1 |

### 4.4.2 Characterization of pDDIs

Some prescriptions had more than one pDDI and thus the total number of DDIs in all the prescriptions were 134. Out of the 134 DDIs, 67(50.0%) were major, 60(44.8%) moderate and 7(5.2%) was minor as shown in figure 4 below.

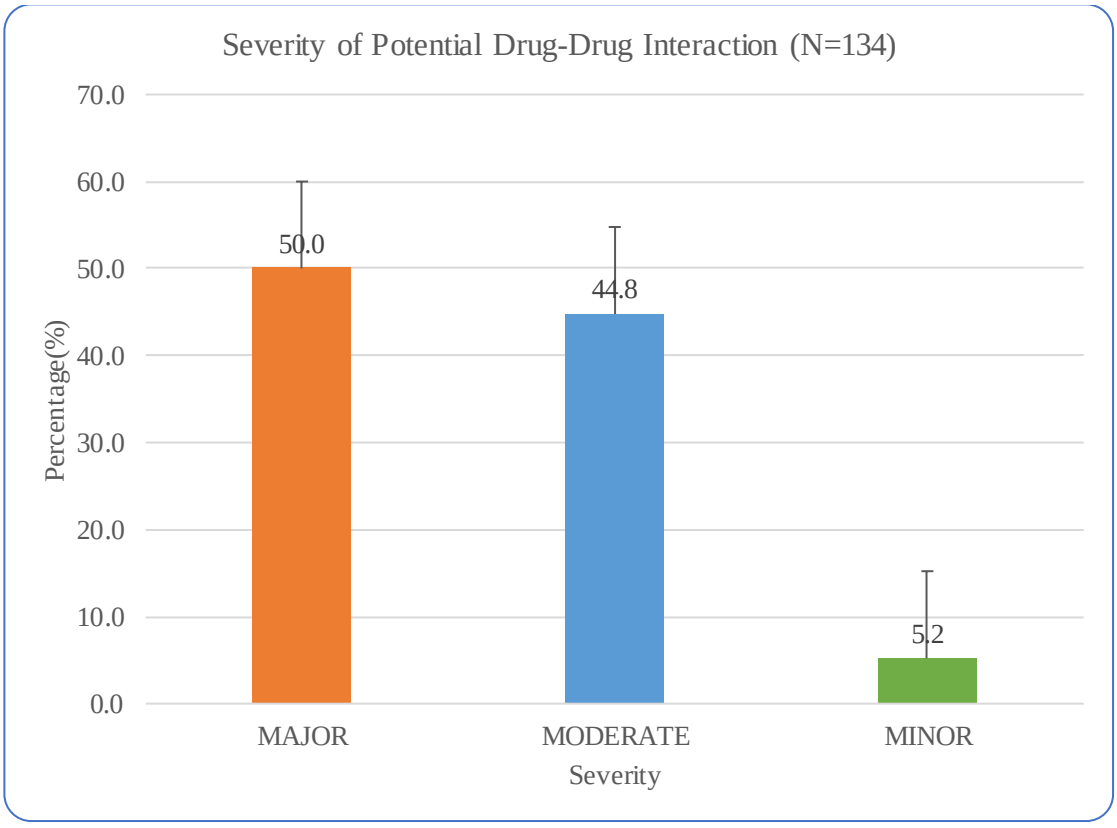


**Figure 3: Characterization and frequency of pDDIs**

### 4.4.3 Number of interacting pairs

The mean of interacting pairs was 2.0±1.5 pairs. Almost a half of the prescriptions that had pDDIs (49.3%) had only one pair of interacting drugs whereas a small proportion (4.5%) had six and above interacting pairs with 29.9% having two interaction pairs. The results are presented in figure 4 below.

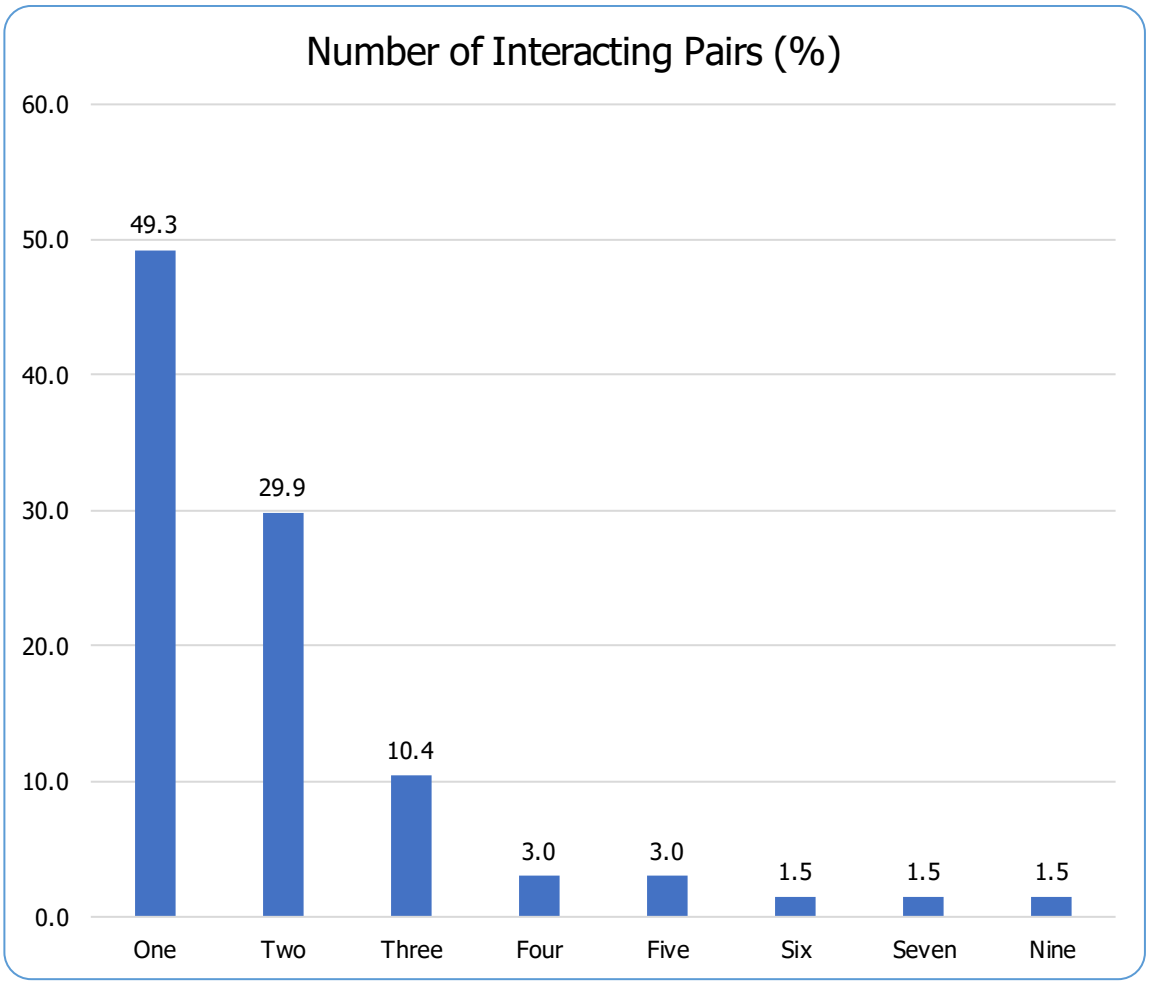


**Figure 4: Number of interacting pairs**

### 4.4.4 Potential drug-drug interaction, severity of interaction; clinical effect

The most frequent potential drug-drug interactions, their severity of interaction, frequency and clinical effects are summarized in table 5 below. All the individual pDDIs, severity of interaction, clinical effect and frequencies are tabulated in Appendix 5.

**Table 5: Types of potential drug-drug interaction and their clinical effects**

| Interacting Pairs | Severity Of Interaction | Clinical Effect | Frequency |
|---|---|---|---|
| Esomeprazole Sodium: Propranolol HCl | Moderate | Increased propranolol exposure | 11 |
| Furosemide: Propranolol HCl | Moderate | Hypotension, bradycardia | 9 |
| Metronidazole: Ondansetron | Major | Increased risk of QT Interval prolongation and arrhythmias; | 6 |
| Ondansetron: Tramadol HCl | Major | increased risk of serotonin syndrome | 5 |
| Esomeprazole Sodium: Ferrous Sulphate | Moderate | Reduced iron bioavailability; | 5 |
| Metoclopramide Hcl: Tramadol Hcl | Major | Increased risk of CNS depression | 5 |
| Octreotide Acetate: Omeprazole | Major | decreased octreotide bioavailability; | 4 |
| Esomeprazole Sodium: Octreotide Acetate | Major | Decreased octreotide bioavailability | 3 |
| Ciprofloxacin: Metronidazole | Major | Increased risk of QT-interval prolongation and arrhythmias | 3 |
| Clarithromycin: Lansoprazole | Minor | Glossitis, stomatitis or black tongue | 3 |
| Omeprazole: Propranolol HCl | Moderate | increased propranolol exposure; | 3 |
| Dolutegravir Sodium: Ferrous Sulphate | Major | decreased dolutegravir exposure and loss of efficacy | 2 |
| Pyrazinamide: Rifampin | Major | Severe hepatic injury | 2 |
| Clarithromycin: Metronidazole | Major | Increased risk of QT Interval prolongation; | 2 |
| Metronidazole: Octreotide Acetate | Major | Increased risk of QT-interval prolongation and arrhythmias. | 2 |
| Ciprofloxacin: Ondansetron HCl | Major | Increased risk of QT-interval prolongation | 2 |
| Morphine Sulphate: Ondansetron | Major | Increased risk of serotonin syndrome | 2 |
| Pantoprazole sodium: Propranolol HCl; | Moderate | Increased propranolol exposure | 2 |
| Furosemide: Insulin Human Isophane | Moderate | Increased risk of hyperglycaemia; | 2 |
| Furosemide: Insulin Human Regular | Moderate | Increased risk of hyperglycaemia; | 2 |
| Iron Sucrose: Omeprazole | Moderate | Reduced non-heme iron bioavailability | 2 |

### 4.5 Independent predictors to potential drug-drug interaction

Table 6 presents the results of factors associated with pDDIs. Participants who had secondary level of education were 4.65 times more likely to be prescribed with drugs with

pDDIs as compared to those who had college/tertiary level of education (a.O.R. 4.65 95% C.I. 1.30; 16.64, p=0.018). For every unit increase in prescription drug, the risk of having a pDDI increase by 1.62 times (a.O.R. 1.62 95% C.I. 1.27; 2.06, p<0.001) i.e., the higher the number of drugs in a prescription the more likely to have pDDIs.

**Table 6: Independent predictors of potential drug-drug interaction (Parsimonious model)**

| Variable | category | Bivariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | **cO. R (95% C.I)** | **p-value** | **aO. R (95% C.I)** | **Sig.** |
| Gender | Male | Ref | | Ref. | |
| | Female | 1.78(0.88-3.60) | 0.108 | 2.02(0.88-4.68) | 0.099 |
| Marital Status | Single/Never married | Ref | | | |
| | Married/Ever Married | 1.27(0.64-2.53) | 0.501 | | |
| Occupation | Business / Self-Employed | 1.47(0.70-3.09) | 0.307 | | |
| | Formal Employment | 0.70(0.26-1.86) | 0.471 | | |
| | Unemployed | Ref | | | |
| Smoking Status | Current Smoker | 2.70(0.66-11.05) | 0.168 | 3.29(0.71-15.19 | 0.126 |
| | Previous Smoker | 1.16(0.51-2.62) | 0.729 | 0.81(0.29-2.22) | 0.677 |
| | Never Smoked | Ref | | Ref. | |
| Alcohol Intake | Currently Drinking | 1.08(0.43-2.75) | 0.866 | | |
| | Previous Drinker | 1.25(0.59-2.65) | 0.560 | | |
| | Never Drunk | Ref | | | |
| Education Level | No Formal Education | 2.50(0.64-9.77) | 0.188 | 2.51(0.52-12.08) | 0.253 |
| | Primary | 2.27(0.78-6.62) | 0.135 | 2.74(0.80-9.32) | 0.107 |
| | Secondary | 4.00(1.27-12.58) | 0.018 | 4.65(1.30-16.64) | **0.018** |
| | College/University | Ref | | Ref. | |
| Presence of comorbidity | No | Ref | | Ref. | |
| | Yes | 2.16(1.06-4.43) | 0.035 | 1.29(0.56-2.99) | 0.549 |
| Age in Years | Mean±SD | 1.00(0.97-1.02) | 0.851 | | |
| Number of Drugs in the prescription | Mean±SD | 1.61(1.30-2.00) | <0.001 | 1.62(1.27-2.06) | **<0.001** |
| Duration of CLD in Years | Mean±SD | 0.97(0.82-1.15) | 0.732 | | |

*Key: cO.R=Crude Odds Ratio; aO.R=Adjusted Odds Ratio; C.I=Confidence Interval*

## CHAPTER FIVE: DISCUSSION, CONCLUSION, AND RECOMMENDATIONS

### 5.1 Discussion

Most participants (89%) were on more than two drugs for chronic liver disease and associated comorbidities. Concurrent use of multiple drugs can cause health risks such as poor compliance, medication errors and adverse drug reactions. The average number of drugs per prescription was a little high compared to a study by Shanmugapriya *et al*(50) and Raza *et al*(51).It was also high compared to a local study that was conducted on prescription patterns in Makueni county referral hospital by Mulwa *et al* that found a mean of 2.7 drugs per prescription(52).

The prescription patterns observed in this study concur with the current recommendations for management of ascites, hepatic encephalopathy and portal hypertension among chronic liver disease patients(53).The most commonly prescribed anticoagulant for deep venous thrombosis prophylaxis was enoxaparin. However, rivaroxaban was prescribed in patients who had portal vein thrombosis.

The prevalence of pDDIs in this study is close to the findings of a study that was conducted in a Brazilian teaching hospital on prevalence of pDDIs and its associated factors.(5). It's also close to the findings of a study that was conducted on the prevalence of pDDIs in patients that were on oral anticancer agents which found a prevalence of 46% (54) as well as a study by Sidra *et al*(55). The findings differs from others studies carried out (7) (56) (57).

Close to half of the prescriptions that had pDDIs had only one pair of interacting drugs. This finding is lower comparing to a study by Sabin *et al* that found that about 60% of the patients had one potentially interacting drug combination(58). The frequency of major pDDIs in this study differ from a Brazilian study that found a quite low prevalence of major pDDIs among the prescriptions(5). It also differs from a study that was conducted on hepatitis patients(55).

In the current study, the most common drug combination that could result into a drug-drug interaction was that of esomeprazole and propranolol, which is a moderate pDDI.

The outcome of this potential drug-drug interaction was increased propranolol plasma concentration which could lead to bradycardia and hypotension. This differs from a study conducted by Straubhaar *et al* in heart failure patients where hyperkalaemia was the most common outcome as a result of concomitant use of ACEI and potassium sparing diuretic(59).

Independent predictors of DDIs were total number of drugs per patient and having secondary level of education. The number of drugs per prescription was identified as a predictor of pDDI in the Brazilian study(5). It was also found as a strong predictor of pDDIs in a study by Santos *et al*(60).

Data on management of potential drug-drug interactions was not available since most of the pDDIs went unnoticed, thus the objective of documenting management of pDDIs was not achieved. However, the first two objectives were achieved in details.

All the prescriptions that were analyzed in this study were retrieved directly from the respective patient files, thus the findings after the analysis are quite reliable. The software that was used for checking out pDDIs in the prescriptions(Micromedex IBM) is considered to be the most reliable by some authors due to its high sensitivity, thus giving more reliable results.

## 5.2 Conclusion

We were able to establish a moderate prevalence of pDDIs among chronic liver disease patients at Kenyatta National Hospital liver clinic. This suggested average management of these patients since they were predisposed to adverse drug reactions due to the pDDIs. Predisposing factors to pDDIs were total number of drugs per patient and having secondary level of education.

## 5.3 Recommendations

### 5.3.1 Recommendations for policy and practice.

The findings of this study should be shared with the respective prescribers to reduce the incidences of concomitant prescription of majorly and moderately interacting drugs.

Polypharmacy should be avoided where possible by the prescribers to reduce the risk of pDDIs due to high number of drugs per prescription.

### 5.3.2 Recommendations for further research

There exist gaps on management and strategies to minimize pDDIs among chronic liver disease patients at KNH liver clinic. Future studies should be done on strategies to minimize and manage pDDIs by the prescribers.

This was a cross-sectional study that was carried out within a relatively short time. In future, prospective cohort studies involving larger populations and longer durations should be done, following up on actual DDIs to provide details on their clinical significance.

**REFERENCES.**


1. Sharma A NS. Chronic Liver Disease. [Updated 2020 Feb 28]. In: StatPearls [Internet] [Internet]. StatPearls Publishing; 2020 [cited 2021 Jan 5]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554597/

2. Asrani SK, Devarbhavi et al. Burden of liver diseases in the world [Internet]. Vol. 70, Journal of Hepatology. Elsevier B.V.; 2019 [cited 2021 Jan 18]. p. 151–71. Available from: https://pubmed.ncbi.nlm.nih.gov/30266282/

3. Setiawan VW, Stram DO, Porcel J, Lu SC, Le Marchand L, Noureddin M. Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: The multiethnic cohort. Hepatology [Internet]. 2016 Dec 1 [cited 2021 Jan 9];64(6):1969–77. Available from: https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/hep.28677

4. Jonker DM, Visser SAG, Van Der Graaf PH, Voskuyl RA, Danhof M. Towards a mechanism-based analysis of pharmacodynamic drug-drug interactions in vivo. Vol. 106, Pharmacology and Therapeutics. Elsevier Inc.; 2005. p. 1–18.

5. Mara Cruciol J, Mara Cruciol-Souza J, Carlos Thomson J. Prevalence of Potential Drug-Drug Interactions and its Associated Factors In a Brazilian Teaching Hospital [Internet]. Vol. 9, Article in Journal of Pharmacy and Pharmaceutical Sciences. 2006 [cited 2021 Jan 23]. Available from: https://www.researchgate.net/publication/6594610

6. Bhagavathula AS, Berhanie A, Tigistu H, Abraham Y, Getachew Y, Khan TM, et al. Prevalence of potential drug-drug interactions among internal medicine ward in University of Gondar Teaching Hospital, Ethiopia. Asian Pac J Trop Biomed. 2014 May 1;4:S204–8.

7. Culafić M, Kovačević SV, Filipović M, Gošnjić N, Vučićević K, Miljković B, et al. CP-193 Drug-drug interactions among patients with chronic liver disease: A snapshot by clinical pharmacist. Eur J Hosp Pharm [Internet]. 2016 Mar 1 [cited 2021 Jan 28];23(Suppl 1):A85.2-A86. Available from: https://ejhp.bmj.com/content/23/Suppl_1/A85.2

8. Embade N, Millet O. Molecular Determinants of Chronic Liver Disease as Studied by NMR-Metabolomics. Curr Top Med Chem [Internet]. 2017 Aug 11 [cited 2021 Jan 12];17(24). Available from: https://pubmed.ncbi.nlm.nih.gov/28685692/

9. Otachi Eo. Potential drug-drug interactions among patients with type 2 diabetes and hypertension in Kisii teaching and referral hospital, kenya. University of Nairobi; 2016 [cited 2021 Jan 23]. Available from: http://erepository.uonbi.ac.ke/handle/11295/98385

10. Makite Sl. Clinically significant potential drug-drug interactions among adult diabetic hypertensive outpatients at Kenyatta National Hospital University of Nairobi; 2019 [cited 2021 jan 23]. Available from: http://erepository.uonbi.ac.ke/handle/11295/109648

11. Jomo SM, Pharm B. Evaluation of Potential Drug-Drug Interactions among Mentally ill Patients Admitted at Mathari Mental Hospital [Internet]. 2014 [cited 2021 Jan 23]. Available from: http://erepository.uonbi.ac.ke/handle/11295/95111

12. Achieng C, Bpharm A(. Risk factors, management and outcomes of drug induced hepatic injury among adult patients with liver disease at Kenyatta National Hospital [Internet]. University of Nairobi; 2015 [cited 2021 Jan 12]. Available from: http://erepository.uonbi.ac.ke/handle/11295/94813

13. Kibuuka HN. A Descriptive study Of chronic hepatitis as seen at Kenyatta National Hospital [Internet]. 1990 [cited 2021 Jan 12]. Available from: http://erepository.uonbi.ac.ke/handle/11295/64206

14. Okoth FA. The pattern of liver cirrhosis at the Kenyatta National Hospital Nairobi. 1984 [cited 2021 Jan 12]; Available from: http://erepository.uonbi.ac.ke/handle/11295/25044

15. Franz CC, Egger S, Born C, Rätz Bravo AE, Krähenbühl S. Potential drug-drug interactions and adverse drug reactions in patients with liver cirrhosis. Eur J Clin Pharmacol [Internet]. 2012 Feb 13 [cited 2021 Jan 23];68(2):179–88. Available from: https://link.springer.com/article/10.1007/s00228-011-1105-5

16. Lucena IM, Andrade RJ, Tognoni G, Hidalgo R, De La Cuesta F. Multicenter hospital study on prescribing patterns for prophylaxis and treatment of complications of cirrhosis. Eur J Clin Pharmacol 2002 586 [Internet]. 2002 [cited 2021 Nov 15];58(6):435–40. Available from: https://link.springer.com/article/10.1007/s00228-002-0474-1

17. Prakash Kolasani B, Sasidharan P, M DC, Jayabal P, Rajaseharan A. Prescribing pattern of drugs in patients with alcoholic liver disease in a tertiary care teaching hospital. Natl J Physiol Pharm Pharmacol [Internet]. 2017 [cited 2021 Nov 15];538. Available from: www.njppp.com

18. Konerman MA, Rogers M, Kenney B, Singal AG, Tapper E, Sharma P, et al. Opioid and benzodiazepine prescription among patients with cirrhosis compared to other forms of chronic disease. BMJ Open Gastroenterol [Internet]. 2019 Apr 1 [cited 2021 Nov 15];6(1):e000271. Available from: https://bmjopengastro.bmj.com/content/6/1/e000271

19. Rubin JB, Lai JC, Shui AM, Hohmann SF, Auerbach A. Patterns of Inpatient Opioid Use and Related Adverse Events Among Patients With Cirrhosis: A Propensity-Matched Analysis. Hepatol Commun [Internet]. 2021 Jun 1 [cited 2021 Nov 15];5(6):1081–94. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/hep4.1694

20. Hong YM, Yoon KT, Heo J, Woo HY, Lim W, An DS, et al. The Prescription Pattern of Acetaminophen and Non-Steroidal Anti-Inflammatory Drugs in Patients with Liver Cirrhosis. J Korean Med Sci [Internet]. 2016 Aug 2 [cited 2021 Nov 15];31(10):1604–10. Available from: https://synapse.koreamed.org/articles/1023109

21. Bang UC, Benfield T, Bendtsen F. Reduced risk of decompensation and death associated with use of statins in patients with alcoholic cirrhosis. A nationwide case-cohort study. Aliment Pharmacol Ther [Internet]. 2017 Oct 1 [cited 2021 Nov 15];46(7):673–80. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/apt.14243

22. Thakrar BT, Grundschober SB, Doessegger L. Detecting signals of drug?drug interactions in a spontaneous reports database. Br J Clin Pharmacol [Internet]. 2007 Oct 1 [cited 2021 Jan 26];64(4):489–95. Available from: http://doi.wiley.com/10.1111/j.1365-2125.2007.02900.x

23. Ren W, Liu Y, Zhang J, Fang Z, Fang H, Gong Y, et al. Prevalence of potential drug–drug interactions in outpatients of a general hospital in China: a retrospective investigation. Int J Clin Pharm. 2020 Aug 1;42(4):1190–6.

24. Dechanont S, Maphanta S, Butthum B, Kongkaew C. Hospital admissions/visits associated with drug-drug interactions: a systematic review and meta-analysis. Pharmacoepidemiol Drug Saf [Internet]. 2014 May 1 [cited 2021 Jan 26];23(5):489–97. Available from: http://doi.wiley.com/10.1002/pds.3592

25. Lubinga SJ, Uwiduhaye E. Potential drug-drug interactions on in-patient medication prescriptions at Mbarara Regional Referral Hospital (MRRH) in western Uganda: Prevalence, clinical importance and associated factors. Afr Health Sci. 2011;11(3):499–507.

26. Kapp PA, Klop AC, Jenkins LS. Drug interactions in primary health care in the George subdistrict, South Africa: A cross-sectional study. South African Fam Pract. 2013;55(1):78–84.

27. Cascorbi I. Drug interactions - Principles, examples and clinical consequences. Dtsch Arztebl Int. 2012;109(33–34):546–55; quiz 556.

28. FASTLANE, Anderson C. Drug Interactions · Part One [Internet]. 2020 [cited 2021 Apr 30]. Available from: https://partone.litfl.com/drug_interactions.html

29. DRUGS.COM. Tenofovir Drug Interactions - Drugs.com [Internet]. 2021 [cited 2021 Apr 30]. Available from: https://www.drugs.com/drug-interactions/tenofovir.html

30. Otachi EO. Potential drug-drug interactions among patients with type 2 diabetes and hypertension in kisii teaching and referral hospital, kenya .University of Nairobi; 2016 [cited 2021 Jan 26]. Available from: http://erepository.uonbi.ac.ke/handle/11295/98385

31. Terrault NA, Lok ASF, Mcmahon BJ, Chang K-M, Hwang JP, Jonas MM, et al.

Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance A he study of liver diseases merican association for. Pract Guid | Hepatol. 2018;67(4).

32. Shadab HA. Schistosomiasis (Bilharzia) Medication: Anthelmintics [Internet]. 2020 [cited 2021 Apr 30]. Available from: https://emedicine.medscape.com/article/228392-medication

33. Roberts EA, Schilsky ML. AASLD PRACTICE GUIDELINES Diagnosis and Treatment of Wilson Disease: An Update. 2008 [cited 2021 Jan 29]; Available from: www.interscience.wiley.com

34. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. 2018;0(0).

35. Dugum M, McCullough A. Diagnosis and management of alcoholic liver disease [Internet]. Vol. 3, Journal of Clinical and Translational Hepatology. Xia and He Publishing Inc.; 2015 [cited 2021 Jan 29]. p. 109–16. Available from: /pmc/articles/PMC4548353/?report=abstract

36. Annette (Gbemudu) Ogbru PM. Benzodiazepines Drug Class: Side Effects, Types & Uses [Internet]. [cited 2021 Jan 30]. Available from: https://www.rxlist.com/benzodiazepines/drug-class.htm

37. Medscape. Viread (tenofovir DF) dosing, indications, interactions, adverse effects, and more [Internet]. 2021 [cited 2021 May 1]. Available from: https://reference.medscape.com/drug/viread-tenofovir-df-342633#3

38. Medscape. Harvoni (ledipasvir/sofosbuvir) dosing, indications, interactions, adverse effects, and more [Internet]. 2021 [cited 2021 May 1]. Available from: https://reference.medscape.com/drug/harvoni-ledipasvir-sofosbuvir-999970#3

39. Medscape. Pediapred, Orapred (prednisolone) dosing, indications, interactions, adverse effects, and more [Internet]. 2021 [cited 2021 May 1]. Available from: https://reference.medscape.com/drug/pediapred-orapred-prednisolone-342745#3

40. Medscape. Xifaxan (rifaximin) dosing, indications, interactions, adverse effects, and more [Internet]. 2021 [cited 2021 May 1]. Available from: https://reference.medscape.com/drug/xifaxan-rifaximin-342685#3

41. Medscape. Enulose, Kristalose (lactulose) dosing, indications, interactions, adverse effects, and more [Internet]. 2021 [cited 2021 May 1]. Available from: https://reference.medscape.com/drug/enulose-kristalose-lactulose-342016#3

42. Medscape. Trental, Pentoxil (pentoxifylline) dosing, indications, interactions, adverse effects, and more [Internet]. 2021 [cited 2021 May 1]. Available from: https://reference.medscape.com/drug/trental-pentoxil-pentoxifylline-342179#3

43. Medscape. Actigall, Urso Forte (ursodiol) dosing, indications, interactions, adverse effects, and more [Internet]. 2021 [cited 2021 May 1]. Available from:

https://reference.medscape.com/drug/actigall-urso-forte-ursodiol-342072#3

44. Tannenbaum C, Sheehan NL. Understanding and preventing drug–drug and drug–gene interactions. Expert Rev Clin Pharmacol [Internet]. 2014 Jul 19 [cited 2021 Jan 30];7(4):533–44. Available from: http://www.tandfonline.com/doi/full/10.1586/17512433.2014.910111

45. Kibathi LW. Quality of adverse event reports in kenya and safety signals for antiretroviral therapy related arrhythmias [Internet]. University of Nairobi; 2020 [cited 2021 Jan 30]. Available from: http://erepository.uonbi.ac.ke/handle/11295/153131

46. Mwangi PN. Incidence, risk factors and management of neutropenia among cancer patientswith solid tumors receiving chemotherapy at Kenyatta national hospital cancer treatment centre. 2016;68. Available from: http://erepository.uonbi.ac.ke/handle/11295/108956

47. Israel GD. Determining Sample Size 1 [Internet]. 2012 [cited 2021 May 1]. Available from: http://edis.ifas.ufl.edu.

48. Roblek T, Vaupotic T, Mrhar A, Lainscak M. Drug-drug interaction software in clinical practice: A systematic review. Eur J Clin Pharmacol [Internet]. 2015 Dec 23 [cited 2021 Jan 28];71(2):131–42. Available from: https://link.springer.com/article/10.1007/s00228-014-1786-7

49. Reis AMM, Cassiani SHDB. Evaluation of three brands of drug interaction software for use in intensive care units. Pharm World Sci [Internet]. 2010 Dec 21 [cited 2021 Jan 28];32(6):822–8. Available from: https://link.springer.com/article/10.1007/s11096-010-9445-2

50. Shanmugapriya S, Saravanan T, Rajee SS, Venkatrajan R, Thomas PM. Drug prescription pattern of outpatients in a tertiary care teaching hospital in Tamil Nadu. Perspect Clin Res [Internet]. 2018 Jul 1 [cited 2021 Oct 1];9(3):133. Available from: /pmc/articles/PMC6058512/

51. Raza UA, Khursheed T, Irfan M, Abbas M, Irfan UM. Prescription Patterns of General Practitioners in Peshawar, Pakistan. Pakistan J Med Sci [Internet]. 2014 [cited 2021 Oct 1];30(3):462. Available from: /pmc/articles/PMC4048486/

52. Mulwa NC, Osanjo GO, Ndwigah SN, Kaburi AN, Muriuki G. Patterns of Prescribing Practices in Makueni County Referral Hospital, Kenya. African J Pharmacol Ther [Internet]. 2015 [cited 2021 Oct 1];4(4). Available from: http://journals.uonbi.ac.ke/ajpt/article/view/1401

53. Heidelbaugh JJ, Sherbondy M. Cirrhosis and Chronic Liver Failure: Part II. Complications and Treatment. Am Fam Physician. 2006 Sep 1;74(5):767–76.

54. van Leeuwen RWF, Brundel DHS, Neef C, van Gelder T, Mathijssen RHJ, Burger DM, et al. Prevalence of potential drug–drug interactions in cancer patients treated with oral anticancer drugs. Br J Cancer 2013 1085 [Internet]. 2013 Feb 14 [cited 2021 Sep 30];108(5):1071–8. Available from:

https://www.nature.com/articles/bjc201348

55. Noor S, Ismail M, Haider I, Khadim F. Drug-Drug Interactions in Hepatitis Patients: Do these Interactions Matter in Clinical Perspectives? Ann Hepatol [Internet]. 2018 Nov 1 [cited 2021 Sep 30];17(6):1001–11. Available from: https://www.elsevier.es/en-revista-annals-hepatology-16-articulo-drug-drug-interactions-in-hepatitis-patients-S1665268119310622

56. Sepehri G, Khazaelli P, Dahooie FA, Sepehri E, Dehghani MR. Prevalence of Potential Drug Interactions in an Iranian General Hospital. Indian J Pharm Sci [Internet]. 2012 Jan [cited 2021 Sep 30];74(1):75. Available from: /pmc/articles/PMC3507350/

57. Kigen G, Kimaiyo S, Nyandiko W, Faragher B, Sang E, Jakait B, et al. Prevalence of Potential Drug-Drug Interactions Involving Antiretroviral Drugs in a Large Kenyan Cohort. PLoS One [Internet]. 2011 [cited 2021 Sep 30];6(2):e16800. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0016800

58. Egger SS, Drewe J, Schlienger RG. Potential drug–drug interactions in the medication of medical patients at hospital discharge. Eur J Clin Pharmacol 2003 5811 [Internet]. 2003 Feb 21 [cited 2021 Oct 8];58(11):773–8. Available from: https://link.springer.com/article/10.1007/s00228-002-0557-z

59. Straubhaar B, Krähenbühl S, Schlienger RG. The Prevalence of Potential Drug-Drug Interactions in Patients with Heart Failure at Hospital Discharge. Drug Saf 6 291 [Internet]. 2012 Nov 20 [cited 2021 Oct 8];29(1):79–90. Available from: https://link.springer.com/article/10.2165/00002018-200629010-00006

60. Santos-Díaz G, Pérez-Pico AM, Suárez-Santisteban MÁ, García-Bernalt V, Mayordomo R, Dorado P. Prevalence of Potential Drug–Drug Interaction Risk among Chronic Kidney Disease Patients in a Spanish Hospital. Pharm 2020, Vol 12, Page 713 [Internet]. 2020 Jul 30 [cited 2021 Oct 8];12(8):713. Available from: https://www.mdpi.com/1999-4923/12/8/713/htm

## APPENDICES

### Appendix 1: Eligibility screening form

### Study title: Potential drug-drug interactions among chronic liver disease patients at the Kenyatta National Hospital

Participant's unique number----------

| CRITERIA | RESPONSE |
|---|---|
| | YES NO |
| 1. Aged 18 or older | |
| 2. patient with a documented diagnosis of CLD | |
| 3. Enrolled for follow up at the KNH liver clinic. | |
| 4. Willing to participate in the study | |
| 5. Not psychiatric | |
| 6. Is not diagnosed with Parkinson's disease | |
| 7. Is not diagnosed with dementia | |

If the responses are all YES, proceed to data collection form.

**Appendix 2a: Consent form for enrollment in the study**

**Title of study: Potential drug-drug interactions among chronic liver disease adult patients at the Kenyatta National Hospital**

| | |
|---|---|
| **PRINCIPAL INVESTIGATOR** | **Dr. Jane Wanjiku Gichuhi**<br>**P.O Box 57-01033, Kagundu-ini, Kenya.**<br>**Email: wanjiku507@gmail.com**<br>**Phone number: 0702532878** |
| **INSTITUTION** | **Department of Pharmaceutics and Pharmacy Practice,**<br>**School of Pharmacy,**<br>**University of Nairobi.**<br>**P.O Box 30197-00400, Nairobi.** |
| **CO-INVESTIGATORS AND INSTITUTIONAL AFFILIATION** | **1. Dr. George Arthur Mugendi,**<br>**Department of pharmaceutics and pharmacy practice,**<br>**School of pharmacy**<br>**University of Nairobi**<br>**Email: george.mugendi@uonbi.ac.ke**<br>**2. Dr. Peter Karimi**<br>**Department of pharmaceutics and pharmacy practice**<br>**School of pharmacy**<br>**University of Nairobi.**<br>**Email: ndirang15@gmail.com** |
| **ETHICAL APPROVAL** | **Requesting approval by Kenyatta National Hospital/University of Nairobi Ethical and Research Committee to conduct the study** |

**Introduction**:

My name is Dr. Jane Wanjiku Gichuhi. I am a postgraduate student at the school of pharmacy, University of Nairobi.

I would like to tell you about a study being conducted by the above listed researchers. The purpose of this consent form is to give you the information you will need to help you decide whether or not to be a participant in the study. Feel free to ask any questions about the purpose of the research, what happens if you participate in the study, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide to be in the study or not. This process is called 'informed consent'. Once you understand and agree to be in the study, I will request you to sign your name on this form.

You should understand the general principles which apply to all participants in medical research: i) Your decision to participate is entirely voluntary

ii) You may withdraw from the study at any time without necessarily giving a reason for your withdrawal

iii) Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities. We will give you a copy of this form for your records.

May I continue? YES / NO

This study will have approval by The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee protocol No. (P101/02/2021)

**What is this study about?**

The researchers listed above are interviewing individuals who have been diagnosed with chronic liver disease at KNH liver clinic. The purpose of the interview is to find out the prescription patterns in chronic liver disease, the prevalence and characteristics of potential drug-drug interactions among those patients and the management of such drug-drug interactions. Participants in this research study will be asked questions about their social demographics and the medicines that they will be using at the entire period of the study.

There will be approximately one hundred and thirty-seven participants in this study randomly chosen. We are asking for your consent to consider participating in this study.

**What will happen if you decide to be in this research study?**

If you agree to participate in this study, the following things will happen:

You will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. The interview will last approximately thirty minutes.

The interview will cover topics such as biodata, comorbidities and medication history.

We will ask for a telephone number where we can contact you if necessary. If you agree to provide your contact information, it will be used only by people working for this study and will never be shared with others. The reasons why we may need to contact you include enquiring more about the medicines that you are using.

**Are there any risks, harms discomforts associated with this study?**

Medical research has the potential to introduce psychological, social, emotional and physical risks. Effort should always be put in place to minimize the risks. One potential risk of being in the study is loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number to identify you in a password-protected computer database and will keep all of our paper records in a locked file cabinet. However, no system of protecting your confidentiality can be absolutely secure, so it is still possible that someone could find out you were in this study and could find out information about you.

Also, answering questions in the interview may be uncomfortable for you. If there are any questions you do not want to answer, you can skip them. You have the right to refuse the interview or any questions asked during the interview.

This study will not involve any laboratory tests, invasive procedures or additional medicine, thus it's not harmful to the participant.

The principal researcher, who will be the interviewer, is a professional with special training in these interviews.

**Are there any benefits being in this study?**

You may benefit by receiving free counselling, health information. The findings of this study will raise awareness of the prescribers on potential drug-drug interactions among

chronic liver disease patients and thus ensure optimal management of the condition among the patients.

**Will being in this study cost you anything?**

Participation in this study will cost of you thirty minutes during your scheduled clinic. However, the benefits of the study in terms of optimizing your management outweighs the thirty minutes that will be used for interview.

**Are there any reimbursements?**

There will not be any incentives or gifts for participation in the study.

**What if you have questions in future?**

If you have further questions or concerns about participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page.

For more information about your rights as a research participant you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke.

The study staff will pay you back for your charges to these numbers if the call is for study-related communication.

**What are your other choices?**

Your decision to participate in research is voluntary. You are free to decline participation in the study and you can withdraw from the study at any time without injustice or loss of any benefits.

If in agreement, kindly sign the participants consent declaration below;

**Consent form**

**Participant's statement**

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw any time. I freely agree to participate in this research study.

I understand that all efforts will be made to keep information regarding my personal identity confidential.

By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study: Yes No

I agree to provide contact information for follow-up: Yes No

Participant printed name:

Participant signature / Thumb stamp Date:

**Researcher's statement**

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher 's Name: Date: 17/11/2021

Gichuhi Jane

Signature: 

Role in the study: Principal Investigator

For more information contact:

Principal Investigator: Dr. Jane Wanjiku Gichuhi on 0702532878

Ethics Committee KNH-UoN ERC on 2726300, Ext 44102

**Appendix 2b: Ridhaa ya kushiriki katika utafiti.**

**Kichwa cha utafiti:**

**Kuchunguza matatizo ya utumiaji pamoja wa madawa tofauti ya tiba kwa wagonjwa ambao ni watu wazima wenye tatizo la ugonjwa sugu wa ini.**

| | |
|---|---|
| Mtafiti Mkuu | Dkt. Jane Wanjiku Gichuhi<br>Sanduku la posta, 57-01033, Kagundu-ini, Kenya.<br>Barua pepe: wanjiku507@gmail.com<br>Nambari ya simu: 0702532878 |
| Taasisi | Idara ya mazoezi ya Famasia,<br>Shule ya Famasia,<br>Chuo Kikuu cha Nairobi,<br>sanduku la posta ,30197-00400, Nairobi |
| Watafiti Wengine pia Wasimamizi | 1.Dkt. George Arthur Mugendi (mhadhiri)<br>Idara ya mazoezi ya Famasia,<br>Shule ya Famasia,<br>Chuo Kikuu cha Nairobi,<br><br>Barua pepe: george.mugendi@uonbi.ac.ke<br><br>2.Dkt. Peter Karimi (mhadhiri)<br>Idara ya mazoezi ya Famasia,<br>Shule ya Famasia,<br>Chuo Kikuu cha Nairobi,<br>Barua pepe: ndirang15@gmail.com |
| Idhini ya Idara ya Adili | Naomba idhini ya kufanya Utafiti huu kutoka Hospitali ya Kitaifa ya Kenyatta ikishirikiana na Kamati ya Adili na Utafiti ya Nairobi. |

**Utangulizi**:

Jina langu ni Dk. Jane Wanjiku Gichuhi. Mimi ni mwanafunzi aliyehitimu katika shule ya famasia, Chuo Kikuu cha Nairobi.

Napenda kukuambia juu ya utafiti unaofanywa na watafiti waliotajwa hapo juu. Madhumuni ya fomu hii ya idhini ni kukupa habari ambayo utahitaji kukusaidia kuamua ikiwa mshiriki katika utafiti. Jisikie huru kuuliza maswali yoyote juu ya madhumuni ya utafiti, nini kinatokea ikiwa unashiriki katika utafiti, hatari na faida zinazowezekana, haki zako kama kujitolea, na kitu kingine chochote juu ya utafiti au fomu hii ambayo haijulikani wazi.

Wakati tumejibu maswali yako yote kwa kuridhika kwako, unaweza kuamua kuwa kwenye masomo au la. Utaratibu huu unaitwa 'idhini iliyo na habari'. Mara tu ukielewa na kukubali kuwa kwenye utafiti, nitakuomba utie saini jina lako kwenye fomu hii.

Unapaswa kuelewa kanuni za jumla zinazotumika kwa washiriki wote katika utafiti wa matibabu:

i) Uamuzi wako wa kushiriki ni wa hiari kabisa

ii) Unaweza kujiondoa kwenye masomo wakati wowote bila kutoa sababu ya kujiondoa

iii) Kukataa kushiriki katika utafiti hautaathiri huduma unayostahiki katika kituo hiki cha afya au vifaa vingine. Tutakupa nakala ya fomu hii kwa rekodi zako.

Naomba niendelee? NDIYO / HAPANA

Utafiti huu utakuwa na idhini ya Hospitali ya Kitaifa ya Chuo Kikuu cha Kenyatta cha Maadili ya Nairobi.

Nambari ya Itifaki (P101/02/2021)

**Utafiti huu unahusu nini?**

Watafiti waliotajwa hapo juu wanahoji watu ambao wamepatikana na ugonjwa sugu wa ini katika kliniki ya ini ya KNH. Madhumuni ya mahojiano ni kuchunguza matatizo ya utumiaji pamoja wa madawa tofauti ya tiba kwa wagonjwa ambao ni watu wazima wenye tatizo la ugonjwa sugu wa ini. Washiriki wa utafiti huu wataulizwa maswali juu ya afya yako na dawa ambazo watakuwa wakitumia katika kipindi chote cha utafiti.

Kutakuwa na washiriki takriban mia moja na thelathini na saba katika utafiti huu waliochaguliwa kwa nasibu. Tunaomba idhini yako ifikirie kushiriki katika utafiti huu.

**Mtindo:**

Ikiwa unakubali kushiriki katika utafiti huu, mambo yafuatayo yatatokea:

Utahojiwa na mhojiwa aliyefundishwa katika eneo la kibinafsi ambalo unajisikia vizuri

kujibu maswali. Mahojiano yatadumu takriban dakika thelathini.

Mahojiano yatashughulikia mada kama vile kuhusu uzima wako kiafya na historia ya dawa.

Tutauliza nambari ya simu ambapo tunaweza kuwasiliana nawe ikiwa ni lazima. Ikiwa unakubali kutoa habari yako ya mawasiliano, itatumiwa tu na watu wanaofanya kazi

kwa utafiti huu na haitashirikiwa tena na wengine. Sababu ambazo tunaweza kuhitaji kuwasiliana nawe ni pamoja na kuuliza zaidi juu ya dawa unazotumia.

**Hatari na madhara**

Utafiti wa matibabu una uwezo wa kuanzisha hatari za kisaikolojia, kijamii, kihemko na kimwili. Jaribio linapaswa kuwekwa kila wakati ili kupunguza hatari. Hatari moja ya kuwa katika utafiti ni upotezaji wa faragha. Tutaweka kila kitu unachotwambia siri kama iwezekanavyo. Tutatumia nambari ya kukutambulisha kwenye hifadhidata ya kompyuta iliyolindwa na nywila na tutaweka rekodi zetu zote za karatasi kwenye baraza la mawaziri la faili lililofungwa. Walakini, hakuna mfumo wowote wa kulinda usiri wako unaweza kuwa salama kabisa, kwa hivyo bado inawezekana kwamba mtu angeweza kujua kuwa ulikuwa kwenye utafiti huu na angeweza kujua habari kuhusu wewe.

Ikiwa kuna maswali yoyote ambayo hutaki kujibu, unaweza kuyaruka. Una haki ya kukataa mahojiano au maswali yoyote yaliyoulizwa wakati wa mahojiano.

Utafiti huu hautahusisha majaribio yoyote ya maabara, taratibu za uvamizi au dawa ya ziada, kwa hivyo sio hatari kwa mshiriki.

Mtafiti mkuu, ambaye ataendeleza mahojiano, ni mtaalamu wa mafunzo maalum katika mahojiano haya.

**Manufaa**:

Unaweza kufaidika kwa kupokea ushauri wa bure na habari ya afya.

Matokeo ya utafiti huu yatakuza uhamasishaji wa maagizo juu ya matatizo ya utumiaji pamoja wa madawa tofauti ya tiba kwa wagonjwa ambao ni watu wazima wenye tatizo la ugonjwa sugu wa ini na hivyo kuhakikisha usimamizi bora wa hali hiyo kati ya wagonjwa.

**Kuna malipo yoyote?**

Ushiriki katika utafiti huu utakugharimu dakika thelathini wakati wa kliniki yako iliyopangwa. Walakini, faida za utafiti katika suala la kuongeza usimamizi wako zinazidi dakika thelathini ambazo zitatumika kwa mahojiano.

Hakutakuwa na motisha au zawadi zozote za kushiriki katika utafiti.

**Na kama utakuwa na maswali baadaye?**

Ikiwa una maswali zaidi au wasiwasi juu ya kushiriki katika utafiti huu, tafadhali piga simu au tuma ujumbe wa maandishi kwa wafanyikazi wa masomo kwa nambari iliyotolewa chini ya ukurasa huu.

Kwa habari zaidi juu ya haki zako kama mshiriki wa utafiti unaweza kuwasiliana na Katibu / Mwenyekiti, Hospitali ya Kitaifa ya Kenyatta ya Maadili ya Nairobi na Simu ya Kamati ya Utafiti Na. 2726300 Ext. 44102 barua pepe uonknh_erc@uonbi.ac.ke.

Wafanyikazi wa masomo watakulipa kwa malipo yako kwa nambari hizi ikiwa simu ni ya mawasiliano yanayohusiana na masomo.

**Ushiriki wa kujitolea**

Uamuzi wako wa kushiriki katika utafiti ni wa hiari. Uko huru kukataa kushiriki katika utafiti na unaweza kujiondoa kwenye utafiti wakati wowote bila ukosefu wa haki au upotezaji wa faida yoyote.

Ikiwa kwa makubaliano,tia saini kwa fomu ya ridhaa ya washiriki hapa chini;

**Fomu ya ridhaa**

Nimesoma na pia kupokea maelezo katika ridhaa hii na nimeyaelewa kikamilifu. Maswali na haja zangu kuhusu huu utafiti yamejibiwa. Manufaa na pia hatari zozote nimepata kuelezwa. Nimefahamu ya kwamba kushiriki kwangu ni kwa hiari na nina uhuru wa kujiondoa bila thuluma au kuathirika kwa huduma ninazopaswa kupokea kwa hosipitali hii au ingine iwayo. Nimefahamu tena ya kwamba, juhudi zote zitafanywa kuweka habari zote kunihusu siri.

Jina la mshiriki: ----------

Tarehe:----------

Sahihi ya mshiriki:----------

**Andiko la mtafiti mkuu**

Nadhibitisha ya kwamba nimemueleza mshiriki habari zote anapaswa kujua kuhusu utafiti huu na amepata kufahamu.

Jina la Mtafiti mkuu:----------Gichuhi Jane

Tarehe:----------17/11/2021

Sahihi ya Mtafiti mkuu:----------

Kwa mawasiliano zaidi ya habari:

Mpelelezi Mkuu: Dk. Jane Wanjiku Gichuhi mnamo 0702532878

Kamati ya Maadili KNH-UoN ERC mnamo 2726300, Ext 44102

**Appendix 3: Data collection questionnaire**

**Study title: Potential drug-drug interactions among chronic liver disease patients at the Kenyatta National Hospital**

DATE: ---------- Participants unique number ----------

**A. Social demographics**

1) Age (Years) ----------

2)Gender: Male (0) Female (1)

3)Weight (Kg)--------- Height (Meters)--------BMI(Kg/m2) ----------

4)Marital status: Single (0) Married (1) Separated (2) Divorced (3) Widowed (4) Others (5)

5) Occupation: Business/ Self-Employment (0) Formal Employment (1) Unemployed (2)

6) Smoking status: Current smoker (0) Previous smoker (1) Never smoked (2)

7) Alcohol intake status: Currently drinking (0) Previously drinking (1) Never drunk (2)

8)Level of Education: Primary (0) Secondary (1) College/University (2) informal (3)

**B. Diagnosis and co-morbidities**

9)Chronic liver disease: Yes (0) No (1)

10)Duration of CLD: -------

11)Comorbidities: Hypertension (0) Heart failure (1) Diabetes mellitus (2) Cancer (3) Others (specify) (4)

## C. Medications

| Indication | Drug name | Dosage | Frequency | Duration |
|---|---|---|---|---|
| CLD | | | | |
| HYPERTENSION | | | | |
| OTHERS(Specify) | | | | |
| Total number of drugs | | | | |

## D. Potential drug-drug interactions and their clinical effects

| Potentially Interacting Pair of Drugs | Type of Potential DDI | Severity of Potential DDI | Clinical Effect of Potential DDI |
|---|---|---|---|
| 1 | | | |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |

**KEY:** Type of potential DDI: Pharmacokinetic (0) pharmacodynamic (1)

Severity of potential DDI: Minor (0) Moderate (1) Major (2)

## E. Strategies to minimize potential drug-drug interaction

**1----------**

**2----------**

**3----------**

**4----------**

## Appendix 4: Dummy tables

### 5.1 Sociodemographic characteristics of the population

| Variable | Characteristic | Participants(n) | Percentage (%) |
|---|---|---|---|
| Gender | Male<br>Female | | |
| Age(years) | 18-30<br>31-50<br>Above 50 | | |
| Marital status | Single<br>Married<br>Separated<br>divorced<br>widowed<br>others | | |
| Body mass index | Ideal<br>Overweight<br>Obese | | |
| Occupation | Business/ Self-Employment<br>Formal Employment Unemployed | | |
| Smoking status | Current smoker Previous smoker Never smoked | | |
| Alcohol intake status | Currently drinking Previously drinking Never drunk | | |
| Level of Education | Primary<br>Secondary<br>College/University Informal | | |

**Appendix 5: Potential drug-drug interaction, severity of interaction, clinical effect and frequency (a total of 134 pDDIs were identified)**

| Interacting Pairs | Severity Of Interaction | Clinical Effect | Frequency |
|---|---|---|---|
| 1. Aspirin: Digoxin | Major | Increased serum concentration of digoxin, prolonged half-life of digoxin | 1 |
| 2. Aspirin: Furosemide | Major | reduced diuretic effectiveness or possible nephrotoxicity | 1 |
| 3. Aspirin: Spironolactone | Major | reduced diuretic effectiveness, hyperkalaemia or possible nephrotoxicity; | 1 |
| 4. Carvedilol: Digoxin | Major | increased digoxin concentrations, increased risk of complete heart block | 1 |
| 5. Digoxin: Spironolactone | Major | increased digoxin exposure through inhibition of active tubular secretion of digoxin; | 1 |
| 6. Dolutegravir Sodium: Ferrous Sulphate | Major | decreased dolutegravir exposure and loss of efficacy | 2 |
| 7. Dolutegravir Sodium: Rifampin | Major | decreased dolutegravir exposure and loss of efficacy | 1 |
| 8. Isoniazid: Rifampin | Major | Hepatotoxicity | 1 |
| 9. Pyrazinamide: Rifampin | Major | Severe hepatic injury | 2 |
| 10. Clarithromycin: Metronidazole | Major | Increased risk of QT Interval prolongation; | 2 |
| 11. Clarithromycin: Ondansetron | Major | Increased risk of QT Interval prolongation, increased ondansetron exposure; | 1 |
| 12. Clarithromycin: Tramadol HCl | Major | increased tramadol exposure and increased risk of respiratory depression; | 1 |
| 13. Metronidazole: Ondansetron | Major | Increased risk of QT Interval prolongation and arrhythmias; | 6 |
| 14. Ondansetron: Tramadol HCl | Major | increased risk of serotonin syndrome | 5 |
| 15. Ciprofloxacin: Octreotide Acetate | Major | increased risk of QT interval prolongation; | 1 |
| 16. Octreotide Acetate: Omeprazole | Major | decreased octreotide bioavailability; | 4 |
| 17. Metformin HCl: Sitagliptin Phosphate | Major | Increased risk of hypoglycaemia; | 1 |
| 18. Isoniazid: Rifampin | Major | Hepatotoxicity; | 1 |
| 19. Metoclopramide Hcl: Tramadol Hcl | Major | Increased risk of CNS depression | 5 |
| 20. Pregabalin: Tramadol HCl | Major | Respiratory depression; | 1 |
| 21. Diazepam: Phenytoin Sodium | Major | Alterations in serum phenytoin concentrations | 1 |
| 22. Esomeprazole Sodium: Octreotide Acetate | Major | Decreased octreotide bioavailability | 3 |

**Appendix 5: Potential drug-drug interaction, severity of interaction, clinical effect and frequency(continued)**

| Interacting Pairs | Severity Of Interaction | Clinical Effect | Frequency |
|---|---|---|---|
| 23. Metformin Hydrochloride: Octreotide Acetate | Major | Impaired glucose regulation | 1 |
| 24. Metronidazole: Octreotide Acetate | Major | Increased risk of QT-interval prolongation and arrhythmias. | 2 |
| 25. Fluconazole: Tramadol HCl | Major | Increased tramadol exposure and increased risk of respiratory depression | 1 |
| 26. Ciprofloxacin: Metronidazole | Major | Increased risk of QT-interval prolongation and arrhythmias | 3 |
| 27. Ciprofloxacin: Ondansetron HCl | Major | Increased risk of QT-interval prolongation | 2 |
| 28. Methotrexate: Omeprazole | Major | Increased risk of methotrexate toxicity | 1 |
| 29. Spironolactone: Trimethoprim | Major | Increased risk of hyperkalaemia; | 1 |
| 30. Itraconazole: Tramadol HCl | Major | Increased tramadol exposure and increased risk of respiratory depression | 1 |
| 31. Haloperidol: Tramadol HCl | Major | Increased risk of respiratory and CNS depression | 1 |
| 32. Ketoprofen: Methyl Prednisolone Sodium Succinate | Major | Increased risk of gastrointestinal ulcer or bleeding | 1 |
| 33. Octreotide Acetate: Ondansetron | Major | increased risk of QT-interval prolongation | 1 |
| 34. Cisplatin: Doxorubicin HCl | Major | Leukemia | 1 |
| 35. Dexamethasone: Doxorubicin HCl | Major | Reduced doxorubicin exposure | 1 |
| 36. Spironolactone: Trimethoprim | Major | Increased risk of hyperkalemia | 1 |
| 37. Hydrochlorothiazide: Ketoprofen | Major | Reduced diuretic effectiveness and possible nephrotoxicity | 1 |
| 38. Morphine Sulphate: Ondansetron | Major | Increased risk of serotonin syndrome | 2 |
| 39. Efavirenz: Metronidazole | Major | Increased risk of QT Interval prolongation | 1 |
| 40. Enoxaparin Sodium: Warfarin Sodium | Major | Increased risk of bleeding | 1 |
| 41. Levofloxacin: Metronidazole | Major | Increased risk of QT Interval prolongation and arrhythmias | 1 |

**Appendix 5: Potential drug-drug interaction, severity of interaction, clinical effect and frequency(continued)**

| Interacting Pairs | Severity Of Interaction | Clinical Effect | Frequency |
|---|---|---|---|
| 42. Diazepam: Phenytoin Sodium | Major | Alterations in serum phenytoin concentrations | 1 |
| 43. Ferrous sulphate: Levothyroxine Sodium | Moderate | Hypothyroidism | 1 |
| 44. Ferrous; Sulphate: Pantoprazole Sodium | Moderate | reduced iron bioavailability | 1 |
| 45. Furosemide: Propranolol HCl | Moderate | Hypotension, bradycardia | 9 |
| 46. Levothyroxine Sodium: Pantoprazole Sodium; | Moderate | Decreased levothyroxine effectiveness | 1 |
| 47. Pantoprazole sodium: Propranolol HCl; | Moderate | Increased propranolol exposure | 2 |
| 48. Pantoprazole Sodium: Warfarin Sodium; | Moderate | Increased INR and prothrombin time | 1 |
| 49. Propranolol HCl: Warfarin Sodium | Moderate | Increased risk of bleeding; | 1 |
| 50. Spironolactone: Warfarin Sodium | Moderate | Decreased anticoagulant effectiveness; | 1 |
| 51. Aspirin: Carvedilol | Moderate | increased blood pressure | 1 |
| 52. Digoxin: Furosemide | Moderate | Increased risk of digoxin toxicity | 1 |
| 53. Esomeprazole Sodium: Ferrous Sulphate | Moderate | Reduced iron bioavailability; | 5 |
| 54. Esomeprazole Sodium: Rifampin | Moderate | Decreased esomeprazole plasma concentrations. | 1 |
| 55. Furosemide: Insulin Human Isophane | Moderate | Altered glucose metabolism leading to increased risk of hyperglycaemia; | 2 |
| 56. Furosemide: Insulin Human Regular | Moderate | Altered glucose metabolism leading to increased risk of hyperglycaemia; | 2 |
| 57. Insulin Human Isophane: Propranolol HCl | Moderate | Altered glucose metabolism and beta blockade leading to increased risk of hyperglycaemia or hypoglycaemia and decreased symptoms of hypoglycaemia; | 1 |
| 58. Insulin Human Regular: Propranolol HCl | Moderate | Altered glucose metabolism and beta blockade leading to increased risk of hyperglycaemia or hypoglycaemia and decreased symptoms of hypoglycaemia | 1 |
| 59. Omeprazole: Propranolol HCl | Moderate | increased propranolol exposure; | 3 |

**Appendix 5: Potential drug-drug interaction, severity of interaction, clinical effect and frequency (continued)**

| Interacting Pairs | Severity Of Interaction | Clinical Effect | Frequency |
|---|---|---|---|
| 60. Empagliflozin: Propranolol HCl | Moderate | May result in hyperglycemia or hypoglycemia, decreased symptoms of hypoglycemia; | 1 |
| 61. Metformin HCl: Propranolol HCl | Moderate | May result in hyperglycemia or hypoglycemia, decreased symptoms of hypoglycemia; | 1 |
| 62. Propranolol HCl: Sitagliptin Phosphate | Moderate | May result in hyperglycemia or hypoglycemia, decreased symptoms of hypoglycemia. | 1 |
| 63. Acetaminophen: Phenytoin Sodium | Moderate | decreased acetaminophen effectiveness and increased risk of hepatotoxicity | 1 |
| 64. Metronidazole: Phenytoin Sodium | Moderate | Increased risk of phenytoin toxicity or decreased metronidazole plasma levels | 1 |
| 65. Esomeprazole Sodium: Fluconazole | Moderate | Increased esomeprazole plasma concentration | 1 |
| 66. L-Methylfolate: Methotrexate | Moderate | Decreased methotrexate and/or l-methylfolate efficacy | 1 |
| 67. Esomeprazole Sodium: Propranolol HCl | Moderate | Increased propranolol exposure | 11 |
| 68. Cholestyramine: Furosemide | Moderate | Decreased furosemide effectiveness; | 1 |
| 69. Cholestyramine: Metronidazole | Moderate | Decreased metronidazole effectiveness. | 1 |
| 70. Haloperidol: Trihexyphenidyl HCl | Moderate | Excessive anticholinergic effects (sedation, constipation, dry mouth) | 1 |
| 71. Ferrous Sulphate: Omeprazole | Moderate | reduced non-heme iron bioavailability | 1 |
| 72. Carvedilol: Dobutamine HCl | Moderate | Decreased dobutamine efficacy | 1 |
| 73. Iron Sucrose: Omeprazole | Moderate | Reduced non-heme iron bioavailability | 2 |
| 74. Levothyroxine Sodium: Warfarin Sodium | Minor | Increased risk of bleeding | 1 |
| 75. Ciprofloxacin: Propranolol HCl | Minor | Bradycardia, hypotension | 1 |
| 76. Calcium Acetate: Ferrous Sulphate | Minor | Decreased iron effectiveness | 1 |
| 77. Clarithromycin: Lansoprazole | Minor | Glossitis, stomatitis or black tongue | 3 |
| 78. Diazepam: Omeprazole | Minor | Enhanced and prolonged diazepam effects | 1 |

**PREVALENCE AND MANAGEMENT OF POTENTIAL DRUG-DRUG INTERACTIONS AMONG CHRONIC LIVER DISEASE PATIENTS AT KENYATTA NATIONAL HOSPITAL**

19/11/2021

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