CHARACTERIZATION OF THE DRUG USE PATTERNS AND POTENTIAL INTERACTIONS AMONG MENTALLY ILL PATIENTS

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U56/12239/2018

A RESEARCH DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF PHARMACY IN CLINICAL PHARMACY OF THE UNIVERSITY OF NAIROBI

JUNE, 2021

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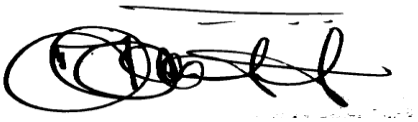
Signature:  **Date: 22/06/2021**

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DEDICATION

I dedicate this write up to my ancestors, the late James Kinyanjui and the late Keziah Njambi

ACKNOWLEDGEMENT

I sincerely appreciate the support and encouragement to pursue this wonderful degree programme from my family, especially my wife Doreen and my son Kester. I appreciate the words of encouragement and support from all my parents, brothers, and sisters.

I appreciate the dedicated efforts of my lecturers to see me through the program, to assist me in growing in knowledge, and to accomplish my academic dreams. Specifically, Dr. G. Nyamu, Dr. P. N. Karimi, Dr. B. Amugune, and Prof Okalebo. I acknowledge the Department of Pharmacy Practice and the whole fraternity of pharmacy school for facilitating the learning process.

I appreciate all my classmates who dedicated their time and resources to share knowledge and make the journey smoother. I thank the Mathari National Teaching and Referral Hospital for facilitating the data collection process.

You all represent the angels that God sent on my path to my destiny. “Behold, I am sending an angel before you to protect you along the way and to bring you to the place I have prepared.”

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AMI	Amitriptyline
AML	Amlodipine
BEN	Benzhexol (Trihexyphenidyl)
BP	Blood pressure
CVS	Cardiovascular system
CNS	Central nervous system
CPZeq	Chlorpromazine equivalents
CPZINJ	Chlorpromazine injection
CLAR	Clarithromycin
CTX	Cotrimoxazole
CPK	Creatinine phosphokinase
DALYs	Daily adjusted life years
DICLO	Diclofenac
DVP	Divalproex
DON	Donepezil
ECG	Electrocardiogram
IFAS	Elemental iron /folic acid
eGFR	Estimated glomerular filtration rate
FBS	Fasting blood sugar
FGA	First-generation antipsychotic
FLX	Fluoxetine
FXOL	Flupentixol injection depot
FLU	Fluphenazine injection depot
FBC	Full blood count
HAL	Haloperidol
INN	International non-proprietary name
INH	Isoniazid
KNH	Kenyatta National Hospital
KNH/UoN ERC	Kenyatta National Hospital/University of Nairobi Ethics and Research Committee
LFTs	Liver function tests
LMIC	Low-and-middle income countries

MNTRH	Mathari National Teaching and Referral Hospital
NICE	National Institute for Health and Care Excellence
NIF	Nifedipine
OLA	Olanzapine
PO	Per oral (orally)
QUE	Quetiapine
RIS	Risperidone
ROA	Route of administration
SGA	Second-generation antipsychotic
SUDs	Substance use disorders
TDF/3TC/DTG	Tenofovir disoproxil/Lamivudine/Dolutegravir
TDF/3TC/EFV	Tenofovir disoproxil/Lamivudine/Efavirenz
UK	The United Kingdom
TCA	Tricyclic antidepressants
BD	Twice daily
US	United States of America
U & E	Urea and electrolyte levels in urine
WHO	World Health Organization
ZUD	Zuclopenthixol

DEFINITION OF TERMS

Adverse effects: A harmful or undesirable result caused by administration of a drug

Chlorpromazine equivalents: The dose of an antipsychotic, which is equivalent to an oral dose of chlorpromazine.

Disability-adjusted life years: A measure of the overall disease burden, expressed in terms of the years lost because of illness, disability, or early death.

Drug-drug interactions: A change in the clinical effects of one drug due to the use of a concomitant drug.

First-generation/typical/classical antipsychotics: they are high-affinity D2 receptor antagonists, which act by reducing dopamine transmission in the mesocortical, mesolimbic, tuberoinfundibular, and nigrostriatal pathways.

Monotherapy: the use of a single drug to treat a defined medical condition

Neuroleptic/Antipsychotic: A drug that can cause emotional quieting, affective indifference, and psychomotor slowing.

Pharmacodynamics: The molecular, physiologic and biochemical effects of a drug on the body. This encompasses binding to receptors, chemical interactions and the post-receptor effects of the drug.

Pharmacotherapy: The use of pharmaceutical agents (drugs) to treat a disorder or disease

Polypharmacy: The concurrent use of two or more drugs to manage one medical condition

Psychopharmacological agents: Drugs that affect the thinking, sensation, mode, and behaviour primarily used in treating mental disorders.

Psychotherapy: Also called talk or psychological therapy, is the use of varying techniques of communication with a patient to assist them to feel better, and resolve psychopathological conditions and restore cognitive function.

Second-generation antipsychotics: Also called atypical antipsychotics are drugs that bind the D2 receptors with lower affinity (rapidly dissociates from the receptor) and the 5HT2A (serotonin) receptors with a higher affinity.

Supramaximal or high dose treatment: A dose of antipsychotic administered to a patient, which exceeds a chlorpromazine equivalent of 1000mg.

Under-dose: A dose of antipsychotic administered to a patient, which is below the minimum effective dose of 200-330mg chlorpromazine equivalents.

ABSTRACT

Background: The chronic use of antipsychotics among mentally ill patients requires a careful balance between effectiveness and the consequential adverse effects or drug-drug interactions. Studies characterizing the prescribing patterns of antipsychotics and the potential drug-drug interactions in resource-constrained settings remain scarce.

Study Objectives: To characterize the drug use patterns and potential drug-drug interactions (pDDIs) among the mentally ill adult patients at Mathari National Teaching and Referral Hospital in Kenya (MNTRH).

Methodology: This was a hospital-based cross-sectional study of 167 patients at MNTRH. A pre-designed semi-structured questionnaire was used to collect the relevant socio-demographic and clinical data, which was coded and entered into Microsoft Excel 2016 for descriptive analysis and then exported to STATA 13. Fischer's exact and Pearson's Chi-square tests were used to identify the association between the predictor and outcome variables. A student t-test and one-way analysis of variance were done to compare the effect of various predictor variables on the outcome investigated. A binomial logistic analysis was done by regressing the patients' profile against the outcome variable to identify the independent predictors. The statistical tests were computed at $P \leq 0.05$ and a 95% confidence level.

Results: The majority of the participants were males (64.7%) and aged below 45 years (76.6%) with a mean age of 36.7 (SD 13.4) years. Most prescriptions contained first-generation antipsychotics (FGAs) (79.2%), and almost half (45.2%) had second-generation antipsychotics (SGAs). Approximately half of the patients (53%) and 38% were on dual and monotherapy antipsychotic, respectively. Only 35.9% of the patients used a standard dose of antipsychotics (≤1000mg of chlorpromazine equivalents), while 53.3% used supramaximal doses. The two most common pDDIs were between olanzapine/carbamazepine and haloperidol/amitriptyline. Patients using supramaximal doses were twice as likely to have pDDIs (OR = 2.23, 95% CI, P=0.023). Having a higher number of FGAs prescribed significantly increased the odds of a patient receiving a supramaximal dose by up to 18 times (P <0.001). The addition of an SGA to a regimen significantly increased the chances of a pDDI (OR=4.01, 95% CI, P<0.001)**.**

Conclusion: Psychiatric disorders were mainly managed using FGAs at a much higher frequency than in developed countries. Polypharmacy contributed to patients receiving supramaximal chlorpromazine dose equivalents and adjunct therapy with anticholinergics. Drug-drug interactions can be minimized by avoiding polypharmacy with SGAs and using lower doses of antipsychotics. Close on-treatment monitoring is essential to reduce adverse drug events.

Recommendations: Psychiatric disorders should be treated with SGAs as opposed to two or more FGA concurrently to ensure that patients benefit from lower doses of CPZeq, which are associated with a lower risk of extrapyramidal side effects. Future studies should come up with a scaled guideline that informs the clinical efficacy of various doses of CPZeq, particularly involving the FGAs to inform practice and policy.

CHAPTER ONE: INTRODUCTION

1.1 Background

Psychiatric disorders are among four of the top ten health conditions that contribute to the highest Disability Adjusted Life Years (DALYs), hence a significant public health priority (1). The treatment options for the mentally ill are still evolving as new evidence-based practices are being fronted, ranging from psychotherapy modalities to the traditionally used pharmacotherapy options. The current practice in the low-and-middle-income countries (LMIC) by clinicians is the use of pharmacotherapy as the first-line treatment. The advantages of using psychopharmacological agents evidentially override the risk of having an untreated mental illness. However, the use of these drugs comes with a potential hazard to a patient's life and an additional financial burden. In this respect, using these drugs in the usual clinical practice needs to be continuously reviewed for effectiveness and safety. Studying the prescribing patterns provides an overview of the therapeutic trends and informs better practice, making medical care rational, safe, and cost-effective, especially for chronic, devastating illnesses (1).

Studies in several developed countries have highlighted the inappropriate use of medicines, terming them wasteful, dangerous, and expensive (2). Studies in different developed countries with clear clinical guidelines, such as the United Kingdom (UK), Australia, and Canada, have revealed that there are still pronounced gaps in adopting evidence-based practices in managing mental illnesses (3,4). Similarly, studies in Asian countries have highlighted several areas that need improvement, particularly in dosing, on-treatment monitoring, adherence to clinical guidelines, and the prevalence of polypharmacy (5). These problems are shared globally, with only a few countries reporting excellent adherence rates to the recommended guidelines and appropriate management of mentally ill patients (6).

The World Bank estimates that in developing countries, 20-50% of the healthcare budget is spent on medicines (7). However, despite the large allocation, more than 50% of the drugs globally are either sold or prescribed wrongly, and 50% of the patients do not use them accurately (7). In the LMIC, inappropriate prescribing is mainly attributed to a lack of awareness of the treatment algorithms among the

prescribers and failure to observe the clinical guidelines (3). In Kenya, the management approaches of mental illnesses are briefly highlighted under the Clinical Management and Referral Guidelines Volume III, released in 2009. However, research done in public health facilities revealed that adherence to standard treatment guidelines is highly inconsistent in Kenya (8).

1.2 Problem Statement

Appropriate management of mentally ill patients could lead to significantly improved and consistent outcomes, enhanced quality of life, and financial benefits for the patients (9,10). The mainstay approach of improving the clinical outcomes of the mentally ill is getting the correct diagnosis, initiating and maintaining the patient on optimal pharmacotherapy or psychotherapy, keen follow up, and social support. Several evidence-based guidelines have been published to promote consistent practices in various geographical settings and utilize healthcare resources more effectively (11). However, poor prescribing habits that deviate from the guidelines are prevalent, which promote unsafe and ineffective treatment, worsen the illnesses, increase chances of harm and distress to patients, and result in unnecessary costs. Some of the ineffective yet prevalent practices include prolonged use of high dose treatment, polypharmacy, and non-evidential treatment options. Inappropriate use of medicine augments the adverse effects for the patients, reduce patient's adherence, increase health care costs, increase morbidity and mortality, and reduce the quality of care (12,13).

Inappropriate management of patients is prevalent but highly variable across the globe. The reported adherence rates to the recommended treatment guidelines and the prescribing patterns are generally far from the recommended standards. In the UK and Canada, where the healthcare system is well developed, polypharmacy and lack of adherence to treatment guidelines is still a present problem. In developing countries, less than 40% of patients treated in public health facilities are treated according to the recommended clinical guidelines (14). Some of the associated reasons include lack of knowledge, skills, or information, overworking of health professionals, and the unrestricted availability of medications (15).

Mental healthcare in Tanzania has similar problems to Kenya, which include insufficient drug supply, inadequate human resources, low priorities, stigma, and

inadequate training, especially in rural settings (16–18). Therefore, this underscores the need to review the current management practices at this psychiatric institution where patients from all counties in Kenya seek care. This study will ascertain whether optimal methods have been adapted and the areas that need improvement. No studies have been published in Kenya on the drug use patterns for mentally ill patients; therefore, this discloses new information in this area.

1.3 Purpose of the Study

This study aims to identify the pharmacotherapy practices among clinicians managing patients with mental illness and to identify discrepancies, if any, between the ideal and the actual prescribing patterns. The study also characterizes the potential drug-drug interactions that may occur among mentally ill patients who are likely to more than one drug concurrently.

1.4 Objectives

1.4.1 Main Objective

To characterize the drug use patterns and potential drug-drug interactions among the mentally ill adult patients at Mathari National Teaching and Referral Hospital

1.4.2 Specific Objectives

i. To characterize the prescribing pattern for patients with mental illnesses at Mathari National Teaching and Referral Hospital (MNTRH)
ii. To characterize the potential drug-drug interactions among the mentally ill patients at Mathari National Teaching and Referral Hospital (MNTRH)
iii. To assess the compliance of the prescriptions with established clinical guidelines

1.5 Research Questions

1. What are the prescribing patterns of the drugs used for mentally ill patients at Mathari National Teaching and Referral Hospital (MNTRH)?
2. What are the characteristics of the potential drug-drug interactions for the mentally ill at Mathari National Teaching and Referral Hospital (MNTRH)?

3. Are the patients' prescriptions at the hospital compliant with the recommended treatment guidelines?

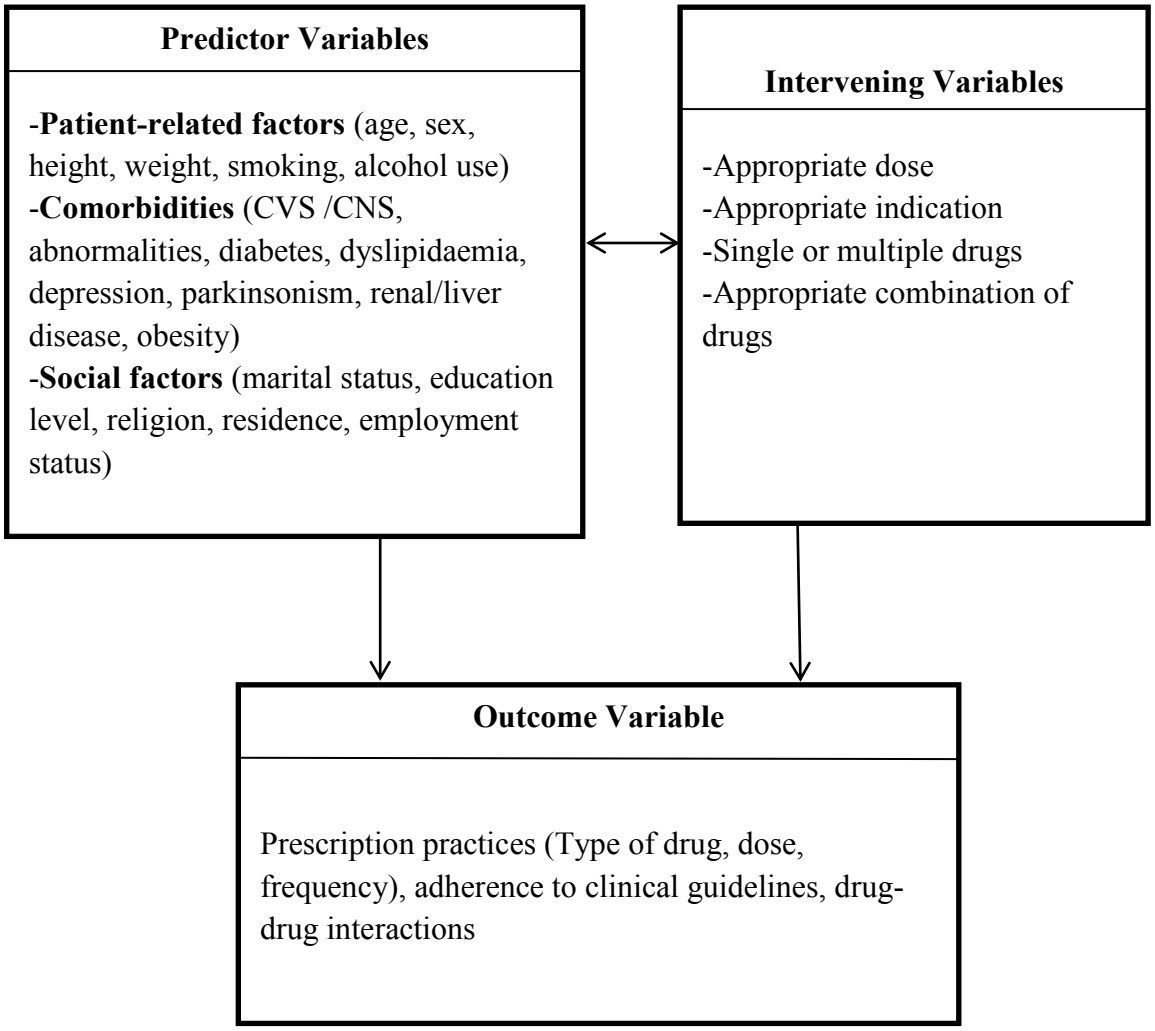
1.6 Justification

Poor prescribing habits promote unsafe and ineffective treatment, prolong or worsen illness, increase chances of harm and distress to patients, and add unnecessary costs (19). On the contrary, appropriate selection of medicines using evidence-based practices ensure the economic viability of healthcare systems, reduce duplication and confusion, reduce chances of adverse effects, and facilitate proper monitoring of side effects (19,20). The assessment of the management patterns of mentally ill patients at the hospital was compared with the globally and nationally endorsed standards to identify compliance or lack thereof. This hospital survey, which reflects the general practice in Kenyan public hospitals, could prompt appropriate corrective actions or improvements to assure optimal medical care for a vulnerable population. These findings fill in the clinical practice gaps in patient management practices of the mentally in Kenya.

1.7 Delimitations

The study was conducted in MNTRH, which is a specialized mental national referral facility with clients drawn from all parts of Kenya. The practices in this hospital were assumed to be representative of other Kenyan public hospitals. The National Institute for Health and Care Excellence (NICE) guidelines were assumed to be the best available evidence-based international recommendations to compare against the current practices in Kenya.

1.8 Conceptual Framework



1.8.1 Predictor Variables:

Patient-related factors- The patient's unique characteristics determine the choice of drugs that can meet the patient's identifiable clinical needs. Firstly, for females who could be pregnant, certain drugs could be contraindicated or need careful use to avoid teratogenicity, unlike males. Secondly, the young and the old need lower doses of antipsychotics and careful monitoring, unlike other age groups whose metabolism rates for drugs are relatively optimal. Thirdly, patients varying pharmacodynamics and pharmacogenetics could cause different responses to similar medication. This could make some patients treatment-resistant to particular medication while others could suffer toxicities at normal therapeutic doses. Fourthly, smoking and alcohol use affects the metabolism of drugs, hence altering their plasma concentration levels. This

creates the need for dose adjustment; otherwise, it could manifest as a lack of response to a potentially helpful drug or toxicity for normal therapeutic doses.

Comorbidities – Patients with mental illnesses usually have concurrent mental and physical illness due to poor health-seeking habits, stress, exposure to traumatic events, and poor eating habits. Physical illnesses such as diabetes imply the need for concomitant use of other drugs and increased potential for drug-drug interactions. The use of several medicines concomitantly augments the side effects, accelerating the deterioration of the patient's health. The presence of comorbidities also makes the drug selection for the patient complicated, and it warrants additional precautions as the clinician strikes a balance between the potential risks versus benefits.

Social factors – a patient's social background plays a significant role in their adherence to drugs, attitude to medication, health-seeking behaviour, and ultimately clinical outcomes. Well-educated and employed clients are likely to be drug-adherent, keen to use medicines correctly, and leading healthy lifestyles. Being married could provide a social support system for the client and motivate them to adhere to medication and lead a healthy lifestyle. The presence of positive influences promotes better clinical outcomes, and by extension, treatment-responsive patients are likely to receive the recommended doses without the need for upward adjustment or polypharmacy. This might not be the case for other patients with different variables.

1.8.2 Intervening Variables:

Appropriate dose: using appropriate doses lessens the risk of adverse drug effects, especially in the long term. Patients are also likely to be adherent and to have improved mental health when taking appropriate doses. High dose treatment increases the risk of adverse drug effects, which could negatively affect treatment adherence.

Appropriate indication: Using the right drug for a condition based on evidence-based approaches improves the patient's health outcome, reduces the need for additional medications, and promotes confidence in conventional therapy. Using the wrong drug is likely to cause undesirable side effects, worsen the original disease, and cause wasteful expenditure.

Single or multiple medications: Most guidelines highly encourage monotherapy in the management of mental illnesses. Using multiple drugs for one condition has not been proven to better the outcomes. The only case where polypharmacy could be considered is when the patient is resistant to clozapine monotherapy, which is regarded as the last line of therapy.

Appropriate drug combination: Using multiple drugs comes with the risk of interactions, which should be assessed and mitigated. Drug-drug interactions could result in minor to severe side effects, which need careful prior consideration and subsequent monitoring.

1.8.3 Outcome Variable

Prescribing patterns, drug-drug interactions and adherence to guidelines: A prescription was considered patient-appropriate if it contains the correct drug for a particular indication as per the guidelines. It should also fall within the recommended dose and carry no serious risk of pDDIs with other concomitant medicines. In case of any foreseeable dangerous interactions, there should be evidence of close monitoring of the appropriate parameters.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

This chapter reviews the burden of mental illnesses globally and locally, prescribing patterns of psychopharmacologic agents, clinicians' adherence to clinical guidelines, and drug-drug interactions. Appropriate use of medicines is crucial to ensure that patients and communities access quality medical care. This review highlights the need for an individual patient to receive appropriate medication that fits his or her clinical needs in the context of the right dose, correct indication, and safe drug combination.

2.2 Mental Illnesses

According to WHO, mental health is a state of wellbeing in which people can realize their capabilities, cope with the normal pressures in life and work effectively and productively to build their community (21). An estimated 971 million persons globally were affected by mental disorders, according to a survey done in 2017, marking a 13.5% increase in number compared to 2007 (22). Mental illnesses have consistently formed more than 14% of the years lived with disability across the globe since 1990, with a prevalence greater than 14% (22). Reports estimate that mental disorders contribute to 32.4% of years lived with disability and 13.0% of DALYs (23). In 2015, mental illnesses were seven among the top twenty-five causes globally of years lived with disability. Both high and LMICs have a similar prevalence for mental diseases despite the differential resource allocation to mental health services (24).

The most prevalent disorders are mood disorders (particularly major depressive disorder), anxiety disorders, and substance use disorders (SUDs). Mental illnesses come with severe limitations in interpersonal relationships, securing employment, and educational attainment. Among the adolescents in the US, half of those who fail to complete high school are usually mentally ill (24).

The WHO has highlighted the need for mental health as a primary agenda in sustainable development, especially in the LMICs. Access to mental healthcare remains inequitable, inadequate, and inefficient in the LMICs, with an estimated 85% treatment gap (those who need treatment and the availability of resources) compared

to 35-50% in the high-income countries (25). In Kenya, about 40% of inpatients and 25% of outpatients at various health facilities have a mental disorder (26). Prevalence of mental illnesses in Kenya, particularly stress and anxiety disorders, depression, and SUDs, are associated with several cases of suicide, domestic violence, and homicides (18). In LMICs, the primary treatment modality is the use of pharmacological agents. In Kenya, especially in rural facilities, mentally ill patients largely depend on the government to provide mental health services and drugs at public health facilities.

2.3 Clinician's Prescribing Patterns for the Mentally Ill

The quality of prescribing by clinicians is a crucial determinant of the way patients use medicines. The choice of drug(s), the dose, the formulation, route of administration, and monitoring is a crucial aspect in the patient's overall confidence in the health system and the resolution of symptoms for patients. Research on the use of antipsychotics is minimal, especially in the LMICs. The World Bank estimates that about 20-50% of the healthcare budget in developing countries is allocated to medicines (7). However, despite the large allocation, more than 50% of the drugs globally are either sold or prescribed wrongly, and 50% of the patients do not use them accurately (7).

Some of the irrational uses of neuroleptics are polypharmacy, using inappropriately high doses, and deviation from the recommended guidelines. The risk of high dosage is exceptionally high in young patients, have a longer duration of illness and have a history of aggression and violence (27). Patients who show inadequate response to medications typically receive an additional antipsychotic or a high dose of an antipsychotic. Some school of thoughts support this practice arguing that due to the varying pharmacodynamics of patients, failure to respond could be due to low drug concentrations reaching the central nervous system (27). Therefore, they prescribe a high dose of antipsychotics that can effectively cross the blood-brain barrier. Other clinicians use high doses inadvertently, whereby the doses are increased progressively during periods of symptoms exacerbation with no subsequent dose de-escalation. Then again, when the maximum licensed dose of one drug is reached, a clinician may opt for an additional drug that together constitutes a supramaximal dose. However, recommendations discourage high doses and instead advise clinicians to switch to an alternative drug altogether in case symptoms do not resolve. Alternatively, they can

top up a depot or long-acting injection with an oral drug for a short period during periods of symptom exacerbation or use a short-term benzodiazepine for sedation (27).

Other clinicians have limited knowledge and are sceptic about the prescribing algorithms. They opt for polypharmacy, intending to target specific symptoms with each drug. Polypharmacy is also practised by clinicians when trying to enhance the speed of therapeutic effects or when they encounter challenging symptoms such as behavioural disturbances and aggression (28). However, evidentially this is likely to augment the side-effects unlike monotherapy. Irrational practices result in increased mortality and morbidity associated with the development of chronic illnesses such as hypertension, diabetes, neurological disorders, and epilepsy (19,27).

2.4 Drug-drug Interactions

Drug-related mortality and morbidity are common, and they come at a high cost. Studies estimate that $177.4 billion is spent annually to handle treatment failure and medication problems resulting from adverse drug events (29). About 40% of patients receiving up to five medications or more suffer from adverse drug effects (30). Drug-drug interaction contributes to roughly 6 – 10% of adverse events, but almost 50 – 84% of these adverse drug effects are preventable events when proper precautions and surveillance systems are in place (29).

Mentally ill patients frequently develop comorbid illnesses such as obesity, hypertension, diabetes, and dyslipidaemia, which increase the need for additional prescription medicines. Drugs for the mentally ill are associated with several interactions with anticancer agents, antiretrovirals, antidiabetics, and contraceptives, among others. For instance, using tricyclic antidepressants (TCA), which is an α-1 blocker with antihypertensive drugs, is likely to exacerbate hypotension, while combining a TCA with adrenaline could cause hypertension (31). Notably, there are numerous drugs in the market, some of which are newly approved, and it is practically impossible to flag all potential interactions. However, health providers can diligently screen for significant drug-drug interactions for every new or change in a prescription. Additionally, monitoring patients closely and measuring the recommended clinical parameters can undoubtedly assist in preventing adverse effects.

Mentally ill patients have an amplified risk of developing physical diseases, which is enhanced by an unhealthy lifestyle, disparities in healthcare utilization and access, and the use of neuroleptics. Adverse effects are highest with antipsychotics, followed by mood stabilizers, then TCAs, and lastly, the new antidepressants (32). This risk is most significant among the elderly, the young, at a high dose of treatment, and with polypharmacy (32). However, appropriate medications are a safer option than the risk of suicide with untreated mental illness.

For drugs that are likely to interact, close on-treatment monitoring of patients is recommended regularly for patients (33). In a study done in India on the use of antipsychotic, none of the patients was monitored as per the guidelines, but 86% of the patients were partly monitored (5). Adequate monitoring of patients should be a major aspect in healthcare provision, especially when patients are using high doses or multiple drugs simultaneously, and there is likely to be an interaction.

Information on drug-drug interactions could be overburden due to the high override rates of alerts of potential interactions, which could cause 'alert fatigue' among practitioners. A systematic study done on the criteria to use for filtering alerts enumerated five key considerations. First, one should consider the severity of interactions in terms of the probability of morbidity, mortality, and likelihood of an intervention that can prevent harm (30). Secondly, consider the prospect of an interaction, which is tied to the timing of administration, route of administration, the pharmacokinetics of the drug, the dose, duration, and the practicality of monitoring (30). Thirdly, reflect on the clinical consequences of the interaction in terms of monitoring required, the burden of managing the interaction, and preparedness for intervening (30). Fourthly, cautiously examine the patient's characteristics such as age, comorbidities, gender, smoking, diet, alcohol use, and concurrent medication (30). Lastly, confirm the quality of evidence supporting the interaction, the quantity of literature on the interaction, and the biological credibility of the alert (30). These criteria were applied to guide the kind of data needed in interpreting the probability of pDDIs.

2.5 Adherence to Standard Treatment Guidelines

Evidence-based practices in mental health are interventions supported by credible scientific approaches proven to improve the clinical outcomes of patients consistently. For instance, the NICE guidelines are renowned globally for producing evidence-based and impartial clinical guidelines. These guidelines are normally developed through a rigorous process to give reliable, consistent, and cost-effective approaches (34). Despite extensive research and publication of clinical guidelines or consensus statements on effective practices in mental health, these recommendations are barely translated into practice in mental health programs. Principally, treatment guidelines are intended to reduce cases of inappropriate care, promote consistent practices in various geographical settings, and utilize healthcare resources more effectively (35).

In mental health care, there are major gaps in adherence to clinical guidelines, particularly in industrialized countries, where there are several studies on this topic. In resource-limited settings, adherence to guidelines largely depends on individual clinicians and the capacity of the healthcare system to provide the enabling personnel, equipment, and medication. In the LMICs, there is little research on this topic, hence not quantifiable. A study done in Chile on adherence to clinical guidelines on managing schizophrenia showed an 86% adherence rate. Similar studies have consistently reported lower rates; for instance, in the Netherlands, for patients being treated for depression or anxiety disorders, only 40% of them received the recommended treatment (35).

A similar study in Quebec (Canada) on adherence to clinical guidelines using specific indicators showed that for nearly half of the measures used, adherence was <60% (36). This Canadian study also demonstrated that adapting clinical guidelines into practice leads to improved quality of care, assists patients in regaining their mental health-related functioning, and increases the chances of retaining employment status for the patients (36). A study in Kenya in public and faith-based hospitals showed that adherence to local guidelines for treating tracers cases was mixed and inconsistent (8). Lack of adherence to guidelines was one major cause for patients failing to fill their prescriptions in public hospitals.

2.6 Studies on Prescribing Patterns

Several studies on the prescribing patterns globally have highlighted the persisting inadequacies in the adoption of evidence-based practices in the actual practice. Studies have consistently shown varying rates of polypharmacy in different countries, the use of supramaximal doses or under-doses and poor adherence to guidelines.

A study in a psychiatric hospital in South London showed that 44% of patients received high-dose antipsychotic medications, with poor observance to the recommended National Institute for Health and Care Excellence (NICE) guiding principles for the use of high doses (37). The use of polypharmacy made clinicians lose sight of the total cumulative dose from simultaneous drugs (37). Studies across the globe reveal a high rate of polypharmacy, with the UK having a prevalence of 48%, Europe 23%, Oceania 16.4%, North America 16%, and 67.3% in Wales (4,33). However, a Canadian study in a community setting involving 435 patients showed that polypharmacy was used in 25.7% of the patients, particularly among patients with schizoaffective disorder (33.7%) followed by schizophrenic patients (31.7%) (38). In a psychiatric clinic in Palestine, where most of the patients had schizophrenia, 70.2% of the patients were on SGA monotherapy, with 10.4% using the depot formulation (39). A study in Oman reported the highest rate of monotherapy at 93%, with 48.1% of these patients using olanzapine (6).

Over the past few decades, prescription patterns in Asian countries have been changing with a notable increase in SGAs usage and a marked reduction in the use of FGAs. Results from a study done in Nagoya University in 2010 involving 527 patients revealed that the rate of monotherapy was 64%, with 53.5% of the patients using FGAs and 46.5% receiving SGAs (40). This study observed that there was a positive correlation between the choice of the antipsychotic and the need for an antiparkinsonian drug. With the increased use of SGA from 1997 to 2007, there was a significant reduction in the use of antiparkinsonian drugs (40). A study on the dosage of antipsychotics in Japan showed that the number of antipsychotics prescribed per person was 1.76 (SD 0.86) drugs, with sedative/hypnotics being used in 60.7% of cases. Among the antipsychotics, risperidone was the most prescribed (47.4% of prescriptions), followed by haloperidol (21.7%) (41). The average dose of antipsychotics used was 798.3 (SD 653.6) mg of CPZeq (41). Among Asian countries

that were sampled, Japan had the highest average of CPZeq, with other Asian countries such as Singapore, Hong Kong, Taiwan and China using between 300 – 600mg of CPZeq. per day.

From a study done in India on antipsychotics use in schizophrenia, 59% of the patients received SGAs, while 3% received FGAs. Some of these patients (13.79%) received supramaximal doses, while another group (24.13%) received suboptimal doses (less than 300mg of CPZeq) (5). Patients receiving combination doses (31%) were mainly the ones receiving supramaximal doses (5). In this study, only 56% of prescriptions used a single antipsychotic. Moreover, only 62% of the prescriptions were concordant with the recommended antipsychotic doses, but 83% followed the recommended guidelines on the use of anticholinergics. Another study in India noted that the rate of SGA in that region was a little lower at 44.26%, where olanzapine (44.26%), risperidone (32.78%), and chlorpromazine (8.19%) were the most commonly used antipsychotics (42). This observation was different from one in Pakistan, where the SGA usage rate (68.1%) was high and the FGAs usage (6.9%) rate was low (43). However, unlike India, the polypharmacy rate was low (25.0%) in Pakistan, and the most common combination was risperidone and olanzapine (43).

From a similar study done in Cape Town, haloperidol, risperidone, and olanzapine were the most common antipsychotic monotherapies. Polypharmacy was prevalent in 28.4% of the patients and closely associated with the use of an FGA in combination with long-acting injectables for the management of schizophrenia (4). In Kenya, polypharmacy with antipsychotics was estimated at 64% from a study done in 2014, with benzhexol, carbamazepine and diazepam being the most common adjunctive medication (44). From this study, haloperidol (57.93%), chlorpromazine (46.95%), and fluphenazine (29.88%) were the most commonly used FGAs, while olanzapine (12.80%) was the most preferred SGA. This study also found an association between the burden of side-effects from antipsychotics and the likelihood of adherence to medication, which infers reduced chances for remission (44). These studies highlighted several areas that need improvement, particularly in the aspects of using high doses, polypharmacy practices, on-treatment monitoring, and adherence to evidential guidelines.

2.7 Literature Gap

Research on mental illnesses has significantly expanded over the last two decades globally, with numerous therapeutic options to improve the quality of life of the mentally ill. However, the translation of evidence-based practices from the theoretical arena into the actual practice has been quite slow. The slow diffusion of recommendation is well documented in the developed countries, where several studies have evaluated the clinicians' practices against the recommendations. In Asia, there is also considerable research on this topic, but in Africa, the literature on the quality of management or the management practices of the mentally ill patient is scarce.

In Kenya, no study has been conducted detailing the drug use patterns among mentally ill patients. This study fills in this literature gap by highlighting the prescribing patterns by clinicians, the pDDIs among patients using psychopharmacologic agents, and the compliance level of the prescribers to established international guidelines.

CHAPTER THREE: METHODOLOGY

3.1 Introduction

This chapter highlights the research design, the study site, the target population, and the study population, including the inclusion and exclusion criteria. Additionally, the following items on methodology have been explained: sampling technique, sample size, research instruments, piloting method, data collection method, data management, data analysis, as well as ethical considerations.

3.2 Research Design

This was a hospital-based cross-sectional study. This study design allowed for an assessment of the prescribing patterns by the clinicians, adherence to the clinical guidelines, and the appropriate use of drugs. The predictor variables included patient-related factors, comorbidities, and social factors. The intervening variables were appropriate drug indication, appropriate dose, single or multiple drug use, and the appropriate drug combinations. The outcome variables were the prescription practices (the type of drug, dosage, and frequency), adherence to NICE guidelines, and pDDIs.

NICE guidelines are a product of the UK government that provide guidance and advice to improve social welfare and healthcare. They maximize the use of evidence-based recommendations for health care, and they are suitable for most people with specific conditions, needs or in particular contexts. They are globally accredited to prevent ill health, improve the quality of services and care, promote and protect good health. Developing standard NICE clinical guidelines take at least 18-24 months from the time its commissioned by the UK Department of Health or the National Health Service Commissioning Board. The royal college of psychiatrists has developed 36 NICE guidelines on mental health, and the WHO has recognized its guidelines twice on schizophrenia as the best internationally on the topic (45).

3.3 Location of the Study

The study site was Mathari National Teaching and Referral Hospital (MNTRH), which is the largest tertiary facility in Kenya, specializing in mental health. The hospital had a bed capacity of 700, with 332 units serving the civil unit and 377 serving the maximum-security centre (46). The hospital had 10 wards, 8 of them being the civil unit wards, and the rest maximum-security units. The eight wards in the civil unit were divided into four male and four female wards. The hospital had 386

staff, 164 nurses, 11 psychiatrists, 2 clinical pharmacists, 8 pharmacists, one pharmaceutical technologist, and five clinical officers as per the Kenyan parliamentary report submitted in 2019 (46). The average occupancy was reported to be slightly above 100%, and the visiting patients were mentally ill persons from different parts of the country. However, this occupation rate was downscaled to about 50% during the Covid-19 pandemic in 2020. The hospital admitted 3540 patients in 2009, with more than half of them being readmissions (46). The outpatient unit received about 1100-1500 patients per month at the OPD (outpatient department) unit in 2019. Additionally, the hospital had weekly outpatient clinics dedicated to the return clients who had been discharged from the various wards serving at least 500 clients monthly.

3.4 Target Population and Study Population

The target population was all mentally ill adult patients being treated in public hospitals in Kenya. The study population was all the adult patients diagnosed and managed for mental illness at MNTRH.

3.4.1. Inclusion Criteria

1. Adult inpatient or outpatient at MNTRH diagnosed with a mental illness according to the recommended diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders (DSM-5).
2. Adult patients or their guardian/caregiver who give informed consent

3.4.2. Exclusion Criteria

1. Patients whose clinical records are incomplete and irretrievable; hence, inadequate to provide information on variables being collected for this study.
2. A patient or caregiver who declines to consent to participate in the study.
3. A patient with no working diagnosis.
4. A patient below 18 years.

3.5 Sampling Technique

The study employed a systematic random sampling method. The required sample size was divided proportionally among the wards, including the OPD unit and the outpatient clinics. All the eight wards in the civil unit were sampled; hence, the sample size required was divided proportionally among 10 units. Each ward was

allocated a target sample size according to the number of patients in that ward or according to the number of patients who visit the unit. A list of the patients admitted to the ward was obtained from the nursing officer. The number of patients currently admitted in a particular ward was divided by the required target number for that ward. The resulting number was used as the sampling interval.

Using the list obtained from the nursing officer, the first patient was chosen randomly, and the rest were chosen according to the sampling interval. Where a patient with complete medical records was chosen but failed to meet the eligibility criteria or declined to consent to the study, the next patient on the list was chosen. For the outpatient unit, the average number of patients that visit every day was be divided by the target sample size. The average number of patients who visit the clinic every week was divided by the target sample size to obtain the sampling intervals. The resulting number was used as the sampling interval. In case the sample size was less than the required from one ward, a new sampling cycle from the list of unsampled files would be started. These files were subjected to a systematic random sampling procedure as described above until the target sample size number was achieved.

First, the patient's file was perused by the investigator for completeness. If the file was incomplete, it was omitted, and the next patient on the list was chosen. A participant or the surrogate was approached, and the clinician would assess the decision-making ability of the participant. If the participant was judged to be competent by the clinician, he or she would be briefed about the study after attending the outpatient clinic or while in the wards. Otherwise, if the patient was not mentally stable and competent, the caregiver or clinician would respond on their behalf. The researcher would then seek consent to proceed with an explanation of the study. Those who agreed to participate were taken through the details of the study, and their informed consent was confirmed when they appended their name and signature to the consent form. After that, the participant or their surrogate (caregiver or clinician) would be interviewed in a private setting, and after the interview, they would be verbally appreciated for participating. The first patient was chosen randomly at the start of the clinic, and then the rest were interviewed as per the sampling interval. For instance, after identifying the first patient (assuming the sampling interval is four), the fifth patient in a row was recruited to the study.

3.5.2. Sample Size

The sample size was based on the estimated prevalence of common mental disorders in Kenya, which is 10.8% (47).

The sample size was estimated using Cochran's formula for calculating sample size

$$n_0 = \frac{z^2 pq}{e^2}$$ …….. Equation 1.1

Where,

n_0 = sample size;

Z = desired confidence level;

p = estimated prevalence of common mental disorders

q = (1− p);

e = desired level of precision

In this case the z = 1.96; p = 0.11; q = 0.89; e = 0.05

Therefore, n_0 = [(1.96^2) * (0.11) * (0.89)] / (0.05^2) = 150.437

The approximate sample size was 151 participants.

An additional 10% of responders were added to address cases of non-responders

In this case, 151 + (10% of 151) = Approximately 167

The targeted number of participants was 167

3.6 Research Instruments

The study used a survey form (Appendix 1) to collect data from the patient or caregiver verbally and from the patient's file. The form collected the patient's socio-demographic data, the diagnosis, the drug corresponding to each diagnosis, any comorbidities present, the drugs used to manage the comorbidities, any major potential drug-drug interactions, and the monitoring parameters employed.

3.7 Pilot Study / Pre-Testing

Sixteen survey forms, representing 10% of the sample size, were pretested at the MNTRH civil unit wards and the outpatient unit to ensure the reliability and validity of the survey form. The survey forms were satisfactory, and they did not need to be updated. Therefore, the forms were used in their original format as approved by the KNH/UoN ERC.

3.8 Validity

Achieving the recommended sample size for this study ensured that the study attains the required statistical significance threshold. A random sampling approach of the participants ensured that each of the eligible participants had an equal chance of being part of the study, eliminating selection bias. Having a standard data collection tool eliminated information bias that could arise at the data collection stage. Drug information was extracted from evidence-based treatment guidelines, particularly the National Institute for Health and Care Excellence Guidelines (NICE). Analysis of pDDIs was done using the IBM Micromedex Drug Interaction mobile-based application (v.2018). The use of validated treatment guidelines and a drug interaction checker application ensured that the study results were credible.

3.9 Reliability

The data collection tool was pretested with 16 patients to ensure that the information collected is reproducible for all the mentally ill patients and across different wards or units. Assuming that data entered into the patients' files were accurate, the forms could reliably collect the same data when repeated by a different researcher.

3.10 Data Collection Techniques

First, the principal investigator explained the research to the participant or their surrogates (caregiver or clinician) and sought informed consent (Appendix 2) in a language that he or she could understand. Data was collected using a structured form (Appendix 1), which is made of 6 sections. Information was extracted from the participants or the surrogates verbally and recorded in the survey form by the investigator. Additional information was extracted from the patient's file after confirming that their name and gender corresponds to that written on the file. Data that needed further clarification or confirmation was clarified verbally. Data on the drugs in current use was extracted from the treatment sheets of inpatients or patients' prescriptions at the pharmacy department.

3.11 Data Management

Data collected from the patient was kept as confidential as possible. In this study, a code number was allocated to each participant and stored electronically in a password-protected computer database. The physical paper records were locked in a file cabinet. Access was limited to the researchers in this study and members of the

KNH/UoN ERC. The results of the study were interpreted anonymously without any reference to a particular participant.

3.12 Data Analysis

The data collected were entered into Microsoft Excel 2016 and analysed using STATA Version 13.0. Descriptive data such as the comorbidities, diagnosis, and patients' socio-demographic information were summarized in frequency tables, pivot tables, graphs, and charts. Fischer's exact or Pearson's Chi-square was used to identify any significant association between the socio-demographic characteristics of participants and the primary diagnosis. A student t-test and one-way analysis of variance were done to compare the effect of various predictor variables on the outcome investigated. A binomial logistic analysis was done by regressing the patients' profile against the outcome variable to identify the independent predictors (having a pDDIs, receiving an SGA/FGA, and receiving a supramaximal dose). The statistical tests were computed at $P \leq 0.05$ and a 95% confidence level.

3.13 Logistical and Ethical Considerations

The proposal was forwarded for review and approval to the KNH/UoN ERC. Approval was granted through protocol number P185/03/2020. Afterwards, authorization was sought from the MNTRH ethics committee through the Medical Superintendent. Once written permission was granted, participants were recruited from the wards and the outpatient units. Before seeking consent from the participants, the attending clinician (clinical officer, medical officer or psychiatrist) assessed the decision-making capacity of the participants. Informed consent was sought from potential participants who were competent and mentally stable. For those adults with diminished cognitive capacity, hence unable to give informed capacity, their caregiver was requested to consent on their behalf. However, in case these patients were unaccompanied, the attending clinician who was not directly involved in the study was requested to give surrogate consent on their behalf. The competent patients or their surrogates (clinician or caregivers) were taken through the consent process and briefed to their full understanding of the contents of the study and their legal rights throughout the study.

The survey was anonymous, and only the patient's file number was recorded. All patients were identified with a unique code to maintain their privacy. The participants

were interviewed confidentially to ensure that the process was done in privacy. Additionally, the filled forms were stored privately under lock and key, and all the information held in confidence.

3.14 Benefits

Participants in this study did not obtain any immediate benefits from this research. However, the research findings could promote quality and harmonized management practices of mental illnesses by the clinicians and improve the prescribing practices for the benefit of current and future patients.

3.15 Risks

This research was non-invasive, and the patients were at no physical risk. However, patients could suffer from loss of privacy by having their information accidentally exposed to other unauthorized persons. The patient's information used for this research was secured in a locked cabinet, and all efforts were made to ensure no breach of confidentiality. Additionally, patients or surrogates could suffer from psychological harm by having to recall past traumatizing or unpleasant events. In case such an event occurred, there was a permanent clinical psychologist at the facility to whom they would be referred. Participation in this research was voluntary, and the patient was at liberty to withdraw from the study at any point without being denied care. Finally, the patient's rights in the research were observed all through, even after they gave their informed consent to participate in the study.

3.16 Dissemination of Research findings

The results of this study were shared with the MNTRH management and the prescribers at the hospital through the continuous medical education department. A summarized version will be published through the University of Nairobi repository and also submitted to a peer-review journal for publication.

CHAPTER FOUR: RESULTS

4.1 Introduction

This chapter highlights the results of the data collected from 167 participants from MNTRH through questionnaires administered by the investigator. The descriptive data is summarized in frequency tables and graphs. Inferential analysis has been done to highlight the association between the predictor and outcome variables.

4.2 Recruitment of Participants

A total of 243 participants who were mentally ill and willing to participate were selected to be part of the study from the list of names provided, but 76 were excluded for various reasons leaving 167 participants. Three of those excluded were below 18 years after perusing their medical records to verify their correct age, 56 of them had incomplete or inconsistent medical records. Seventeen participants were unable to concentrate all through the interview. This resulted in 110.6% attainment of the target sample size.

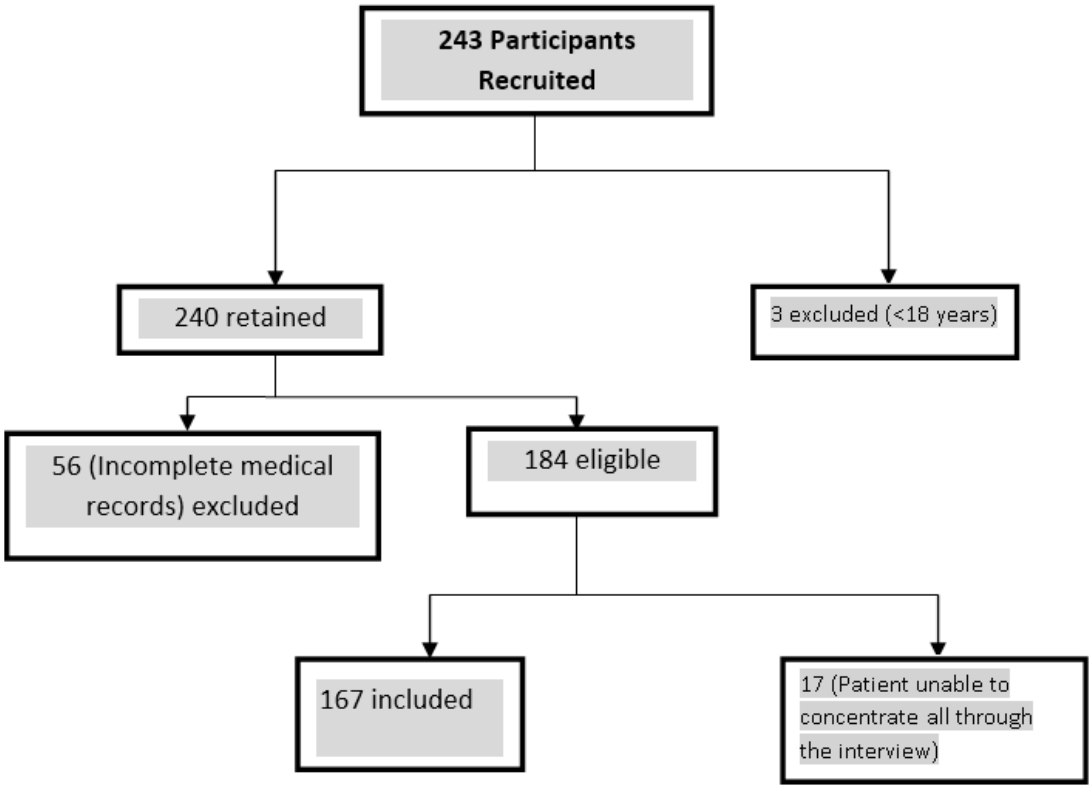


Figure 1: Consort Diagram Illustrating Participant's Recruitment

4.3 Socio-demographic Characteristics

The majority of participants were male (n =108, 64.7%), as seen in Table 1. The age of the participants was skewed towards the 18 to 45 years' age brackets (n=128, 76.6%). The median age was 34 years (IQR 27, 44), with a range of 18 to 87 years. A majority of the participants had healthy weight (n=87, 52.1%), but slightly less than half of the population was above the healthy weight limit (n=71, 42.5%). The mean BMI was 36.7kg/m^2, while the median BMI was 24.2 kg/m^2 (IQR 22.6, 27.4). More than half of the participants (n=103, 61.6%) had a history of psychiatric admission; only 64 (38.3%) participants had never been admitted.

Table 1: Sociodemographic Characteristics of the Participants (N=167)

Variable	Frequency, n (%)
Sex	
Male	**108 (64.7%)**
Female	59 (35.3%)
Age (Years)	
18 – 31	**69 (41.3%)**
32 – 45	59 (35.3%)
46 -59	29 (17.4%)
>60 years	10 (6.0%)
Median (IQR)	34(27-44)
Mean ±SD	36.7±13.4
BMI (kg/m^2)	
Underweight (<18.5)	9 (5.4%)
Healthy weight (18.5 – 24.9)	87 (52.1%)
Overweight (25.0 – 29.9)	**49 (29.3%)**
Obese (≥30.0)	22(13.2%)
Mean ± SD	24.9 ± 4.5
Median (IQR)	24.2 (22.6 – 27.4)
Previous Psychiatric Admissions	
None	64 (38.3%)
1-3 times	56 (33.5%)
More than three times	47 (28.1%)
Marital Status	
Single	**93 (55.7%)**
Married	38 (22.8%)
Divorced	3 (1.8%)
Separated	27 (16.2%)
Widowed	6 (3.6%)
Education	
Informal	15 (9.0%)
Primary	51 (30.5%)
Secondary	**69 (41.2%)**
College	21 (12.6%)
University	11 (6.6%)
Smoking Tobacco	
Non-smoker	72 (43.1%)
Smoker	**95 (56.9%)**
Alcohol	
No alcohol use	84 (50.3%)
Uses alcohol regularly	83 (49.7%)
Religion	
Christian	**142 (85.0%)**
Muslim	16 (9.6%)
Other	9 (5.4%)
Residence	
Rural	62 (37.1%)
Urban	50 (30.0%)
Semi-urban	55 (32.9%)
Employment Status	
Student	10 (6.0%)
Unemployed	**108 (64.7%)**
Self-employed	34 (20.3%)
Full-time employee	15 (9.0%)

KEY: BMI – Body Mass Index, IQR – Interquartile Range, SD – Standard deviation

More than half of the participants were single (n=93, 55.7%), and only 38 (22.8%) of them were married. The rest of the participants were either separated or divorced (n=30, 18.0%). The majority of the participants (n=69, 41.2%) had at least a secondary school level of education, 51 (30.5%) had attained primary education, 21 (12.6%) had graduated from college, and 11 (6.6%) had attended university education.

The majority of participants were active smokers, or they used to smoke before admission (n=72, 56.9%). Furthermore, almost half of the participants (n=83, 49.7%) reported using alcohol occasionally or regularly. Most of the participants ascribe to Christianity (n=142, 85.5%), and the rest were Muslims or had different religious affiliations. The places of residence were almost equally distributed among rural, urban, and semi-urban settings. A majority of the participants were unemployed (n=108, 64.7%), and only 9.0% of them had permanent jobs, especially from the outpatient unit (n=15). Some participants were still students in colleges or universities (n=10, 6.0%), while 20.3% of the participants owned informal businesses such as hawking and carpentry.

4.4 Prevalence of Mental Illnesses

The majority of the participants were diagnosed with schizophrenia (n=73, 43.7%). The other illnesses included drug-induced psychosis (n=45, 26.9%), bipolar disorder (n=33, 19.8%), schizoaffective disorder (n=16, 9.6%), acute psychosis (n=11, 6.6%), major depressive disorder (n=8, 4.8%), postpartum psychosis (n=3, 1.8%), post-traumatic stress disorder (n=2, 1.2%), and psychosis due to a medical condition (n=2, 1.2%) as seen in Figure 2. Two of the participants were diagnosed with generalized anxiety disorder and borderline personality disorder. The above illnesses occurred either in isolation or combined, as seen in Appendix 6 list of mental illnesses.

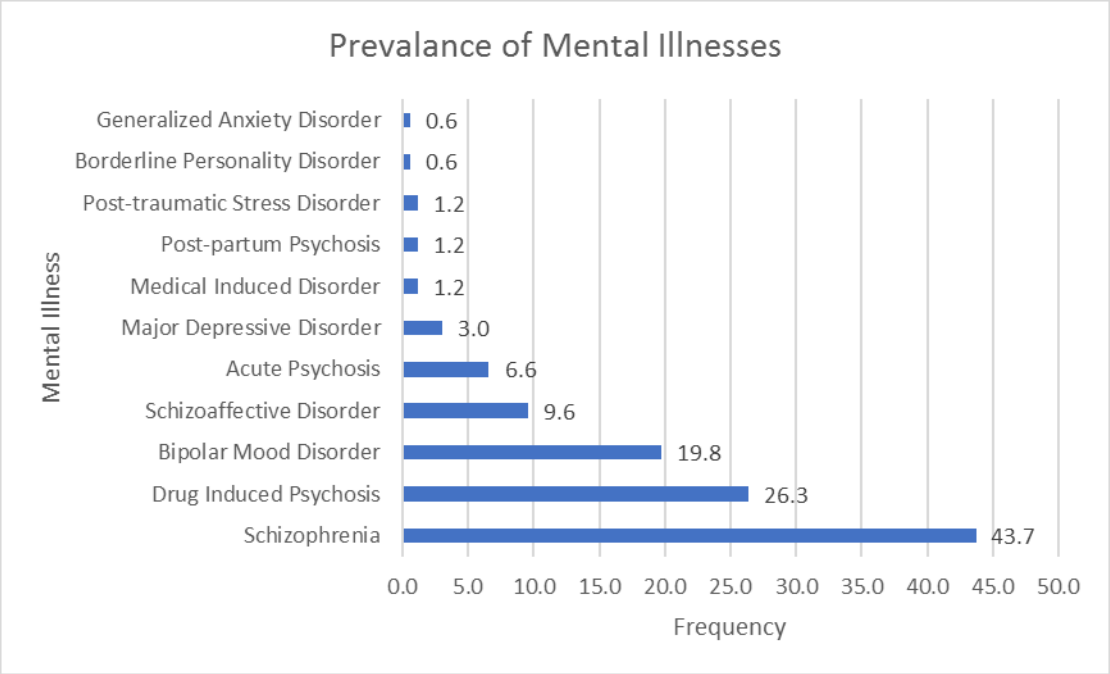


Figure 2: Distribution of Mental Illnesses among Participants

4.4.1 Years Lived with Disability

Mental illnesses that affected at least five participants were recorded in Table 2, illustrating the average number of years of mental illness. Participants diagnosed with schizophrenia had lived for at least 12.2 years with the disease. Cumulatively, this contributed to 683.7 years lived with the disability for this category of participants. Those with schizophrenia (SZA) and comorbid drug-induced psychosis had lived with the condition for an average of 10.5 years, cumulatively contributing to 126.5 years lived with illness. Participants diagnosed with schizoaffective disorder (SAD) had lived with the disease for an average of 10.2 years, while those with bipolar disorder (BMD) had lived with the condition for an average of 8.3 years. Finally, those with drug-induced psychosis (DIP) and acute psychosis (APY) had lived with the disease for an average of 6.6 and 0.9 years, respectively.

Table 2: Average Number of Years Lived with Mental Illness

Mental Illness	Average of No Years ± SD	Number of participants (N=148)	Total Duration of Illness
SZA	12.2 ± 10.11	56.0	683.7
SZA/DIP	10.5 ± 10.71	12.0	126.5
SAD	10.2 ± 8.34	16.0	163.8
BMD	8.3 ± 7.24	28.0	231.8
DIP	6.6 ± 5.16	27.0	178.2
APY	0.9 ± 1.66	9.0	8.2
Grand Total	**9.4**	**148.0**	**1392.2**

Key: SZA – Schizophrenia, SZA/DIP – Schizophrenia and comorbid drug-induced psychosis, SAD - Schizoaffective disorder, BMD – Bipolar disorder, DIP – Drug-induced psychosis, APY – Acute psychosis.

4.4.2 Age of Onset

The average age of onset for mental illnesses was 27.6 ±12.1 years. DIP was most prevalent among the younger age group, with the lower and upper quartile ranging from 21.8 to 28.0 years, respectively (Figure 3). SZA had the highest variability of the age of onset, with the lower and upper quartiles ranging from 19.3 to 35.8 years. SZA with comorbid DIP had the lowest average age of onset with a median age of 20 years (IQR, 17.0, 26.8). SZA had the lowest minimum age of onset at ten years, while SAD had the highest maximum age of onset at 54.5 years.

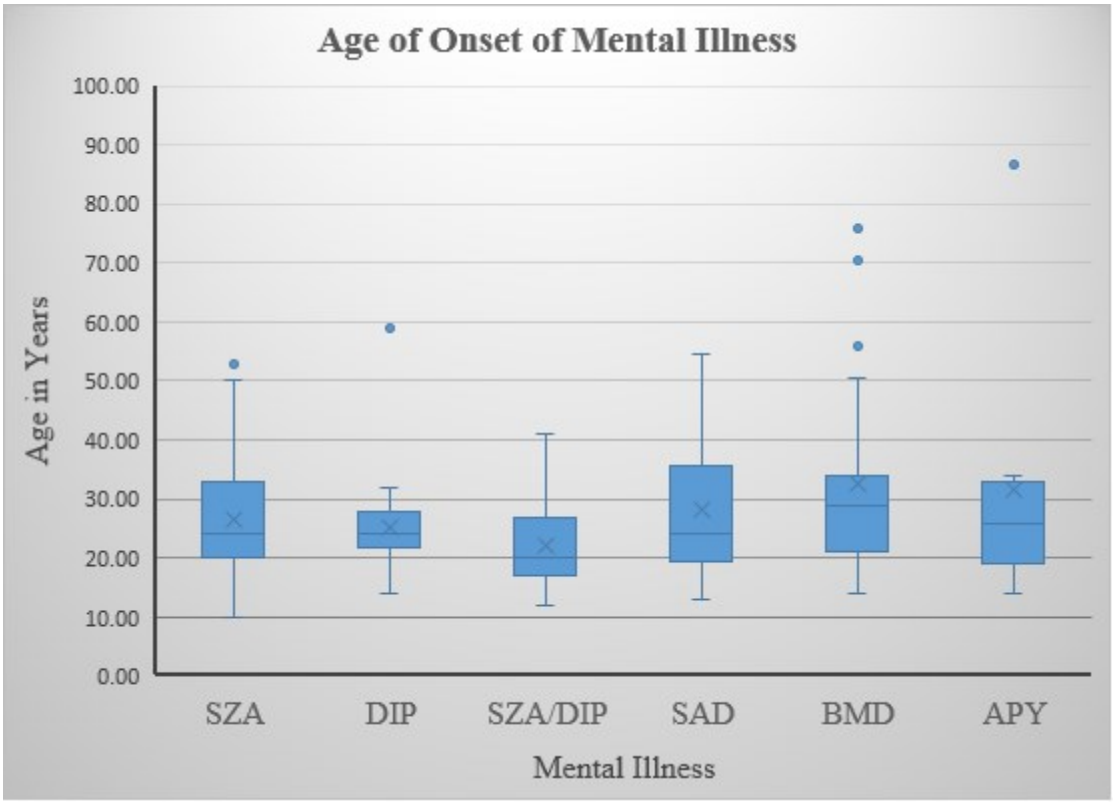


Figure 3: Age on Onset of Mental Illness

4.5 Drug Use Patterns

All participants received the correct drug for the respective indications based on the NICE clinical guidelines (Appendix 6). Additionally, all participants received the correct dose of individual antipsychotics, and none of the drugs exceeded the recommended maximum effective dose of an individual drug. The rate of use of FGAs was 79.2%, and that of SGAs was 47.2%.

Antipsychotics were commonly prescribed for almost all participants, as shown in Figure 4, and only four participants (2.4%) were not using an antipsychotic. One of the participants was on a drug holiday, while the other three had no indication for an antipsychotic. About 37.7% (n=63) of all the participants were on monotherapy, 53.3% (n=89) were using two antipsychotics, and 6.0% (n=10) were using three antipsychotics concurrently. One participant who was diagnosed with SZA was using four antipsychotics.

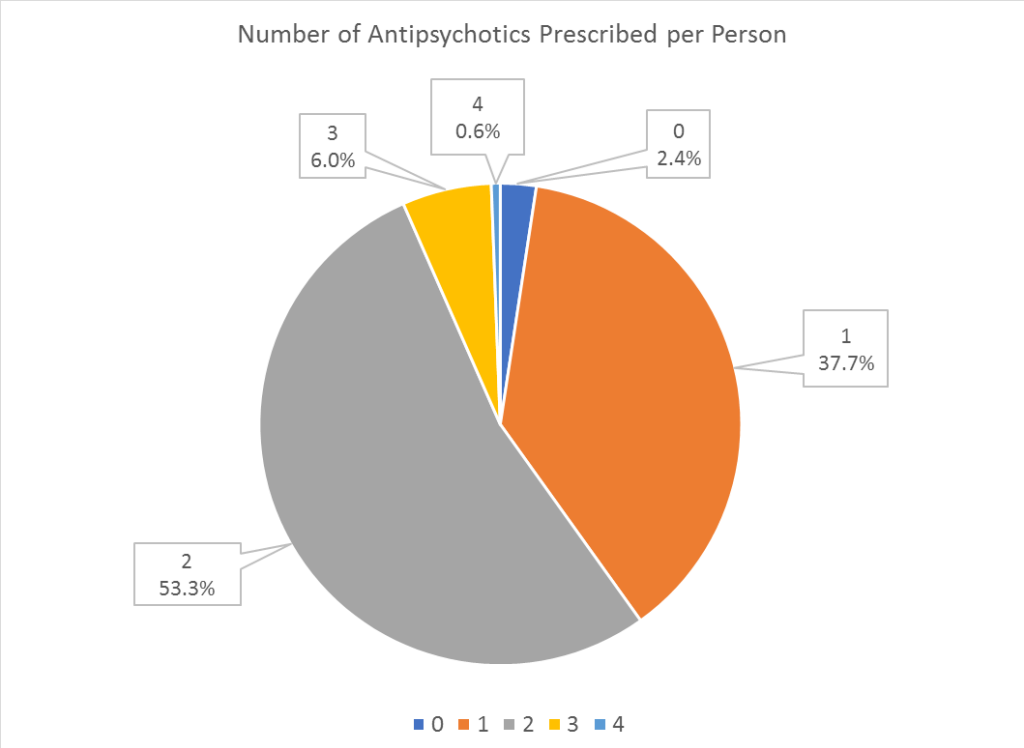


Figure 4: Number of Antipsychotics Prescribed per Person

4.5.1 Average Number of Drugs and Dose Prescribed per Person

Participants with schizophrenia as the only diagnosis (n=56) received an average of 1.7 antipsychotics, as shown in Figure 5 below. Participants with SZA were the least likely to receive second-generation antipsychotics (SGAs), having the lowest average of 0.3 SGAs per person. However, they were likely to receive FGAs, having the highest average of 1.4 FGAs per person. Notably, participants with schizophrenia and those with schizophrenia and comorbid drug-induced psychosis received the highest number of FGAs (1.4 per person). Each of the drugs prescribed to a patient was converted into its CPZeq using the approximate equivalent doses displayed in Appendix 8. All the CPZeq for all the drugs prescribed per patient were added up to get the cumulative dose of CPZeq prescribed. The average dose of antipsychotics prescribed for all the participants was 1021.0mg per person (Table 3).

Patients diagnosed with bipolar disorder (n=28) received 1.6 antipsychotics per person. They also received the highest number of SGAs (0.6 drugs per person), together with patients diagnosed with APY and SZD. Participants diagnosed with schizoaffective disorder received the lowest number of FGAs (0.4 per person).

Table 3: Average of CPZ Equivalents Prescribed for Various Mental Illnesses

Mental Disorder	Average of CPZ Equivalents (mg) ± SD
Acute psychosis	1038.9 ± 739.8mg
Schizophrenia	1021 ± 608.0mg
Drug-induced psychosis	965.7 ± 647.8mg
Schizoaffective disorder	910.9 ± 702.4mg
Schizophrenia/Drug-induced psychosis	900 ± 673.9mg
Bipolar disorder	829.5 ± 548.8mg

From this study, 10.2% (n=17) of the participants were under-dosed (<200mg CPZ equivalents), 35.9% (n=60) used standard doses, while 53.3% (n=88) used supramaximal doses (>1000mg CPZ equivalents). Participants with BMD received the lowest dose of antipsychotics, whereby each patient received an average of 829.5mg ± 548.8mg of CPZeq.

Those diagnosed with SZA/DIP received a relatively low dose of antipsychotics (900.0 ± 673.9mg CPZ equivalents), but paradoxically this was accompanied by having the highest number of anticholinergics prescribed (0.3 per person). Those diagnosed with acute psychosis (n=9) received the highest number of antipsychotics (1.9), which corresponded to having the highest average dose of antipsychotics per person (1038.9 ± 739.8mg of CPZeq). Unexpectedly, these participants received the lowest of anticholinergics (0.2 per person).

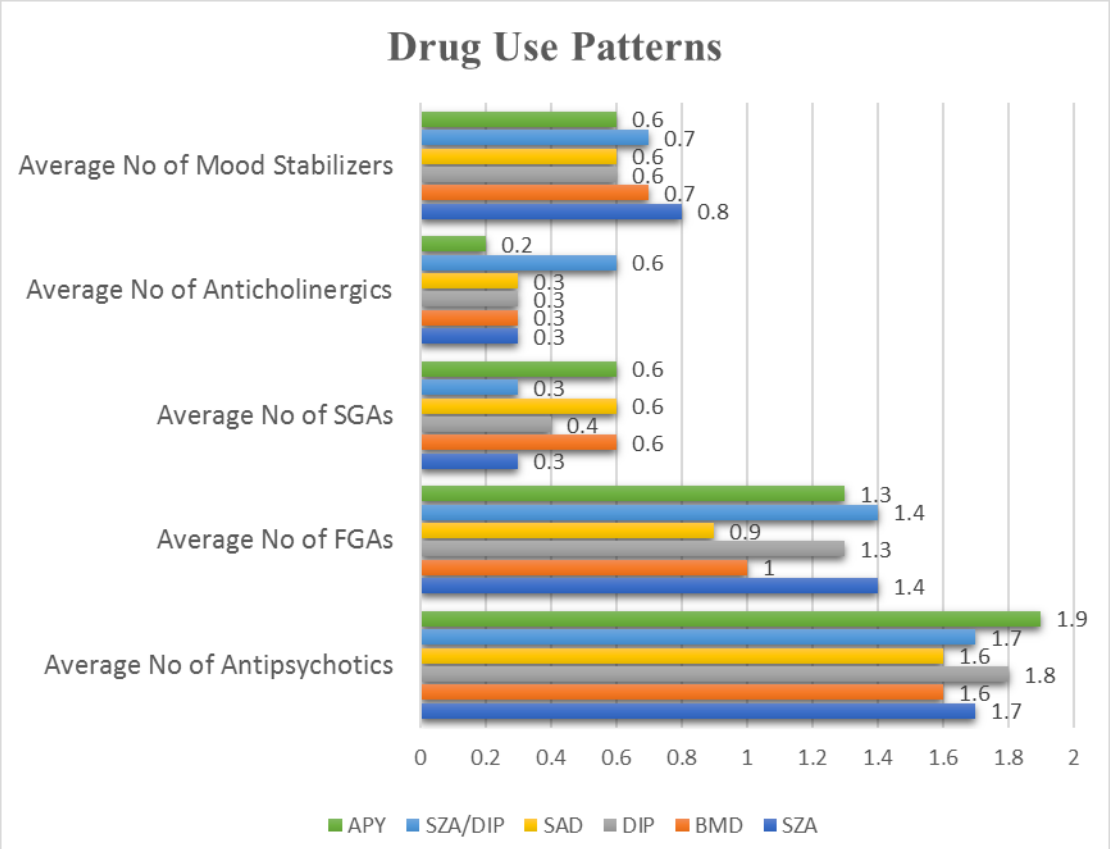


Figure 5: Average Number of Drugs Prescribed per Person
KEY: No - number, FGAs - First Generation Antipsychotics, SGAs - Second Generation Antipsychotics, APY – Acute Psychosis, SZA – Schizophrenia, SAD – Schizoaffective Disorder, DIP – Drug-Induced Psychosis, BMD – Bipolar Disorder

4.5.2 Prescribed Antipsychotics

Among the 163 participants medicated with antipsychotics, 47.2% (n=77) received oral haloperidol, representing the most commonly used FGA. Fluphenazine decanoate injection was the most preferred intramuscular depot, administered to 42.3% (n=69) of the participants. The most preferred anticholinergic was trihexyphenidyl (benzhexol) oral formulation used on a *PRN* (as needed) basis. The most prescribed SGA was the oral formulation of olanzapine, which was issued to 25.2% (n=41) of the patients. Risperidone was the second most preferred SGA, which was given to 20.2% (n=33) of the participants. Oral chlorpromazine was issued to 16.0% (n=26) of the participants, while only 1.8% (n=2) received oral quetiapine. Some of the other long-acting injectables that were used included zuclopenthixol decanoate (n=15, 9.2%) and flupentixol decanoate (n=12, 7.4%).

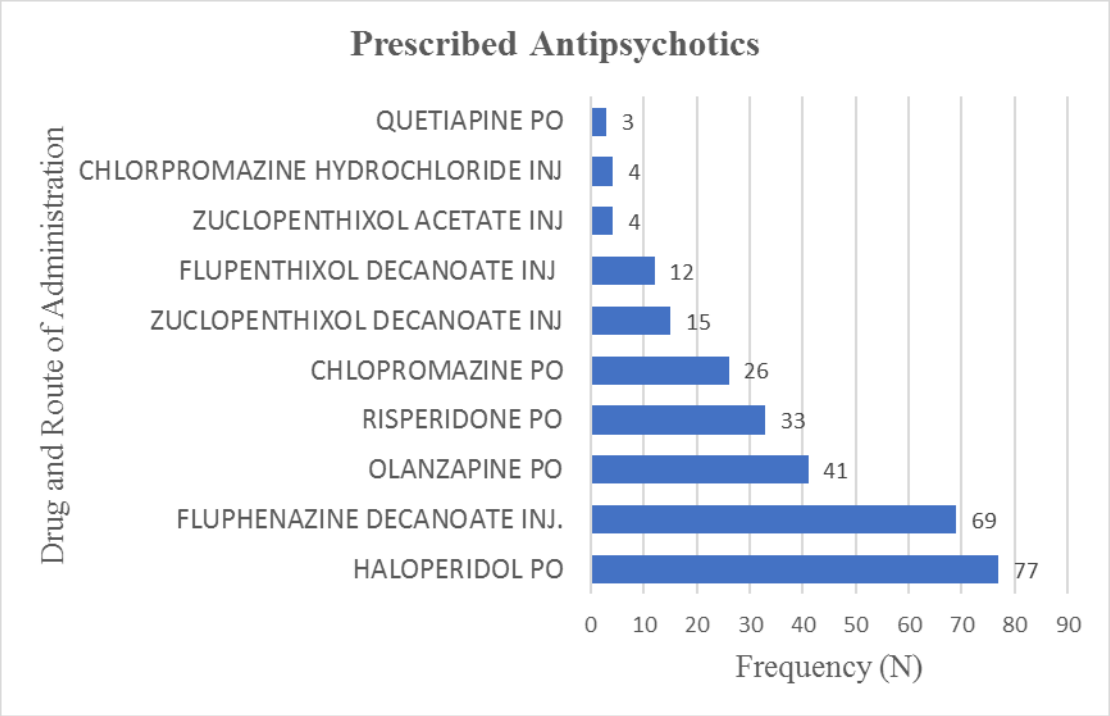


Figure 6: Commonly Prescribed Antipsychotics
KEY: PO – Per oral, INJ – Intramuscular injection

Some of the adjuvant drugs used with the antipsychotics included sodium valproate/valproic acid, topiramate, carbamazepine, trihexyphenidyl (benzhexol), amitriptyline, and fluoxetine.

4.5.3 Dose of Antipsychotics Used

Each antipsychotic prescribed was converted into the approved CPZeq using the internationally accepted consensus (Appendix 7). The mean dose of CPZeq was 930.4 ± 617.5mg for all participants (n=163) using antipsychotics. The median dose of antipsychotics was 1100mg (IQR, 250,1100), ranging from 50mg to 2650mg CPZeq.

4.6 Comorbidities among the Study Population

4.6.1 Prevalence of Comorbidities

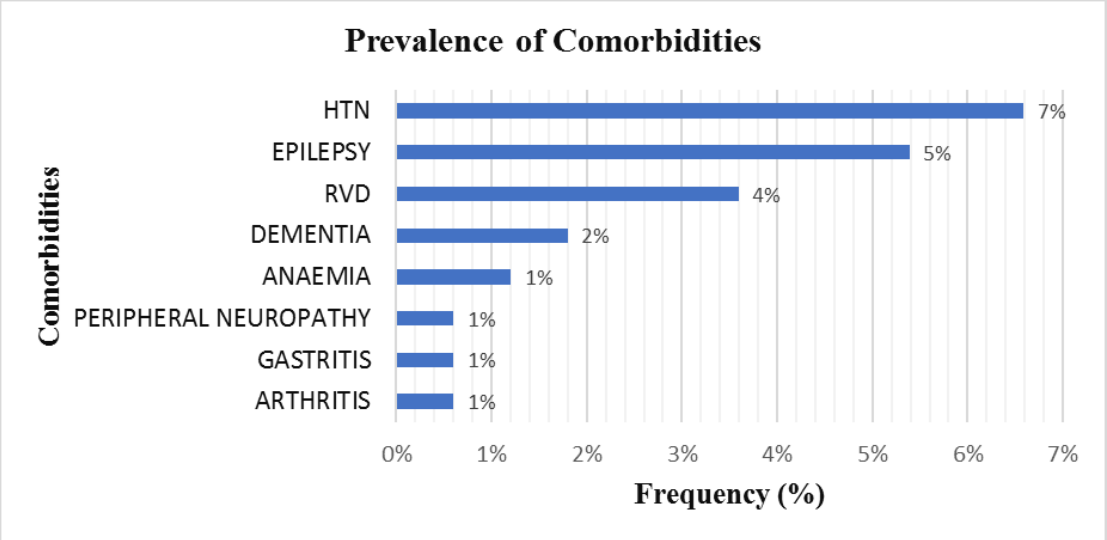


Figure 7: Prevalence of Comorbidities

KEY: HTN – Hypertension, RVD – Retroviral Disease

Out of the 167 participants, 35(21.0%) had comorbidities. The most common comorbidities were hypertension (n=11, 6.7%), epilepsy (n=9, 5.3%), and dementia (n=3, 1.8%). The others included anaemia, peripheral neuropathy, chronic gastritis, and arthritis.

4.6.2 Drugs Used for the Comorbidities

The most commonly used pharmacological agents for participants with comorbidities included nifedipine (antihypertensive), hydrochlorothiazide (antihypertensive) and TDF/3TC/DTG (fixed dose of antiretroviral). Other drugs included donepezil, iron and folic acid, clarithromycin, isoniazid, pyridoxine, cotrimoxazole, phenobarbitone and diclofenac.

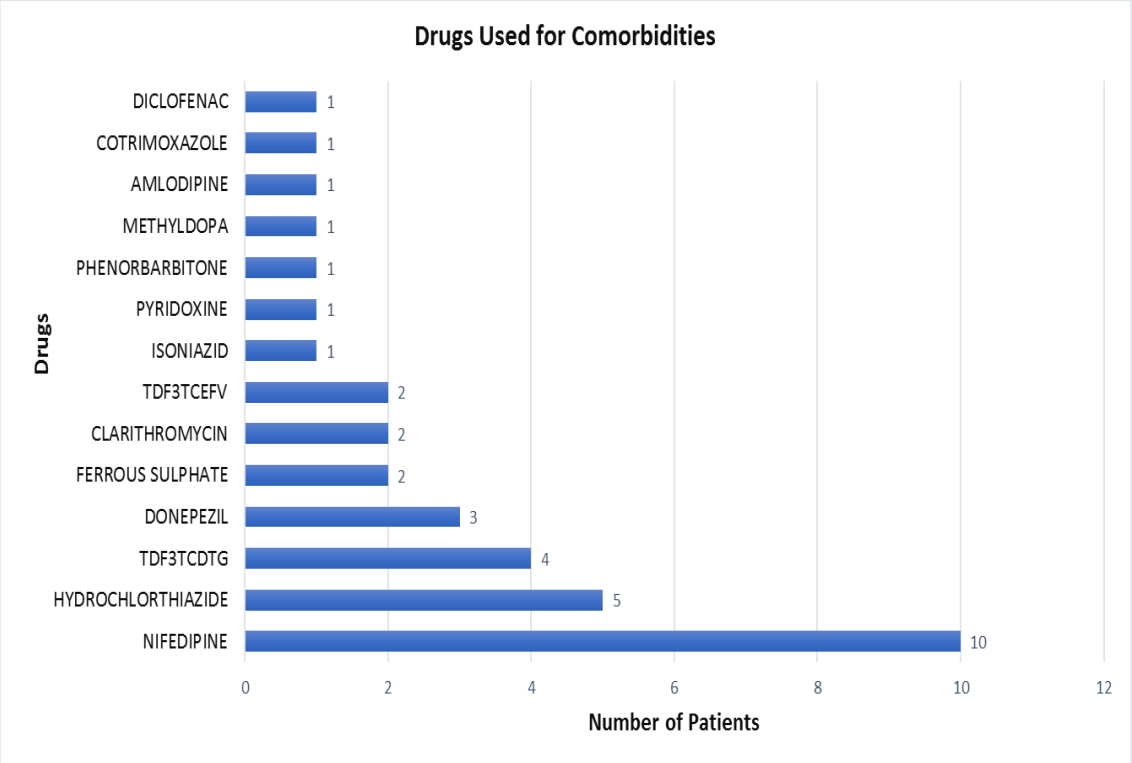


Figure 8: Drug Used to Manage Comorbidities

KEY: TDF3TCEFV - Tenofovir Disoproxil 300mg/Lamivudine 300mg/Efavirenz 400mg, TDF3TCDTG- Tenofovir Disoproxil 300mgm/Lamivudine 300g/Dolutegravir 50mg.

4.7 Potential Drug-drug Interactions

4.7.1 Drug-drug Interactions and Outcomes

All drugs prescribed to a patient were screened for pDDIs using the IBM Micromedex Drug Interaction Checker (version 2018). Ten possible major pDDIs were identified. Among the 167 participants, 49.1% (n=82) were at risk of experiencing major drug-drug interactions. The most common interactions affected the cardiovascular system. The pDDIs included QT-interval prolongation (QTPROL) [n=27, 16.2%], cardiac toxicity (CADTOX) [n=24, 14.4%] and carbamazepine toxicity (CBZOLA) [n=23, 13.8%]. QT-interval prolongation resulted from different drug-drug interactions such as chlorpromazine and amitriptyline, haloperidol and risperidone and many others, as highlighted in details in Appendix 5.

Table 4: Possible Drug-drug Interactions and Outcomes

Type of Drug Interaction	Possible Outcomes	Frequency (N = 167)	Percentage of Participants
QTPROL	Increased risk of QT-interval prolongation	28	16.8
CADTOX	Increased risk of cardiotoxicity (torsade's de pointes/QT-interval prolongation and cardiac arrhythmias)	24	14.4
CBZOLA	Reduced efficacy of olanzapine and increased risk of carbamazepine toxicity	23	13.8
BLEED	Increased risk of bleeding	1	0.6
CBZDTG	Decreased efficacy of dolutegravir	1	0.6
CBZINH	Increased risk of carbamazepine toxicity and increased risk of isoniazid-induced hepatoxicity	1	0.6
CBZNIF	Decreased nifedipine efficacy	1	0.6
CBZQUE	Decreased quetiapine efficacy	1	0.6
FLXHAL	Increased risk of haloperidol exposure, haloperidol toxicity, QT-interval prolongation, and torsade's de pointes	1	0.6
SERSYND	Increased risk of anticholinergic side effects (serotonin syndrome)	1	0.6
Total		**82**	**49.1**

KEY: - QTPROL -QT-interval prolongation; CADTOX – cardiac toxicity; CBZOLA – carbamazepine-olanzapine interaction; BLEED – bleeding risk; CBZDTG – carbamazepine-dolutegravir interaction; CBZINH – Carbamazepine-isoniazid interaction; CBZNIF – carbamazepine-nifedipine interaction; CBZQUE – carbamazepine-quetiapine interaction; FLXHAL – fluoxetine-haloperidol interaction; and SERSYND – serotonin syndrome.

CADTOX (cardiac toxicity) was associated with several drug-drug interactions such as chlorpromazine and haloperidol, and risperidone and amitriptyline, among others. Other possible manifestations of drug-drug interactions were increased risk of bleeding, serotonin syndrome, decreased efficacy of some antipsychotics due to increased metabolism, and haloperidol toxicity.

4.7.2 Drugs Likely to Cause Interactions

The most common pDDIs were between olanzapine/carbamazepine (n=23, 28.0%) and haloperidol/amitriptyline (n=9, 11.0%). Olanzapine was involved in 39.0% (n=32) of all pDDIs noted in Table 5. Similarly, carbamazepine was involved in several pDDIs (n=31, 37.8%). These two drugs contributed to more than 75% of all pDDIs. Other major contributors to the drug-drug interactions were haloperidol, risperidone, zuclopenthixol, amitriptyline, and chlorpromazine.

Table 5: Drugs that were Likely to Cause Drug-drug Interactions

Commonly Interacting Drugs	Number of interactions (n = 82)	Percentage (%)
Interactions involving olanzapine	32	39.0
Interactions involving carbamazepine	31	37.8
Interactions involving haloperidol	26	20.7
Interactions involving risperidone	17	18.3
Interactions involving zuclopenthixol	18	22.0
Interactions involving amitriptyline	15	18.3
Interactions involving chlorpromazine	13	15.9
Interactions involving fluoxetine	7	8.5

4.8 Monitoring of Adverse Effects of Antipsychotics

All the participants' blood pressure, pulse rate, and temperature were routinely monitored at least once every day. The nurses made daily entries of these parameters in the patient's files using a daily monitoring chart. These were the only routing tests conducted on the participants. The other tests that were conducted occasionally on participants for other diagnostic reasons included full blood count (FBC), fasting blood sugar (FBS), urea, potassium levels, toxicology screening, lipid levels, and electroencephalogram (EEG). FBC and FBS/HBA1C were the most commonly done

routine tests, but they were not specific to any regimen used. Some of the participants suspected to have drug-induced psychosis underwent toxicology screening. Screening involved investigating the plasma levels of cocaine, amphetamine, methamphetamine, marijuana, methadone, morphine, opiate, phencyclidine, barbiturates, and benzodiazepines.

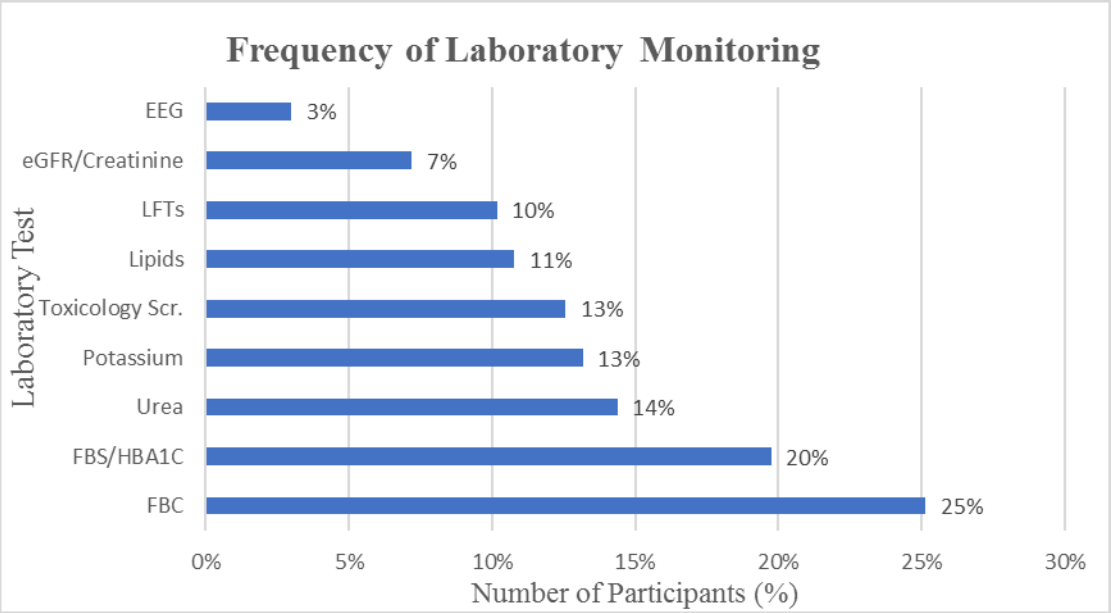


Figure 9: Proportions of Participants with Laboratory Results Records

KEY: EEG – Electroencephalogram, LTFs – Liver functions tests, Toxicology scr. – Toxicology screening, FBS/HbA1C – Fasting blood sugar/Haemoglobin A1C, FBC – Full blood count

4.9 Correlation of the Sociodemographic and Clinical Characteristics with Various Diagnoses

Fischer's exact or Pearson's Chi-square at $P \leq 0.05$ was done to identify any significant association between socio-demographic characteristics of participants and the primary diagnosis. The primary diagnosis was significantly associated with the gender $\chi 2\ (5) = 25.8$ ($P < 0.001$), whereby the concentration of certain mental illnesses such as DIP was more prevalent in males than females. There was also a significant association between the diagnosis and the various classes of BMI $\chi 2\ (15) = 40.90$ ($P < 0.001$). Notably, most mental illnesses were more concentrated in those who had an ideal body weight. There was a significant association between a history of previous admission and the primary diagnosis $\chi 2\ (10) = 34.29$ ($P < 0.001$). Some mental

conditions such as APY were more common among patients who have never been admitted before.

There was a significant association between the marital status of an individual and the diagnosis $\chi 2$ (20) = 33.02 (P < 0.034), whereby most mental illness except BMD was most common among unmarried patients. There was also a significant association between the education level of the participants and the diagnosis $\chi 2$ (20) = 33.18 (P = 0.032). Notably, a high number of patients with DIP had a secondary school level of education compared to other levels of education. Other factors that were related to the primary diagnosis included the use of alcohol $\chi 2$ (5) = 34.58 (P<0.001) and the smoking status $\chi 2$ (5) = 26.13 (P < 0.001). Patients with DIP mainly were those who smoked and also used alcohol regularly.

Table 6: Covariates of Mental Illnesses

Variable	Primary Diagnosis		
	df (degrees of freedom)	χ^2	P-Value
Age (Years) 18 – 31 32 – 45 46 -59 ≥59 years	15	23.08	0.082
Sex Female Male	5	25.80	**P<0.001**
BMI (kg/m^2) Underweight (<18.5) Healthy weight (18.5 – 24.9) Overweight (25.0 – 29.9) Obese (≥30.0)	15	40.90	**P<0.001**
Previous Admissions None 1-3 times More than three times	10	34.29	**P<0.001**
Marital Status Single Married Divorced Separated Widowed	20	33.02	**0.034**
Education Informal Primary Secondary College University	20	33.18	**0.032**
Religion Christian Muslim Other	15	19.82	0.179
Residence Rural Urban Semi-urban	15	21.35	0.126
Comorbidity None Existing	5	5.88	0.318
Alcohol use No Yes	5	34.58	**P < 0.001**
Smoking No Yes	5	26.13	**P < 0.001**

4.10 Covariates of the Dose of Antipsychotics Prescribed

Using a student t-test at $P \leq 0.05$, the average doses of CPZeq administered between groups were compared for any significant difference, as shown in Table 7. There was a significantly higher chance of participants using a mood stabilizer to receive a relatively high dose of CPZeq ($P = 0.0001$). Similarly, participants receiving an anticholinergic drug had a higher chance of being on a high dose of antipsychotics ($P = 0.004$). Those participants who had no comorbidity has a significantly higher chance of receiving a high dose of antipsychotics ($P = 0.002$). Finally, there was a significant association between the dose of CPZeq and the occurrence of a pDDI ($P = 0.023$). Participants who had pDDIs had a higher average of CPZeq than those who did not have an interaction.

Table 7: Covariates of the Dose of Antipsychotics Prescribed

Variable	Dose of CPZeq			
	Mean	**SD**	**t (165)**	**P value**
Sex				
Female	1.69	0.75	-1.0206	0.309
Male	1.58	0.61		
Employment Status				
Student/Unemployed	925	643.98	-0.1745	0.862
Self-employed/Full-time employee	943.37	554.59		
Smoking tobacco				
Non-smoker	1.58	0.58	-1.0820	0.281
Smoker	1.69	0.72		
Alcohol				
Uses alcohol regularly	1.69	0.66	0.8624	0.390
No alcohol use	1.60	0.66		
Mood stabilizer				
None	1.36	0.65	-4.0660	**0.001**
Currently using	1.78	0.62		
Anticholinergics				
None	1.55	0.66	-2.9049	**0.004**
Currently using	1.87	0.61		
Comorbidity				
None	1.73	0.67	3.1985	**0.002**
Existing	1.36	0.54		
Drug-drug Interactions				
No	832.61	612.01	-2.2954	**0.023**
Yes	1050.33	606.87		

A one-way analysis of variance was done to establish the association between the socio-demographic and clinical characteristics with the dose of antipsychotics. The analysis showed no statistically significant variance among the various groups regarding the dose of antipsychotics administered, as shown in Table 8.

Table 8: Covariates of the Dose of Antipsychotics Prescribed

Variable	Chlorpromazine Equivalents (mg)		
	df (degrees of freedom)	F	P-Value
Age (Years) 18 – 31 32 – 45 46 -59 >60 years	[3,163]	1.18	0.982
BMI (kg/m^2) Underweight (<18.5) Healthy weight (18.5 – 24.9) Overweight (25.0 – 29.9) Obese (>30.0)	[3,163]	0.45	0.318
Previous Admissions None 1-3 times More than 3 times	[2,164]	2.78	0.558
Marital Status Single Married Divorced/Separated/Widowed	[2,164]	0.49	0.372
Education Informal Primary Secondary College University	[4,162]	0.60	0.664
Religion Christian Muslim Other	[2,164]	0.72	0.808
Residence Rural Urban Semi-urban	[2,164]	1.38	0.412
Diagnosis APY BMD BMD/DIP DIP MDD MIP PPP SAD SZA SZA/DIP SZA/MDD	[10,147]	0.79	0.888
Duration of Illness (years) 1-2.9 3 – 5.9 6 – 14.9 >15	[3,163]	0.70	0.714

4.11 Bivariate Analysis of the pDDIs

A bivariate logistic analysis was done to assess any association between the various categorical variables and pDDIs. The odds of having a pDDI was 2.23 higher in patients receiving a supramaximal dose compared to those who received a standard dose (OR =2.23, P = 0.012).

Table 9: Covariates of Potential Drug-drug Interactions

Variable	Potential Drug-drug Interactions	
	Bivariate Analysis Crude OR (CI 95%)	**P-Value**
Age (Years) Below 35 years Above 35 years	1.65 (0.80, 3.42)	0.398
Sex Male Female	1.41 (0.64, 3.11)	0.838
BMI (kg/m^2) Below 25 Above 25	1.38 (0.71, 2.68)	0.346
Previous Admissions Never admitted Previously admitted	0.67 (0.32, 1.41)	0.291
Marital Status Single Married	1.36 (0.63, 2.94)	0.79
Education Below secondary Secondary and above	1.97 (0.978, 3.97)	0.058
Religion Non-Christian Christian	1.44 (0.56, 3.73)	0.450
Residence Urban/Semi-urban Rural	1.17 (0.56, 2.46)	0.670
Comorbidity None Existing	1.22 (0.60, 2.51)	0.55
Alcohol use No Yes	0.87 (0.38, 1.99)	0.751
Smoking No Yes	1.30 (0.58, 2.90)	0.432
Supramaximal dose ≤1000mg CPZeq >1000mg CPZeq	2.23 (1.19, 4.17)	**0.012**
Duration of Illness ≤8 years Above 8 years	0.98 (0.54, 1.83)	0.951

4.12 Bivariate Analysis of FGA's Use

A bivariate logistic analysis was done by regressing the number of FGAs prescribed against the various independent variables to identify any association (Table 10). A higher number of FGAs prescribed significantly increased the odds of a patient receiving a supramaximal dose by up to 18 times (P <0.001).

Table 10: Covariates of the Number of FGAs Prescribed

Variable	Number of FGAs Prescribed	
	Bivariate Analysis Crude OR (CI 95%)	**P-Value**
Age (Years) ≤ 35 years > 35 years	1.41 (0.65, 3.05)	0.382
Sex Male Female	1.86 (0.87, 4.00)	0.863
BMI (kg/m^2) ≤25 > 25	1.07 (0.50, 2.30)	0.860
Previous Admissions Never admitted No admission	2.89 (1.33, 6.26)	0.071
Marital Status Single Married	0.64 (0.27, 1.49)	0.302
Education Below secondary Secondary and above	0.57 (0.25, 1.29)	0.180
Religion Non-Christian Christian	0.88 (0.25, 3.15)	0.850
Residence Urban/Semi-urban Rural	2.08 (0.714, 6.08)	0.179
Comorbidity None Existing	0.53 (0.17, 1.66)	0.279
Alcohol use No Yes	1.36 (0.44, 4.23)	0.584
Smoking No Yes	0.56 (0.178, 1.76)	0.322
Supramaximal Dose ≤1000mg CPZeq >1000mg CPZeq	18.04 (0.50, 1.65)	**P <0.001**
Duration of Illness ≤8 years Above 8 years	2.30 (0.85, 6.22)	0.101
Drug-drug Interactions No Yes	1.30 (0.48, 3.53)	0.301

4.13 Bivariate Analysis of SGA's Use

A bivariate logistic analysis of the number of SGAs prescribed was done against various independent variables to identify any association (Table 11). Having a secondary education and below was associated with the probability of receiving fewer SGAs (OR = 0.28, P=0.010). Additionally, the higher the number of SGAs prescribed, the higher the chances of having a pDDI (OR =4.01, P<0.001).

Table 11: Covariates of the Number of SGAs Prescribed

Variable	Number of SGAs Prescribed	
	Bivariate Analysis Crude OR (CI 95%)	**P-Value**
Age (Years) Below 35 years Above 35 years	1.59 (0.66, 3.81)	0.301
Sex Male Female	0.82 (0.34, 1.99)	0.663
BMI (kg/m^2) Below 25 Above 25	1.58 (0.74, 3.36)	0.240
Previous Admissions Never admitted No admission	0.65 (0.27, 1.55)	0.330
Marital Status Single Married	1.89 (0.79, 4.51)	0.151
Education Below secondary Secondary and above	0.28 (1.28, 6.11)	**0.010**
Religion Non-Christian Christian	0.51 (0.18, 1.43)	0.201
Residence Urban/Semi-urban Rural	0.71 (0.31, 1.63)	0.424
Comorbidity None Existing	0.52 (0.21, 1.29)	0.159
Alcohol use No Yes	0.56 (0.22, 1.44)	0.233
Smoking No Yes	1.40 (0.57, 3.42)	0.461
Supramaximal Dose ≤1000mg CPZeq >1000mg CPZeq	0.63 (0.30, 1.34)	0.232
Duration of Illness ≤8 years Above 8 years	0.49 (0.20, 1.22)	0.125
Drug-drug Interaction None Yes	4.01 (1.90, 8.47)	**P<0.001**

4.14 Association between Participants' Profiles and Supramaximal Doses

A bivariate logistic analysis of the prescription of a supramaximal dose against various variables to identify any significant relationship showed that those who received supramaximal doses were less likely to have comorbidities (OR=0.28,

P=0.003). Secondly, those receiving supramaximal doses were 2.12 times more likely to have pDDIs than those receiving a standard antipsychotic dose (P = 0.013).

Table 12: Covariates of the Prescription of a Supramaximal Dose

Variable	Prescription of a Supramaximal Dose	
	Bivariate Analysis Crude OR (CI 95%)	**P-Value**
Age (Years) Below 35 years Above 35 years	0.84 (0.38, 1.90)	0.682
Sex Male Female	0.94 (0.41, 2.15)	0.882
BMI (kg/m^2) Below 25 Above 25	1.03 (0.51, 2.07)	0.941
Previous Admissions Never admitted No admission	2.00 (0.87, 4.58)	0.101
Marital Status Single Married	1.56 (0.68, 3.58)	0.300
Education Below secondary Secondary and above	0.62 (0.29, 1.30)	0.206
Religion Non-Christian Christian	1.39 (0.52, 3.71)	0.505
Residence Urban/Semi-urban Rural	1.28 (0.60, 2.73)	0.523
Comorbidity None Existing	0.28 (0.12, 0.64)	**0.003**
Alcohol use No Yes	0.993 (0.99, 0.45)	0.988
Smoking No Yes	0.92 (0.39, 2.13)	0.838
Drug-drug Interactions No Yes	2.12 (1.18, 4.13)	**0.013**
Duration of Illness ≤8 years Above 8 years	0.94 (0.50, 1.75)	0.839

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Introduction

This chapter discusses the findings from the data analysis section, concludes the main observations, and makes recommendations for further research. The discussion incorporates findings from similar previous research work, noting the differences and similarities in the observations.

5.2 Discussion

5.2.1 Sociodemographic Data

There was male predominance (64.7%) among the participants, showing that mental illnesses mostly affected males more than females. This was similar to other study done in Kenya (55.49%) and Sudan (57%), where the majority were male (18,44,48). Mental illnesses were more prevalent among those aged below 45 years. The median age was 34 years suggesting that the disease afflicts the middle-aged Kenyan population, similar to another study in Kenya where the median age was 31 (44).

The majority of the patients were within the recommended BMI range of 18.5 – 25.0kg/m^2. However, a substantial percentage of the patients were not within the healthy weight category, with 42.5% being overweight or obese. The estimated global prevalence of overweight individuals is 40%, with nearly 30% being obese. In this study, with 42.5% overweight participants and 29.3% being obese, there was a close match with the global statistics (33). The slight difference could be attributed to the use of SGAs which is associated with weight gain. However, studies have not established a close association between obesity and most mental illnesses, except for depression, where depression and obesity are related reciprocally (33). The majority of the patients had a positive history of previous psychiatric admission (61.6%), pointing to the chronic and relapsing nature of mental illnesses. Perhaps, the chronic nature of the disease renders patients to chronic antipsychotic medications, which could also have precipitated weight gain, as revealed in other studies (30).

The majority of the patients were single and have never been married (55.7%), and only 38% were married. This observation was similar to studies done in India and the USA, where 58.99% and 76.3% were single, respectively (49). The poor premorbid adjustment could explain why the mentally have limited ability to form consistent and long-term social engagements, the occupational and social disability that arises from the illness, and the early onset of the disease when most young adults acquire spouses (49). In this study, where the average age of onset for mental illnesses was 27.6 ±12.1 years, most of these single adults would be unable to form long term relationships, hence putting them at a social disadvantage.

Mental illnesses are significantly associated with school termination before completing primary school, high school, college entry, and college graduation. A study conducted in the USA found the odds for school termination among the mentally ill to be 1.3 to 7.0 compared to the rest of the population, with the highest terminations being seen in high school (50). More than 90% of the patients had at least a primary level of education, but less than half of them (41.2%) had attained secondary school education. Even much less of them (12.6%) had college, and few had a university education (6.6%). This could be explained by the early onset of mental illnesses, which consistently hinders educational attainment, particularly for disorders involving externalising behaviour (50).

The use of alcohol, especially heavy drinking, is closely linked with depressive symptoms, which explains why alcohol use was significantly associated with certain psychiatric disorders more than others at MNTRH ($P<0.001$). A study done in Norway comparing 566 adolescents with psychiatric disorders to 8137 adolescents from the general population showed that alcohol use among the mentally ill was much lower than the general population (51). Alcohol among the mentally ill is a 'self-medication', especially for anxiety and depression. Alcohol helps to induce sleep and temporarily reduces the feeling of depression and anxiety (51). Notably, patients with mood disorders have high frequencies of using alcohol, smoking, and abusing illicit drugs.

However, smoking among the mentally ill in the Norway study was much higher, and they had a four times odds ratio of having engaged in illicit drugs (51). In this study, the smoking rate was 43.1%, compared to the Kenyan rate of tobacco use which is 6.0

– 19.1%. In Africa, the rate of tobacco use is about 20% compared to the global usage rate of 15% (52). Therefore, the prevalence of tobacco use at MNTRH was more than two times that of the general population. Smoking diminishes the negative affect among the mentally ill, and individuals with anxiety disorders and depression have demonstrated higher smoking rates than the general population (51). In another study, people with schizophrenia were shown to have significantly higher smoking rates than the general population (53). This explains the findings at MNTRH, where there was a significant association between the diagnosis and being a smoker ($P<0.001$), whereby people with particular mental illness were more likely than others to be smokers.

Most of the participants were Christians (85.0%), and only 9.6% were Muslims. In Kenya, approximately 83% of the citizens are Christians, 11% are Muslims, while 25% belong to other religions (54). The predominance of Christians in the institution was congruent with the Kenyan demographics.

Mentally ill patients were unlikely to secure full-time employment, with only 9.0% of them being full-time jobs. The majority of the patients were unemployed (64.7%), while those who were self-employed were 20.3%. Similar studies showed low employment rates for patients with schizophrenia. For instance, in the UK, the employment rate was 12.9%, 30.2% in Germany, and 11.5% in France (55). This could be attributed to the chronic nature of the disease, positive and negative symptoms, especially in a work environment, and alcohol and substance abuse.

There was a significant variance of the diagnosis between males and females, with some mental illnesses being disproportionally spread across the two ($P<0.001$). For instance, males were more likely to be diagnosed with DIP, which could be explained by the higher rates of substance abuse among males than females (43). This is supported by research works showing that women are more vulnerable to anxiety and depressive disorders, while men suffer more from substance use disorders and antisocial personality disorders (56).

The BMI category was also likely to predict the kind of diagnosis ($P<0.001$). Studies have shown that obesity is significantly associated with an increased lifetime risk of bipolar disorder (OR=1.47), major depression (OR = 1.21), and substance use disorder (OR 0.78) (57). Another significant covariate of the diagnosis was the

number of previous admissions (P<0.001), which could be explained by the high rates of relapses associated with certain mental disorders. Schizophrenia is associated with a 3.5% risk of relapse, and approximately 40% of schizophrenia patients experience relapse after one year of admission (58). Another study in Ethiopia also concluded that schizophrenia (81.92%) and bipolar disorder (88.12%) have a high rate of relapses and readmission (58).

The marital status was a covariate of the diagnosis in the study done at MNTRH (P<0.001). The marital status of an individual affects the coping mechanisms of an individual with psychological stresses. Separated, divorced, and widowed individuals with mental illnesses had a relatively lower well-being score than married or 'coupled' individuals (59). Being married could reduce the chances of relapses of mental conditions such as bipolar disorder and schizophrenia due to social support in adherence to medication, proper nutrition, and prompt seeking of psychiatric help when signs of relapses are noted.

5.2.2 Prevalence of Mental Illnesses

Schizophrenia was highly prevalent, affecting 43.7% of the patients, slightly lower than a study done in the same institution in 2014 when the prevalence was 46.95% (44). The prevalence of BMD in 2014 (14.63%) was comparable to 19.8% in 2020. The 2014 study at MNTRH drew its sample from the outpatient department only, as opposed to both the inpatient and outpatient department. This could have resulted in varying prevalence rates of mental illnesses. Notably, drug-induced psychosis seems to have risen from 12.2% according to a study done in 2014 (44) to 26.3% in 2020. The use of alcohol, smoking, and substance abuse has been on the rise globally as well as in Kenya, especially among the young. Substance use has been on a global rise across all genders, accompanied by drug use disorders (60), which could explain the reason for the substantially increased prevalence of DIP at MNTRH between 2014 and 2020. In sub-Saharan Africa, substance use disorders are projected to increase by 130% in 2050 (61). This is further aggravated by a lack of adequate budgetary support, treatment and prevention systems in Kenya (61).

Mental illnesses are chronic, with the major ones (SZA, DIP, SAD, and BMD) lasting for at least ten years. Psychotic illnesses rarely occur before 14 years but are more

prevalent in the age of 15-17 years. Schizophrenia which is the most common psychotic illness, begins at the age of 15 -35 years. In this study, the earliest age of onset was ten years for schizophrenia and 13 years for schizoaffective disorder. For drug-induced psychosis, bipolar disorder, and acute psychosis, the age of onset was about 14 years, corresponding to the average global age of onset (62). Some studies suggest that early intervention for early-onset mental illnesses could reduce disease severity and reduce the progression of secondary psychiatric disorders (62). The average age of onset of the mental disorders was 27.6 ±12.1 years, which corresponds to the peak age of onset of 14/18 years of all mental disorders(63). The average age of onset of schizophrenia, personality disorder, bipolar disorder, and PTSD averages 30 to 35 years globally, which was almost similar to the average age of onset for these conditions in this study. Substance use disorders were associated with a lower age of onset of 21.8 to 28.0 years, which is higher compared to other studies that estimate it to be 17 to 22 years (63).

5.2.3 Prescription Patterns

Patients received drugs recommended for treating their primary diagnosis, with every clinician showing variance in their preferred choice of drugs, but all of them were consistent with guidelines. Most of the switches between drugs and the decision that informed prescribing particular drugs could not be interrogated for correctness since the rationale behind the treatments was not detailed in the patients' files. All the drugs prescribed to the patients did not exceed the maximum effective dose recommended by the British National Formulary.

The dose of CPZeq is a measure of whether a patient received a standard dose of antipsychotics (≤1000mg of CPZeq) or a higher than normal dose of antipsychotics (>1000mg of CPZeq, also known as a supramaximal dose). In all cases, the maximum effective dose of an individual drug was within the allowed limit; however, the cumulative CPZeq dose, which was calculated by adding up all the drugs prescribed per patient, was higher than the standard dose. Participants who used standard doses were 35.9% (n=60), while those who used supramaximal doses were 53.3% (n=88). The high prevalence of supramaximal doses could be attributed to the high rate of polypharmacy, especially with FGAs.

The rate of use of FGAs at MNTRH was 79.2%, and that of SGAs was 45.2%. The rate of SGAs use was substantially lower than other developed countries in the world, such as Arab countries (95.6%), China (86.6%), Turkey (96.9%), Korea (93%), India (93.5%) (49) and New Zealand (87.0%). The same remarkable difference was noticeable in the use of FGAs, where the use was markedly high at 79.2% at MTNRH compared to other countries such as Arabian countries (23.4%), Turkey (17.2%), New Zealand (13.0%), India (33.81%) and Korea (7%) (49). This could be explained by the exorbitant costs of SGAs in the Kenyan population with low affordability by the patients. This is despite the fact that SGAs are perceived to be much safer than the FGAs because they have a reduced risk of causing extrapyramidal effects.

Receiving a higher number of FGAs significantly increased the chances of receiving a supramaximal dose by up to 18 times ($P < 0.001$). Supramaximal doses have been correlated with the number of antipsychotics prescribed (64,65), implying that polypharmacy and high-dose prescriptions are inextricably related. This could also be attributed to the high usage of fluphenazine decanoate injection (42% of patients), which has a high CPZeq conversion factor. Most patients who received fluphenazine injection also received oral medications contributing to supramaximal doses. FGAs (compared to the SGAs) contributed to higher CPZ equivalents of 930.4 ± 617.5mg. This is in contrast to other countries that had a much lower mean dose of CPZeq, such as Qatar with a mean CPZ equivalent of 577.8mg, Korea 732.1mg (66), and Turkey 684.1mg (67). The plausible explanation would be that the high-income countries that predominantly used SGAs would enjoy the benefit of lower doses of CPZeq.

The polypharmacy rate in the present study was at 60%, whereby 53% of the patients received two antipsychotics, 6% three antipsychotics, and 1% quadruple therapy. This rate of polypharmacy was almost similar to a study in Qatar at 58.8% (68). Polypharmacy is a common practice globally, as observed in several studies in Asia with a sample size of more than 2000; 45.7% of the prescriptions had more than one antipsychotic (68). A study in the USA had a polypharmacy rate of 57% (69), Japan 69% (70), while Korea had the lowest rate at 9.0% (22). Some studies support the use of polypharmacy with findings suggesting that combining some drugs such as clozapine and aripiprazole could reduce rehospitalisation (71). Polypharmacy is applicable in exceptional instances such as during cross-titration of antipsychotics,

augmenting the efficacy of clozapine, and when managing particular side-effects, and when rapid tranquilization is needed (72). However, in routine practice, there is no conclusive evidence for this practice, and clinical guidelines largely emphasize monotherapy.

Haloperidol was the most commonly used FGA, while fluphenazine was the most common injectable, an observation that was congruent with a similar study in Sudan (48) and Korea (22). Olanzapine was the most preferred SGA, issued to 25% (n=41) of the participants, followed by risperidone at 20%. Although both olanzapine and risperidone are well tolerated and efficacious, olanzapine has been consistently associated with a greater reduction in the severity of psychiatric illnesses and improvement of negative symptoms (22), and it has fewer extrapyramidal effects (73). The low usage of SGAs could be attributed to budgetary constraints from the ministry of health, affecting the supply chain of these drugs at the hospital (46). Most patients could not afford the SGAs from external sources, and the supply of these commodities was erratic at the pharmacy. Noting that olanzapine was involved in 39% of the drug-drug interactions, it should be used cautiously, with the appropriate drug combinations and adequate monitoring.

Patients using antipsychotics received adjunct therapy, particularly carbamazepine, amitriptyline, fluoxetine, sodium valproate, topiramate, and valproic acid. The use of high doses could present a higher risk of extrapyramidal side effects. Therefore, the use of an anticholinergic such as trihexyphenidyl could be closely associated with the occurrence of side effects that increase proportionally to the dose of antipsychotics. This could be the reason why patients on higher doses of chlorpromazine equivalents were most likely to use anticholinergics (P=0.004). Studies have found that the use of anticholinergics is a correlate of antipsychotic polypharmacy. Notably, high usage of SGAs is associated with not taking anticholinergics. In this setting where FGA usage was high, most patients also used an anticholinergic (trihexyphenidyl) on a PRN basis.

A high dose of CPZeq was associated with the use of a mood stabilizer (P=0.001). A combination of a mood stabilizer and an antipsychotic is commonly indicated for relapsing cases of mental illnesses (patient with four or more acute episodes in a year) (74). Having a history of admission was significantly associated with using a mood

stabilizer (P=0.003), which points to the high likelihood of relapsing patients receiving a mood stabilizer. These findings are intertwined in that patients who relapse (higher rates of readmission) are likely to receive a higher dose of antipsychotics to stabilize them. This was likely to be accompanied by a mood stabilizer as well.

One of the patients was on a drug holiday. This practice is thought to "re-sensitize" neurons to the acute pharmacological activities of antipsychotics, and it is also helpful in treating tardive dyskinesia (75) and neuroleptic malignant syndrome (31). However, this comes with the risk of poor compliance to therapy, destabilizing a patient, and difficulty in distinguishing discontinuation and rebound effects (75).

Having a secondary education and below was associated with the probability of receiving fewer SGAs (OR = 0.28, P=0.010). However, the influence of the education level of the patients on the prescribing patterns of antipsychotics has not been studied. It could be that patients with a low level of education are likely to fall in the low economic class, hence not able to afford the SGAs, whose prices are exorbitant. Since clinicians prescribe drugs that are tailored to the patient's circumstances, it is possible that prescribers opted for FGAs, which are more accessible to them.

5.2.4 Comorbidities

The pharmacological agents used for managing the comorbidities included nifedipine, amlodipine, methyldopa, and hydrochlorothiazide for the hypertensive participants. Several studies have shown hypertension is normally prevalent in clozapine use and relatively low with other antihypertensives. It is estimated that in the long term, 30-40% of patients using antipsychotics develop hypertension (31). Additionally, hypertension is closely related to stressful conditions and unemployment. The stress-related conditions cause elevated cortisol levels, which increases arteriosclerotic deposition, narrowing of the blood vessels intima, and ultimately elevated arterial pressure (76). Therefore, patients with mental illnesses require frequent monitoring of their blood pressure.

One significant finding was that a supramaximal dose was administered to those with no comorbidities (OR=0.28, P=0.003). This finding was similar to another study

where patients with diabetes mellitus, cerebrovascular, cardiovascular, and kidney diseases were less likely to receive high dose prescriptions (41). It might be the presence of comorbidities prompted the clinicians to be more careful with the dose of antipsychotics to avoid adding the burden of any side effects to already ill patients.

5.2.5 Potential Drug-drug Interactions

The occurrence of pDDIs was positively associated with the administration of higher doses of CPZ equivalents (P=0.023). A high cumulative dose of antipsychotics could be because of combining several drugs that interacted with each other. Drug interactions, especially for chronic usage in mental illnesses, can lead to poor tolerability, reduced efficacy of antipsychotics, and adverse events (77). Some of the signs and symptoms recorded that suggested QT-prolongation or cardiotoxicity included light-headedness, dizziness, and tachycardia.

Ten possible outcomes of pDDIs were noted, with the most common PDIs being prolonging the QT-interval (16.2%). QT prolongation is one of the most common reasons for market drug withdrawal. One study involving 6417 patients, QT-interval prolongation or QT seizure was experienced in nearly 25% of the participants using antipsychotics (29). Ordinarily, this requires monitoring of the cardiac rhythm to detect changes before and after administration of a drug. The possible manifestation of this outcome is rapid and chaotic heartbeats leading to ventricular fibrillation, syncope, seizures, and sudden death.

The second most common interaction at 14.4% was the risk of cardiac toxicity, which combines the risk of QT-prolongation with cardiac arrhythmias and an elevated risk of torsades de pointes. One of the established risk factors for torsades de pointes is the presence of QT-prolonging agents among others. When more than two QT-prolonging antipsychotics are used concurrently, they create an additive effect to the risk of cardiac toxicity. The risk of cardiotoxicity does not have a precise relationship, but it comes with the rare unexpected risk of sudden death twice more likely than the normal population (78). Notably, 30% of the pDDIs affected the heart functionality, and they carried life-threatening outcomes.

Another main outcome was from the carbamazepine and olanzapine interaction. This could lead to reduced efficacy of olanzapine (CYP3A4 inhibitor) and increased serum levels of carbamazepine (CYP3A4 substrate), leading to carbamazepine toxicity. Some of the possible outcomes of carbamazepine toxicity are ataxia, disorientation, aggression, hallucinations, seizures, and coma. The use of alternative mood stabilizers such as topiramate and lamotrigine has been associated with less clinically significant interactions, hence better patient safety (77). A study involving 11 healthy volunteers, using olanzapine and carbamazepine concurrently resulted in a 46% increase in olanzapine clearance and a 36% decrease in the area under the curve (AUC) of olanzapine (79). This exposes patients to subtherapeutic doses of antipsychotics and the need for higher doses. Carbamazepine is a potent inducer of several cytochrome P450 isoenzymes involved in drug metabolism; therefore, when given concomitantly, the dose of olanzapine should be adjusted.

The other interactions were the increased risk of bleeding, decreased efficacy of co-administered drugs, hepatotoxicity, and anticholinergic effects. These interactions emphasise the need for prompt and frequent monitoring to ensure patient's safety.

Prescribing a higher number of SGAs resulted in increased drug-drug interaction chances (OR =4.01, $P<0.001$). Most antipsychotics are metabolized by hepatic cytochrome p450 isoenzymes, especially CYP1A2, CYP2D6, and CYP3A4 (80). The frequency of cytochrome-mediated interactions is high among psychiatric patients. Olanzapine is metabolized by CYP1A2, CYP2D6, and flavin mono-oxygenase 3 (80). Inducers of CYP3A4 like carbamazepine are likely to interact with olanzapine through this isoenzyme, explaining why olanzapine and carbamazepine recorded a high number of interactions. These major interactions by the SGAs could be because olanzapine was implicated in most of the interactions.

Like other study findings, olanzapine and haloperidol combinations were highly likely to cause harmful drug-drug interactions (77). The inclusion of some specific drugs in any regimen was highly likely to cause major drug-drug interactions such as fluoxetine and amitriptyline. For instance, 17 prescriptions had amitriptyline, 88.2% of which led to major drug-drug interactions. Similarly, fluoxetine was prescribed 16 times, but it resulted in 7 interactions, meaning it caused pDDIs in 43.8% of the

incidences it was prescribed. Therefore, some of the drugs that are more likely than others to cause drug-drug interactions should be administrated cautiously.

5.2.6 Monitoring

The recommended on-treatment monitoring parameters after administering any parenteral antipsychotic are temperature, pulse rate, blood pressure, and respiratory rate (31). However, this was not routine practice in the institution after administering the injectables. Patients who were antipsychotic naïve or been switched to alternative ones should have their baselines such as the BMI and waist circumference noted and repeated at least every six months (31). This monitoring aspect was missing in all patients, especially among the patients using drugs that are likely to cause rapid weight gain. Weekly BMI monitoring is recommended for the first three months.

None of the patients was monitored for the QT interval changes using an ECG, despite having some patients with elevated risks for QT-interval prolongation. In a similar study done in Sudan, only 4.1% of the patients had an ECG (48). ECG monitoring in several facilities could be complicated by lack of expertise by psychiatrists in ECG interpretation, lack of ECG machines, low inter-rater reliability, lack of adequate time for ECG determination, especially in the outpatient unit, and difficulty in performing baseline ECG in acutely disturbed patients (28). Patients with extreme ages, metabolic abnormalities, currently using antibiotics, antimalarials or antiarrhythmics and those with cardiac abnormalities need a baseline and frequent monitoring of the QT interval (31). The potential risk of cardiac arrhythmias was alarming since there was no routing monitoring of electrolytes for high-risk patients such as those with acute psychosis during admission.

Drugs that are given intravenously are classified as having a ‘high effect’ on QT-interval prolongation. In contrast, haloperidol and chlorpromazine are classified as having a moderate effect on the QT interval. For moderate and high effect drugs, routine monitoring should be paramount. However, most of the other drugs used at the institution are in the ‘low effect’ category, such as aripiprazole, flupentixol, fluphenazine, olanzapine, and risperidone, which possibly explain the low incidence of cardiotoxicities.

Other recommended monitoring parameters are prolactin levels, liver function tests, urea and electrolytes, blood lipids, full blood count, weight gain, creatinine phosphokinase, and plasma glucose (31). Most of these tests should be done at baseline, after 3-6 months, and annually, but there was no evidence of any recommended tests occurring at the required frequency, including the blood pressure. The absence of baseline parameters was similarly observed in another study in Sudan, where the weight, lipid profiles, prolactin levels, and other crucial tests were not done as recommended by the clinical guidelines (48). Additionally, monitoring is essential for acute cases, especially among the outpatients who could have abused substances such as cannabis, heroin/methadone, cocaine, amphetamine, and alcohol, among other substances. Injecting them with tranquillizers or oral antipsychotics could worsen their clinical picture, especially their blood pressure, heart rhythm, temperature, and breathing rate (31). For this category of high-risk patients, monitoring was not done.

5.3 Strengths and Limitations

This was the first study to describe the prescription patterns at MNTRH, the largest mental health facility in the country; hence its patient management modalities widely reflect the pharmacotherapy practices in the country. Some of the data were collected prospectively by the investigator allowing for verification and clarification of any inaccuracies, which reduced errors from the data collected. The random sampling process and use of validated tools (NICE guidelines and a piloted questionnaire) minimized bias and assured the internal and external validity of the study.

This study, however, was limited to a small sample of 167. A bigger sample size would have allowed the study to capture more data on the various variables, giving it more statistical power. Secondly, there was limited information on the files about the rationale of switching or prescribing specific regimens, making it difficult to assess whether the indication was correct. Having more detailed information on the justification for using specific drugs and polypharmacy would have enriched the study. Finally, the study was largely dependent on the medical records entered in patient's files by the healthcare team, and any erroneous entries or omissions could have given inaccurate data for this study.

5.4 Conclusion

The majority of the prescriptions (79.2%) contained FGAs, while SGAs were found in 45.2% of the prescriptions. Patients on monotherapy were 38%, while those on dual therapy were 53%. The practice of polypharmacy contributed to 35.9% of the patients having a standard dose of antipsychotics, while 53.3% of the patients received supramaximal doses. The odds of a patient receiving a supramaximal dose was associated with having a higher number of FGAs.

About half of the patients had pDDIs that were highly likely to be caused by interactions with olanzapine, carbamazepine, and haloperidol, among others. The occurrence of pDDIs was positively associated with the administration of higher doses of CPZeq. Additionally, the higher the number of SGAs prescribed, the higher the chances of having a drug-drug interaction and the possible outcomes for the interactions were related to QT-prolongation and other forms of cardiac toxicity.

5.5 Recommendation for Policy and Practice

We recommend the use of monotherapy instead of polypharmacy with antipsychotics to ensure that patients receive a lower dose of CPZeq and lower the chances of pDDIs. Polypharmacy involving FGAs should be avoided to ensure patients do not receive a supramaximal dose and, by extension, a pDDI. Alternatively, clinicians should routinely monitor cardiac functions for mentally ill patients on high dose antipsychotics.

Considering the potentially harmful effects of major drug-drug interactions or long-term side effects of antipsychotics, clinicians should also be encouraged to carry out routine on-treatment monitoring of patients for adverse drug effects and pDDIs. A combination of carbamazepine (adjunct) and olanzapine should be avoided, and an alternative adjunct drug considered to reduce chances of a clinically significant drug-drug interaction.

5.6 Recommendation for Further Research

Future studies should develop a scaled guideline that informs the clinical efficacy of various doses of CPZeq, particularly for the FGAs.

Future prospective studies should establish the clinical efficacy of monotherapy versus polypharmacy in antipsychotics use to inform the future practice of coadministration of drugs.

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Appendix 1: Data Collection Form
Instructions

1.Please write in the provided blank spaces

2. Where a code has been assigned, please fill in the code in the space provided

3. Fill in the data using the specified units of measurement

4. Fill out the full generic (INN) names of the drugs as illustrated in the form

5. If the required information is not available from the file or the participant/surrogate, indicate Not Available [N/A]

6. This information should only be collected after obtaining informed consent from a mentally stable and competent participant or their surrogates.

Investigator:					**Date:**	
PART 1: SOCIODEMOGRAPHIC DATA						
Patient ID	**Unique Code**	**Prescription Date [dd/mm/yyyy]**	**Sex [F/M] F = 0 M = 1**	**Age (yrs.)**	**Weight (Kgs)**	**Height (cm)**

No. of previous admissions 0 = None 1 = 1 -3 times 2 = > 3 times	**Marital Status** 0 = Single 1 = Married 2 = Divorced 3 = Separated 4 = Widowed	**Education** 0 = Informal 1 = Primary 2 = Secondary 3 = College 4 = University	**Smoking (cigarette)** 0 = Non-Smoker 1 = Smoker
Alcohol use 0 = Uses alcohol 1 = No alcohol use	**Religion** 0 = Catholic 1 = Protestant 2 = Muslim 3 = Other	**Residence** 1 = Rural 2 = Urban 3 = Semi-urban	**Employment status** 0 = Student 1 = Unemployed 2 = Self-employed 3 = Full-time employee

PART 2: DIAGNOSIS		**Duration of illness (years)**
Diagnosis	**1.**	

(Mental or behavioural disorder):	**2.**	
	3.	
	4.	

PART 3: APPROPRIATENESS OF DRUG					
Diagnosis (Mental or behavioural disorder):	**Psychopharmacological agent administered (INN name, dose (mg), frequency, ROA, and preparation), e.g., Haloperidol 5mg BD PO TABLETS**	**Total Daily Dose (mg)**	**CPZ eq (mg)**	**Correct Indication 0 = No 1 = YES**	**Correct Dose 0 = No 1 = YES**
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					

PART 4: COMORBIDITIES			
Diagnosis	**Drug administered (INN name, dose (mg), frequency, ROA, and preparation) e.g., Enalapril 10mg BD PO TABLETS**	**Correct Indication 0 = No 1 = YES**	**Correct Dose 0 = No 1 = YES**
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			

PART 5: DRUG INTERACTIONS		
Are there any potential drug interactions? [NO = 0, YES = 1]		
Interacting drugs		**Consequences of drug-drug interactions**
1		
2		

3.		
4.		
5.		
6.		

PART 6: PATIENT LABORATORY MONITORING (TICK APPRPOPRIATELY)		
□ Bicarbonate **□ BP** **□ Calcium** **□ CPK** **□ ECG** **□ eGFR** **□ FBC** **Other…….**	**□ FBS/HbA1c** **□ LFTs** **□ Lipids** **□ Magnesium** **□ Potassium** **□ Phosphorous** **□ Plasma levels** **Other…….**	**□ Prolactin** **□ Pulse** **□QT prolongation** **□ Urea** **□ Weight** **□ Thyroid function test** **□ Waist Circumference** **Other…….**

KEY: BP- Blood pressure, CPK - creatine phosphokinase, ECG - Electrocardiogram, eGFR - Estimated glomerular filtration rate, FBC - Full blood count, FBS - Fasting blood sugar, HbA1c - Haemoglobin A1c, and LFTs - Liver function tests.

Appendix 2: Participant Information and Consent Form (English/Kiswahili Version)

ADULT PARTICIPANT INFORMATION AND CONSENT FORM FOR ENROLLMENT IN THE STUDY

Title of Study: CHARACTERIZATION OF THE DRUG USE PATTERNS AND POTENTIAL INTERACTIONS AMONG MENTALLY ILL PATIENTS

Principal Investigator\and Institutional Affiliation:

Kevin Kinyanjui Matheri, Master of Pharmacy in Clinical Pharmacy student, Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi

Supervisors/Co-Investigators and Institutional Affiliation:

1. Dr G.D. Nyamu, Senior Lecturer, Department of Pharmaceutics, and Pharmacy Practice, School of Pharmacy, University of Nairobi.
2. Dr B. Amugune, Senior Lecturer, Department of Pharmaceutical Chemistry, School of Pharmacy, University of Nairobi

Introduction:

I request your attention to explain about an ongoing study by the researchers listed above as part of the requirement. This study is part of my assessment for a degree in master of pharmacy in clinical pharmacy at the University of Nairobi. This consent form will inform you about this research and enable you to decide whether to participate in the study. You are free to ask questions related to the study such as, what will happen to you as a participant, the potential risks or benefits, the rights you have as a participant or any other information. When you feel satisfied with the study, you are free to enrol to the study by giving your consent. The name of this process is 'informed consent.' When you understand and decide to join in the study, you will sign your name on this form as proof of consent.

Some of the universal principles in medical research, which apply to participants are:

i) Participation in this study is totally voluntary

ii) At any point in this study, you are free to withdraw without necessarily explaining your withdrawal

iii) In case you decline to be a participant in the research, you will still enjoy all the normal services you are entitled to. A copy of this form will be provided to you for your records.

May I continue? **YES / NO**

The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee has approved this study via protocol No._____

What is this study about?

This research is targeting adult patients with any mental illness. This study wants to assess the drug use patterns of mentally ill patients at this facility. Participants will be asked about their socio-demographic data, past medical history, and current medications. About 170 patients will be randomly chosen to participate in this study.

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

If you agree to part of this study, you will be interviewed privately, answering questions relevant to this study. You will answer questions on your social, medical, and medication history. This interview takes approximately 15 minutes. Additionally, the interviewer will access information from your medical file related to your social, medical, and medication history. The interviewer may request your telephone number or address in case further clarification is needed for this study. Your number will only be used by people working for this study and will not be shared with any other person.

Are there any risks or harms discomforts associated with this study?

From this study, you could suffer a loss of privacy. However, everything you mention will be kept confidential. In this study, a code number will be used to refer to you in a computer database that is password-protected, and all paper records will be kept in a well-secured cabinet. Please note it could still be possible that someone gains access

to the study records and finds out that you were one of the participants since no data storage system can be absolutely secure.

Collecting personal information about you in a public setting could create discomfort, and the investigators will ensure that it is done privately and professionally.

In case you do not want to answer some questions asked from this interview, you could skip them. Remember that you have the right to decline the interview or any questions asked during the interview.

Are there any benefits to being in this study?

By being part of this study, you may not receive an immediate and direct benefit. However, the results of this study will be useful for improving the quality of care received by you and future patients.

Will being in this study cost you anything?

This study will require you to spare about 15minutes to answer questions relevant to this study. However, participating in this study will not cost you any money.

Will you get a refund for any money spent as part of this study?

Since there is no foreseeable expenditure for participating in this study, there will be no compensation arising from being a participant.

What if you have questions in the future?

In case you have any additional concerns about being part of this study, please send a text message, or call the investigator on the following number: Kevin Matheri (+254729138121). You may also contact my supervisor, Dr G.D. Nyamu (+254722403671). If you need additional information about your rights as a research participant, please contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee through the telephone number 2726300 Ext. 44102 or the email address: uonknh_erc@uonbi.ac.ke. The study has ethical approval from this entity.

The researchers in this study should compensate you for the charges you incur if you call these numbers for study-related queries.

What are your other choices?

Participating in this research is voluntary. You have the option to decline to participate or to withdraw from this study at any point without suffering any injustice or losing any benefits and services usually enjoyed at the hospital.

Researcher's statement

Having explained all the relevant details of this study to the above participant, I trust that he/she has understood and voluntarily given his/her consent to participate.

Researcher's Name: _____

Date: _____

Signature: _____

Role in the study: _____

CONSENT FORM

Participant's statement

This is to confirm that I have read this consent information or have been read to me. I have discussed with the study counsellor in details about this research, and my questions have been addressed in a language that I understand. I am aware of the benefits or risks of being one of the participants. It is clear to me that my participation is voluntary, and at any given point in this study, I am free to withdraw. Therefore, I have agreed to participate in this study freely.

I understand that the research staff will make all efforts possible to maintain the confidentiality of my personal records and identity. I understand that by consenting to this study, I have not foregone my legal rights, which I am entitled to as a study participant.

Participant/Caregiver printed name: _____

Participant/Caregiver signature / Thumb stamp:

Date: _____

For more information, contact the investigators, Kevin Matheri, at cell phone number: 0729138121 from 8 am to 5 pm during the weekdays.

MUHTASARI WA UHUSIKA WA MTU MZIMA NA FOMU YA IDHINI KWA AJILI YA UTAFITI HUU

Kichwa cha utafiti: **UCHAMBUZI WA UTUMIZI WA DAWA ZA MATIBABU NA MAATHIRIANO KATI YA MADAWA ZENYEWE KWA WALIO NA MAGONJWA YA KIAKILI**

Mpelelezi mkuu \ na ushirika wa kitaasisi: Kevin Kinyanjui Matheri, Mwanafunzi wa shahada ya uzamili ya Madawa, Idara ya Pharmaceutics and Pharmacy Practice, Shule ya Famasia, Chuo Kikuu cha Nairobi

Wasimamizi / Wachunguzi wa ushirikiano na ushirika wa kitaasisi:

1. Dr G.D. Nyamu, Mhadhiri Mwandamizi, Idara ya Pharmaceutics and Pharmacy Practice, Shule ya Famasia, Chuo Kikuu cha Nairobi
2. Dr B. Amugune, Mhadhiri Mwandamizi, Idara ya Kemia ya Madawa, Shule ya Famasia, Chuo Kikuu cha Nairobi

Utangulizi:

Naomba umakini wako nikueleze juu ya utafiti unaoendelea na watafiti waliotajwa hapo juu kama sehemu ya mahitaji. Utafiti huu ni sehemu ya tathmini yangu kwa shahada ya uzamili katika ya dawa katika Chuo Kikuu cha Nairobi. Njia hii ya idhini itakujulisha juu ya utafiti huu na kukuwezesha kuamua ikiwa unaweza kushiriki katika utafiti. Uko huru kuuliza maswali yanayohusiana na utafiti kama vile, nini kitakachokukuta kama mshiriki, hatari zinazoweza kutokea, au faida, haki uliza nazo kama mshiriki, au habari nyingine yoyote. Unapojisikia kuridhika na utafiti huo, uko huru kujiandikisha kwenye utafiti huu kwa kutoa idhini yako. Utaratibu huu unaitwa 'ridhaa iliyo na habari'. Mara tu utakapoelewa na kuamua kushiriki katika utafiti, utasaini jina lako kwenye fomu hii kama uthibitisho wa idhini.

Baadhi ya kanuni za jumla zinazotumika kwa washiriki wote katika utafiti wa matibabu ni:

i) Kushiriki katika utafiti huu ni hiari kabisa

ii) Unaweza kujiondoa kutoka kwa utafiti huu wakati wowote bila kutoa sababu ya kujiondoa kwako

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

Naweza kuendelea? **NDIO** au **LA**

Kamati ya Kitaifa ya Hospitali ya Maadili na Utafiti ya Kenya ya Kenyatta na Chuo Kikuu cha Nairobi imeidhinisha utafiti huu kupitia itifaki nambari_____

Je! Utafiti huu ni nini?

Utafiti huu unawalenga wagonjwa wazima walio na magonjwa yoyote ya akili. Utafiti huu unataka kutathmini mifumo ya utumiaji wa dawa za wagonjwa wanaougua kiakili katika kituo hiki. Washiriki wataulizwa juu ya data yao ya kijamii, historia ya matibabu ya zamani na dawa za sasa. Karibu wagonjwa mia moja na sabini watachaguliwa kwa nasibu kushiriki katika utafiti huu.

Je! Nini kitatokea ikiwa utaamua kuwa katika utafiti huu?

Ikiwa unakubali kushiriki kwa utafiti huu, utahojiwa kibinafsi kujibu maswali yanayohusiana na utafiti huu. Utajibu maswali kuhusu historia yako ya kijamii, matibabu na dawa. Mahojiano haya itachukua takriban dakika kumi na tano. Kwa kuongeza, mtafiti atapata habari kutoka kwa faili yako ya matibabu inayohusiana na historia yako ya kijamii, matibabu, na dawa. Mtafiti anaweza kuuliza nambari yako ya simu au anwani ili ladba kesi ikitaka kufafanuliwa zaidi baadaye. Nambari yako itatumiwa tu na watu wanaofanya kazi kwa utafiti huu na hawatashirikiwa na mtu mwingine yeyote.

Je! Kuna hatari au athari mbaya zinazohusiana na utafiti huu?

Kutoka kwa utafiti huu, unaweza kupata hasara ya faragha. Walakini, kila kitu unachosema kitahifadhiwa kwa siri iwezekanavyo. Katika utafiti huu, kodi maalum itatumika kukutambulisha katika hifadhidata ya kompyuta iliyolindwa na nywila na rekodi zote za karatasi zitafungwa kwenye kabati la faili.

Walakini, hakuna mfumo wa kulinda usiri wako unaweza kuwa salama kabisa, kwa hivyo bado inawezekana kwamba mtu angegundua kuwa ulikuwa kwenye utafiti huu na anaweza kupata habari juu yako.

Kukusanya habari za kibinafsi juu yako katika mpangilio wa umma kunaweza kukupa usumbufu, na wachunguzi watahakikisha kuwa inafanywa kwa faragha na taaluma.

Ikiwa hutaki kujibu maswali kadhaa yaliyoulizwa kutoka kwa mahojiano haya, unaweza kuyaruka. Kumbuka kuwa unayo haki ya kukataa mahojiano au maswali yoyote yaliyoulizwa wakati wa mahojiano.

Je! Kuna faida yoyote kuwa katika utafiti huu?

Kwa kushirika kwa utafiti huu, huwezi kupokea faida yoyote ya haraka na moja kwa moja. Walakini, matokeo ya utafiti huu yatakuwa muhimu kwa kuboresha huduma bora inayopokelewa na wewe na wagonjwa wa siku zijazo.

Je! Kuwa katika utafiti huu kutagharimu chochote?

Utafiti huu utahitaji kupumzika dakika kumi na tano ili kujibu maswali yanayohusiana na utafiti huu. Walakini, kushiriki katika utafiti huu hautakugharimu pesa yoyote.

Je! Utarudishiwa pesa yoyote inayotumika kama sehemu ya utafiti huu?

Kwa kuwa hakuna matumizi dhahiri ya kushiriki katika utafiti huu, hakutakuwa na fidia inayotokana na kuwa mshiriki.

Je! Ikiwa una maswali katika siku zijazo?

Ikiwa una wasiwasi zaidi juu ya kushiriki katika utafiti huu, tafadhali piga simu au tuma ujumbe wa maandishi kwa mpelelezi kwa nambari ifuatayo: Kevin Matheri (+254729138121). Unaweza pia kuwasiliana na msimamizi wangu, Dk. G.N. Nyamu (+254722403671). Kwa habari zaidi juu ya haki zako kama mshiriki wa utafiti, tafadhali wasiliana na Katibu / Mwenyekiti, Hospitali ya Kitaifa ya Hospitali ya Kitaifa ya Chuo Kikuu cha Maadili cha Kenya na Kamati ya Utafiti kwa Namba

2726300 Ext. 44102, au barua pepe: uonknh_erc@uonbi.ac.ke. Utafiti una idhini ya maadili kutoka kwa hii taasisi.

Watafiti watakulipa gharama itakayoambatana na kuwasiliana na nambari hizi ikiwa simu ni ya mawasiliano yanayohusiana na masomo.

Chaguo zako zingine ni nini?

Kushiriki katika utafiti huu ni hiari. Una chaguo la kukataa kushiriki au kujiondoa kutoka kwa utafiti huu wakati wowote bila kuteseka, bila kupoteza haki yoyote, au kupoteza faida na huduma ambazo kawaida hupatikana hospitalini.

Taarifa ya mtafiti

Baada ya kuelezea maelezo yote muhimu ya utafiti huu kwa mshiriki wa hapo juu, nina imani kuwa ameelewa na kwa hiari kupeana ridhaa yake ya kushiriki.

Jina la mtafiti:_____

Tarehe:_____

Sahihi:_____

Jukumu katika somo:_____

FOMU YA IDHINI

Taarifa ya Mshiriki

Hii ni kuhakikisha kuwa nimesoma habari hii ya idhini au imenisomewa. Nimejadiliana na mshauri wa masomo kwa maelezo juu ya utafiti huu, na maswali yangu yameshughulikiwa kwa lugha ambayo naelewa. Ninaelewa faida au hatari ya kuwa mmoja wa washiriki. Ni wazi kwangu kwamba ushiriki wangu ni wa hiari na wakati wowote wa utafiti huu, niko huru kujiondoa. Kwa hivyo, nakubali kwa uhuru kushiriki katika utafiti huu.

Ninaelewa kuwa juhudi zote zitafanywa kuweka habari yangu ya kibinafsi kwa siri na faragha. Ninaelewa kuwa kwa kukubali utafiti huu, sijakatizwa kufurahia haki zangu za kisheria ambazo ninazo kama mshiriki wa utafiti.

Mshiriki / mwangalizi aliyechapishwa jina:

_____

Mshiriki / saini ya mwangalizi / muhuri wa kidole cha gumba:

_____

Tarehe: _____

Kwa habari zaidi, wasiliana na wachunguzi, Kevin Matheri kwa nambari ya simu +254729138121 kutoka saa mbili asubuhi hadi saa kumi na moja jioni siku za kazi.

Appendix 3: Research Proposal Approval

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

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

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

Ref: KNH-ERC/A/250

6th August 2020

Kevin Kinyanjui Matheri
Reg. No.U56/12239/2018
Dept.of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Kevin

RESEARCH PROPOSAL – CHARACTERIZATION OF THE DRUG USE PATTERNS AND POTENTIAL DRUG-DRUG INTERACTIONS AMONG THE MENTALLY ILL ADULT PATIENTS AT MATHARI NATIONAL TEACHING AND REFERRAL HOSPITAL IN KENYA (P185/03/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 6th August 2020 – 5th August 2021.

This approval is subject to compliance with the following requirements:

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

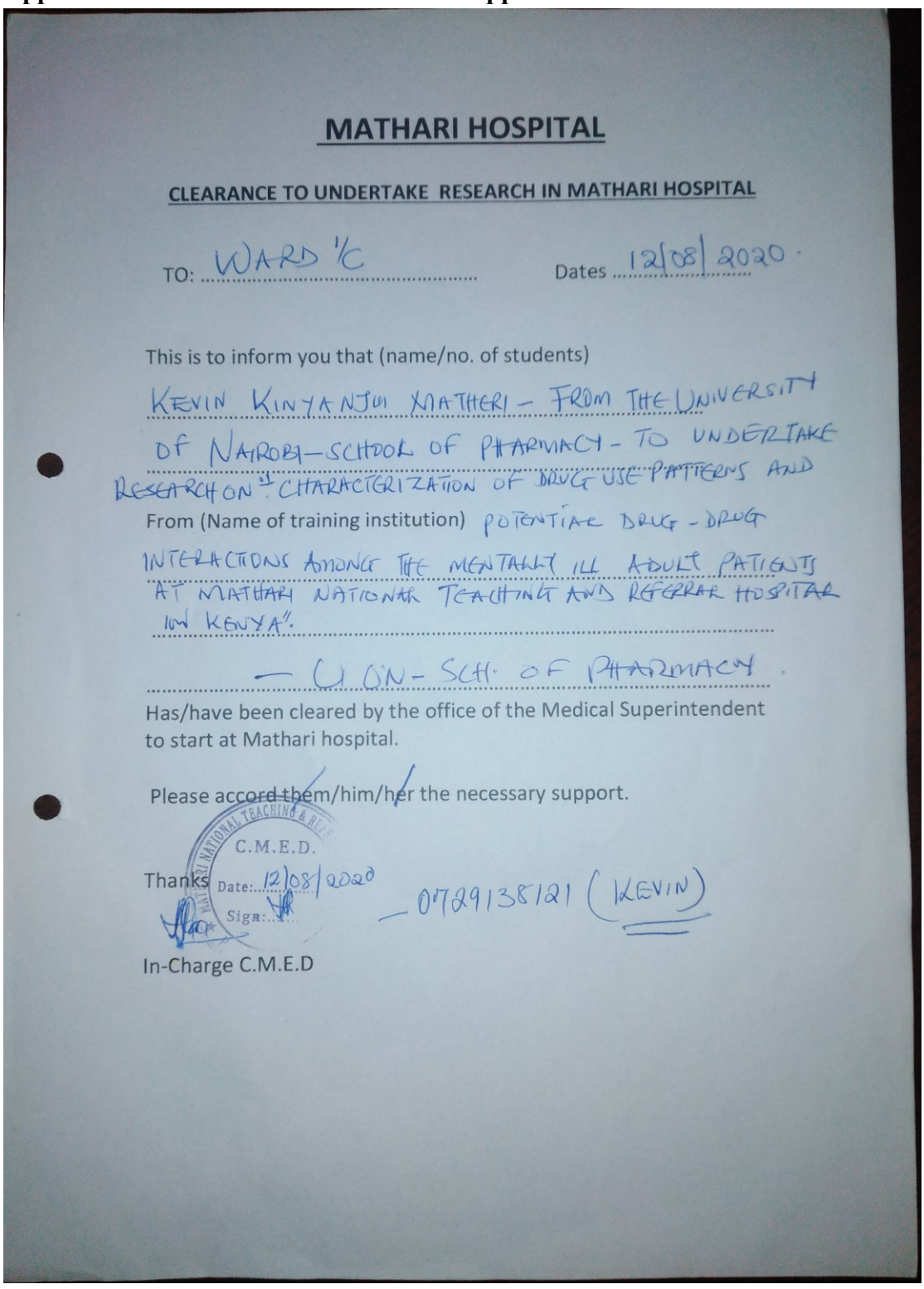
For more details consult the KNH- UoN ERC website**http://www.erc.uonbi.ac.ke**

Yours sincerely,

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

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmaceutics and Pharmacy Practice, UoN
Supervisors: Dr David G. Nyamu(UoN), Dr. Beatrice Amugune(UoN)

Appendix 4: MNRTH Ethics Committee Approval



MATHARI HOSPITAL

CLEARANCE TO UNDERTAKE RESEARCH IN MATHARI HOSPITAL

TO: WARD 1/C Dates 12/08/2020.

This is to inform you that (name/no. of students)

KEVIN KINYANJUI MATHERI – FROM THE UNIVERSITY OF NAIROBI – SCHOOL OF PHARMACY – TO UNDERTAKE RESEARCH ON "CHARACTERIZATION OF DRUG USE PATTERNS AND POTENTIAL DRUG – DRUG INTERACTIONS AMONGST THE MENTALLY ILL ADULT PATIENTS AT MATHARI NATIONAL TEACHING AND REFERRAL HOSPITAL IN KENYA".

From (Name of training institution) – U.O.N – SCH. OF PHARMACY.

Has/have been cleared by the office of the Medical Superintendent to start at Mathari hospital.

Please accord them/him/her the necessary support.

C.M.E.D. Date: 12/08/2020 Sign:

Thanks – 0729135121 (KEVIN)

In-Charge C.M.E.D

Appendix 5: Detailed Drug-drug Interactions

DRUG INTERACTIONS	No of Interactions
INCREASED RISK OF BLEEDING	**1**
FLX/DICLO	1
INCREASED RISK OF CARDIOTOXICITY	**25**
CLAR/AMI/RIS/ZUD	1
CPZ/HAL	4
FLX/DON/OLA	1
FLX/HAL/FLU	1
HAL/AMI	9
HAL/CPZ	2
HAL/RIS/CPZ	1
HAL/FLU	1
OLA/HAL/FLX	1
RIS/AMI	1
RIS/FLX/CPZ	1
RIS/FLX/DON	1
ZUD/RIS/CPZ/AMI	1
DECREASED EFFICACY OF DOLUTEGRAVIR	**1**
CBZ/DTG	1
INCREASED RISK OF CARBAMAZEPINE TOXICITY AND INCREASED RISK OF ISONIAZID-INDUCED HEPATOXICITY	**1**
CBZ/INH	1
DECREASED EFFICACY OF NIFEDIPINE	**1**
CBZ/NIF	1
REDUCED EFFICACY OF OLANZAPINE AND INCREASED RISK OF CARBAMAZEPINE TOXICITY	**23**
CBZ/OLA	23
DECREASED QUETIAPINE EFFICACY	**1**
CBZ/QUE	1
INCREASED RISK OF HALOPERIDOL EXPOSURE, HALOPERIDOL TOXICITY, QT-INTERVAL PROLONGATION AND TORSADES DE POINTES	**1**
FLX/HAL	1
INCREASED RISK OF ANTICHOLINERGIC SIDE EFFECTS	**1**
QUE/FLU	1
QT-INTERVAL PROLONGATION	**27**
CPZ/AMI	1

CPZ/EFV/HAL/ZUD	1
ESC/OLA	2
FLX/FXOL/CPZ/AMI	1
FLX/OLA	2
HAL/CLAR	1
HAL/EFV	1
HAL/RIS	1
RIS/DON	1
RIS/FLX/FXOL	1
RIS/OLA/ZUD	1
RIS/ZUD	4
ZUD/CPZ	1
ZUD/HAL	3
ZUD/OLA	2
ZUD/QUE	1
ZUD/RIS	3
INCREASED RISK OF SEROTONIN SYNDROME	**1**
AMI/FLX	1
Grand Total	**83**

KEY: AMI – Amitriptyline, AML – Amlodipine, BEN – Benzhexol (Trihexyphenidyl), CLAR – Clarithromycin, CPZ – Chlorpromazine, DICLO - Diclofenac, DON – Donepezil, FLU – Fluphenazine, FLX – Fluoxetine, FXOL - Flupentixol, HAL – Haloperidol, INH – Isoniazid, NIF -Nifedipine, OLA – Olanzapine, QUE – Quetiapine, RIS – Risperidone, EFV – Efavirenz, ZUD - Zuclopenthixol

Appendix 6: Drugs used to Manage Various Mental Illnesses

Mental Illness		
Drugs	**Route of Administration**	**Dosage (Range)**
Acute Psychosis		
Chlorpromazine	Oral	100mg
Divalproex	Oral	500mg
Fluoxetine	Oral	20mg
Haloperidol	Oral	5-10mg
Olanzapine	Oral	10mg
Risperidone	Oral	2mg
Trihexyphenidyl	Oral	5mg PRN
Carbamazepine	Oral	400mg
Chlorpromazine	Intramuscular	200mg
Zuclopenthixol decanoate	Intramuscular	200mg
Fluphenazine decanoate	Intramuscular	25mg
Bipolar Disorder		
Amitriptyline	Oral	25mg
Carbamazepine	Oral	400 – 800 mg
Chlorpromazine	Oral	100 - 200mg
Divalproex	Oral	500mg
Enchorate Chrono (Sodium valproate/ Valproic acid)	Oral	300mg
Escitalopram	Oral	10mg
Fluoxetine	Oral	20mg
Haloperidol	Oral	2.5-10mg
Olanzapine	Oral	5 - 10mg
Quetiapine	Oral	300mg
Risperidone	Oral	2 – 8mg
Sodium valproate	Oral	500mg
Topiramate	Oral	25mg
Trihexyphenidyl	Oral	5mg PRN
Chlorpromazine	Intramuscular	100mg
Flupentixol	Intramuscular	40mg
Fluphenazine	Intramuscular	25mg
Zuclopenthixol acetate	Intramuscular	100mg
Zuclopenthixol decanoate	Intramuscular	200mg
Drug Induced Psychosis		
Fluoxetine	Oral	20mg
Risperidone	Oral	2 – 8mg
Olanzapine	Oral	5 - 10mg
Amitriptyline	Oral	25mg
Haloperidol	Oral	5-10mg
Trihexyphenidyl	Oral	5mg PRN
Carbamazepine	Oral	400 – 800 mg
Zuclopenthixol acetate	Intramuscular	100mg
Zuclopenthixol decanoate	Intramuscular	200mg
Chlorpromazine	Intramuscular	100-200mgPRN

Fluphenazine	Intramuscular	25mg
Major Depressive Disorder (MDD)		
Escitalopram	Oral	10
Flupenthixol decanoate	Intramuscular	20
Fluoxetine	Oral	20
Generalized Anxiety Disorder (GAD)		
Fluoxetine	Oral	20
Post-partum Psychosis (PPP)		
Haloperidol	Oral	5
Olanzapine	Oral	10
Carbamazepine	Oral	400
Flupentixol	Intramuscular	40
Post-traumatic Stress Disorder/Major Depressive Disorder		
Risperidone	Oral	2mg
Bipolar Disorder/Major Depressive Disorder		
Fluoxetine	Oral	20mg
Olanzapine	Oral	10 -20mg
Flupentixol	Intramuscular	40mg
Psychosis due to a Medical Condition		
Fluoxetine	Oral	20
Olanzapine	Oral	2.5
Flupentixol	Intramuscular	40
Schizoaffective Disorder (SAD)		
Fluoxetine	Oral	20mg
Risperidone	Oral	2 – 8mg
Divalproex	Oral	300mg
Olanzapine	Oral	10 -20mg
Haloperidol	Oral	2.5-20mg
Trihexyphenidyl	Oral	5mg PRN
Carbamazepine	Oral	400 – 800 mg
Amitriptyline	Oral	25mg
Escitalopram	Oral	10mg
Flupentixol	Intramuscular	40mg
Zuclopenthixol decanoate	Intramuscular	200mg
Chlorpromazine	Intramuscular	100mg
Fluphenazine	Intramuscular	25mg
Schizophrenia (SZA)		
Amitriptyline	Oral	25mg
Carbamazepine	Oral	200 – 800 mg
Chlorpromazine	Oral	100 - 200mg
Divalproex	Oral	500 - 1000mg
Enchorate Chrono (Sodium valproate/ Valproic acid)	Oral	300mg
Escitalopram	Oral	10mg
Fluoxetine	Oral	20mg
Haloperidol	Oral	2.5-20mg
Olanzapine	Oral	5 - 10mg
Quetiapine	Oral	300mg

Risperidone	Oral	2 – 8mg
Sodium valproate	Oral	500mg
Topiramate	Oral	25mg
Trihexyphenidyl	Oral	5mg PRN
Chlorpromazine	Intramuscular	100mg
Flupentixol	Intramuscular	20-40mg
Fluphenazine	Intramuscular	25mg
Zuclopenthixol acetate	Intramuscular	100mg
Zuclopenthixol decanoate	Intramuscular	200mg
Schizophrenia/ Drug Induced Psychosis		
Fluoxetine	Oral	20mg
Chlorpromazine	Oral	200 - 400mg
Olanzapine	Oral	2.5 - 10mg
Amitriptyline	Oral	25mg
Haloperidol	Oral	5-10mg
Trihexyphenidyl	Oral	5mg PRN
Carbamazepine	Oral	200 – 800 mg
Chlorpromazine	Intramuscular	5-100mg
Fluphenazine	Intramuscular	25mg

Appendix 7: First and Second-generation Antipsychotics: Approximate Equivalent Doses

Chlorpromazine	**Approximate Equivalent Dose 100 mg/day**	**Literature reference range** (81–83)
First Generation Antipsychotics		
Chlorpromazine	100 mg/day	Reference
Flupentixol depot	10 mg/week	10–20 mg/week
Fluphenazine	2 mg/day	1–5 mg/day
Fluphenazine depot	5 mg/week	1–12.5 mg/week
Haloperidol	2 mg/day	1.5–5 mg/day
Haloperidol depot	15 mg/week	5–25 mg/week
Pericyazine	10 mg/day	10 mg/day
Perphenazine	10 mg/day	5–10 mg/day
Pimozide	2 mg/day	1.33–2 mg/day
Pipotiazine depot	10 mg/week	10–12.5 mg/week
Sulpiride	200 mg/day	133–300 mg/day
Trifluoperazine	5 mg/day	2.5–5 mg/day
Zuclopenthixol	25 mg/day	25–60 mg/day
Zuclopenthixol depot	100 mg/week	40–100 mg/week
Second Generation Antipsychotics		
Amisulpride	200mg	200mg
Aripiprazole	7.5mg	7.5mg
Asenapine	5mg	5mg
Brexpiprazole*	1mg	1mg
Cariprazine*	1.5mg	1.5mg
Clotiapine†	50mg	50mg
Iloperidone*	6mg	6mg
Lurasidone	40mg (74mg)	40mg (74mg)
Molindone*	50mg	50mg
Olanzapine	5mg	5mg
Paliperidone LAI	37.5mg/month	37.5mg/month
Quetiapine	150mg	150mg
Risperidone oral	1.5mg	1.5mg
Risperidone LAI	18.75mg/2weeks	18.75mg/2weeks
Ziprasidone	40mg	40mg

KEY: LAI: Long-Acting injection