University of Nairobi

Department of Pharmacology and Pharmacognosy

Evaluation of Potential Drug-Drug Interactions among Mentally ill Patients Admitted at Mathari Mental Hospital

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A research thesis submitted in partial fulfillment of the requirement for the award of Master of Pharmacy (Pharmacoepidemiology and Pharmacovigilance) by the University of Nairobi

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DECLARATION

This is my original thesis. It has not been submitted for award of a degree or any other award in any University.

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DEDICATION

I dedicate this work to my grandmother Kemuma Ogwangi, my mother Milkah Bochere, my dad Jomo Ogwangi, my brothers Dan, Oscar and Charles my sister Sheila, my wife Leonida and my daughter Kayla for making this possible.

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LIST OF ABBREVIATIONS AND ACRONYMS

ADR	Adverse Drug Reaction
ADE	Adverse Drug Event
AIDS	Acquired Immunodeficiency Syndrome
AIC	Akaike Information Criterion
CNS	Central Nervous System
CYP 450	Cytochrome P 450
DALY	Disability Adjusted Lost Years
DDI	Drug-Drug Interactions
DNA	Deoxyribonucleic Acid
EMA	European Medicines Agency
ERC	Ethics and Research Committee
HIV	Human Immunodeficiency Virus
KNH	Kenyatta National Hospital
MAOIs	Mono Amine Oxidase Inhibitors
pDDI	Potential Drug Drug Interactions
PLWH	People Living with HIV/AIDS
SMI	Serious Mental Illness
SSRI's	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
UNAIDS	United Nations Acquired Immunodeficiency Syndrome
UON	University of Nairobi
WHO	World Health Organization
WMH	World Mental Health

OPERATIONAL DEFINITIONS

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

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

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

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

ABSTRACT

Background: Mental health refers to a wider range of activities directly or indirectly related to the mental well-being. Multiple social, psychological and biological factors determine the level of mental health of a person at any given time. Mentally ill patients are prone to a high risk of polypharmacy, complex therapeutic regimen and frequent modification of therapy. Hence an increase in the likelihood of potential drug-drug interactions, which are, estimated to account for 11% of adverse related hospital admissions. This necessitates a need to explore the overall pattern of potential drug interactions and their risk factors among mentally ill inpatients at Mathari Mental Hospital.

Objective: To evaluate potential drug-drug interactions among mentally ill patients admitted at Mathari Mental Hospital

Study Area: Mathari Mental Hospital is a national referral and teaching psychiatric hospital in Kenya, it mainly admits patients whose behavioral disturbances and mental cases cannot be managed within the community.

Study design: A retrospective descriptive cross-sectional study of medical records data of patients who had undergone mental treatment and were admitted at Mathari Mental Hospital between July and December 2013. Prescriptions were obtained by systematic random sampling method and checked using medscape drug interaction checker for any potential drug-drug interaction.

Study Population: The study comprised of all mentally ill patients who were admitted and put on medication during the study period at Mathari Mental Hospital, were of either gender and aged between 13 to 75 years.

Results: One hundred and seventy five patient files were sampled, married and unemployed patients had a statistically significant ($p<0.05$) association with potentially serious drug interactions. The average drugs prescribed per prescription was six. Participants with bipolar mood disorder had a statistically significant association with potentially serious drug interactions [OR 4.39 CI (1.09, 17.46) $p = 0.04$]. There was a statistically significant association of

potentially serious drug interactions with fluphenazine [OR 10.38 CI (4.66, 23.10) p<0.01) haloperidol [OR 4.39 CI (2.29, 8.41) p<0.01] and amitriptyline [OR 3.39 CI (1.36, 8.41) p=0.01].

Conclusion and recommendation: Married, unemployed and patients on fluphenazine, haloperidol, amitriptyline and chlorpromazine were at a higher risk of having potentially serious drug-drug interactions. These drugs exhibited both pharmacodynamic and pharmacokinetic drug interaction mechanisms. There is need to use second generation antidepressants mainly because of their improved tolerability and safety profile. We recommend continuous electrocardiogram for patients on specific antipsychotics like haloperidol.

CHAPTER ONE

Introduction

1.1 Background

Mental health refers to a wider range of behavioral activities directly or indirectly related to the psychological well-being of an individual. The World Health Organisation (WHO) defines health as: " A state of complete physical, mental and social well being, and not merely the absence of disease". Mental health is thus a state of well-being that encompasses the prevention of mental disorders and treatment and rehabilitation of people affected by mental disorders [1].

In most cases, care providers for mentally ill patients encounter clinical situations which require medications. These clinical situations require familiarity with a broad category of these medications. It includes the basic understanding of indications, adverse effects and drug-drug interactions. In particular, it is very important to recognize the many potential interactions associated with cytochrome P450 metabolism, which is common to many psychotropics and other central nervous system (CNS) drugs [2]. Mentally ill patients have a high risk of polypharmacy hence increase in the likelihood of drug-drug interactions. This may cause partial or complete abolishment of treatment efficacy, thus underlining the importance of understanding the potential drug-drug interactions and the adverse drug reactions associated with them [3].

Potential drug-drug interactions are based on the risk-benefit evaluation of a medicinal product and incidences of adverse events, reduced efficacy or increased toxicity which are often predictable, avoidable or manageable [4]. This risk benefit evaluation needs more attention in the case of hospitalized patients due to severity of disease, polypharmacy, co-morbid conditions, chronic diseases, complex therapeutic regime and frequent modification in therapy. Results from different studies have estimated the prevalence of hospital admissions due to drug-drug interactions drug interactions to be between 1 % to 21 % (an average of 11 %) [5-6].

Studies are needed to explore the overall pattern of potential drug-drug interactions (pDDIs) in psychiatric patients along with their levels and correlation with different risk factors. Hence the main aim of this study was to determine the prevalence and risk factors associated with pDDIs in hospitalized mentally ill patients in Mathari Mental Hospital.

1.2 Problem statement and study justification

Mental and behavioral disorders are common and affect more than 25 % of all people at some time during their lives. The WHO estimates that about 10 % of the adult and child population at any given time suffer from at least one mental disorder. In addition, at least 20 % of all patients seen by primary health care professionals have one or more mental disorders. It is projected that by 2020, the burden of mental and behavioral disorders will account for 15 % of the total Disability- Adjusted Lost Years (DALYs) up from 12 % in the year 2000 [7].

Mentally ill patients take non-prescribed and prescribed drugs and are more likely than other individuals to have more complex medication regimens. This can result in polypharmacy and drug-drug interactions (DDIs) which may lead to undesired medication effects and serious, potentially fatal adverse drug events (ADEs) which could have been prevented or easily managed [8]. To evaluate drug interactions patients aged between 13 and 75 years were studied since they are considered to be in the productive bracket.

Drug interaction is a potential problem among mentally ill patients both economically and socially. It is important to consider drug interactions when initiating drug therapy, changing a dose, changing the route of administration or stopping a therapy. There is need to determine the extent of this problem among hospitalized mentally ill patients in Kenya as a measure towards improving therapy outcomes. Mathari hospital being the national mental referral hospital in Kenya was chosen as the study site.

1.3 Objectives

1.3.1 Broad objective

The main objective of this study was to evaluate potential drug-drug interactions associated with the use of psychotropic drugs among mentally ill patients admitted at Mathari Mental Hospital.

1.3.2 Specific objective

i) Determine the prevalence of potential drug-drug interactions in mentally ill inpatients.

ii) Determine the severity of potential drug-drugs interactions in mentally ill inpatients.

iii) Determine the underlying mechanisms of potential drug-drug interactions in mentally ill inpatients.

iv) Identify risk factors associated with potentially serious drug-drug interactions among mentally ill inpatients.

CHAPTER TWO

Literature Review

2.1 Drug-drug interactions

A drug-drug interaction is defined as a pharmacological or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone [9]. There two main mechanisms of interactions, pharmacodynamic or pharmacokinetic. Pharmacodynamic drug interaction occurs when one drug modulates the pharmacologic effect of another by additive, synergistic or antagonistic effect. It is occurs in drugs which compete with each other at the pharmacological target and/or have similar or opposing pharmacodynamic effects. In pharmacokinetic interactions, one drug alters the concentration of another drug by altering its absorption, distribution, metabolism or excretion. Pharmacokinetic interactions occur if there are indications that the interaction profile may not be adequately predicted from and *in vivo* interaction data for the separate drugs [10, 11].

2.2 Pharmacokinetic interactions of psychotropic drugs

Most psychotropic drugs exhibit the two types of pharmacokinetic drug interaction mechanisms.

2.2.1 Metabolism and Distribution

Drugs compete for binding sites differently, protein-binding interactions may be significant for drugs with a small volume of distribution or where a temporary increase in plasma may result in unacceptable adverse effect and includes drugs like phenytoin. Most psychotropics are protein bond to a certain extent with the exception of lithium and gabapentin [10-11].

Metabolic drug interactions involve, enzyme induction or inhibition, which may affect the substrate drug and their plasma levels. This is exhibited when carbamazepine and quetiapine are used together, carbamazepine decreases the effect of quetiapine by affecting hepatic enzyme

CYP 3A4 [12]. Metabolic drug interactions are also significant for drugs with low ratio between a therapeutic and toxic dose, notable drugs include phenytoin and theophyline [13].

Many psychotropic drugs interact with each other in this manner since most are metabolised in the liver by Cytochrome P450 and may therefore cause inhibition or induction of enzyme Cytochrome P450 resulting in increased or decreased effect [14,15]. Table 2.1 outlines the common psychotropic drugs that are substrates, inhibitors and inducers of CYP450 isoenzyme.

Table 2.1: Psychotropic drugs that are substrates, inhibitors and inducers of CYP 450 isoenzymes

CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP2D6	CYP3A4,5,7
Substrates					
Amitriptyline Chlorpromazine Clomipramine Clozapine Fluvoxamine Haloperidol Imipramine Methadone Olanzapine	Bupropion Methadone	Amitriptyline Citalopram Clomipramine Diazepam Imipramine Moclobemide Phenobarbitone	Amitriptyline Fluoxetine Phenytoin	Amitriptyline Amphetamine Chlorpromazine Clomipramine Desipramine, Donepezil, Fluoxetine, Fluvoxamine Galantamine, Haloperidol Imipramine, Nortriptyline Olanzapine, Paroxetine Risperidone, Sertraline Zuclopenthixol	Alprazolam, Amitriptyline Carbamazepine Clomipramine Clonazepam, Clozapine Diazepam, Donepezil Haloperidol Imipramine, Methadone Midazolam, Mirtazapine Pimozide, Quetiapine Triazolam
Inhibitors					
Fluvoxamine		Fluoxetine Fluvoxamine Modafinil Paroxetine Valproate	Fluoxetine Fluvoxamine Paroxetine	Bupropion Chlorpromazine Doxepin, Duloxetine Fluoxetine Haloperidol, Methadone Moclobemide, Paroxetine Reboxetine, Sertraline Thioridazine, Valproate	Fluoxetine, Fluvoxamine Valproate
Inducers					
Barbiturates,	Phenobarbitone Modafinil	Carbamazepine	Barbiturates		Carbamazepine Modafanil, Phenytoin

2.3 Pharmacodynamic interactions

The most commonly encountered interactions in practice are pharmacodynamic interactions. Clinically significant pharmacodynamic drug interactions with psychotropic drugs are based on antagonistic, additive or synergistic drug interactions.

2.3.1 Antagonistic interactions

Antipsychotropics that are potent dopamine D2 antagonists oppose the effect of dopamine agonists in management of Parkinson's disease. When used together, the therapeutic effect of both drugs will be diminished [16]. Drugs with anticholinergic properties can pharmacodynamically oppose the effects of anticholinesterase drugs used in Alzheimer's disease. Cyproheptadine antagonizes postsynaptic serotonin receptors hence concomitant use of cyproheptadine with drugs that possess serotonin-enhancing properties might be expected to result in a pharmacodynamic interaction. Reduction in antidepressant efficacy has been reported when cyproheptadine was administered concurrently with fluoxetine and paroxetine [17].

2.3.2 Additive pharmacodynamic interactions

Additive pharmacodynamic interactions involving psychotropic drugs resulting in various forms of adverse reactions are; over sedation, seizures, serotonin syndrome, hypertension, anticholinergic effects, hypotension, QTC prolongation and hematological effects.

Over sedation due to the additive effects of drugs with sedative properties is often encountered when psychotropic drugs like chlorpromazine and fluphenazine are combined. Over sedation may also occur as the result of inhibition of metabolism of the sedating drug through CYP450 metabolism [18].

Concurrent use of lithium and antipsychotic drugs or carbamazepine may result in neurotoxicity characterized by weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brain damage. This interaction is rare and is more likely to occur with higher plasma levels of lithium [19].

Seizures may result from the additive effects of two or more drugs that lower the seizure threshold. Most antipsychotic drugs and antidepressants can reduce the seizure threshold. Antipsychotics such clozapine and chlorpromazine have the greatest epileptogenic potential whereas among the antidepressants, the tricyclic antidepressants (TCAs) pose the greatest risk.

Patients that require a combination of drugs that reduce the seizure threshold should be maintained on the lowest effective dose, with careful introduction and withdrawal of high-risk drugs [20].

Serotonin syndrome can occur with one or more serotonergic drugs. Serotonin syndrome is a potentially life threatening condition characterized by mental state changes, myoclonus, tremor, hyper reflexia, fever, sweating, shivering and diarrhoea. All of the antidepressants, except reboxetine, can contribute to serotonin syndrome and there is a greater risk of serotonin syndrome with combinations of selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) or SSRIs and serotonergic TCAs (clomipramine, amitriptyline, and imipramine). Other drugs such as opioids (tramadol, pethidine, and dextromethorphan), stimulants (phentermine, diethylpropion, amphetamines, and sibutramine), $5HT_1$ agonists (sumatriptan, naratriptan, and zolmitriptan) and others (illicit drugs, selegiline, trytophan, buspirone, lithium, linezolid and St John's wort) can also contribute to serotonin syndrome. Combined use of serotonergic drugs should be avoided or monitored carefully [21].

The concomitant use of MAOIs and tyramine containing food, or drugs that increase the level of monoamines (serotonin, noradrenaline, or dopamine) can result in interactions that have the potential to cause hypertensive condition. Combinations of monoamine oxidase inhibitors (MAOIs) and these drugs are contraindicated. The severity and consequences of such interactions may vary among individuals. If substantial and rapid increases in blood pressure (an increase of 30 mm Hg or more in systolic blood pressure within 20 minutes) occur, patients may experience symptoms associated with subarachnoid haemorrhage or cardiac failure [22].

Caution should be taken when combining drugs with anticholinergic properties like alprazolam, amitriptyline, diazepam and flurazepam due to enhanced anticholinergic effects such as dry mouth, urinary retention and constipation. There is also an increased risk of developing paralytic ileus, or central anticholinergic delirium characterised by cognitive changes as well as symptoms such as dry skin, dry mucous membranes, dilated pupils, tachycardia and absent bowel sounds [23].

Caution should be taken when combining drugs with an antihypertensive effect. Hypotension is a common adverse effect of many psychotropic drugs due to alpha-adrenergic blockade common with prazosin, doxazosin and phenoxybenzamine. Hypotension is a dose related and additive adverse effect that is a potentially serious due to the risk of falls, cerebral ischaemia or myocardial ischaemia [24].

Many psychotropic drugs including certain antidepressants, antipsychotics and lithium have been associated with lengthening of the cardiac QTC interval, which increases the risk of ventricular arrhythmias such as torsades de pointes. Psychotropic drugs with the greatest effect on QTC interval include chlorpromazine, haloperidol, doperidol, pimozide and thioridazine. The risk of cardiac arrhythmia and sudden death may be increased further when these drugs are used concomitantly with other QTC prolonging drugs like astemizole, cisapride, erythromycin and sotalol. QTC prolongation is a dose dependent effect; hence inhibition of drug metabolism is also an important interaction to consider. Indirect pharmacodynamic interactions with psychotropic drugs that prolong the QTC interval should also be considered. These interactions involve drugs that affect the electrolyte balance or that cause bradycardia, thereby increasing the risk of arrhythmia [25,26].

Psychotropic drug-induced haematological effects are rare however, additive drug effects are noted on white blood cells and platelets among patients on clozapine and drugs known to be myelosupressive. Due to the risk of agranulocytosis, these combinations are contraindicated. Many other psychotropic drugs have also been associated with agranulocytosis, most notable drugs are carbamazepine and the phenothiazines. Serotonergic drugs and valproate can affect platelet function. SSRIs can inhibit serotonin reuptake into the platelets, reducing platelet's ability to aggregate. When SSRIs are used in combination with NSAIDs or anticoagulants the risk of bleeding may increase although this interaction is usually uneventful. Sodium valproate can inhibit the second stage of platelet aggregation and increase bleeding time. Caution is required when valproate is used with other drugs that affect coagulation or platelet function [27,28].

CHAPTER THREE

Methodology

3.1 Research design

The study was a retrospective descriptive cross sectional study. Whereby documented prescriptions in the existing patient files of mentally ill patients admitted in the wards within July 2013 to December 2013 were obtained by systematic random sampling. All drugs prescribed for each patient were noted and checked for any potential drug-drug interactions using, the Medscape drug interaction checker.

3.2 Study site

The study was conducted at Mathari Mental Hospital, which is the national referral and teaching mental hospital in Kenya located in Nairobi, the capital city of Kenya. It mainly admits patients whose behavioral disturbances and mental conditions cannot be managed within the community. Mathari Hospital has about 600 beds, and at any given time there are about 300 patients admitted in the hospital. It is served by nine psychiatrists, two of who carry out administrative duties on a full-time basis [29].

3.3 Target population

All mentally ill patients who were admitted and were on medication between July 2013 to December 2013 in Mathari Mental Hospital were targeted in the study. This study period was the latest period in which the study could be conducted.

3.4 Inclusion and Exclusion criteria

In-patients (both new and readmitted cases) aged between 13 to 75 years (which was deemed to be the normal age bracket for a healthy person) for both male and female were included in the

study. They were to be on more than one drug in a given prescription issued during the study period.

Patients were excluded from the study if they had one drug in their prescription and were aged below 13 years or above 75 years.

3.5 Sampling

3.5.1 Sample size

The sample size was determined based on the average prevalence rate of drug-drug interactions which is estimated to be about 11 % from a previous studies cited in the study background [5,6]. Using Fischer's formula for sample size determination [30]. The following formula was used;

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

Where:
N is the total sample required for the study
Z is the standard normal deviation corresponding to 95 % confidence level ($Z = 1.96$).
P is the prevalence which is estimated to be 11 %
d is the level of the confidence (set at 5 %)
Therefore by substitution:

$$N=150.4 (\sim 150 \text{ patients})$$

An allowance of 10 % was included in calculating the target sample size in anticipation of unforeseen anomalies. For this study, the total number of sampled patient files were 175.

3.5.2 Sampling technique

Systematic random sampling technique was used. A total of 1164 patients were admitted between July and December 2013. To get the sampling fraction, the total patients admitted over the period was divided with the required sample size of 200. A sampling fraction of every sixth patient file was applied. Out of which 194 patient files obtained, 19 files didn't meet inclusion criteria hence excluded from the study and a total of 175 patients files were studied.

3.5.3 Exposure measures

Study predictors of potential drug-drug interactions (pDDIs) extracted from the patient's medical records include; mental diagnosis, patient characteristics (gender, age), prescribed drugs and social demographic factors like residential place, level of education and marital status.

3.6 Data collection procedures

3.6.1 Data quality assurance

A pilot of 10 sampled patients was done and the findings used to improve the design of data collection tools and the standard operating procedures. Any significant shortcomings in the design of the tools were noted and adjustments were made to the tools to eliminate any ambiguities, improve clarity and the quality of data collected.

All data entries were counterchecked against the source document by the investigator. The raw data generated during the course of the study and the final report was subjected to inspection and quality audit for conformity to set protocols by the investigator.

3.6.2 Extraction of patient files

The sampled patient medical files were retrieved and the following information abstracted; patient demographic characteristics like gender, age, marital status and level of education, the type of mental illness, co morbidities and any documented medication history.

3.6.3 Medscape drug interactions checker

Medscape drug interaction checker is an online medical tool in which drugs prescribed in a given prescription are entered to predict the nature of the interactions. Medscape gives an output of interactions based on severity (serious, significant, minor or none), mechanism of drug interactions (pharmacokinetic or pharmacodynamic drug interactions) [31].

Using Medscape drug interaction checker the nature of potential drug interactions were observed and classified as; pharmacokinetic interactions in which absorption, distribution, metabolism or elimination interaction mechanisms were observed and pharmacodynamic interactions which included synergistic, antagonism or additive interaction mechanism as shown in appendix one.

3.7 Case definition and variables

Potential drug-drug interactions were obtained using Medscape drug interaction checker which classified the outcomes based on severity of potential drug-drug interactions as shown in Table 3.7 and mechanism of potential drug-drug interactions [31].

Severity	Action	Explanation
Serious	Avoid combination Consider therapy modification	The drugs are contraindicated for concurrent use, The interaction may be life threatening and/or require medical intervention to minimize or prevent serious adverse events
Significant	Monitor therapy	The interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy
Minor	No action needed	The interaction would have limited clinical effects. May include an increase in the frequency or severity of side effects but generally would not require a major alteration in therapy

Table 3.7 Severity of potential drug-drug interactions

Mechanisms of potential drug-drug interactions were cartegorized into two broad categories, namely pharmacodynamic and pharmacokinetic. Pharmacodynamic potential drug-drug interactions were classified into synergism, antagonism and additive. Synergism effect occurs when a pharmacological response is facilitated by concomitant use of two or more drugs resulting in a total effect greater than the sum of their independent actions. Antagonism when two drugs on the same physiological system exhibit opposing actions. Additive effect occurs when the total pharmacological effect of two or more drugs administered together is equivalent to the sum of their individual pharmacological actions. Most psychotropic drugs exhibited metabolic pharmacokinetic potential drug interactions in which physiological factors like enzyme levels may modify the effects of drugs [32].

There were three predictor variables in the study namely, social demographic factors (gender, residence, education, marital status and occupation), prescribed psychotropic drugs and mental diagnosis.

3.8 Data analysis

Data was collected, coded and entered into computer excel database where data analysis was done in three steps namely descriptive analysis, bivariate analysis and multivariate analysis.

Descriptive statistical analysis described the outcomes in patient demographic factors using percentages or frequency for categorical variables. In continuous variables like age the mean and standard deviation was used to describe the distribution.

Bivariate analysis compared the outcomes and predictor variable using logistic regression analysis where odds ratio with 95 % confidence intervals (95 % CI) were calculated and probability (p) values of 0.05 or less were considered to be statistically significant.

A multivariate analysis of a parsimonious forward stepwise model building was done to determine the drugs with best predictor variables for potentially serious drug-drug interactions. All statistical analyses were done out using Stata® 10.0 version statistical software.

3.9 Ethical considerations

Approval to carry out the study was granted by the Kenyatta National Hospital and University of Nairobi Ethical Research Committee (KNH/UON-ERC) (approval letter in appendix two). The in-charge of Mathari Mental Hospital gave consent to the principal investigator to access patient files (consent letter appendix three and four). Patient informed consent was not required since all required information was abstracted from patient files. There were no direct benefits for the patients whose files were used in the study. Confidentiality of the patients' medical records was maintained and no names were included during data collection. Patients were assigned study numbers in place of patient identification numbers. A link log was created and kept under lock and key accessible only by the principle investigator. The link log will be destroyed on publication of the study findings. All the original records pertaining to the study were also kept under lock and key accessible only by the principle investigator and the research supervisors. Good clinical practice (GCP) guidelines were adhered to as outlined by the International Conference on Harmonization and the Nuremburg Code and Declaration of Helsinki (1964) [33].

CHAPTER FOUR

Results

4.1 Social demographic characteristics of study participants

One hundred and seventy five files for patients who were aged between 13 to 75 years were sampled, with a mean age of 34.2 years and a standard deviation (SD) of (±13.8). Male patients were 101 (57.7 %), while most of the patients 133 (76.0 %) were residing in the rural area, majority had secondary school level of education 94 (53.7 %), most of them were single 78 (44.6 %), and were self-employed or in business 54 (30.9 %) as outlined in Table 4.1.

Table 4.1: Social demographic characteristics of study participants (N = 175)

Parameters	Observations	Parameters	Observations
Age in years		**Marital status**	
Mean	34.2 (SD ± 13.8)	Single	78 (44.6)
Gender	**Number (%)**	Married	64 (36.6)
Male	101 (57.7)	Separated	25 (14.3)
Female	74 (42.3)	Divorced	6 (3.4)
Residence		Widowed	2 (1.1)
Urban	42 (24.0)	**Occupation**	
Rural	133 (76.0)	Farmer	40 (22.9)
Level of education		Business/self employed	54 (30.9)
None	2 (1.1)	Formal employment	16 (9.1)
Primary	28 (16.0)	Unemployed	65 (37.1)
Secondary	94 (53.7)		
Tertiary	36 (20.6)		
University	6 (3.4)		
Unknown	9 (5.1)		

4.2 Clinical conditions of study participants

Bipolar mood disorder and schizophrenia were the most common mental conditions among study participants at 58 (33.1 %) and 48 (27.4 %) respectively. Majority of the patients did not have co-morbidities 116 (92.0 %) however hypertension accounted for 8 (4.6 %) of the study participant as shown in Table 4.2.

Table 4.2: Clinical conditions of study participants (N = 175)

Parameters	Observations
Mental diagnosis	
Unipolar disorder	13 (7.4)
Bipolar mood disorder	58 (33.1)
Schizophrenia	48 (27.4)
Epilepsy	20 (11.4)
Alcohol use disorder	15 (8.6)
Alzheimer and other dementia	11 (6.3)
Substance abuse Disorder	10 (5.7)
Co-morbidities	
None	161 (92.0)
Diabetes	1 (0.6)
HIV	1 (0.6)
Hypertension	8 (4.6)
Dyspepsia	1 (0.6)
Tuberculosis	1 (0.6)
Neuropathy	1 (0.6)
Pneumonia	1 (0.6)

4.3 Drugs prescribed to study participants

Forty-six different drugs were prescribed, the average number of drugs per prescription was found to be 6.5. these drugs included psychotropic drugs 18 (39 %), antihypertensives 7 (15 %), analgesics 6 (13 %), anti-retrovirals 4 (9 %), anti-tuberculosis 4 (9 %), antibiotics 1 (2 %) and other drugs 6 (13 %). Figure 4.3 shows the classification of prescribed drugs.

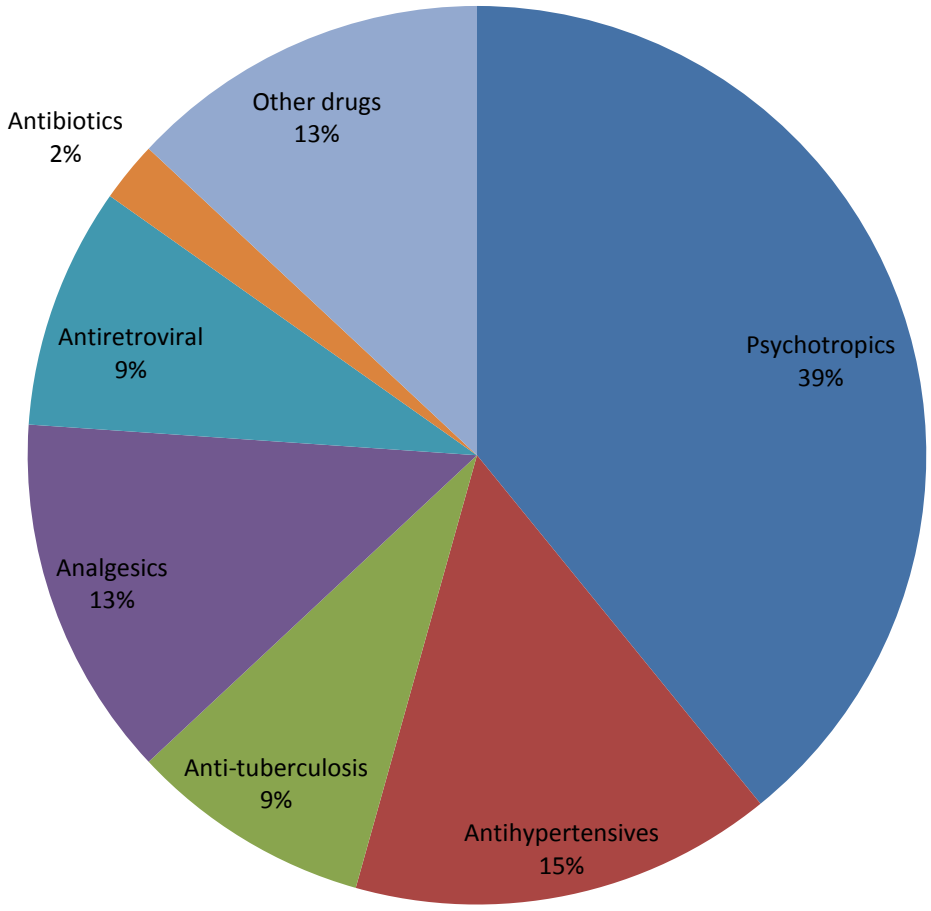


Figure 4.3: Classification of prescribed drugs

Among the psychotropic drugs carbamazepine and benzhexol accounted for 114 (22.6 %) and 82 (16.2 %) prescriptions respectively as shown in table 4.3.

Table 4.3: Drugs prescribed to study participants in Mathari Mental Hospital

Drug	N, (%)	Drug	N, (%)
Psychotropics		**Antihypertensives**	
Amitriptyline	24 (4.8)	Methyl dopa	1 (6.25)
Benzhexol	82 (16.2)	Atenolol	3 (18.75)
Carbamazepine	114 (22.6)	Hydrochlorthiazide	5 (31.25)
Chlorpromazine	41 (8.1)	Frusemide	1 (6.25)
Zuclopenthixol	17 (3.4)	Lorsatan	2 (12.5)
Diazepam	14 (0.8)	Enalapril	1 (6.25)
Donepezil	12 (2.4)	Nifedipine	3(18.75)
Duloxetine	1(0.2)	**Total prescriptions**	**16**
Flupentixol	8 (1.6)	**Anti Tuberculosis**	
Fluoxetine	11 (2.2)	Ethambutol	1 (25.0)
Fluphenazine	48 (9.5)	Rifampicin	1 (25.0)
Haloperidol	69 (13.7)	Pyrazinamide	1 (25.0)
Olanzapine	32 (6.3)	Isoniazid	1 (25.0)
Phenobarbitone	8 (1.6)	**Total prescriptions**	**4**
Phenytoin	3 (0.6)	**Analgesics**	
Quetiapine	3 (0.6)	Diclofenac	1 (10.0)
Risperidone	16 (3.2)	Meloxicam	2 (20.0)
Valproic acid	2 (0.4)	Paracetamol	2 (20.0)
Total prescriptions	**505**	Tramadol	1 (10.0)
Antiretrovirals		Aspirin	1 (10.0)
Abacavir	1(11.1)	Ibuprofen	3 (30.0)
Lamivudine	1(11.1)	**Total prescriptions**	**10**
Nevirapine	1(11.1)	**Other drugs, 6**	**(n=24)**
Acyclovir	6(66.7)	Salbutamol	1 (4.2)
Total prescriptions	**9**	Chlorpheniramine	1 (4.2)
Antibiotics		Vincamine	1 (4.2)
Amoxicillin & Clavulanic acid	3 (100)	Omeprazole	1 (4.2)
Total prescriptions	**3**	Pabrinex®	3 (12.5)
		Multvitamins®	17(70.8)
		Total prescriptions	**24**
		TOTAL 46 DRUGS	

4.4 Severity of potential drug-drug interactions

There were 151 (30 %) incidents in which psychotropic drugs were involved in potentially serious drug-drug interactions, potentially significant drug-drug interactions accounted for most of the interactions at 262 (52 %) while minor drug-drug interactions were at 72 (14 %) and 21 (4 %) had no drug-drug interactions as outlined in Figure 4.4.

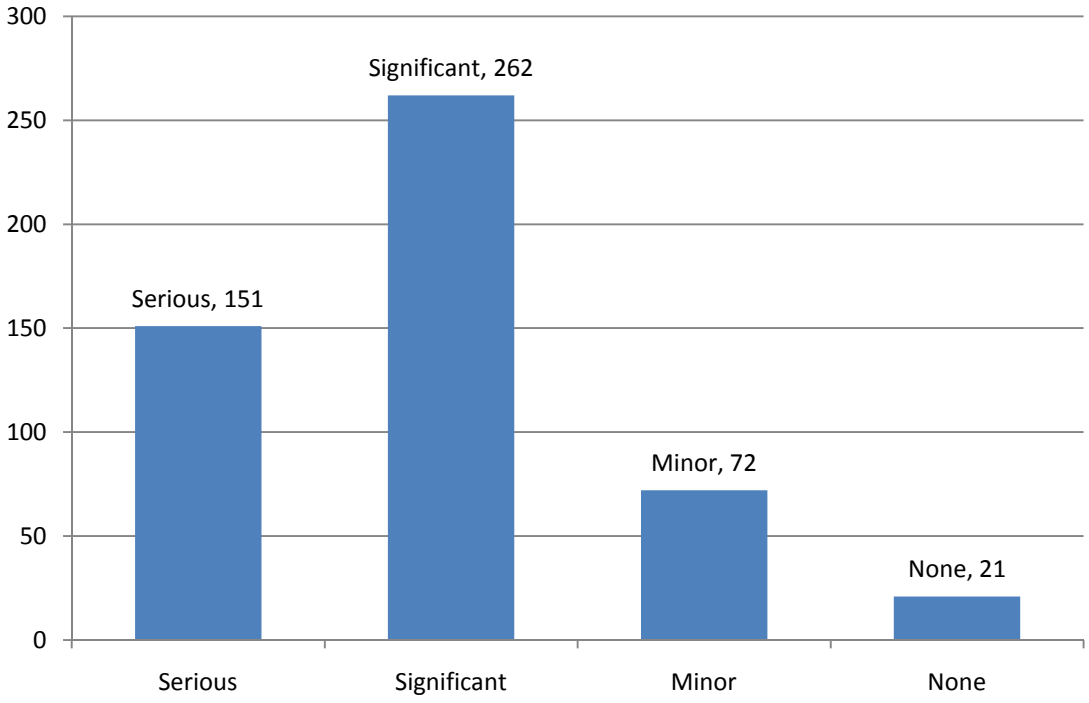


Figure 4.4: Severity of potential drug-drug interactions

Among the psychotropic drugs most potentially serious drug-drug interactions were attributed to haloperidol (28.5 %) and fluphenazine (25.2 %) use. Potentially significant drug interactions were attributed to carbamazepine (25.6 %) and benzhexol (27.5 %) use while most minor drug interactions were due to carbamazepine related drug interactions at (28.6 %) as shown in Table 4.4.

Table 4.4: Psychotropic drugs and severity of potential drug interactions

Drug	Serious (n=151) (%)	Significant (n=262) (%)	Minor (n=72) (%)	None (n=21)(%)
Haloperidol	43 (28.5)	21 (8.0)	4 (5.6)	1 (4.8)
fluphenazine	38 (25.2)	7 (2.6)	3 (4.2)	0 (0.0)
Chlorpromazine	21 (13.9)	19 (7.3)	1 (1.4)	0 (0.0)
Amitriptyline	16 (10.6)	6 (2.3)	1 (1.4)	1 (4.8)
Carbamazepine	13 (8.6)	67 (25.6)	28 (38.9)	6 (28.6)
Diazepam	8 (5.3)	6 (2.3)	0 (0.0)	0 (0.0)
Fluoxetine	5 (3.3)	3 (1.1)	5 (6.9)	1 (4.8)
Risperidone	3 (2.0)	8 (3.1)	4 (5.6)	1 (4.8)
Benzhexol	2 (1.3)	72 (27.5)	7 (9.7)	1 (4.8)
Quetiapine	2 (1.3)	2 (0.8)	0 (0.0)	1 (4.8)
Olanzapine	0 (0.0)	24 (9.2)	3 (4.2)	5 (23.8)
Zuclopenthixol	0 (0.0)	8 (3.1)	8 (11.1)	1 (4.8)
Donepezil	0 (0.0)	7 (2.6)	4 (5.6)	1 (4.8)
Flupentixol	0 (0.0)	5 (1.9)	1 (1.4)	2 (9.5)
Phenobarbital	0 (0.0)	2 (0.8)	2 (2.8)	0 (0.0)
Phenytoin	0 (0.0)	2 (0.8)	1 (1.4)	0 (0.0)
Valproic acid	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Duloxetine	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

4.5 Pharmacodynamic and pharmacokinetic potential drug-drug interactions

Pharmacodynamic interactions accounted for most potential drug-drug interaction mechanism whereby carbamazepine benzhexol, haloperidol and fluphenazine attributing to over 10 % of synergistic, additive and antagonistic drug interactions. In pharmacokinetic interactions slightly over 25 % of metabolic interactions were attributed to carbamazepine as shown in Table 4.5.

Table 4.5: Psychotropic drugs and mechanism of interaction

	Pharmacodynamic			Pharmacokinetic
Drugs	**Synergism (n=335) (%)**	**Additive (n=278) (%)**	**Antagonism (n=197) (%)**	**Metabolism (n=351) (%)**
Carbamazepine	72 (21.5)	53 (19.1)	39 (19.8)	90 (25.6)
Benzhexol	79 (23.6)	44 (15.8)	49 (24.9)	53 (15.1)
Haloperidol	44 (13.1)	46 (16.5)	22 (11.2)	62 (17.7)
Fluphenazine	36 (10.7)	43 (15.5)	29 (14.7)	37 (10.5)
Chlorpromazine	32 (9.6)	22 (7.9)	29 (14.7)	15 (4.3)
Olanzapine	17 (5.1)	14 (5.0)	6 (3.0)	23 (6.6)
Amitriptyline	15 (4.5)	20 (7.2)	5 (2.5)	16 (4.6)
Zuclopenthixol	12 (3.6)	5 (1.8)	5 (2.5)	10 (2.8)
Risperidone	9 (2.7)	6 (2.2)	4 (2.0)	9 (2.6)
Diazepam	4 (1.2)	9 (3.2)	2 (1.0)	8 (2.3)
Donepezil	2 (0.6)	3 (1.1)	2 (1.0)	8 (2.3)
Phenobarbital	3 (0.9)	3 (1.1)	0 (0.0)	7 (2.0)
Flupentixol	4 (1.2)	3 (1.1)	3 (1.5)	3 (0.9)
Fluoxetine	2 (0.6)	3 (1.1)	0 (0.0)	4 (1.1)
Quetiapine	1 (0.3)	2 (0.7)	2 (1.0)	2 (0.6)
Phenytoin	1 (0.3)	2 (0.7)	0 (0.0)	3 (0.90
Duloxetine	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Valproic acid	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

4.6 Description of potentially serious drug-drug interactions

Drug interaction between fluphenazine and haloperidol attributed to 32.5 % of potentially serious drug-drug interactions while a combination of fluphenazine and chlorpromazine accounted for 14.3 % of potentially serious drug-drug interactions which leads to an increase in QTC interval as shown in Table 4.6.

Table 4.6: Serious drug-drug interactions

Serious Drug Interactions	Prescriptions with interactions (n=77)	Effect of drug-drug interactions
Fluphenazine + Haloperidol	25(32.5)	Both drugs increase QTC interval
Chlorpromazine + Fluphenazine	11(14.3)	Both drugs increase QTC interval
Carbamazepine + Diazepam	8(10.4)	Carbamazepine decrease the effect of diazepam by affecting hepatic enzyme CYP3A4
Amitriptyline + Haloperdol	8(10.4)	Both drugs increase QTC interval
Chlorpromazine + Haloperidol	7(9.1)	Both drugs increase QTC interval
Chlorpromazine + Amitriptyline	3(3.9)	Both drugs increase QTC interval
Amitriptyline + Fluoxetine	3(3.9)	Both increase serotonin levels and fluoxetine increase the effect of amitriptyline by affecting hepatic enzyme CYP2C19
Carbamazepine + Quetiapine	2(2.6)	Carbamazepine decrease the effect of quetiapine by affecting hepatic enzyme CYP3A4
Haloperidol + Benzhexol	2(2.6)	Haloperidol increases the effects of benzhexol by Pharmacodynamic synergism
Fluphenazine + Amitriptyline	2(2.6)	Both drugs increase QTC interval
Fluoxetine+ Risperidone	2(2.6)	Fluoxetine increases the effect of risperidone by affecting hepatic enzyme CYP2D6
Carbamazepine + Hydrochlorthiazide	2 (2.6)	Carbamazepine, Hydrochlorothiazide either increases the effect of the other by pharmacodynamic synergism Increases the risk of hyponatremia
Risperidone + Methyldopa	1(1.3)	Risperidone decreases effect of methyldopa by pharmacodynamic antagonism
Carbamazepine + Haloperidol	1(1.3)	Carbamazepine decreases the level of haloperidol by increasing metabolism

4.7 Association between social demographic factors with serious drug interactions

Participants who were married had a statistically significant association with serious drug interaction [OR 2.25(1.13,4.48) p=0.02] while unemployed participants had [OR 0.31(0.14,0.39) p<0.01]. Most of the p-values indicated that social demographic factors have no statistical significant association with potentially serious drug interactions as shown in Table 4.7.

Table 4.7: Association between social demographic factors with serious drug interactions (n=175)

Parameter	Serious (%)	Not-Serious (%)	OR (95% CI)	P-Value*
Overall	72 (41.1)	103 (58.9)	_	_
Sex				
Male	39 (22.3)	62 (35.4)		
Female	33 (18.9)	41 (23.4)	1.28(0.70,2.36)	0.43
Residence				
Urban	17 (9.7)	26 (14.9)	1.09(0.54,2.20)	0.81
Rural	55 (31.4)	77 (44)		
Education				
None	1 (0.6)	1 (0.6)		_
Primary	7 (4)	21 (12)	0.33(0.02,6.55)	0.46
Secondary	43 (24.6)	51 (29.1)	0.84(0.05,13.87)	0.91
Tertiary	17 (9.7)	19 (10.9)	0.90(0.05,11.82)	0.94
University	1 (0.6)	5 (2.8)	0.20(0.01,6.69)	0.37
Unknown	3 (1.7)	6 (3.4)	0.50(0.02,11.13)	0.66
Marital Status				
Single	24 (13.7)	54 (30.9)		_
Married	32 (18.3)	32 (18.3)	2.25(1.13,4.48)	**0.02**
Separate	11 (6.3)	14 (8)	1.77(0.70,4.44)	0.23
Divorce	3 (1.7)	3 (1.7)	2.25(0.42,11.94)	0.34
Widowed	2 (1.1)	0 (0.0)		_
Occupation				
Farmer	22 (12.6)	18 (10.3)		_
Self employed	26 (14.9)	28 (16)	0.77(0.34,1.73)	0.52
Formal employment	6 (3.4)	10 (5.7)	0.49(0.15,1.62)	0.24
Unemployed	18 (10.3)	47 (26.8)	0.31(0.14,1.39	**<0.01**

* Significant p values are in **bold**.

4.8 Mental diseases associated with serious drug interactions

Most of the patients with serious drug interactions were diagnosed with bipolar mood disorder 33 (18 %), and had a statistically significant association [OR 4.39(1.09,19.64) p=0.04] with potentially serious drug-drug interactions as shown in Table 4.8.

Table 4.8: Association between mental disease with serious drug interactions

Mental diagnosis	(n=175) Patients	Serious (n=72) (%)	Not-Serious (n=103) (%)	OR (95% CI)	p-value*
Bipolar mood disorder	58	33 (45.8)	25 (24.3)	4.39(1.09,17.64)	**0.04**
Schizophrenia	48	26 (36.1)	22 (21.3)	3.94(0.96,16.12)	0.06
Substance abuse disorder	10	5 (6.9)	5 (4.9)	3.32(0.55,19.89)	0.19
Unipolar disorder	13	3 (4.2)	10 (9.7)	_	_
Alcohol use disorder	15	3 (4.2)	12 (11.7)	0.84(0.14,5.05)	0.84
Epilepsy	20	1 (1.4)	19 (18.4)	0.18(0.02,1.92)	1.15
Alzheimer and dementia	11	1 (1.4)	10 (9.7)	0.33(0.03,3.78)	0.38

*Significant p values are in **bold**

4.9 Psychotropic drugs associated with synergistic drug interactions

Potential synergistic interactions were more common and statistically significant among patients who were on benzhexol [OR 90.02(25.79, 314.19) p<0.01] and carbarmazepine [OR 2.01(1.07, 3.70) p=0.03], chlorpromazine, diazepam, donepezil, fluphenazine and fluoxetine were statistically significant (p<0.05) with synergistic potential drug-drug interactions as shown in table 4.9.

Table 4.9: Association between psychotropic drugs with synergistic drug interactions

Drug	Synergism (n=335) (%)	No-Synergism (n=170) (%)	OR (95% CI)	p-value*
Benzhexol	79 (23.6)	3 (1.8)	90.02(25.79,314.19)	< **0.01**
Carbamazepine	72 (21.5)	42 (24.7)	2.01(1.07,3.70)	**0.03**
Haloperidol	44 (13.1)	25(14.7)	1.57(0.84,2.92)	0.15
Fluphenazine	36 (10.7)	12 (7.1)	2.94(1.40,6.17)	< **0.01**
Chlorpromazine	32 (9.6)	9 (5.3)	3.46(1.54,10.49)	< **0.01**
Olanzapine	17 (5.1)	15 (8.8)	0.82(0.38,1.77)	0.06
Amitriptyline	15 (4.5)	9 (5.3)	1.30(0.53,3.13)	0.57
Zuclopenthixol	12 (3.6)	5 (2.9)	1.92(0.64,2.10)	0.25
Risperidone	9 (2.7)	7 (4.1)	0.96(0.34,2.69)	0.94
Diazepam	4 (1.2)	10 (5.9)	0.27(0.08,0.90)	**0.03**
Flupentixol	4 (1.2)	4 (2.4)	0.740(0.18,3.06)	0.68
Phenobarbital	3 (0.9)	5 (2.9)	0.43(0.10,1.88)	0.26
Donepezil	2 (0.6)	10 (5.9)	0.13(0.03,0.63)	**0.01**
Fluoxetine	2 (0.6)	9 (5.3)	0.15(0.03,0.71)	**0.02**
Phenytoin	1 (0.3)	2 (1.2)	0.37(0.03,4.14)	0.42
Duloxetine	1 (0.3)	0(0.0)	_	_
Quetiapine	1 (0.3)	2 (1.2)	1.51(0.13,16.95)	0.74
Valproic acid	1 (0.3)	1 (0.6)	0.75(0.05,12.18)	0.84

* Significant p values are in **bold**.

4.10 Psychotropic drugs associated additive drug interactions

Table 4.10 below outlines potential additive interactions, which were common among patients on carbamazepine (10.5 %) and haloperidol (9.1 %). These interactions were statistically significant with haloperidol [OR 3.42(1.80,6.49)p<0.01], fluphenazine [OR 17.46(6.42,46.99)p<0.01], and amitriptyline [OR 6.62(2.16,20.29) p<0.01] and zuclopenthixol [OR 0.29(0.09,1.07) p=0.04].

Table 4.10: Association between psychotropic drugs with additive drug interactions

Drug	Additive (n=278) (%)	No-Additive (n=227) (%)	OR (95% CI)	p-value*
Carbamazepine	53 (10.5)	61 (12.1)	0.79(0.42,1.46)	0.45
Haloperidol	46 (9.1)	23 (4.6)	3.42(1.80,6.49)	**< 0.01**
Benzhexol	44 (8.7)	38 (7.5)	1.46(1.23,2.66)	0.20
Fluphenazine	43 (8.5)	5 (1.0)	17.46(6.42,46.99)	**< 0.01**
Chlorpromazine	22 (4.4)	19 (3.8)	1.31(0.09,2.64)	0.46
Amitriptyline	20 (4.0)	4 (0.8)	6.62(2.16,20.29)	**< 0.01**
Olanzapine	14 (2.8)	18 (3.6)	0.79(0.36,1.70)	0.55
Diazepam	9 (1.8)	5 (1.0)	2.01(0.64,6.30)	0.23
Risperidone	6 (1.2)	10 (2.0)	0.61(0.21,1.75)	0.36
Zuclopenthixol	5 (1.0)	12 (2.4)	0.29(0.09,1.07)	**0.04**
Donepezil	3 (0.6)	9 (1.8)	0.33(0.09,1.26)	0.11
Flupentixol	3 (0.6)	5 (1.0)	0.63(0.14,2.69)	0.53
Fluoxetine	3 (0.6)	8 (1.6)	0.38(0.11,1.46)	0.16
Phenobarbital	3 (0.6)	5 (1.0)	0.63(0.14,2.69)	0.53
Phenytoin	2 (0.4)	1 (0.2)	2.14(0.19,24.05)	0.54
Quetiapine	2 (0.4)	1 (0.2)	2.14(0.19,24.05)	0.54
Duloxetine	0(0.0)	1 (0.2)	_	_
Valproic acid	0(0.0)	2 (0.4)	_	_

*Significant p values are in **bold**

4.11 Psychotropic drugs associated with antagonistic drug interactions

Potential antagonistic drug interactions were common among patients on benzhexol (24.8 %) with a statistically significant association [OR 18.17(7.54,44.26) p<0.01]. Other drugs with significant association with antagonistic drug interactions were chloropromazine [OR 9.58(4.35,21.12) p<0.01], fluphenazine [OR 5.64(3.00,11.52) p<0.01] as shown in Table 4.11.

Table 4.11: Association between psychotropic drugs with antagonistic interactions

Drug	Antagonism (n=197) (%)	No-Antagonism (n=308) (%)	OR (95% CI)	p-value*
Benzhexol	49 (24.8)	33 (10.7)	18.17(7.54,44.26)	**< 0.01**
Carbamazepine	39 (19.8)	75 (24.4)	1.34(0.68,2.66)	0.39
Chlorpromazine	29 (14.7)	12 (3.9)	9.58(4.35,21.12)	**< 0.01**
Fluphenazine	29 (17.7)	19 (6.2)	5.64(3.00,11.52)	**< 0.01**
Haloperidol	22 (11.2)	47 (15.3)	1.99(1.93,2.90)	0.98
Olanzapine	6 (3.0)	26 (8.4)	0.43(0.17,1.12)	0.08
Amitriptyline	5 (2.5)	19 (6.2)	0.52(0.18,1.46)	0.21
Zuclopenthixol	5 (2.5)	12 (3.9)	0.88(0.29,2.61)	0.81
Risperidone	4 (2.0)	12 (3.9)	0.68(0.21,2.23)	0.53
Flupetixol	3 (1.5)	5 (1.6)	1.30(0.30,5.53)	0.73
Diazepam	2 (1.0)	12 (3.9)	0.33(0.07,1.52)	0.16
Donepezil	2 (1.0)	10 (3.2)	2.48(0.09,1.92)	0.25
Quetiapine	2 (1.0)	1 (0.3)	4.35(0.39,48.91)	0.23
Phenytoin	0(0.0)	3 (1.0)	_	_
Duloxetine	0 (0.0)	1 (0.3)	_	_
Fluoxetine	0 (0.0)	11 (3.6)	_	_
Phenobarbital	0 (0.0)	8 (2.6)	_	_
Valproic acid	0 (0.0)	2 (0.6)	_	_

*Significant p values are in **bold**

4.12 Psychotropic drugs associated with metabolic interactions

Table 4.21 outline potential metabolic interactions which were common among patients on carbamazepine (15.4 %) and with statistically significant association of [OR 5.75(2.92,11.47) p<0.01], haloperidol (35.2 %), [OR 9.30(3.86,21.98) p<0.01] and chlorpromazine [OR 0.88(0.28,1.43) p<0.01].

Table 4.12: Association Psychotropic drugs with metabolic interactions

Drug	Metabolism (n=351) (%)	No-Metabolism (n=154) (%)	OR (95% CI)	p-value*
Carbamazepine	90 (25.6)	24 (15.6)	5.75(2.92,11.47)	**< 0.01**
Haloperidol	62 (17.6)	7 (4.5)	9.30(3.86,21.98)	**< 0.01**
Benzhexol	53 (15.1)	29 (18.8)	1.04(0.51,11.47)	0.90
fluphenazine	37 (10.5)	11 (7.1)	2.18(1.02,4.66)	**0.04**
Olanzapine	23 (6.6)	9 (5.8)	1.48(0.67,3.39)	0.39
Amitriptyline	16 (4.6)	8 (5.2)	1.08(0.44,2.69)	0.87
Chlorpromazine	15 (4.3)	26 (16.9)	0.88(0.28,1.43)	**< 0.01**
Zuclopenthixol	10 (2.8)	7 (4.5)	0.74(0.27,2.05)	0.57
Risperidone	9 (2.6)	7 (4.5)	0.24(0.23,1.88)	0.44
Diazepam	8 (2.3)	6 (3.9)	0.69(4.39,2.10)	0.51
Donepezil	8 (2.4)	4 (2.6)	1.07(0.31,3.71)	0.91
Phenobarbital	7 (2.0)	1 (0.6)	3.94(0.47,32.79)	0.21
Fluoxetine	4 (1.1)	7 (4.5)	0.28(0.08,1.00)	**0.05**
Phenytoin	3 (0.9)	0 (0.0)	_	_
Flupentixol	3 (0.9)	5 (3.2)	0.30(0.07,1.31)	0.11
Quetiapine	2 (0.6)	1 (0.6)	1.07(0.10,12.06)	0.96
Duloxetine	1 (0.3)	0 (0.0)	_	_
Valproate	0 (0.0)	2 (1.2)	_	_

*Significant p values are in **bold**

4.13 Psychotropic drugs associated with potentially serious drug interactions

Bivariate analysis showed that there was a statistically significant association of haloperidol [OR 4.39(2.29,8.41) p<0.01], fluphenazine [OR 10.38(4.66,23.10) p<0.01], and amitripytline [OR 3.39(1.36,8.41) p=0.01] with potential serious drug-drug interactions as outlined in Table 4.13.

Table 4.13: Association between psychotropic drugs with serious drug interactions

Drug	Serious (n=151) (%)	Not-Serious (n=354) (%)	OR (95% CI)	P-Value*	AIC
Haloperidol	43 (28.5)	26 (7.3)	4.39(2.29,8.41)	< **0.01**	219.15
fluphenazine	38 (25.2)	10 (2.8)	10.38(4.66,23.10)	< **0.01**	**200.69**
Chlorpromazine	21 (13.9)	20 (5.6)	1.72(0.84,3.46)	**0.14**	238.86
Amitriptyline	16 (10.6)	8 (2.3)	3.39(1.36,8.41)	**0.01**	233.69
Carbamazepine	13 (8.6)	101 (28.5)	1.25(0.66,2.36)	0.49	240.62
Diazepam	8 (5.3)	6 (1.7)	2.01(0.67,6.11)	0.21	239.49
Fluoxetine	5 (3.3)	6 (1.7)	0.30(0.06,1.42)	**0.13**	238.25
Risperidone	3 (2.0)	13 (3.7)	0.30(0.08,1.09)	**0.07**	237.08
Artane	2 (1.3)	80 (22.6)	1.49(0.82,2.75)	**0.19**	239.36
Quetiapine	2 (1.3)	1 (0.3)	2.92(0.26,32.79)	0.39	240.27
Phenytoin	0 (0.0)	3 (0.9)	_	_	_
Zuclopenthixol	0 (0.0)	17 (4.8)	_	_	_
Donepezil	0 (0.0)	12 (3.4)	_	_	_
Duloxetine	0 (0.0)	1 (0.3)	_	_	_
Flupentixol	0 (0.0)	8 (2.3)	_	_	_
Olanzapine	0 (0.0)	32 (9.0)	_	_	_
Phenobarbital	0 (0.0)	8 (2.3)	_	_	_
Valproic acid	0 (0.0)	2 (0.6)	_	_	_

***** P values less than 0.2 and the lowest AIC are in **bold**

4.14 Multvariate analysis

Forward stepwise model building was done to identify a set of exemplary variables that best predict the outcome through a simple regression of each predictor variable verses the outcome. Akaike information criterion (AIC) was used as a statistical tool for parsimonious statistical model evaluation since it considers multiple models before selecting the best model and can assess a complex model with multiple relationships simultaneously. A bivariate analysis of predictors with a p-value of less than 0.2, which was considered to be a more relaxed threshold was selected alongside those with the lowest Akaike information criterion (AIC) as the base for a multivariate model building. The variable that improved the model most was selected and a three variable regression carried out. The process was repeated until there was no further improvement in the model. The best predictor variables for the outcome were fluphenazine, haloperidol, amitriptyline and chlorpromazine. As outline in Appendix five.

CHAPTER FIVE

Discussion, Conclusion and Recommendations

5.1 Discussion

This retrospective study analyzed potential drug-drug interactions in a population of hospitalized mentally ill patients at Mathari Mental Hospital between July and December 2013. The participants in study were nearly evenly distributed gender wise with a male preponderance and a mean age of 34.2 years. The average number of prescribed drug per patient was 6.5 this shows that poly pharmacy was high. The prevalence of potential serious drug-drug interaction at 30% was considered to be high, this was observed mostly in participant with secondary level of education and married participants. Married participants had a statistically significant association with potentially serious drug-drug interaction ($p=0.02$) and unemployed participants having a statically significance of ($p<0.01$).

There is no scientific evidence to explanation this association of married and unemployed with potential serious drug-drug interactions. However married and unemployed people may have stress due to the burdens associated with their social life. This explains the high number of these patients with mental illness captured in the study and significant association with potential drug interactions. However most social demographic characteristics in this study were not statistically associated with potentially serious drug-drug interactions. This findings concurs with a previous study where no associations were noted between demographic parameters including age, gender, marital or educational status and psychotropic drugs [34]. In this study demography appears to have a minimum impact on cross-sectional prescribing patterns in psychiatry patients so effort should be geared towards achieving rational, yet pragmatic treatment guidelines and logarithms to minimize risks while maximizing the benefits to these patients.

Ninety two percent of the participants did not have co-morbidities other than the diagnosed mental illness, hypertension accounted for 8% of the total patients. This seems not to concur with a similar study where the findings indicate that people with severe mental illnesses, such as depression or bipolar disorder have a higher cardiovascular mortality attributed to an increased risk of the modifiable coronary heart disease risk factors such as diabetes and hypertension [35]. In this study the low numbers of participants with diabetes and hypertension could be attributed to the fact that most of the sampled patients had a mean age of 34.2 years hence less prone to diabetes and hypertension conditions which are known to be prevalent in old age.

Most of the participants with potentially serious drug-drug interactions were diagnosed with bipolar mood disorder and schizophrenia. This explains the high use of haloperidol and fluphenazine, which had a statistically significant association with potentially serious drug-drug interactions. The use of fluphenazine as a monthly injection and haloperidol or chlorpromazine oral medication was common in this study. These drugs are known to prolong QTC interval of the heart which may lead to dizziness, syncope or cardiac arrest. The findings implies that patients on these drugs need close monitoring and periodic electro cardiogram (ECG) checkups [36,37] which were a compulsory requirement among mentally ill patients who were on haloperidol and fluphenazine at Mathari Mental Hospital. There was no statistically significant association of potentially serious drug-drug interactions associated with the use of quetiapine or risperidone. This concurs with findings where the two drugs were found to have no association with prolongation of QTC interval [38]. To date, all antipsychotic drugs have the potential for serious adverse events. Balancing these risks with the positive effects of treatment poses a challenge for psychotherapy.

In this study, potentially serious pharmacokinetic drug interactions in patients on a combination of carbamazepine and diazepam were observed. Carbamazepine decreases the effect of diazepam by affecting CYP 3A4 metabolism. Significant pharmacokinetic metabolic interactions were observed in patients on carbamazepine and haloperidol. This could be attributed to the fact that these drugs are affected by cytochrome P450 (CYP) enzyme system. This findings concurs with a study where clinically significant pharmacokinetic drug interactions with antipsychotics and antidepressant drugs. The knowledge of substrates, inhibitors inducers of CYP isoenzyme may

help clinicians to anticipate and avoid psychotherapeutic drug interactions and improve rational prescribing practices [39].

There was a significant additive pharmacodynamic drug interactions in first generation anti-depressant (amitriptyline) compared to second generation anti-depressant fluoxetine. This explains the results in a similar study where the potentially harmful pharmacodynamic drug interactions with first-generation anti-depressants had contributed to a gradual decline of their use in clinical practice. And second generation antidepressants have gradually replaced tricyclic antidepressants (TCAs) mainly because of their improved tolerability and safety profile [40].

A bivariate data analysis of drugs with serious drug interactions indicated that most of the drugs with a statistically significant association with the outcome were substrates, inhibitors and inducers of cytochrome P450 isoenzyme with higher odds of developing a serious drug interaction in patients on fluphenazine. Forward step wise model building analysis indicated that the best predictor variables for serious drug interactions were fluphenazine, haloperidol, amitriptyline and chlorpromazine. According to WHO guidelines on pharmacological treatment of mental disorders in primary healthcare, the findings obtained in this study suggest necessity for continuous electrocardiogram monitoring which is mandatory in some countries for specific antipsychotics for example haloperidol. Further monitoring of full blood count, urea and electrolytes and liver function tests, blood glucose levels is crucial in an effort to balance the risks and benefits of the drugs before using them [41].

5.2 Implications for public health/ treatment guidelines

This study has demonstrated that potentially serious drug interactions are common with drugs used in mental illness. This was observed mostly in the use of first generation antidepressants. The results confirm that second generation antidepressants have less potentially serious drug interactions. This implies that treatment guidelines in Kenya should shift towards the use of second generation antidepressants as first line therapy for mentally ill patients.

5.3 Study limitations

The study achieved its main objective to evaluate potential drug-drug interactions among hospitalized mentally ill patients, however there were several limitations encountered within this study. There were no documented previous studies done on the same subject in Kenya for comparison. This being a retrospective study it was limited to obtaining first hand information that may have contributed to the observed differences such as genetic polymorphism.

5.4 Conclusion

The obtained results shows that the prevalence of potentially serious drug interactions was high among admitted patients at Mathari Mental Hospital. Married and unemployed patients were more likely to have potentially serious drug interactions. Patients on fluphenazine, haloperidol, amitriptyline and chlorpromazine are at a higher risk of having potential serious drug-drug interactions. This drugs exhibited both pharmacodynamic and pharmacokinetic interaction mechanisms.

5.5 Recommendation

Based on this study's findings, it is recommended that second generation antidepressants be used due to their beneficial effects and reduced drug interactions. There is need to have continuous monitoring of patients parameters such as: electrocardiogram, full blood count, liver function tests and blood glucose levels to balance the risks and benefits before using antipsychotropic drugs. Future prospective cohort studies or randomized controlled trials with large sample size may be necessary in order to provide more evidence.

REFERENCES

1. World Health Organization, Mental health: A state of well being, 2012. http://www.who.int/topics/mental_disorders/en/

2. Faragon J, Psychiatric Medications and HIV Antiretroviral; A drug interactions guide for clinicians, Adult management 2013 page 3-22.

3. Ramin M, Mark O. National Trends in Psychotropic medication, polypharmacy in office based psychiatry; Arch Gen Psychiatry. 2010; 67(1) 26-36.

4. European Medicines Agency (EMA) Guidelines on the investigation of Drug interactions (EMA/CHMP/EWP/125211/2010) Page 4.

5. Jankel C, Fitterman L. Epidemiology of drug-drug interactions as a cause of hospital admissions. Drug Saf 1993; 9: 51–9.

6. Pirmohamed M, James S, Meakin S, Green C, Scott A, Walley T, Farrar K, Park B, Breckenridge A. Adverse drug reactions as a cause of admission to hospital: prospective analysis of 18 820 patients. Br Med J 2004; 329: 15–9.

7. World Health Report, 2001 Mental Health; New understanding, New Hope. World Health Organization 2001 page 19.

8. Preskon S.H, Flockhart D. 2011 Guide to Pyschiatri drug interactions, Primary Psychiatry 2009; 16 (12); 45-74.

9. Tatro DS (Ed.) Drug Interaction Facts. J.B. Lippincott Co. St. Louis 1992. Page 12.

10. Penzak R. S, Drug Interactions, National Institute of Health, Dec 2010 page 4.

11. North Metropolitant Area Mental Health Service, Psychotropic Drug Interactions, Graylands Hospital Drug Bulletin July 2006 Vol. 14 (2), ISSN 1323-1251.

12. Casrberg I. Quetiapine and drug interactions: evidence for a routine therapy drug monitoring service. J Clin Psychiatry 2007 Oct; 68(10) 1540-5.

13. Mesdjian E. Metabolism of carbamazepine by CYP3A6: a model for *in vitro* drug interactions studies. Life Sci. 1999; 64(10): 827-35.

14. Karina K, Uldall. HIV and Psychiatric medication Interactions, HIV/AIDS Research programme, University of Washington, April 2003 Page 8-9.

15. Michael L, Jolene R and Marie A. How to Prevent Adverse Drug Events, Current Psychiatry July 2011 Vol. 10 (7).

16. Tetsuya S, Yoshiro O, Fumikiko Y. Decreased Dopamine D_2 Receptor binding in the anterior cingulated cortex in Schizophrenia. Arch. Gen. Psychiatry 2002; 59: 25-30.

17. Nordberg A, Suensson A, Cholinesterase inhibitors in the treatment of Alzheimer's Disease, a comparison of tolerability and pharmacology, Drug Safety 1998 Dec; 9(6): 465-480.

18. Michalets E, Clinically significant cytochrome P-450 Drug interactions, Pharmacotherapy Volume 18, Number1, 1998 page 91-95.

19. Boeker H, Seldl A, Schopper C. Neurotoxicity related to combined treatment with Lithium Antidepressants and atypical antipsychotics, A series of cases (case report) page 19.

20. David W, Kimford J. Cognitive and Behavioral Effects of Epilepsy Treatment, Dept of Neurology, medical college of Georgia, USA. Epilepsia, 42 (suppl.8): 24-32, 2004.

21. Dvir Y, Smallwood P. Serotonin Syndrome: A complex but easily avoidable condition. Gen Hospital Psychiatry. 2008 May-June; 30(3) 284-287.

22. Schmitz N, Kruse J. Mental Disorders and Hypertension: Factors associated with awareness and treatment of hypertension in General population of Germany; Psychosocial medicine 68: 246-252.

23. Larry E. Anticholinergic Effects of Medication in Elderly Patients, J. Clinical Psychiatry 2001; 62 (suppl 21): 11-14.

24. Gugger J, Antipsychotic Pharmacotherapy and Orthostatic Hypotebsion; Identification and Management, CNS drugs 2011 Aug; 25(8): 659-671. www.ncbi.nlm.nil.gov/pubmed/20790209

25. Jeff C. Huffman, Theodoro A, QTC Prolongation and the use of Antipsychotics: A case Discussion. Primary care companion J. Clinical Psychiatry 2003; 5(6).

26. Badshah A, Mirza B, Janjua M, Nair R, Steinman R. T. Amiodarone induced Torsande de Pointes in a Patient with Wolff-Parkinson-White Syndrome; Hellenic. J. Cardiol; 2009 May-June; 50(3): 224-226. www.ncbi.nim.nih.gov/pubmed/19465366

27. Acharya S, Bussel J. Heamatological toxicity of sodium valproate. J. Pediatric Heamatology Oncology; 2000 Jan-Feb; 22(1): 62-65. www.ncbi.nlm.gov/pubmed/10695824

28. Oyesanmi O, Elisabeth J. Hematologic side effects of Psychotropics. Psychosomatics Volume 40, issue 5, Sept-Oct 1999 page 414-421.

29. Republic of Kenya, Ministry of medical services, Republic of Kenya. The Mental Health Policy, October 2012, Page 14-15.

30. Browner S. Warren, Newman B. Thomas, Hulley B. Stephen, Estimating Sample Size and Power; Applications and Examples Page 91.

31. Drug Interactions Checker - For Drugs, Food & Alcohol [Internet]. [cited 2014 Oct 6]. Available from: http://www.drugs.com/drug_interactions.html.

32. Satoskar R, Bhandarkar S. Ainapure S. Pharmacology and Pharmacotherapeutics, Revised 17th edition, June 2002 page 49-50.

33. World Medical Association declaration of Helsinki adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964.

34. Joseph L, Roy K, Brar J. Psychotropic drug prescription patterns among patients with bipolar disorder. I.J of psychiatry and neurosciences; Vol 2 June 2000 page 120-130

35. Hert M, Dekker J, wood D, Kahl K. Cardiovascular disease and diabetes in people with severe mental illness, position statement from European Psychiatric Association. European Psychiatry 24 (2009) 412-424.

36. Wayne A. Sarah M, Purushattam B, Keith G. Antipsychotic and Risk of Sudden Cardiac Death. Arch Gen Psychiatry, 2001; 58(12) 1161-1167.

37. Alexander H. Antipsychotic drugs: prolonged QTC interval, Torsande de pointes and sudden death, AMJ psychiatry 2001; 158: 1774-82

38. Jakub Z. tolerability profiles of atypical antipsychotics in treatment of bipolar disorders. J. Clin Psychiatry 2005; 66 [suppl 3]: 28-36.

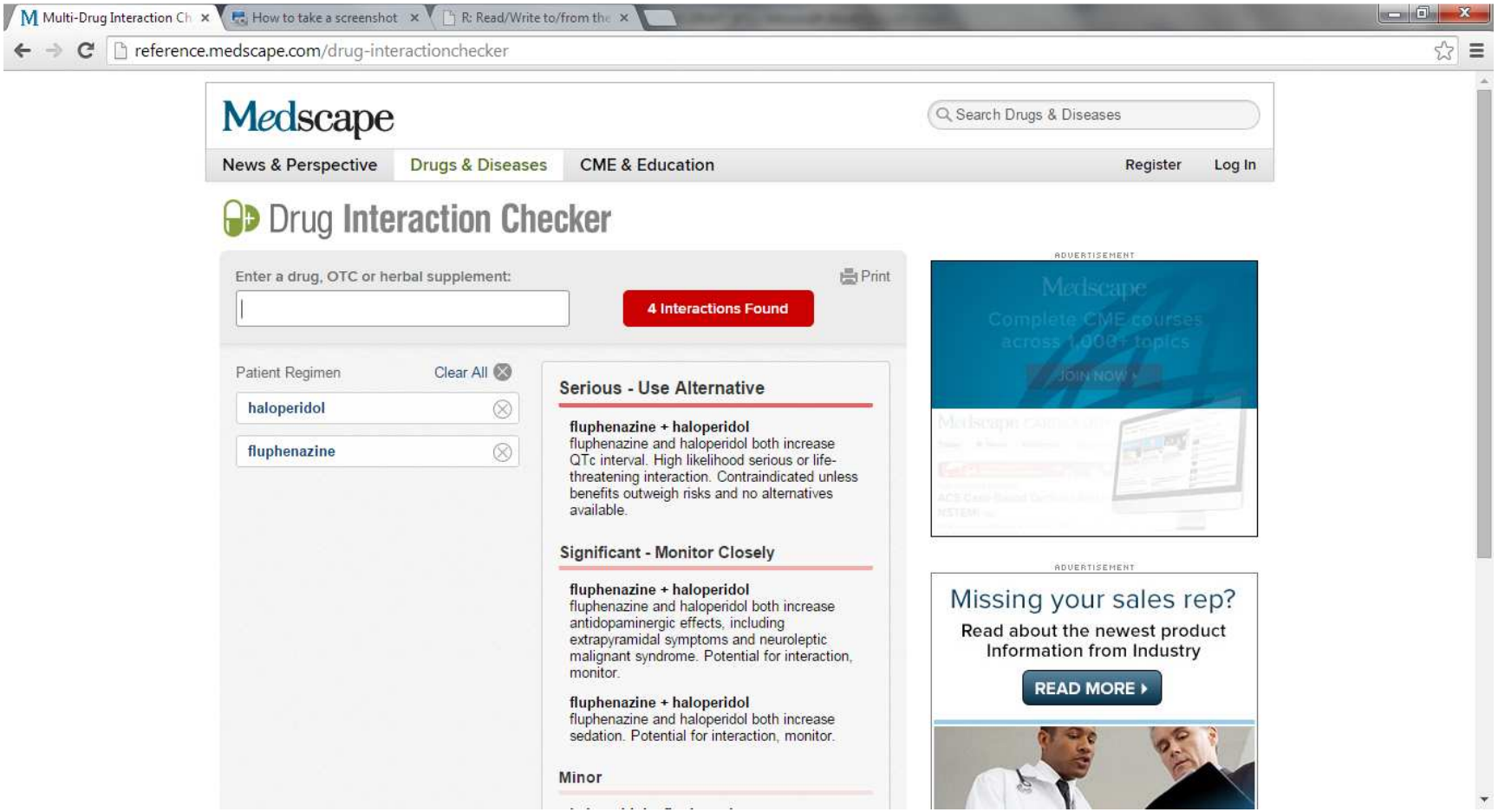
39. Tanaka E, Hisawa S. Clinically Significant Pharmacokinetic drug interactions with Psychoactive drugs: antidepressant and antipsychotic and cytochrome P 450 system. Journal of clinical pharmacy and therapeutics 2006: (24) 7-16.

40. Eckert A. Clinically relevant drug interactions with new generation antidepressants and antipsychotics. Umsch, 2009 June: 66(6); 485-92.

41. WHO, Pharmacological treatment of mental disorders in primary healthcare. 2009 pg 14.

APPENDICES

APPENDIX 1: MEDSCAPE DRUG INTERACTION CHECKER TOOL



APPENDIX 2: LETTER OF APPROVAL

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355

KNH/UON-ERC
Email: uonknh_erc@uonbi.ac.ke
Website: www.uonbi.ac.ke

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/166 **Link:www.uonbi.ac.ke/activities/KNHUoN** 29th May 2014

Dr. Jomo Seth Maganya
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
University of Nairobi

Dear Dr. Maganya

RESEARCH PROPOSAL: EVALUATION OF DRUG-DRUG INTERACTIONS AMONG MENTALLY ILL PATIENTS ADMITTED IN MATHARI MENTAL HOSPITAL (P33/01/2014)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 29th May 2014 to 28th May 2015.

This approval is subject to compliance with the following requirements:

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

For more details consult the KNH/UoN ERC website **www.uonbi.ac.ke/activities/KNHUoN.**

Protect to Discover

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chairperson, KNH/UoN-ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chairman, Dept.of Pharmacology and Pharmacognosy, UoN
Supervisors: Dr. K.A.Sinei, Dr. Margaret Oluka, Dr. Beatrice Amugune

APPENDIX 3: CONSENT EXPLANATION

My name is Dr Jomo Seth from the University of Nairobi doing a study on Evaluation of drug-drug interactions among mentally ill patients admitted in Mathari mental hospital. I intend to access patient files who were admitted in Mathari hospital during the study period (July 2013 to December 2013) and find out if they may have been prescribed with drugs likely to cause a drug-drug interaction.

At the end of the study recommendations will be made that will hopefully positively influence the prescribing patterns, policy formulations concerning mental health care in our hospitals. There are a few points i would like to highlight before you make a decision on whether or not you will allow me to access the patient files in your institution.

1) Patient files will be accessed only within the records department.
2) The patient name shall not be used anywhere in this study and all information gathered from the patient file shall be used for purposes of this study only.
3) The final research findings will be shared with the institutions in-charge.

If you agree to allow me conduct this study in your institution, I would request you to sign the statement below after reading through it.

APPENDIX 4: CONSENT FORM

I the undersigned do hereby give consent for the researcher to access patient files during this study whose nature and purpose have been fully explained to me by Dr Jomo. I understand that all the information gathered will be kept confidential and used for purposes of this study only.

Signed by facility in-charge……

Date……

APPENDIX 5: MODEL BUILDING TABLES

Table 1: Two variable model building

VARIABLE	AIC*
Fluphenazine	200.6945
fluphenazine amitriptyline	192.5149
fluphenazine Benzhexol	202.4588
fluphenazine chlorpromazine	197.0331
fluphenazine fluoxetine	202.2067
fluphenazine haloperidol	**185.8012**
fluphenazine risperidone	202.0538

*Predictor with the lowest AIC value is in **bold**

Table 2: Three variable model building

VARIABLE	AIC*
fluphenazine haloperidol	185.8012
fluphenazine haloperidol amitriptyline	**173.5819**
fluphenazine haloperidol benzhexol	187.7642
fluphenazine haloperidol chlorpromazine	176.0813
fluphenazine haloperidol risperidone	187.779

*Predictor with the lowest AIC value is in **bold**

Table 3: Four variable Model building

VARIABLE	AIC*
fluphenazine haloperidol amitriptyline	173.5819
fluphenazine haloperidol amitriptyline benzhexol	175.2613
fluphenazine haloperidol amitriptyline chlorpromazine	**160.3943**

*Predictor with the lowest AIC value is in **bold**