Clozapine usage in a public sector psychiatric hospital in the Nelson Mandela Metropole

M Moolman

23298685

Dissertation submitted in partial fulfillment of the requirements for the degree *Magister Pharmaciae* in Pharmacy Practice at the Potchefstroom Campus of the North-West University

Supervisor: Dr JC Lamprecht

Co-supervisors: Prof Dr MS Lubbe

Dr R Joubert

Dr W Esterhuysen

November 2013

It all starts here ™

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT ®

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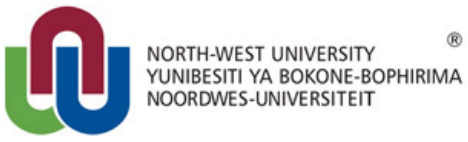

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- Above all, my almighty, loving and ever-present God. I know that everything I could ever accomplish is only through the power of Jesus Christ.

DECLARATION

I, Mari-san Moolman (23298685), hereby declare that the work on which this dissertation is based is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part thereof has been or is being submitted for another degree at this or any other university.

Mari-san Moolman

SUMMARY

Clozapine usage in a public sector psychiatric hospital in the Nelson Mandela Metropole

Key words:

schizophrenia, clozapine, drug utilisation, Nelson Mandela Metropole, prescribing patterns, psychiatric hospital.

About 30.00% of schizophrenic patients fail to respond to conventional antipsychotics. Clozapine shows superior efficacy, for both the positive and negative symptoms of schizophrenia, over conventional antipsychotics. The reputation of clozapine lies mainly with its repeated proven efficacy in the treatment of refractory schizophrenia.

However, clozapine has quite a severe side effect profile. Patients receiving clozapine therapy may develop serious adverse effects such as agranulocytosis, neutropenia and metabolic syndrome. Therefore guidelines are required which recommend that regular haematological and metabolic monitoring be performed. These monitoring guidelines should assist medical practitioners in the early detection and reporting of serious adverse effects associated with clozapine therapy.

South Africa lacks uniform provincial or national guidelines regulating practices in the treatment of mental disorders. International guidelines may be considered, which are not specifically adapted for the South African setting. These guidelines recommend both the haematological and metabolic monitoring of clozapine. At present there are no South African guidelines recommending the metabolic monitoring of clozapine.

The general aim of the study was to determine the prescribing and monitoring patterns of clozapine at Elizabeth Donkin Hospital in the Nelson Mandela Metropole. Due to the

absence of specific South African guidelines and the severe side effect profile of clozapine, some of the research objectives were to determine whether the initiation of clozapine, as well as the haematological and metabolic monitoring performed, was compliant with international clinical guidelines.

In this pharmacoepidemiological study a retrospective drug utilisation review was performed. The study was observational in design and included quantitative data. Data were collected from the files of 65 patients (N=65) discharged on clozapine between 1 December 2010 and 29 February 2012. Follow-up investigations were performed at the clinics and long-term care centres both three months and six months after discharge.

In 52.30% (n=34) of the cases clozapine was previously prescribed. Compliance with the National Institute for Health and Clinical Excellence (NICE) guidelines for the appropriate initiation of clozapine was 63.10% (n=41). Compliance with the Standard Treatment guidelines for the initiation of clozapine by a psychiatrist was 63.10% (n=41). Non-compliance with the recommended guidelines for haematological monitoring occurred in 77.40% of patients in the hospital setting (n=48) as well as in 95.70% of patients during the three-month follow-up at the clinics (n=44). Non-compliance with the guidelines for metabolic monitoring occurred in all the observed patients in the hospital setting (n=62) as well as in 45.70% of patients in the clinic setting (n=21). It was found that 71.00% (n=46) of patients were still on clozapine three months after discharge and 65.00% (n=42) were still on clozapine six months after discharge from hospital, resulting in discontinuation rates of 29.00% and 35.00% respectively.

It was found that clozapine was inadequately monitored although in most cases the initiation of clozapine was compliant with the recommended guidelines. However, practitioners should be trained on the existing prescribing and monitoring guidelines to promote the rational use of clozapine in the public health sector of South Africa.

OPSOMMING

Gebruik van klosapien in ‘n openbare sektor psigiatriese hospitaal in die Nelson Mandela Metropool

Sleutelwoorde:

skisofrenie, klosapien, geneesmiddelverbruik, Nelson Mandela Metropool, voorskryfpatrone, psigiatriese hospitaal

Ongeveer 30.00% van skisofrenie-pasiënte reageer nie op konvensionele antipsigotika nie. Klosapien is meer doeltreffend vir beide die positiewe en negatiewe simptome van skisofrenie as konvensionele antipsigotika. Klosapien is bekend vir herhaalde bewese doeltreffendheid in die behandeling van behandelings-weerstandige skisofrenie.

Klosapien het egter ‘n beduidende newe-effekprofiel. Pasiënte wat klosapienterapie ontvang, kan ernstige nadelige newe-effekte soos agranulositose, neutropenie en metaboliese sindroom ontwikkel. Daarom word riglyne vereis wat aanbeveel dat gereelde hematologiese en metabolise monitering uitgevoer word. Hierdie moniteringsriglyne moet mediese praktisyns help met die vroeë identifisering en rapportering van ernstige nadelige newe-effekte wat met klosapienterapie gepaardgaan.

Suid-Afrika ontbreek aan eenvormige provinsiale of nasionale riglyne wat praktyke in die behandeling van geestesversteurings reguleer. Internasionale riglyne, wat nié spesifiek vir die Suid-Afrikaanse omgewing aangepas is nie, kan oorweeg word. Hierdie riglyne beveel beide die hematologiese as metaboliese monitering van klosapien aan. Tans is daar geen Suid-Afrikaanse riglyne wat die metaboliese monitering van klosapien aanbeveel nie.

Die algemene doel van die studie was om voorskryf- en moniteringspatrone van klosapien by die Elizabeth Donkin Hospitaal in die Nelson Mandela Metropool te bepaal. Weens die

afwesigheid van spesifieke Suid-Afrikaanse riglyne, sowel as die ernstige newe-effekprofiel van klosapien, was ván die navorsingsdoelwitte om vas te stel of die inisiëring van klosapien, asook die hematologiese en metaboliese monitering daarvan, in ooreenstemming met internasionale kliniese riglyne was.

In dié farmako-epidemiologiese studie is ‘n retrospektiewe oorsig uitgevoer van geneesmiddelverbruik. Daar is gebruik gemaak van ‘n kwantitatiewe navorsingsontwerp en die studie was observerend van aard. Data is ingesamel van die lêers van 65 pasiënte (N=65) wat tussen 1 Desember 2010 en 29 Februarie 2012 op klosapien ontslaan is. Opvolgondersoeke is by klinieke en langtermyn-sorgsentrums drie maande en ses maande na ontslag gedoen.

In 52.30% (n=34) van die gevalle was klosapien voorheen voorgeskryf. Dit is bevind dat in 63.10% (n=41) van die gevalle was daar voldoen aan die National Institute for Health and Clinical Excellence (NICE)-riglyne ten opsigte van die inisiëring van klosapien. Die nakoming van die Standaard Behandelingsriglyne vir die inisiëring van klosapien deur ‘n psigiater was 63.10% (n=41). Nie-nakoming van die aanbevole riglyne vir hematologiese monitering het by 77.40% pasiënte in die hospitaalopset (n=48) en 95.70% pasiënte gedurende die driemaandelikse opvolgbesoek by die klinieke voorgekom (n=44). Nie-nakoming van die riglyne vir metaboliese monitering het by ál die waargenome pasiënte in die hospitaalopset (n=62) en in 45.70% van die pasiënte by klinieke voorgekom (n=21). Daar is bevind dat 71.00% (n=46) van die pasiënte drie maande en 65.00% (n=42) ses maande na ontslag uit die hospitaal steeds op klosapien was, met ‘n gevolglike stakingskoers van 29.00% en 35.00% onderskeidelik.

Daar is bevind dat klosapien onvoldoende gemoniteer was alhoewel die inisiëring daarvan in die meeste gevalle aan die aanbevole riglyne voldoen het. Nietemin, praktisyns moet opgelei word in die bestaande voorskryf- en moniteringsriglyne om sodoende die korrekte gebruik van klosapien in die openbare gesondheidsektor in Suid-Afrika te bevorder.

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CHAPTER 1

INTRODUCTION AND PROBLEM STATEMENT

1.1 INTRODUCTION

A pharmacoepidemiological study investigates the use and effects of drugs in large numbers of people (Strom & Kimmel, 2006:3). This dissertation serves as a descriptive report on the usage of clozapine in the public sector of the Nelson Mandela Metropole.

Particular emphasis was placed on the prescribing and monitoring of clozapine. The prevalence of drug interactions and adverse effects was investigated and current practices were evaluated against available local and international guidelines. This chapter provides an outline of the background to the study, problem statement, primary aim and research objectives, and the chapter layout.

1.2 BACKGROUND TO THE STUDY

Currently, more than 450 million people worldwide suffer from mental disorders (WHO, 2010). According to the South African Stress and Health (SASH) study conducted in 2009, about 16,50% of South Africans suffer from some form of mental illness (Herman *et al.*, 2009:342).

Between 1% and 3% of the South African population are likely to suffer from a mental health problem severe enough to require hospitalisation. Many factors including communicable disease, substance abuse, political violence, poverty and urbanisation may contribute to the high prevalence of mental health disorders in South Africa (SA Health Info, 2008).

This study focuses on the use of clozapine in the treatment of mental disorders. Clozapine is classified as a second generation antipsychotic (SGA) agent and is registered with the Medicines Control Council (MCC) of South Africa for the following indications:

- “Patients with treatment-resistant schizophrenia,

- Reducing the risk of recurrent suicidal behaviour in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behaviour based on history and recent clinical state; and
- Patients with drug-induced psychosis during the course of Parkinson's disease in cases where standard treatment has failed" (Novartis, 2006).

Clozapine was discovered in 1958 in Bern, Switzerland, and was used for the first time in animal experiments in May 1960 (Sadock *et al.*, 2009:3207; Schatzberg & Nemeroff, 2004:443). Clozapine was first introduced on to the market in Europe in the 1970s (Crilly, 2007:39). Clozapine became available in South Africa in 1974 (Hempill *et al*., 1975:2121). Clozapine was voluntarily withdrawn by the manufacturer in 1975, since it was associated with agranulocytosis. Thereafter, clozapine was again released on to the market in 1989 after studies indicated that it was more effective in treatment-resistant schizophrenia than other antipsychotics (Healy, 2004:238).

A study conducted in 1988 by John Kane, Herbert Meltzer and others in which the efficacy of clozapine was compared with that of chlorpromazine in 268 treatment-resistant patients established that clozapine was superior to chlorpromazine in terms of a number of outcomes, including psychosis, mood and anxiety. The results from this study and others led to the approval of clozapine in the United States in 1990 and subsequently in other countries for schizophrenia patients who are resistant to treatment with other antipsychotics (Sadock *et al*., 2009:3207).

Despite its proven efficacy in treatment-resistant schizophrenia it is also commonly used off-label for various other indications such as: resistant mania, post-traumatic stress disorder and intermittent explosive disorder (Kant *et al.,* 2004:57).

About 30.00% of schizophrenic patients fail to respond to conventional antipsychotics (Porter & Kaplan, 2011:1564). Clozapine provides the possibility of significant help for at least 60% of patients with schizophrenia who fail to respond adequately to conventional antipsychotics (Dipiro *et al*., 2011:1156). On the other hand, due to its side-effect profile and the need for regular blood monitoring, the use of clozapine has been relatively limited (Meltzer, 2000:1277).

International clinical practice guidelines such as the National Institute for Health and Clinical Excellence (NICE) guidelines, as well as other international guidelines, are widely available for the treatment of mental disorders. In South Africa, there are no uniform provincial or national guidelines regulating practices in the treatment of a mental illness such as schizophrenia. Currently, our standards are international guidelines which are not specifically adapted for the South African setting (Koen *et al.*, 2008:287).

Clozapine has shown superior efficacy, for both the positive and negative symptoms of schizophrenia, over conventional antipsychotics. The reputation of clozapine lies mainly with its repeated proven efficacy in the treatment of refractory schizophrenia (Chandrasekaran, 2008:96). Clozapine can almost be considered a 'last resort', since it is used mainly for treatment-resistant cases (Schatzberg & Nemeroff, 2004:453).

1.3 MOTIVATION AND PROBLEM STATEMENT

Internationally and locally strict guidelines recommend the haematological monitoring of clozapine. The Standard Treatment Guidelines Hospital Level: Adults suggest that a psychiatrist should initiate clozapine therapy and that haematological monitoring should be performed as is instructed on the package insert (Department of Health, 2012:298).

At present there are no South African guidelines recommending the metabolic monitoring of clozapine. This is, however, a concern, since the incidence of agranulocytosis in patients initiated on clozapine is 1-2% (Chandrasekaran, 2008:96) whereas 53.80% of patients develop metabolic syndrome while on clozapine therapy (Lamberti *et al.,* 2006:1273). Therefore, the metabolic monitoring of clozapine should also be considered as important.

NICE guidelines suggest that before a patient is initiated on clozapine treatment, at least two other antipsychotics, at adequate doses, should be tried. At least one of these two drugs should be a non-clozapine second generation antipsychotic (NICE, 2009:10).

Clozapine has quite a severe side effect profile. The more serious adverse effects of clozapine are summarised in Table 1.1 (Novartis, 2006; Rossiter, 2012:475; Taylor *et al.*, 2012:76).

Table 1.1 Serious adverse effects of clozapine

Haematological	Agranulocytosis, neutropenia, leukopenia and eosinophilia
Metabolic	Weight gain, hypercholesterolemia and hyperglycaemia
Anticholinergic	Constipation, blurred vision, urinary incontinence and retention
Cardiovascular	Orthostatic hypotension, tachycardia, myocarditis and cardiomyopathy
Nervous system	Sedation and seizures

Hence, to ensure patient safety, regular haematological and metabolic monitoring is required to assist in the early detection and reporting of serious adverse effects associated with clozapine therapy.

The haematological monitoring requirements for clozapine are summarised in Table 1.2 (Novartis, 2006; Rossiter, 2012:475; Taylor *et al*., 2012:93).

See next page

Table 1.2 Haematological monitoring requirements for clozapine

Pre-treatment	White blood cell counts (total and differential) must be normal before clozapine therapy can be initiated.
After initiating therapy	• Monitor white blood cell counts weekly for the first eighteen weeks. • Then every two weeks for the remainder of the year. • Thereafter, the blood monitoring is usually performed monthly.
Withdraw therapy if leucocyte count drops below 3000/mm³ or absolute neutrophil count below 1500/mm³	

According to Honigfield (cited by Naheed & Green, 2001:223), when performing periodic white blood cell count monitoring the risk of agranulocytosis is less than 0.38%. When a patient is initiated on clozapine in the United Kingdom, the patient must immediately be registered with the Clozaril Patient Monitoring Services (CPMS). No patient can receive clozapine without a recent satisfactory haematological result and only psychiatrists registered with CPMS are allowed to prescribe it (Naheed & Green, 2001:224).

Physical disease in patients with schizophrenia tends to be seriously undetected and underdiagnosed (Sadock *et al*., 2009:1459). Schizophrenic patients are at an increased risk for developing metabolic abnormalities (McCarron *et al*., 2009:81). Obesity and the concomitant metabolic syndrome involving insulin resistance are becoming increasingly common problems in patients with schizophrenia (Sadock *et al*., 2009:1459). Metabolic syndrome is the development of a cluster of metabolic abnormalities associated with raised fasting triglyceride levels and low high density lipoprotein (HDL) cholesterol levels, elevated fasting plasma glucose, high blood pressure and weight gain (American Heart Association, 2011; Wells *et al*., 2012:908).

The metabolic monitoring requirements for clozapine are summarised in Table 1.3 (Taylor *et al.*, 2012:95).

Table 1.3 Metabolic monitoring requirements for clozapine

Baseline	Weight, lipids, plasma glucose, blood pressure, body mass index (BMI) and waist circumference
After one month of therapy	Weight, plasma glucose, BMI and waist circumference
After 3 months of therapy	Weight, lipids, BMI and waist circumference
After 4-6 months of therapy	Weight, lipids, plasma glucose, BMI and waist circumference
After 12 months of therapy	Weight, lipids, plasma glucose, BMI and waist circumference

Many psychotropic drugs, including both first generation antipsychotics (FGAs) and SGAs, antidepressants and mood stabilizers are associated with metabolic adverse effects (Usher *et al*., 2009:176). Phenothiazines such as chlorpromazine and fluphenazine are some of the FGAs with metabolic adverse effects (Taylor *et al*., 2012:151). However, the SGAs such as clozapine, olanzapine and risperidone can be strongly linked to metabolic syndrome (Usher *et al*., 2009:177). Unfortunately these metabolic disturbances often go undetected or unreported in patients with schizophrenia (Usher *et al*., 2009:178). The main focus for mental health care practitioners is to obtain improvement in the patient's mental state, but in the process the physical health of the patient is often neglected (Maj, 2009:2). A need is therefore identified to determine whether the metabolic and haematological monitoring of clozapine is regularly performed, since according to evidence in the literature it may be easily overlooked.

Patients suffering from psychiatric conditions such as schizophrenia already have a poor quality of life due to the debilitating effect of their disease. Recent literature indicates that the average life expectancy for patients with schizophrenia is from 10 to more than 30

years shorter than that of the general population (Sadock *et al*., 2009:1573). At present the leading causes of premature death in patients with schizophrenia are suicide, accidents, and comorbid physical illness (Sadock *et al.*, 2009:1460). If a patient develops metabolic syndrome as a result of clozapine therapy he/she is at high risk of early death due to stroke, cerebrovascular disease or coronary heart disease (Sadock *et al*., 2009:1573). Therefore, it is very important that the screening of metabolic markers be performed regularly to assist in the early detection of physical health problems associated with clozapine therapy. Ultimately, the appropriate management of these metabolic symptoms will help in reducing negative outcomes such as coronary heart disease and cerebrovascular disease.

Patients suffering from psychiatric illness are very vulnerable; therefore special care is needed when treating these patients. These patients can often not inform the health care professional taking care of them that they are not feeling well, since they are sometimes not fully aware of their surroundings while they are acutely ill (Krüger, 2012:176). Therefore, it is of the utmost importance that investigations be performed to prevent future incidents that could threaten patient safety and hence negatively affect the quality of life of patients.

The motivation for this study is to assess the safe and effective use of clozapine, through performing a pharmacoepidemiological investigation on the prescribing and monitoring patterns followed in a tertiary hospital, using a public sector psychiatric hospital and associated community psychiatric clinics as a model.

1. 4 PRIMARY AIMS AND RESEARCH OBJECTIVES

This study aimed to investigate the prescribing and monitoring patterns of clozapine at Elizabeth Donkin Hospital in the Nelson Mandela Metropole.

The general objective of the study was to determine whether clozapine is rationally used, for the treatment of psychotic disorders at Elizabeth Donkin Hospital. Elizabeth Donkin

Hospital was the preferred setting to conduct this study, since the primary investigator is currently employed as a pharmacist at the particular institution. Therefore the need for the correct monitoring of psychiatric patients on clozapine treatment was identified and hence the motivation for this study.

1.4.1 Specific objectives for the literature study

The specific research objectives for the literature study included the following:

- To obtain information from the literature on the use of clozapine in patients with schizophrenia and other psychotic disorders.
- To gain knowledge from the available literature on psychotic disorders including schizophrenia, where clozapine therapy can be considered as a treatment option.
- To conceptualise drug utilisation review, its purpose and applications.

1.4.2 Specific objectives for the empirical study

The specific research objectives for the empirical study included the following:

- To determine the general prescribing patterns of clozapine at Elizabeth Donkin Hospital.
- To determine compliance with the recommended guidelines for the initiation of clozapine therapy.
- To investigate the presence and severity of any adverse reactions that could be associated with clozapine therapy.
- To identify possible drug interaction(s) when clozapine is used in combination with other agents.
- To assess the extent of compliance with the recommended guidelines for haematological and metabolic monitoring of clozapine both at Elizabeth Donkin Hospital as well as the community psychiatric clinics and long-term care centres after discharge from hospital.
- To determine the total monetary costs involved when admitting a patient and initiating the patient on clozapine therapy.

- To determine the discontinuation rate of clozapine both three months as well as six months after discharge from Elizabeth Donkin Hospital.

1.5 RESEARCH METHODOLOGY

A short overview of the research methodology employed in this study will be provided below.

1.5.1 Research design

An observational pharmacoepidemiological investigation in the form of a descriptive cross-sectional study was performed. Methodological concepts of a drug utilisation review study were also employed.

A retrospective drug utilisation review was performed on the use of clozapine in a public sector psychiatric hospital in the Nelson Mandela Metropole. As part of the study, follow-up investigations, using questionnaires were performed at the clinics and long-term care facilities to which the patients were discharged.

The research method used in this investigation consisted of the following phases, namely: a literature review and an empirical study.

1.5.2 Literature review

The aim of this study was to analyse the use, monitoring and prescribing patterns of clozapine through performing a pharmacoepidemiological investigation. Hence, a comprehensive literature review had to be conducted to determine which local and international treatment guidelines or protocols exist for initiating and monitoring clozapine.

The main objective of the literature review was to gain background pharmacological knowledge on clozapine and its use in psychiatric conditions. The methodology employed

for the literature review consisted of the development of a theoretical framework as well as a conceptual framework. Gaps in the current literature were also identified.

The literature review was conducted from August 2011 to January 2013. Information was obtained on the pharmacological classification, mechanism of action, dosages, drug interactions, recommended metabolic and white cell count monitoring as well as adverse effects of clozapine.

Various reference sources were consulted. The primary sources accessed included original articles published in professional journals (local and international). The secondary sources accessed included prescribing guidelines and abstracts. The tertiary sources accessed for information included textbooks as well as reliable internet websites.

The following electronic online databases were used to search for journal articles: EBSCOhost®, Science Direct®, Medline® and Pubmed®.

An in-depth overview of the literature study is provided in Chapter Two.

1.5.3 Empirical study

The research methodology employed in the empirical study is discussed in Chapter Three.

1.5.4 Study population

In February 2011 there were 475 patients that received clozapine therapy at Elizabeth Donkin Hospital and the surrounding community psychiatric clinics, in the public sector of the Nelson Mandela Metropole. The study sample included a total number of 65 patients. Patients discharged on clozapine from Elizabeth Donkin Hospital were identified through the collection of discharge summaries received by the pharmacy department.

1.5.5 Research instruments

The following research instruments were used in the study:

- Data collection tool
- Three-month follow-up questionnaire
- Six-month follow-up questionnaire

1.5.6 Data collection

Data were collected as previously mentioned through using data collection forms and questionnaires. The data collection forms were used to obtain information from patient files at Elizabeth Donkin Hospital. The questionnaires completed by nurses in the community psychiatric clinics and long-term care centres were used to obtain information about the patient after discharge from hospital. The primary investigator of the study collected data from the patients' files.

1.5.7 Data analysis

The data recorded on the data collection forms and questionnaires were captured in an Excel spreadsheet using the programme Microsoft Office Excel® 2007. The data in the Excel spreadsheet were then exported to the computer programme SAS® 2012 version 9.3 for statistical analyses (SAS, 2012).

1.5.8 Study variables

Some of the variables included: age, gender, race, family history and smoking history.

1.5.9 Study measurements

Some of the study measurements investigated included: co-morbid disease states, diagnosis, dosages, cost and compliance with the recommended treatment and monitoring guidelines.

1.5.10 Ethical aspects

Approval for this study was granted by the Research Ethics Committee of the North-West University with the ethics number: NWU-0003-12-A2. Approval was also received from the Eastern Cape Department of Health to conduct this study in public health care institutions in the Eastern Cape.

1.6 CHAPTER LAYOUT

Chapter Two serves as a literature review. The clinical use of clozapine is outlined in this chapter. Primary and secondary psychotic disorders are discussed. Special emphasis is placed on literature regarding the use of clozapine in the management of refractory schizophrenia. Drug utilisation review is defined and the different types of drug utilisation review studies are briefly discussed. The purpose and applications of drug utilisation reviews are mentioned shortly.

Chapter Three outlines the methodology employed for the drug utilisation review. The processes involved in conducting the empirical study are explained, including amongst others: obtaining, analysing and interpreting the data. The ethical considerations of the study are also stipulated in this chapter.

Chapter Four gives a report and discussion of the results that were obtained from the drug utilisation review performed.

Chapter Five is a concluding chapter in which final conclusions were stated. The limitations of the study are also mentioned. The recommendations are presented at the end of Chapter Five.

1.7 SUMMARY OF CHAPTER ONE

This concludes the introductory chapter. A brief outline of the study was provided in this chapter. The problem statement and primary aim and research objectives were discussed in detail. The following chapter will provide an overview of the literature study performed.

CHAPTER 2

CLOZAPINE AS NEUROLEPTIC AGENT

2.1 CLINICAL USE OF CLOZAPINE

2.1.1 INTRODUCTION

Clozapine was the first second-generation antipsychotic (SGA) released onto the market (Sadock *et al*., 2009:3207). Clozapine has played a critical role in the history of therapeutics for psychosis (Schatzberg & Nemeroff, 2004:443).

The discovery that clozapine is an effective antipsychotic with minimal extrapyramidal side effects (EPS) led to reassessment of models for developing antipsychotic agents. Moreover, attempts to understand the mechanism of action of clozapine have placed focus on current views of the pharmacology of schizophrenia and other psychotic disorders (Schatzberg & Nemeroff, 2004:443).

Consensus of opinion is rare in psychiatry. One issue for which there is a widespread consensus is the unique place that clozapine occupies in the treatment of severe mental illnesses, particularly refractory schizophrenia. This molecule is distinct because of its effectiveness, numerous and sometimes mysterious pharmacologic characteristics, serious side effects and underuse (Joober & Boksa, 2010:147).

Historically, clozapine was distinguished by one of its dangerous and sometimes lethal side effects, namely agranulocytosis, which almost caused its complete removal from the psychiatric pharmacopoeia. It was only rescued when it demonstrated superior therapeutic effects compared to chlorpromazine amongst patients with refractory schizophrenia (Joober & Boksa, 2010:147).

2.1.2 PHARMACOLOGICAL PROFILE

2.1.2.1 Pharmacological classification

Clozapine is a dibenzodiazepine derivative SGA agent (Semple & Smyth, 2009:202).

2.1.2.2 Mechanism of action

The explanation for the unique clinical profile of clozapine remains controversial (Sadock *et al*., 2009:3207). A number of characteristics could explain how clozapine can reduce psychosis without causing EPS (Schatzberg & Nemeroff, 2004:445).

Clozapine mainly blocks D_1 and D_4 dopamine receptors and its antagonism of D_2 receptors is relatively less than conventional antipsychotics. Clozapine also has a high affinity for 5-HT_{2A} and 5-HT_{1C} serotonin receptors (Schatzberg & Nemeroff, 2004:445). Clozapine also blocks 5-HT_3, 5-HT_6, 5-HT_7 serotonin receptors, M_1 muscarinic, H_1 histamine and α_1-adrenergic receptors (Stahl, 2012:29). The lower affinity of clozapine for D_2 receptors may partially explain its lack of EPS and hyperprolactinaemia (Semple & Smyth, 2009:202). Moreover, serotonin can modulate dopamine neurons in the substantia nigra, which in turn may decrease EPS (Schatzberg & Nemeroff, 2004:445).

Clozapine does have significant anticholinergic, antihistaminergic, and anti-adrenergic activity which can be accountable for its common adverse effects (Semple & Smyth, 2009:202). The superior efficacy of clozapine for refractory schizophrenia may be due to its additional blockade of 5-HT_2 receptors. Clozapine's affinity for 5-HT_2 receptors is among the highest for antipsychotic drugs (Sadock *et al*., 2009:3208).

Seeman and Kapur (cited by Schatzberg & Nemeroff, 2004:445) proposed that the lack of EPS with clozapine and other SGAs is related to their fast dissociation from the D_2 receptor. Conventional antipsychotics tend to have a greater affinity for dopamine receptors than dopamine itself. Whereas the affinity of the dopamine receptors for clozapine is lower than that of dopamine and clozapine can more easily dissociate from the receptor in the presence of dopamine. Therefore as a result clozapine can permit more normal dopaminergic transmission (Sadock *et al*., 2009:3209).

2.1.2.3 Pharmacokinetics

Clozapine is only available as an oral preparation. The absorption of orally administered clozapine is 90-95%, the rate or extent of absorption is not influenced by food (Novartis, 2006).

Peak plasma levels are reached approximately 2 hours after oral administration (Schatzberg & Nemeroff, 2004:444). The elimination half-life is about 12 hours (Stahl, 2012:32). As a result twice-daily dosing results in steady-state plasma concentrations in less than one week (Sadock *et al*., 2009:3207).

Clozapine has a large volume of distribution (mean of 2.0 to 5.1 L/kg; range 1.0-10.2 L/kg) although lower than that of other antipsychotic drugs (Schatzberg & Nemeroff, 2004:444).

Clozapine is subject to extensive first-pass metabolism in the liver and gut, resulting in an absolute bioavailability of 27 to 47% (Sadock *et al*., 2009:3207). Clozapine is approximately 95% bound to plasma proteins (Novartis, 2006). N-desmethylclozapine, the active metabolite of clozapine represents 40-80% of the concentration of clozapine (Wells *et al*., 2012:899).

Clozapine is almost completely metabolised prior to excretion. Less than 5% of unchanged drug are detected in the urine and approximately 80% of the administered dose is excreted as metabolites in the urine and faeces (Schatzberg & Nemeroff, 2004:444).

Measuring plasma concentrations may be useful in monitoring patients treated with clozapine. Patients are more likely to respond when their clozapine plasma levels are > 350 µg/L (Schatzberg & Nemeroff, 2004:445).

Clozapine plasma levels are broadly related to daily dose, but there is sufficient variation to make impossible any precise prediction of plasma level (Taylor *et al*., 2012:5). Plasma levels are influenced by factors such as smoking, hepatic metabolism, gastric absorption, age and possibly gender (Semple & Smyth, 2009:203). The plasma levels of older adults may be twofold higher than those of younger adults (Sadock *et al*., 2009:3209). Plasma

levels are generally lower in males and smokers and higher in Asian patients (Taylor *et al*., 2012:5). A series of algorithms has been developed for the approximate prediction of clozapine levels according to patient factors and is highly recommended. However, algorithms cannot account for other influences on clozapine plasma levels such as changes in adherence, infection and inflammation (Taylor *et al.*, 2012:5).

Time to steady state clozapine plasma levels is 2-3 days (Taylor *et al*., 2012:3). A typical total daily dose of 300-400 mg is associated with levels ranging between 200 and 400 µg/L (Sadock *et al*., 2009:3209). In those not responding to clozapine the dose should be adjusted to give plasma levels in the range 350-500 µg/L. Those not tolerating clozapine may benefit from a reduction to a dose giving plasma levels in this range. As expected, there seems to be a correlation between plasma level and clozapine-related adverse effects (Taylor *et al.*, 2012:5).

Onset of antipsychotic effect may take several weeks, but maximum effects can require several months of therapy (Semple & Smyth, 2009:203).

2.1.3 INDICATIONS

2.1.3.1 Treatment-resistant schizophrenia

Clozapine is indicated in patients with treatment-resistant schizophrenia i.e. patients with schizophrenia who failed trials with other antipsychotics (Novartis, 2006; Sadock *et al*., 2009:3212).

“Treatment-resistant” describes a patient who has had inadequate symptom response from multiple antipsychotic trials (Dipiro *et al*., 2011:1156). Traditionally treatment resistance has been defined as lack of improvement in positive symptoms, but it can be defined by poor improvement in negative symptoms, or even by medication intolerance (Dipiro *et al*., 2011:1156).

The National Institute for Health and Clinical Excellence (NICE) (2002:8) defines treatment resistance as “a lack of significant clinical improvement despite the sequential use of the recommended doses for 6 to 8 weeks of at least two antipsychotics, one of which must be an atypical antipsychotic”.

Between 10% and 30% of patients receive minimal symptomatic improvement after various attempts of conventional antipsychotic monotherapy trials (Dipiro *et al*., 2011:1156). An additional 30% to 60% of patients on antipsychotic therapy have partial but inadequate improvement in symptoms or experience unacceptable side effects. In those patients failing two or more pharmacotherapy trials, a treatment-resistant evaluation should be performed to re-examine diagnosis, substance abuse, medication adherence and psychosocial stressors. Targeted cognitive behavioural therapy or other psychosocial augmentation strategies should be considered to improve the clinical outcome (Dipiro *et al.*, 2011:1156).

Only clozapine has shown superiority over other antipsychotics in randomised clinical trials for the management of treatment-resistant schizophrenia (Wells *et al*., 2012:902). Symptomatic improvement with clozapine often occurs slowly in treatment-resistant patients and as many as 60% of patients may improve if clozapine therapy is continued for up to six months (Wells *et al*., 2012:902).

2.1.3.2 Risk of recurrent suicidal behaviour

Clozapine is also indicated for reducing the risk of recurrent suicidal behaviour in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behaviour, based on history and recent clinical state (Novartis, 2006; Sadock *et al*., 2009:3212).

The International Prevention of Suicide (InterSePT) study conducted in 2003, proved that clozapine had a significant advantage over olanzapine in decreasing suicidal behaviours in patients with schizophrenia and schizoaffective disorder (Meltzer *et al*., 2003:82). This led

to the U.S. Food and Drug Administration (FDA) approval for this indication of clozapine. Clozapine is the only antipsychotic with this particular indication (Sadock *et al*., 2009:3212).

2.1.3.3 Drug-induced psychosis during the course of Parkinson's disease

Clozapine is indicated in psychotic disorders (secondary to dopaminomimetic agents) occurring during the course of Parkinson's disease, in cases where standard treatment has failed (Novartis, 2006; Sadock *et al*., 2009:3211).

According to Wolters (cited by Schatzberg & Nemeroff, 2004:448) psychosis with delusions and hallucinations occurs in about 25% of patients with Parkinson's disease and although other SGAs can be used in treating psychosis in Parkinson's disease, clozapine is generally the preferred agent.

2.1.4 CONTRAINDICATIONS

The following contraindications are associated with clozapine therapy (Novartis, 2006; Rossiter, 2012:475; Turner *et al*., 2010:461):

- Known hypersensitivity to clozapine
- Uncontrolled epilepsy
- Impaired bone marrow function
- History of toxic or drug-induced granulocytopenia or agranulocytosis (with the exception of granulocytopenia or agranulocytosis from previous chemotherapy)
- Concomitant use of clozapine and carbamazepine
- Severe renal or cardiac disease (e.g. myocarditis, pericarditis or cardiomyopathy)
- Active liver disease, progressive liver disease, hepatic failure
- Patients that cannot undergo regular blood tests
- Glaucoma
- Circulatory collapse
- Paralytic ileus

- Children under the age of 16 years
- Patients at risk for venous thromboembolism

2.1.5 PREGNANCY AND LACTATION

Women with pre-existing mental illnesses become pregnant each year, while others develop a mental illness during pregnancy. Many of these women will need to use psychiatric medication at some stage during their pregnancy (Usher *et al*., 2009:130).

Exposure of the foetus to medication is common, especially during the first trimester of pregnancy (Owen, 2011:1005). About 50-65% of all pregnancies are usually unplanned and the foetus may be exposed to a variety of drugs during the first trimester before the mother realises that she is pregnant (Owen, 2011:1005). Surveys estimate that 80% of pregnant women take prescription medications and 21-33% is exposed to psychiatric medication during pregnancy (Owen, 2011:1005).

Foetal risks associated with the use of antipsychotics during pregnancy include teratogenicity, direct toxicity, perinatal effects, and possible long-term effects on behaviour and development. Both the known and possible risks of pharmacotherapy must be balanced against the risks to the foetus if withholding therapy (Dipiro *et al*., 2011:1164). Exacerbation of the mother's psychiatric illness may endanger the foetus in utero through maternal self-harm, suicide, malnutrition, lack of proper prenatal care, or excessive exposure to risks through impulsivity, delusions, disorientation, or denial of the pregnancy (Owen, 2011:1005; Usher *et al*., 2009:130). Health care professionals caring for pregnant women are challenged by minimising the risks to the unborn foetus while ensuring the safety and well-being of the mother (Usher *et al*., 2009:131).

SGAs are commonly prescribed for women who experience psychoses during pregnancy or immediately after delivery (Dipiro *et al*., 2011:1164). SGAs have not yet been proven safe in pregnancy and their use in pregnancy is not based on evidence from randomised clinical trials (Usher *et al*., 2009:130). Potential risks to the infant associated with SGAs

taken during pregnancy include respiratory complications, cardiovascular defects, hypotonia, and low birth weight (Wells *et al.*, 2012:910). Where possible, women using SGAs should be changed to first generation antipsychotics (FGAs) such as haloperidol during the first trimester of pregnancy (Usher *et al*., 2009:134).

There are concerns that clozapine may be associated with a high rate of congenital malformations (Usher *et al*., 2009:132). The risk for weight gain and potential risk for gestational diabetes associated with clozapine should be considered in drug selection (Dipiro *et al*., 2011:1164). Additional concerns include the known risks of agranulocytosis and orthostatic hypotension associated with clozapine use, which may also have harmful effects on the foetus (Usher *et al*., 2009:132).

Clozapine carries a category B risk in pregnancy (Rossiter, 2012:475). In drugs with a category B risk animal studies may have shown adverse effects, but there were none that have been replicated in controlled studies in pregnant women. However, reproduction studies in animals have revealed no evidence of impaired fertility or harm to the foetus due to clozapine, but the safe use of clozapine in pregnant women has not yet been established. Clozapine should be used only if the benefit outweighs the risk (Novartis, 2006; Rossiter, 2012:475; Turner *et al*., 2010: 461).

About 60% of mothers usually choose to breast-feed their babies and many will wish to do so while taking psychiatric medication (Owen, 2011:1005). If informed that a particular medication is contraindicated when breast-feeding a mother may decide to continue breast-feeding and then discontinue her psychiatric medication. Recurrence of the psychiatric disorder is not only dangerous for the mother but may place the infant at greater risk than that posed by breast-feeding while the mother is taking medication (Owen, 2011:1005). The use of medication during pregnancy and breast-feeding, including the risks, benefits, and treatment alternatives must be discussed with the patient. Failure to fully inform the patient may result in the discontinuation of treatment because of excessive fear of risk to the foetus or neonate (Owen, 2011:1006).

Antipsychotics appear in breast milk, with milk to plasma ratios of 0,5:1 (Wells *et al*., 2012:910). However, 1-week post-delivery clozapine milk concentrations were found to be

as much as 279% of serum concentrations (Dipiro *et al*., 2011:1164). Animal studies also revealed that clozapine is excreted in breast milk (Dipiro *et al*., 2011:1164). This may be a concern due to the possible risk for agranulocytosis, sedation, cardiovascular instability and seizures (Owen, 2011:1006). Use of clozapine during breastfeeding is therefore not recommended (Novartis, 2006; Turner *et al*., 2010:461; Wells *et al.*, 2012:910).

Some female patients treated with antipsychotics other than clozapine may become amenorrheic. A return to normal menstruation may occur due to switching from other antipsychotics to clozapine. Adequate contraceptive measures must therefore be ensured in women of childbearing potential (Novartis, 2006). However, according to the literature generally a female patient older than 45 years of age is already in menopause and hence contraception is no longer a priority (Beksinska *et al.*, 2011:133).

2.1.6 DOSAGES

2.1.6.1 Initiation of clozapine

According to the Leponex® package insert the dosage must be adjusted individually and is different for the individual indications (Novartis, 2006). For each patient the lowest effective dose should be used. Dosage adjustments are necessary in patients receiving drugs that interact with clozapine e.g. benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) (Novartis, 2006).

Many of the adverse effects of clozapine are dose dependent and associated with the speed of titration (Taylor *et al*., 2012:64). Due to risks of orthostatic hypotension, bradycardia, syncope and seizures; clozapine is usually titrated more slowly than other antipsychotics (Sadock *et al*., 2009: 3207).

The following table summarises the recommended dosing and administration of clozapine (adapted from Rossiter, 2012:475; Sadock *et al*., 2009:1096; Stahl, 2012:30; Taylor *et al*., 2012:64).

Table 2.1 Dosing and administration of clozapine

Initial dose: Day 1	Second dose: Day 2	Titration	Target dose	Dose range	Maximum dose
12,5 mg administered once or twice	25 mg administered once or twice	25-50 mg/day very 2-3 days	300 mg/day within 2-3 weeks of initial dose	200-450 mg/day may be given in divided doses with larger dose given at bedtime	900 mg/day

Clozapine should normally be started at a dose of 12,5 mg once or twice on the first day, followed by 25 mg once or twice on the second day.

If well tolerated the daily dose may then be increased slowly in increments of 25 mg to 50 mg in order to achieve a dose level of up to 300 mg/day within two to three weeks.

Thereafter, if required, the daily dose may be further increased in increments of 50 mg to 100 mg at half-weekly or preferably weekly intervals (Novartis, 2006; Rossiter, 2012:475; Taylor *et al*., 2012:64).

Slower titration may be necessary where sedation is severe. If the patient is not tolerating a particular dose, decrease to one that was previously tolerated. If the adverse effects resolve, increase the dose again but at a slower rate (Taylor *et al.*, 2012:65)

The following table summarises the recommended starting regimen for clozapine (adapted from Taylor *et al*., 2012:65).

Table 2.2 Clozapine starting regimen for inpatients

Day	*Morning dose (mg)*	*Evening dose (mg)*
1	-	12,5
2	12,5	12,5
3	25	25
4	25	25
5	25	50
6	25	50
7	50	50
8	50	75
9	75	75
10	75	100
11	100	100
12	100	125
13	125	125
14	125	150
15	150	150
18	150	200
21	200	200
28	200	250

2.1.6.2 Clozapine dosages in special population groups

2.1.6.2.1 Clozapine use in the elderly

It is recommended to initiate treatment at a particularly low dose (12,5 mg given once on the first day) and to restrict dosage increases to 25 mg per day.

Clinical studies did not include a sufficient number of patients in the age category 65 years and older to establish whether or not they respond differently to clozapine compared to younger patients (Novartis, 2006).

Increased mortality is evident in elderly patients with dementia who are treated with antipsychotics. Clozapine is not approved for the treatment of dementia-related behavioural disturbances in the elderly (Novartis, 2006).

2.1.6.2.2 Clozapine use in paediatric patients

The safety and efficacy of clozapine in patients under the age of 16 years has not yet been established (Novartis, 2006).

2.1.6.2.3 Clozapine use in hepatic impairment

Clozapine should be administered with caution in patients with hepatic impairment and regular monitoring of liver function tests should be performed (Novartis, 2006).

2.1.6.3 Therapeutic dosages

2.1.6.3.1 Target dose

In most patients, antipsychotic efficacy can be expected with dosages between 200 mg to 450 mg per day. Some patients may require doses up to 600 mg/day. The total daily dose may be divided unevenly, with the larger portion given at bedtime (Novartis, 2006; Rossiter, 2012:475).

Lower doses are required in the elderly, females and non-smokers and those patients that are prescribed certain enzyme inhibitors that alter clozapine metabolism (Taylor *et al.*, 2012:66).

2.1.6.3.2 Maintenance dose

After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is therefore recommended. With daily doses

not exceeding 200 mg, a single administration in the evening may be appropriate (Novartis, 2006; Stahl, 2012:30).

The average dose of clozapine in the United Kingdom is approximately 450 mg/day. The average dose of clozapine normally varies between 250 mg/day (e.g. female non-smoker) and 550 mg/day (e.g. male smoker) (Taylor *et al*., 2012:66).

2.1.6.3.3 Maximum dose

A few patients, however, may require larger doses to obtain maximum therapeutic benefit, in which case judicious increments (not more than 100 mg per increment) are allowed to a maximum dose of 900 mg per day. The possibility of increased adverse reactions, especially seizures, which usually occur at doses over 450 mg/day, should be considered (Novartis, 2006; Rossiter, 2012:475, Taylor *et al*., 2012:17).

2.1.6.4 Discontinuation and re-initiation of clozapine

2.1.6.4.1 Therapy cessation

In the event of planned termination of clozapine therapy, a gradual reduction in dose is recommended over a 2-4 week period (Sadock *et al*., 2009:3214). If abrupt discontinuation of therapy is necessary e.g. due to agranulocytosis or neutropenia the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea and diarrhoea (Novartis, 2006; Sadock *et al*., 2009:3214; Semple & Smyth, 2009:205).

2.1.6.4.2 Re-starting therapy

If for any reason a patient misses less than two days' clozapine, restart at the dose prescribed before the event (Taylor *et al*., 2012:65). In patients in whom the interval since the last dose of clozapine exceeds two days, treatment should be re-initiated with 12.5 mg given once or twice on the first day. If this dose is well tolerated, it may be feasible to

perform dosage titration at a faster rate than is recommended for initial treatment (Novartis, 2006; Taylor *et al*., 2012:65)

2.1.6.4.3 Switching from a previous antipsychotic to clozapine

The switching regimen will be largely dependent on the patient's mental state (Taylor *et al*., 2012:93).

When clozapine is to be initiated in a patient that was on oral antipsychotic therapy, the dosage of the previous antipsychotic should be reduced or discontinued by gradual downwards tapering. Risks for additive side effects as well as possible drug interactions should be evaluated before cross-tapering with clozapine. All depot antipsychotic medication should be discontinued before clozapine can be initiated (Novartis, 2006; Taylor *et al*., 2012:93).

2.1.7 CLOZAPINE AUGMENTATION

Clozapine augmentation has become common practice because inadequate response to clozapine monotherapy is a frequent clinical event (Taylor *et al.*, 2012:66). Clozapine augmentation is usually recommended when 3-6 months of optimised clozapine monotherapy showed no improvement (Taylor *et al*., 2012:66).

The evidence base supporting augmentation strategies is weak and not clearly sufficient to allow the development of any algorithm or schedule of treatment options (Taylor *et al.*, 2012:66).

If clozapine monotherapy fails, a time-limited combination trial may be attempted. If there is no improvement within 6 to 12 weeks, the augmenting agent should be tapered and discontinued (Wells *et al.*, 2012:902).

In some cases, the addition of an augmenting agent may reduce the severity of some adverse effects or allow a reduction in clozapine dose. The addition of aripiprazole to clozapine may be particularly effective in reversing its metabolic effects (Taylor *et al.*, 2012:66). SSRIs have been used in combination with clozapine for obsessive-compulsive symptoms that worsen or arise during clozapine treatment (Wells *et al*., 2012:902).

The following table summarises the suggested options for augmenting clozapine (adapted from Taylor *et al.*, 2012:67).

Table 2.3 Suggested clozapine augmentation options

Drug:	**Dose:**
Amisulpride	400-800 mg/day
Aripiprazole	15-30 mg/day
Haloperidol	2 -3 mg/day
Lamotrigine	25-300 mg/day
Risperidone	2-6 mg/day
Sulpiride	400 mg/day
Topiramate	200-300 mg/day
Ziprasidone	80-160 mg/day

2.1.8 PRECAUTIONS

Clozapine has five black box warnings. Boxed warnings, commonly referred to “black box” warnings are notices issued by the FDA that feature in the labelling of drugs associated with serious adverse reactions. The following warnings appear on the package insert of clozapine: agranulocytosis, seizures, myocarditis, severe cardiovascular and respiratory events and increased mortality in elderly patients with dementia (FDA, 2005).

2.1.8.1. Agranulocytosis

Agranulocytosis due to clozapine therapy is a potentially fatal condition that requires immediate medical attention (Schatzberg & Nemeroff, 2004:445).

The risk of agranulocytosis increases with age and is higher in women (Sadock *et al*., 2009:3212). The risk for agranulocytosis is 0.73% during the first year of treatment and reduces to 0.07% in the second year of treatment (Sadock *et al*., 2009:3212).

The risk for this adverse effect is greatest during the first eighteen weeks of treatment, but a significant risk remains during the first year of treatment and perhaps, indefinitely (Taylor *et al*., 2012:77).

The risk for neutropenia is 2.32% in the first year of treatment and 0.69% in the subsequent year (Sadock *et al*., 2009:3212).

2.1.8.2 Seizures

Rapid dosage escalation during the first weeks of clozapine treatment may increase the likelihood of seizures (Taylor *et al*., 2012:77). Approximately 5-10% of patients treated with clozapine will develop seizures (Sadock *et al*., 2009:3213). The risk is clearly related to dosage, with an increased risk at dosages greater than 450 mg/day (Rossiter, 2012:475).

Head trauma or a pre-existing seizure disorder places the patient at even higher risk (Sadock *et al*., 2009:3213).

The occurrence of seizures associated with clozapine should not be seen as a reason to discontinue clozapine therapy. However, lowering the dosage of clozapine and adding an antiepileptic agent (e.g. topiramate or sodium valproate) is usually sufficient to protect patients against additional seizures (Taylor *et al*., 2012:77).

2.1.8.3 Myocarditis

There is an increased risk of myocarditis associated with clozapine, especially during the first month of therapy (Taylor *et al*., 2012:81).

The incidence of myocarditis is very low (approximately 2.8/100 000 patient-years) but there have been at least 17 deaths reported (Sadock *et al*., 2009:3212).

Symptoms include unexplained fatigue, dyspnoea, tachypnea, fever, chest pain, palpitations, and other evidence of cardiac failure (Taylor *et al*., 2012:81). Early detection and treatment is vital, since mortality from myocarditis approaches 40% (Sadock *et al*., 2009:3212).

2.1.8.4 Severe cardiovascular and respiratory events

Clozapine can cause severe episodes with orthostatic hypotension and possible syncope that have been associated with cardiac or respiratory arrest. However, these events occur rarely and are more likely to present early in treatment when the dose is titrated upwards (Sadock *et al*., 2009:3213).

2.1.8.5 Increased mortality in elderly patients with dementia related psychosis

In 2005 the FDA issued a black box warning stating that the treatment of behavioural disorders in elderly patients with dementia with SGAs medications (including clozapine) is associated with increased mortality (FDA, 2005). Therefore, clozapine is not approved for the treatment of patients with dementia-related psychosis.

2.1.9 ADVERSE EFFECTS

2.1.9.1 Common adverse effects of clozapine

Clozapine has a wide range of adverse effects, many of which are serious or potentially life-threatening (Taylor *et al*., 2012:75). The adverse effects of clozapine make it one of the most challenging psychotropics for psychiatrists to prescribe (Schatzberg & Nemeroff, 2004:448).

The common adverse effects of clozapine include the following: constipation, dry mouth, blurred vision, difficult micturition, hypotension, sexual dysfunction, sedation, weight gain, nausea, vomiting, headache, fatigue, hypersalivation, tachycardia, hypertension, fever, seizures, neutropenia/agranulocytosis and dizziness (Semple & Smyth, 2009:206).

The following table summarises the adverse effects of clozapine into five categories, namely very common, common, uncommon, rare and very rare (adapted from Novartis, 2006; Rossiter, 2012:475; Taylor *et al.*, 2012:76; Turner *et al*., 2010:461).

(See next page)

Table 2.4 Adverse effects of clozapine

Organ system	Very common	Common	Uncommon	Rare	Very rare
Haematological disorders		Neutropenia, leukopenia, eosinophilia, leukocytosis	Agranulocytosis	Anaemia	Thrombocytopenia
Metabolic disorders		Weight gain		Diabetes mellitus aggravated	Hypercholesterolemia, severe hyperglycaemia, hypertriglyceridemia
Cardiovascular disorders	Tachycardia	ECG changes		Circulatory collapse, arrhythmias, pericarditis, myocarditis	Cardiomyopathy
Vascular system disorders		Postural hypotension, hypertension, syncope			Thromboembolism
Nervous system disorders	Sedation	Blurred vision, tremor, rigidity, headache, seizures, akathisia, extrapyramidal symptoms		Confusion and delirium	Tardive dyskinesia, obsessive compulsive symptoms
Psychiatric disorders		Dysarthria		Agitation, restlessness	

Respiratory disorders				Aspiration of ingested food	Respiratory depression/arrest
Gastro-intestinal disorders	Constipation, hypersalivation	Nausea, vomiting, dry mouth		Dysphagia	Intestinal obstruction/ paralytic ileus / faecal impaction
Hepatobiliary disorders		Elevated liver enzymes		Cholestatic jaundice, hepatitis and pancreatitis	Fulminant hepatic necrosis
Renal and urinary disorders		Urinary incontinence, urinary retention,			Interstitial nephritis
Reproductive system disorders					Priapism
Skin disorders					Skin reactions
General disorders		Fever, fatigue, disturbances in sweating/ temperature regulation	Neuroleptic malignant syndrome (NMS)		Sudden unexplained death
Investigations				Raised CPK	

The following table displays the scale that was used to rank the adverse effects associated with clozapine therapy (adapted from Council for International Organisations of Medical Sciences (CIOMS, 2000:8).

Table 2.5 Rating scale for occurrence of adverse effects

Incidence	**Occurrence of events**
Very common	An event that occurs in ≥ 1 in 10 exposures
Common	Events that occur < 1 in 10 but ≥1 in 100 exposures
Uncommon	Events that occur < 1 in 100 but ≥1 in 1000 exposures
Rare	Events that occur < 1 in 1000 but ≥1 in 10 000 exposures
Very rare	Events that occur < 1 in 10 000 exposures

2.1.9.2 MANAGEMENT OF COMMON ADVERSE EFFECTS

More extensive pharmacoepidemiological monitoring is associated with clozapine than with any other drug used in psychiatry. Awareness of adverse effects related to clozapine treatment is therefore enhanced (Taylor *et al*., 2012:75).

The management of common adverse effects associated with clozapine will be discussed briefly.

2.1.9.2.1 Sedation

Time course

- Usually occurs within the first few months.
- May persist but usually wears off.

Treatment

- Give a smaller dose in the morning.
- Reduce the dose if necessary.
- Patients should be advised not to drive or operate any machinery, especially during the initial weeks of therapy

(Novartis, 2006; Semple & Smyth, 2009:207; Taylor *et al*., 2012:76).

2.1.9.2.2 Hypersalivation

Time course

- First few months.
- May persist, but sometimes wears off.
- This is often very troublesome at night.

Treatment

- In the UK hyoscine hydrobromide 300 µg is given to the patient that should be sucked and swallowed at night

(Semple & Smyth, 2009:207; Taylor *et al*., 2012:76).

2.1.9.2.3 Constipation

Time course

- Usually persists.

Treatment

- Encourage a high fibre diet and adequate fluid intake.
- Bulk forming laxatives and stimulants should be used.
- Effective treatment or prevention of constipation is essential as death may result

(Novartis, 2006; Semple & Smyth, 2009:207; Taylor *et al*., 2012:76).

2.1.9.2.4 Hypotension

Time course

- First four weeks.

Treatment

- Advise patient to take time when standing up.
- Close medical supervision is required.
- Reduce dose or slow down rate of dose escalation. If severe consider using moclobemide and Bovril

(Novartis, 2006; Rossiter, 2012:475; Semple & Smyth, 2009:207; Taylor *et al*., 2012:76).

2.1.9.2.5 Fever

Time course

- First three weeks.

Treatment

- Clozapine induces an inflammatory response.
- The fever is generally benign but occasionally it may be associated with an increase or decrease in white blood cell (WBC) count.
- Patients should be carefully monitored for the early detection of agranulocytosis and neuroleptic malignant syndrome.
- Provide symptomatic relief through giving an antipyretic but check full blood count (FBC) and reduce the rate of clozapine dosage titration

(Novartis, 2006; Semple & Smyth, 2009:207; Taylor *et al*., 2012:77).

2.1.9.2.6 Weight gain

Time course

- Usually during the first year of treatment.

Treatment

- Dietary and exercise counselling is essential.
- Advice may be more effective if given before weight gain occurs. Weight gain is common and often profound (> 4.5 kg).
- Weight gain increases the risk of thromboembolism and therefore immobilisation of the patient should be avoided

(Novartis, 2006; Semple & Smyth, 2009:207; Taylor *et al*., 2012:76).

2.1.9.2.7 Nausea

Time course

- Occurs during the first six weeks.

Treatment

- Consider the use of an antiemetic.
- Avoid prochlorperazine and metoclopramide if previous problems with EPS.
- Ondansetron is usually a good choice

(Novartis, 2006; Semple & Smyth, 2009:207; Taylor *et al.*, 2012:77).

2.1.9.2.8 Neutropenia/agranulocytosis

Time course

- First eighteen weeks – but can occur at any time.

Treatment

- Stop clozapine, admit patient to hospital if agranulocytosis is confirmed

(Novartis, 2006; Semple & Smyth, 2009:207; Taylor *et al.*, 2012:77).

2.1.9.2.9 Seizures

Time course

- May occur at any time.

Treatment

- Usually related to increases in clozapine dosage above 600 mg.
- Consider use of a prophylactic agent such as sodium valproate if on high dose of clozapine or with high plasma level of clozapine.
- Caution should be used when clozapine is administered to patients with a history of seizures or other predisposing factors. Patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others. (e.g. swimming, climbing and driving)

(Novartis, 2006; Rossiter, 2012:475; Taylor *et al*., 2012:77).

2.1.9.2.10 Neuroleptic malignant syndrome (NMS)

Neuroleptic malignant syndrome (NMS) is a rare but potentially serious or even fatal adverse effect of all antipsychotics (Taylor *et al*., 2012:110).

NMS occurs in 0.5% to 1% of patients taking conventional antipsychotics and has been reported with SGAs as well, including clozapine, but this is less frequent than with conventional antipsychotics (Wells *et al*., 2012:906).

Although widely seen as an acute, severe syndrome, NMS may in many cases have few signs and symptoms, 'full-blown' NMS may thus represent the extreme of a range of non-malignant related symptoms. Certainly, asymptomatic rises in plasma creatine kinase (CK) are fairly common (Taylor *et al*., 2012:110).

Signs and symptoms

Usually the symptoms develop within the first two weeks of antipsychotic drug treatment (McPhee *et al*., 2012:1032). A catatonia-like state manifested by hyperpyrexia, rigidity, confusion, tachycardia, elevated CK, leukocytosis, altered liver function tests, fluctuating blood pressure and consciousness. NMS may lead to stupor, coma and death (McPhee *et al*., 2012:1032; Wells *et al*., 2012:907).

Treatment

- Withdraw antipsychotic therapy.
- Monitor the patient's temperature, blood pressure and pulse.
- Control the patient's fever and provide fluid support.
- Consider using benzodiazepines (e.g. lorazepam injected intramuscularly)
- Dopamine agonists (e.g. bromocriptine) and skeletal muscle relaxants (e.g. dantrolene) can also be used.
- Electroconvulsive therapy (ECT) can be considered in resistant cases of NMS

(McPhee *et al*., 2012:1032; Taylor *et al.*, 2012:111).

Restarting antipsychotic therapy

Stop administration of the antipsychotic drug for at least 5 days, but preferably longer. Allow time for symptoms and signs to resolve completely (Taylor *et al.*, 2012:906).

Begin with very small dose and increase very slowly with close monitoring of temperature, blood pressure and pulse. CK monitoring may be used but is controversial. Close monitoring of physical and biochemical parameters is effective in reducing progression to full-blown NMS (Taylor *et al.*, 2012:111; Wells *et al*., 2012:907).

Clozapine demonstrated relative safety and fair success as an antipsychotic drug for patients who suffered from NMS in the past (McPhee *et al*., 2012:1032).

2.1.9.2.11 Tardive dyskinesia

Tardive dyskinesia (TD) is characterised by abnormal involuntary movements occurring with chronic antipsychotic therapy and is sometimes irreversible (Porter & Kaplan, 2011:1562). Predisposing factors include older age, cigarette smoking, many years of treatment with neuroleptics and diabetes mellitus (McPhee *et al*., 2012:1033). Clinical presentation includes lip smacking, sucking, and puckering as well as facial grimacing. Other movements may include irregular movements of the limbs, particularly choreoathetoid-like movements of the fingers and toes, and slow, writhing movements of the trunk (Sadock *et al*., 2009:1552). Dosage reduction or discontinuation of antipsychotic treatment may have a significant effect on the outcome achieved and in some patients the symptoms may disappear completely if a timeous intervention is performed (Wells *et al*., 2012:906).

The risk of TD associated with clozapine therapy appears to be less than that for other antipsychotics (McPhee *et al*., 2012:1033). The first-line treatment strategy for patients with TD is switching them to clozapine therapy, especially in those patients with moderate to severe dyskinesias (Wells *et al*., 2012:906).

2.1.10 MONITORING REQUIREMENTS

2.1.10.1 Metabolic monitoring

Accumulating evidence suggests that clozapine has a marked effect on various metabolic markers when compared to other neuroleptics (American Diabetes Association, 2004; Lamberti *et al*., 2006:1273).

The Maudsley Prescribing Guidelines recommend the following metabolic monitoring protocol for clozapine (adapted from Taylor *et al*., 2012:95).

Table 2.6 Metabolic monitoring

Baseline	Weight, lipids, plasma glucose, body mass index (BMI) and waist circumference
After one month of therapy	Weight, plasma glucose, BMI and waist circumference
After 3 months of therapy	Weight, lipids, BMI and waist circumference
After 4-6 months of therapy	Weight, lipids, plasma glucose, BMI and waist circumference
After 12 months of therapy	Weight, lipids, plasma glucose, BMI and waist circumference

Measurements of body mass index (BMI) expressed in kg/m^2, take into account the weight of a patient relative to his or her height. The waist circumference and BMI are important parameters to measure because they are both predictors of cardiovascular risk (Schatzberg & Nemeroff, 2004:449).

There is a strong association between clozapine and hyperglycaemia, impaired glucose intolerance and diabetic ketoacidosis (Taylor *et al*., 2012:132).

The following warning was published by the Medicine Control Council in 2005 and has to be stated on the package insert of all SGAs agents, including clozapine:

Warning on Hyperglycaemia and Diabetes Mellitus with SGA agents

"Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with clozapine. Patients with an established diagnosis of diabetes mellitus who are started on clozapine should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with clozapine should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with clozapine should undergo fasting blood glucose testing" (MCC, 2005:1).

While cholesterol levels can rise the most profound effect of clozapine seems to be on triglycerides. Mean triglyceride levels have been shown to double and cholesterol levels to increase by at least 10% after 5 years' treatment with clozapine. Patients treated with clozapine have triglyceride levels that are almost double those of patients who are treated with conventional antipsychotics (Taylor *et al*., 2012:139).

Particular care should be taken before prescribing clozapine for patients who are obese, diabetic or known to have pre-existing hyperlipidaemia (Taylor *et al.*, 2012:139).

2.1.10.2 Haematological monitoring

Because of a non-dose-dependent risk of agranulocytosis associated with clozapine, the following precautionary measures are mandatory (adapted from Novartis, 2006; Rossiter, 2012:475; Taylor *et al*., 2012:95).

Table 2.7 Haematological monitoring

Pre-treatment	White blood cell counts (total and differential) must be normal before clozapine therapy can be initiated
After initiating therapy	• Monitor white blood cell counts weekly for the first eighteen weeks • Then every two weeks for the remainder of the year • Thereafter, the blood monitoring is usually performed monthly

Before starting clozapine therapy a white blood cell (WBC) and a differential blood count should be performed within 10 days prior to initiation. Initiation of treatment must be restricted to patients with a WBC count ≥ 3.5 x 10^9/L and an absolute neutrophil count (ANC) ≥ 2,0 x 10^9/L and within standardised normal limits (Novartis, 2006).

The normal range of total WBC count is 4.0-10.0 x 10^9/L and absolute neutrophil count (ANC) is 2.0-7.5 x 10^9/L (NHLS, 2012).

In the United Kingdom (UK), Australia and the United States (US) before clinicians can treat patients with clozapine the eligible patient should be registered with the relevant clozapine monitoring system (Sadock *et al*., 2009:3212).

The requirement for WBC count monitoring is continued for as long as the patient receives clozapine therapy and weekly monitoring must be performed for at least one month after clozapine discontinuation (McPhee *et al*., 2012:1029; Novartis, 2006; Turner *et al*., 2010:461).

Patients who have low WBC counts because of benign ethnic neutropenia should be given special consideration and may be started on clozapine only after agreement by a haematologist (Novartis, 2006).

The following table summarises the action required according to the results obtained for the haematological parameters that were investigated (adapted from Novartis, 2006; Rossiter, 2012:475).

Table 2.8 Haematological parameters

White blood cell count	Absolute neutrophil count	Procedure to follow
> 3.5 x 10^9/L	> 2.0 x 10^9/L	Continue clozapine treatment
3.0 x 10^9/L – 3.5 x 10^9/L	1.5 x 10^9/L – 2.0 x 10^9/L	Continue clozapine treatment, sample blood twice weekly until counts stabilise or increase
< 3.0 x 10/L ^{9}	< 1.5 x 10^9/L	Immediately stop clozapine treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

An experienced haematologist should take over the management of the patient's condition if the WBC count further falls below 2.0 x 10^9/L and/or the ANC decreases below 1.0 x 10^9/L following clozapine withdrawal (Novartis, 2006).

Confirmation of the blood results is recommended by performing two blood counts on two consecutive days. However, it is advised that clozapine be discontinued after obtaining the first result. If clozapine therapy had to be discontinued in a patient due to a negative effect on the WBC count, that patient should never be re-exposed to clozapine (Novartis, 2006).

Although the FDA allows US patients to be rechallenged if the WBC count is between 2.0 x 10^9/L and 3.0 x 10^9/L and the ANC is between 1.0 x 10^9/L and 1.5 x 10^9/L, the regulatory authorities in the UK and Australia do not allow a rechallenge of clozapine (Sadock *et al*., 2009:3212).

The following table summarises the additional haematological monitoring precautions for clozapine (adapted from Novartis, 2006).

Table 2.9 Additional haematological monitoring

Eosinophilia
It is recommended to discontinue clozapine if the eosinophil count rises above 3.0 x 10^9/L and to restart therapy only after the eosinophil count has fallen below 1.0 x 10^9/L.
Thrombocytopenia
It is recommended to discontinue clozapine if the platelet count falls below 50.0 x 10^9/L.

Patients should also be monitored for the development of signs and symptoms of agranulocytosis which include the following:

- Sore throat
- Fever
- Painful mouth ulcers
- Anal ulcers
- Flu-like symptoms

(Novartis, 2006; Rossiter, 2012:475).

An immediate differential blood count should be performed if any symptoms or signs of an infection occur (Rossiter, 2012:475).

2.1.10.3 Additional physical health monitoring requirements

The following table summarises the additional physical health monitoring requirements for clozapine (adapted from Churchward *et al*., 2009:453; Taylor *et al*., 2012:95).

Table 2.10 Additional physical health monitoring

Blood pressure	• Baseline blood pressure • Hourly blood pressure monitoring for at least three hours after the first dose of clozapine. • Then daily blood pressure monitoring for the first two weeks of treatment followed by weekly monitoring for the remainder of the first month of treatment. • Thereafter blood pressure should be assessed annually.
Temperature	• Hourly monitoring for at least three hours after the first dose of clozapine. • Then daily temperature monitoring for the first two weeks of treatment followed by weekly monitoring for the remainder of the first month of treatment.
Pulse	• Hourly monitoring of the pulse for at least three hours after the first dose of clozapine. • Then daily monitoring of the pulse for the first two weeks of treatment followed by weekly monitoring for the remainder of the first month of treatment. • Thereafter the patient's pulse should be assessed annually.
Liver function	• Baseline liver function tests (LFTs) should be performed

Liver function	• LFTs should again be performed 6 months after initiation of clozapine therapy. • Thereafter annually.
Thyroid function	• Baseline thyroid function tests should be performed. • Thereafter annually.
Urea and electrolytes	• Baseline urea and electrolytes should be performed. • Thereafter annually.
Electrocardiogram	• Baseline electrocardiogram should be performed. • Thereafter annually.

2.1.11 DRUG INTERACTIONS

2.1.11.1 Pharmacodynamic-related interactions

Clozapine may enhance the central effects of alcohol, mono-amine oxidase inhibitors and central nervous system depressants such as narcotics, antihistamines and benzodiazepines (Semple & Smyth, 2009:203).

Because of the possibility of additive effects, caution is essential when substances possessing anticholinergic, hypotensive, or respiratory depressant effects are given concomitantly with clozapine (Novartis, 2006).

2.1.11.1.1 Clozapine and benzodiazepines

Level of interaction	Onset	Severity	Effects
Level 1	Rapid	Major	Suspected

Result:

- The pharmacologic or toxic effects of certain benzodiazepines may be increased.

Mechanism:

- Unknown

Management:

- Consider monitoring vital signs and observing patients for excessive adverse reactions when clozapine and benzodiazepines are co-administered

(Tatro, 2011:246).

Discussion:

- A handful of reports describe severe hypotension, respiratory depression, unconsciousness and potentially fatal cardiac and/or respiratory arrest in patients on benzodiazepines and clozapine. Dizziness and sedation are also increased (Baxter, 2010:873; Novartis, 2006).

2.1.11.1.2 Clozapine and bone marrow suppressants

Caution need to be exercised when clozapine is used with other drugs that can cause bone marrow suppression. Low white cell counts have been seen in patients on clozapine and chloroquine, co-trimoxazole, nitrofurantoin and olanzapine (Baxter, 2010:875, Novartis, 2006).

Result:

- Co-administration with clozapine is associated with increased risk and/ or severity of bone marrow suppression (Novartis, 2006).

Discussion:

- Clozapine should not be co-administered with other agents known to suppress bone marrow function. Agranulocytosis has been reported with the concurrent use of clozapine and co-trimoxazole (Novartis, 2006; Turner *et al*., 2010:460).

2.1.11.1.3 Clozapine and anticholinergics

The anticholinergic effects of clozapine are additive with those of other anticholinergic drugs, which can lead to urinary retention and delirium in susceptible patients (Baxter, 2010:873).

Result:

- Clozapine potentiates the anticholinergic activity of these agents (Novartis, 2006).

Discussion:

- Patients should be observed for anticholinergic side effects e.g. constipation, especially when anticholinergics drugs are used to help control hypersalivation (Novartis, 2006).

2.1.11.1.4 Clozapine and lithium

Concomitant use of clozapine and lithium or other central nervous system agents may increase the risk of development of neuroleptic malignant syndrome (Novartis, 2006).

Level of interaction	Onset	Severity	Documentation
Level 4	Delayed	Moderate	Possible

Result:

- Diabetic ketoacidosis may occur.

Mechanism:

- Unknown

Management:

- Diabetic ketoacidosis: Based on available data, no special precautions are warranted.

- NMS: Patients should be monitored for signs and symptoms of NMS (Tatro, 2011:1103).

2.1.11.1.5 Clozapine and valproic acid/ sodium valproate

Level of interaction	Onset	Severity	Documentation
Level 4	Delayed	Moderate	Possible

Result:

- Serum clozapine concentrations may be slightly elevated; increasing sedation, functional impairment and occurrence of seizures amongst non-epileptic patients (Novartis, 2006).

Mechanism:

- Unknown

Management:

- No precautions other than usual monitoring of the patient are needed. If an interaction is suspected, it may be necessary to discontinue valproic acid/ sodium valproate (Tatro, 2011:479).

2.1.11.1.6 Clozapine and antihypertensives

There are isolated cases of apparent interactions between clozapine, and enalapril, lisinopril as well as propranolol. Additive hypotensive effects are possible with clozapine and any antihypertensive agent (Baxter, 2010:873).

Result:

- Clozapine potentiates the hypotensive effect of these drugs.

Discussion:

- Caution is needed when clozapine is co-administered with antihypertensives and patients need to be advised of the risk of hypotension, especially during the initial dosage titration period. When clozapine is co-administered with propranolol it can result in dizziness, sedation, significant hypotension and respiratory depression (Turner *et al*., 2010:460).

2.1.11.1.7 Clozapine and angiotensin-converting enzyme (ACE) inhibitors

Level of interaction	Onset	Severity	Documentation
Level 4	Delayed	Moderate	Possible

Result:

- The pharmacologic and toxic effects of clozapine may be increased.

Mechanism:

- Unknown

Management:

- Observe the clinical response, monitor clozapine plasma concentrations and adjust the dose of clozapine as needed when starting, stopping or changing the dose of the ACE inhibitor (Tatro, 2011:464).

2.1.11.1.8 Clozapine and depot formulations of conventional antipsychotics

Concomitant administration of clozapine and flupenthixol decanoate or fluphenazine decanoate or zuclopenthixol decanoate can result in neutropenia. Therefore, it is advised not to use these depot formulations in combination with clozapine (Turner *et al*., 2010:462).

2.1.11.2 Pharmacokinetic-related interactions

Clozapine is a major substrate for many cytochrome P450 isoenzymes, in particular 1A2 and 3A4. Caution is called for in patients receiving concomitant treatment with other drugs, which are either inhibitors or inducers of these enzymes (Novartis, 2006; Tatro, 2011:xxi).

2.1.11.2.1 Clozapine and hormonal contraceptives

Level of interaction	**Onset**	**Severity**	**Documentation**
Level 4	Delayed	Moderate	Possible

Result:

- Clozapine plasma concentrations may be elevated, leading to increased pharmacologic and adverse effects.

Mechanism:

- Inhibition of clozapine metabolism by oral contraceptives is suspected.

Management:

- Observe the clinical response of the patient and adjust the dose of clozapine as needed when oral contraceptives are started or stopped. Monitoring of clozapine plasma levels may assist in managing the patient (Tatro, 2011:468).

2.1.11.2.2 Clozapine and caffeine

Level of interaction	***Onset***	***Severity***	***Documentation***
Level 2	Rapid	Moderate	Suspected

Result:

- Elevation of serum clozapine levels which may increase the incidence of clozapine adverse effects (Baxter, 2010:874, Novartis, 2006).

Mechanism:

- Caffeine may inhibit clozapine metabolism (CYP1A2).

Management:

- If an interaction is suspected, advise patients to avoid beverages and other products that contain caffeine.

Discussion:

- Acute exacerbations of psychotic episodes may be experienced when clozapine is taken with caffeinated beverages. According to the literature clozapine plasma concentration is decreased by nearly 50% following a 5-day caffeine-free period (Novartis, 2006; Tatro, 2011:466).

2.1.11.2.3 Clozapine and carbamazepine

Level of interaction	Onset	Severity	Documentation
Level 4	Delayed	Moderate	Possible

Result:

- The pharmacologic effects of clozapine may be decreased by co-administration of carbamazepine (Turner *et al*., 2010:460).

Mechanism:

- Induction of hepatic microsomal enzymes (CYP3A4) by carbamazepine is suspected.

Management:

- Monitor serum clozapine levels when carbamazepine therapy is started or stopped. When discontinuing carbamazepine observe the patient for signs of clozapine toxicity and adjust the dose accordingly. Cases of NMS as well as pancytopenia have been reported with concurrent use of clozapine and carbamazepine (Turner *et al*., 2010:460).

- The administration of an alternative anticonvulsant agent such as valproic acid or valproic acid derivatives may overcome this problem (Novartis, 2006; Tatro, 2011:467).

2.1.11.2.4 Clozapine and ciprofloxacin

Level of interaction	Onset	Severity	Documentation
Level 2	Delayed	Moderate	Suspected

Effects:

- Clozapine plasma concentrations may be elevated, increasing the risk of adverse effects.

Mechanism:

- Inhibition of clozapine metabolism (CYP1A2) by ciprofloxacin is suspected.

Management:

- Observe the clinical response of the patient and adjust the dose of clozapine as needed when ciprofloxacin is started or stopped (Tatro, 2011:475).

Discussion:

- An isolated report describes the development of agitation in an elderly man on clozapine, probably attributed to elevated serum levels caused by an interaction with ciprofloxacin. A study supports this observation (Baxter, 2010:878).

2.1.11.2.5 Clozapine and rifampicin

Level of interaction	Onset	Severity	Documentation
Level 4	Delayed	Moderate	Possible

Result:

- Rifampicin may decrease clozapine serum concentrations, resulting in decreased therapeutic effect (Turner *et al*., 2010:462).

Mechanism:

- Rifampicin may increase the metabolism of clozapine by enzyme induction (CYP3A4).

Management:

- Monitor serum clozapine concentrations and observe the clinical response of the patient when rifampicin is started or stopped. If rifampicin is discontinued, observe the patient for signs of clozapine toxicity. Adjust the dose of clozapine as needed (Tatro, 2011:476).

Discussion:

- An isolated report describes a marked fall in the serum levels of a patient on clozapine when he was treated with rifampicin (Baxter, 2010:879).

2.1.11.2.6 Clozapine and risperidone

Level of interaction	Onset	Severity	Documentation
Level 4	Delayed	Major	Possible

Result:

- The pharmacologic effects and adverse effects of clozapine may be increased.

Mechanism:

- Unknown.

Management:

- Observe the clinical response of the patient, monitor clozapine serum concentrations and adjust the dose of clozapine as indicated when risperidone is started or stopped (Tatro, 2011:477).

Discussion:

- The concurrent use of clozapine and risperidone can be effective and well tolerated but two isolated reports describe a rise in serum clozapine levels when risperidone was added and another describes the development of atrial ectopics. Dystonia has been seen when clozapine was replaced by risperidone. Neuroleptic malignant syndrome (NMS) and neutropenia have been reported (Baxter, 2010:879; Turner *et al*., 2010:462).

2.1.11.2.7 Clozapine and haloperidol

Level of interaction	Onset	Severity	Documentation
Level 4	Delayed	Moderate	Possible

Result:

- Haloperidol plasma levels may be elevated increasing the risk of side effects.

Mechanism:

- Inhibition of haloperidol metabolism (CYP2D6) by clozapine is suspected.

Management:

- Observe the clinical response of the patient to haloperidol when starting or stopping clozapine. Neutropenia has been reported following the concurrent use of haloperidol and clozapine (Tatro, 2011:878; Turner *et al*., 2010:460).

2.1.11.2.8 Clozapine and selective serotonin re-uptake inhibitors (SSRIs)

Level of interaction	Onset	Severity	Documentation
Level 1	Delayed	Major	Established

Result:

- Serum clozapine levels may be elevated, resulting in increased pharmacologic and toxic effects (Turner *et al*., 2010:462).

Mechanism:

- Certain SSRIs inhibit clozapine hepatic metabolism (CYP1A2).

Management:

- Monitor clozapine serum levels and observe the clinical response. Adjust the dose of clozapine as needed (Tatro, 2011:478).

Discussion:

- Fluoxetine, paroxetine, sertraline and possibly citalopram can raise serum clozapine levels. Particularly large increases can occur with fluvoxamine. Clozapine toxicity has been seen in some patients (Baxter, 2010:880).

2.1.11.3 Effect of smoking on clozapine plasma levels

The potential for the pharmacokinetics and pharmacodynamics of a drug to be altered by cigarette smoking is significant (Tatro, 2011:xxxix).

Induction of liver enzymes by polynuclear aromatic hydrocarbons in cigarettes can increase drug metabolism. This is the most common mechanism by which smoking alters the pharmacokinetics of a drug. The effects of smoking on drug metabolism are greater in younger smokers than in older smokers. The effects of smoking on drug metabolism can persist for months after the person has stopped smoking (Tatro, 2011:xxxix).

2.1.11.3.1 Effect of smoking on clozapine metabolism

Nicotine reduces clozapine plasma levels by up to 50% due to increased hepatic metabolism (CYP1A2) (Novartis, 2006; Tatro, 2011:xli; Taylor *et al.*, 2012:616).

Two reports of elevated clozapine plasma concentrations following smoking cessation could be found in the literature. In the first patient elevated plasma concentrations of clozapine (3004 µg/L) occurred six days after a 16-day stay in a hospital in which smoking was prohibited. In the other patient, smoking cessation resulted in extreme sedation and fatigue within two weeks, and there was a three-fold increase in clozapine levels (Tatro, 2011:xli).

Smoking seven to 12 cigarettes daily may be sufficient for maximum induction of clozapine metabolism. Non-smokers may require a 50% lower starting dose of clozapine than smokers (Tatro, 2011:xli).

2.1.11.3.2 Smoking cessation

- Take plasma level before quitting.
- On stopping reduce clozapine dose gradually over one week until 75% of the original dose is reached.
- Repeat plasma level one week after stopping. Consider further dose reductions. (Taylor *et al.*, 2012:616).

2.1.11.3.3 Patient starts to smoke again

- Take plasma level before restarting.
- Increase dose to previous smoking dose over one week.
- Repeat plasma level (Taylor *et al.*, 2012:616).

2.1.12 CLOZAPINE DISCONTINUATION RATES

A study conducted by Taylor *et al*. (2009:165) compared the reasons for discontinuation of clozapine with reasons for discontinuation of risperidone long-acting injection in age-matched individuals treated in the same clinical environment. The study found that adverse effects and death were more commonly observed as reasons for discontinuation of clozapine than of risperidone. Clozapine was less likely to be withdrawn because of ineffectiveness than was risperidone. Standardised mortality ratio (SMR) was significantly raised for patients receiving clozapine (SMR=4.17, 95% CI 2.78–6.26). The number and causes of death in the clozapine group highlight the importance of prevention and early detection and management of physical illness in patients receiving clozapine therapy.

Another retrospective observational study conducted by Taylor *et al*. (2008:240) which aimed to compare the patterns of use and discontinuation of commonly used SGAs showed that clozapine had a significantly lower discontinuation rate in individuals with schizophrenia when compared to amisulpride, olanzapine, quetiapine, and risperidone.

However, a benchmark clinical trial conducted by McEvoy *et al*. (2006) known as phase 2 of the CATIE study (in which patients who left phase 1 of the CATIE study prematurely were re-randomised to either double-blinded risperidone, olanzapine or quetiapine or to open-label clozapine), revealed that clozapine outperformed the other SGAs and was found most effective as measured by time to all-cause discontinuation. The results indicated that 44% of the patients who changed to clozapine stayed on it for the rest of the 18-month study, compared with 18% of patients who had changed to the other medications.

On average, patients stayed on clozapine for 10 months, while patients on any of the other medications stayed on them for only 3 months. Therefore, clozapine seems to be the only effective treatment option for patients who have failed treatment with a conventional antipsychotic or an SGA. However, clozapine remains underused, probably because of lower tolerability and need for continuous haematological monitoring (McEvoy *et al*., 2006:600).

2.1.13 ALTERNATIVE TREATMENT OPTIONS

Clozapine is the established treatment of choice for refractory schizophrenia. Where treatment resistance is established, clozapine treatment should not normally be delayed or withheld. Where clozapine cannot be used (because of toxicity or patient refusal) other drugs or drug combinations may be tried but the clinical outcome is usually disappointing (Taylor *et al*., 2012:69).

The following table provides a list of possible alternatives to clozapine therapy for refractory schizophrenia (adapted from Taylor *et al*., 2012:70).

Table 2.11 Alternatives to clozapine

Treatment	Dose	Comments
Amisulpride	up to 1200 mg/day	Uncommon in practice
Aripiprazole	15-30 mg/day	Moderate effect
Quetiapine	> 1200 mg/day	Very limited evidence
Ziprasidone	80-160 mg/day	Disappointing results in practice
Electroconvulsive therapy (ECT)	Three sessions per week	Moderate effect and often reserved for last line treatment in practice

2.1.14 COST OF THERAPY

Two studies have examined the cost-effectiveness of clozapine in treatment-resistant schizophrenia. Revicki (1999) reported that by the second year of treatment, total costs had decreased more than $24 000.00 per year in 86 treatment-resistant schizophrenic patients. In a prospective study, Meltzer (2000) compared the total costs of treatment for 2 years before and 2 years after clozapine treatment in 37 treatment-resistant schizophrenic patients.

The median total cost for 2 years decreased from $42 934.00 to $23 772.00, a decrease of $19 162.00. These studies suggest that large savings are possible with clozapine treatment for treatment-resistant schizophrenic patients who have had frequent hospitalisations (Meltzer, 2000:1282).

The cost of clozapine therapy has reduced remarkably, since the expiration of the patent on clozapine in 2007 (Joober & Boksa, 2010:147).

The 2012 cost of one month's clozapine (e.g. Clozaril®) therapy based on the maximum dosage of clozapine i.e. 900 mg/day in the U.S. was about $899.10 (McPhee *et al*., 2012:1028), whereas in South Africa the 2012 cost of one month's clozapine (e.g. Aspen Clozapine®) therapy at the maximum daily dosage based on the single exit price (SEP) was about R1658.50 (Aspen Pharmacare, 2012).

The use of clozapine provides overall savings in health care costs, mainly through reductions in admissions and hospital stay (Taylor *et al*., 2002:21).

A study conducted by Woodall *et al.* (2004:285) between 1996 and 2001 in the United Kingdom investigated the use of clozapine in treatment-resistant schizophrenia and its impact on hospitalisation rates when prescribed in accordance with the NICE guidelines. The study found that the annual hospitalisation rate for patients that were receiving clozapine was 13.50 days compared to 34.00 days for those who were not receiving clozapine. Hence, long-term treatment with clozapine was associated with a mean reduction in hospitalisation of 20.50 days which represents a 60.00% reduction in the annual hospitalisation rate. Thus, the benefits of clozapine include quality of life gains as a result of reduced hospitalisation, given the preference of most patients for community living.

2.1.15 CONCLUSION

The suboptimal use of clozapine is currently one of the more serious problems in the treatment of schizophrenia and needs urgent attention. Identifying new molecules to treat schizophrenia is a very important task but optimizing the use of molecules proven to be effective at individual and population levels is equally, if not more, important. However, conducting further research to determine the precise mechanism for clozapine's superior efficacy (compared to other antipsychotics) might provide some insight on how to develop safer and more effective medications for the treatment of schizophrenia in the future (Joober & Boksa, 2010:148).

Clozapine demonstrates better efficacy and effectiveness than other antipsychotics and is useful when concerns exist over suicidality, aggression and comorbid substance abuse. A number of factors including a severe side effect profile, clinicians' negative perceptions and routine haematological monitoring may contribute to the delayed use and underutilisation of clozapine. Additionally, clozapine is a commercial orphan, neither marketed nor promoted. Despite these factors clozapine maintains an important place in the treatment of severe psychosis and can sometimes transform an individual's life (Farooq & Taylor, 2011:248).

2.2 PSYCHOTIC DISORDERS

2.2.1 INTRODUCTION

Mental health should be considered as an integral and essential component of health. The World Health Organization (WHO) constitution states the following: “Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. Thus, mental health is not merely the absence of mental disorders or disabilities, but is a state of well-being in which an individual realizes his or her own abilities, is able to cope with the normal stresses of life and can work productively in order to make a positive contribution to his or her community (WHO, 2010).

According to the World Health Report 2001, about one in four of the world’s population will suffer from some form of mental illness during their lifetime (WHO, 2001:19). Another burning issue highlighted in this report was the fact that mental and behavioural disorders are estimated to account for 12% of the global burden of disease, yet the mental health care budgets of most countries constitute less than 1% of their total health care expenditures. The relationship between disease burden and disease spending is clearly unreasonable (WHO, 2001:3).

It is estimated that by the year 2015 the global burden of disease from all neuropsychiatric illnesses will reach 14.14% and by 2030, it will escalate to 14.42% (Gelder *et al*., 2009:10). Furthermore, the World Health Report showed that mental disorders accounted for 6 of the 20 leading causes of disability worldwide for people between the ages of 15 and 44 years - those who are supposed to be active in the work place (WHO, 2001:27).

The burden of psychotic disorders is considerable. They are associated with significant disability, morbidity, and mortality, resulting in drastically reduced life expectancy (Heckers, 2009:848).

Psychosis is a mixture of symptoms that can be associated with many different psychiatric disorders, but it is not a specific disorder itself. At the least, psychosis

means delusions and hallucinations. It generally also includes symptoms such as disorganised behaviour, disorganised speech and gross distortions of reality testing (Stahl, 2008:248).

Therefore, psychosis can be considered to be a set of symptoms in which a person's mental capacity, affective response, and capacity to recognise reality, communicate, and relate to others are impaired. Psychotic disorders have psychotic symptoms as their defining features, but there are, other disorders in which psychotic symptoms may be present but are not necessary for diagnosis (Stahl, 2008:248).

Based on the diagnosis, psychotic disorders can be classified into two groups namely (McCarron *et al*., 2009:80):

- **Primary psychotic disorders**
- **Secondary psychotic disorders**

2.2.2 PRIMARY PSYCHOTIC DISORDERS

Primary psychotic disorders are conditions in which psychosis is a cardinal symptom and not directly caused by another disorder (McCarron *et al*., 2009:80). Currently, there are seven defined disorders: schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, delusional disorder, shared delusional disorder, and psychotic disorder not otherwise specified (McCarron *et al*., 2009:81).

2.2.2.1 SCHIZOPHRENIA

Of the psychotic disorders, schizophrenia has received the greatest attention in terms of research (Semple & Smyth, 2009:170). Schizophrenia is a severe form of mental illness responsible for tremendous morbidity and reduced quality of life and productivity. Currently, schizophrenia affects about 24 million people worldwide (WHO_a, 2013).

2.2.2.1.1 Definition of schizophrenia and refractory schizophrenia

The *Pharmacotherapy Handbook* by Wells *et al.* (2012:894) defines schizophrenia as: "a chronic heterogeneous syndrome of disorganised and bizarre thoughts, delusions, hallucinations, inappropriate affect, cognitive deficits, and impaired psychosocial functioning".

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) states the following definition for schizophrenia: "The essential features of schizophrenia are a mixture of characteristic signs and symptoms (both positive and negative) that have been present for a significant portion of time during a 1-month period (or for a shorter time if successfully treated) with some signs of the disorder persisting for at least 6 months" (American Psychiatric Association, 2000:298).

Defining the term "refractory" in schizophrenia can be fairly difficult (Ballon & Lieberman, 2010:475).

Treatment refractoriness has been defined by the International Psychopharmacology Algorithm Project (IPAP) as:

- "no period of good functioning in the previous five years,
- prior non-response to at least two antipsychotic drugs of two different chemical classes for at least 4-6 weeks each at doses ≥ 400 mg equivalents of chlorpromazine or 5 mg/day risperidone, and
- moderate to severe psychopathology, especially positive symptoms: conceptual disorganisation, suspiciousness, delusions, or hallucinatory behaviour" (IPAP, 2008).

The above criteria mainly focus on the positive symptoms of schizophrenia, but IPAP also considers continued negative or cognitive symptoms, violence, suicidality and recurrent mood symptoms as elements of treatment refractoriness (IPAP, 2008).

It is estimated that about 30% of schizophrenic patients can be considered as treatment-resistant cases, with some estimates being even higher, toward 50-60% (Ballon & Lieberman, 2010:475).

The ultimate goal of therapy for any disease is not just the remission of symptoms but a full functional recovery from that disease and schizophrenia should not be an exception (Ballon & Lieberman, 2010:475).

2.2.2.1.2 Prevalence and onset of schizophrenia

Schizophrenia has a worldwide lifetime prevalence of 0.6-1.9% and hence represents one of the most serious global health challenges (Dipiro *et al.*, 2011:1147; Lambert & Naber, 2009:117).

Schizophrenia affects about 7 per thousand of the adult population, mostly in the age group 15-35 years (WHO, 2010).

"The worldwide prevalence of schizophrenia is remarkably similar among most cultures" (Dipiro *et al*., 2011:1147). The WHO International Pilot Study of Schizophrenia and its successor the WHO 10-country epidemiological study were the first systematic investigations of the comparative incidence, clinical manifestations, and course of schizophrenia in both developing and developed countries. The WHO programme was an impetus for similar studies in India, China, the Caribbean, and Australia (Jablensky & Sartorius, 2008:253). However, the incidence of schizophrenia varies both geographically and temporally. (Stilo & Murray, 2010:305). A systematic review showed that the incidence rate of schizophrenia ranged from 7.7 to 43.0 per 100 000 (Stilo & Murray, 2010:305).

The lifetime risk for schizophrenia seems to be equal in both males and females, although the age of onset tends to be a few years earlier in men (Dipiro *et al.*, 2011:1147; Schatzberg & Nemeroff, 2004:885). The onset tends to be more acute in women compared with the more subtle onset in men, and women tend to have a higher level of premorbid functioning (Schatzberg & Nemeroff, 2004:889). It was found that

males most frequently have their first episode during their early twenties, whereas in females it usually occurs during their late twenties to early thirties (Dipiro *et al.,* 2011:1147).

"The first symptoms of schizophrenia tend to start in young adulthood, but can occur at any age" (NICE, 2009:5). Childhood onset i.e. onset by the age of 12 years is rare. Up to 1% of all schizophrenia spectrum disorders manifest before the age of 10 years, 5% before the age of 15 years and almost 20% below the age of 18 years. In 30-40% of the cases onset is in early adulthood, between the age of 18 and 25 years. However, some people experience late-onset schizophrenia i.e. onset above the age of 40 years. Some people can also experience very-late-onset schizophrenia-like psychosis i.e. after the age of 60 years (Lambert & Naber, 2009:117).

The diagnosis of schizophrenia is still associated with limited public understanding, stigma, bias and fear. The first few years after onset can be particularly upsetting and chaotic, and are associated with a higher risk of committing suicide. Often an acute episode of illness is followed by problems such as difficulties forming new relationships, social exclusion as well as reduced opportunities to get back to work or study (NICE, 2009:5).

2.2.2.1.3 Aetiology of schizophrenia

Although the specific cause of schizophrenia is unknown, it has a biological basis. Evidence indicates alterations in brain structure (e.g. enlarged cerebral ventricles, decreased size of the anterior hippocampus and the other brain regions) and changes in neurotransmitters, especially altered activity of dopamine and glutamate. Accumulating evidence suggests that schizophrenia is a neurodevelopmental disorder and some experts suggest that the onset, remission, and recurrence of symptoms are the result of interactions between neurodevelopmental vulnerabilities and environmental stressors (Porter & Kaplan, 2011:1559; Schatzberg & Nemeroff, 2004:889).

"The cause of schizophrenia is likely multifactorial, that is, multiple pathophysiologic abnormalities can play a role in producing the similar but varying clinical phenotypes we refer to as schizophrenia" (Dipiro *et al.*, 2011:1147).

According to recent evidence, schizophrenia is probably not related to a single biological defect. Rather, it is suggested that an interaction of different pathological mechanisms, including intrinsic and extrinsic risk factors, is more likely. These risk factors can be associated with a higher vulnerability for the development of schizophrenia. The pathways between risk factors and the diagnosis and course of schizophrenia are not yet fully researched and many questions remain unanswered about the diagnostic specificity and aetiological significance of these associations (Lambert & Naber, 2009:118).

Intrinsic and extrinsic risk factors may include the following (Lambert & Naber, 2009:118):

- Genetic predisposition (e.g. family history of psychosis)
- Intrauterine complications (e.g. viral infections) and/or birth complications (e.g. hypoxia), certain patterns of family interaction and life events (e.g. expressed emotion)
- An illness that is combined with severe central nervous system dysfunctions (e.g. multiple sclerosis)
- CNS dysfunctions caused by various substances (e.g. methamphetamine induced psychosis)
- Environmental factors (e.g. substance abuse or developmental stress)

Most of these risk factors may occur early in life, especially during the perinatal period. This may lead to disturbances in the development of the brain and hence a greater vulnerability to experience stress (Lambert & Naber, 2009:118).

It has been hypothesized that disruptions in brain development, especially during the second and third trimester of pregnancy, may contribute to the pathophysiology of schizophrenia (Schatzberg & Nemeroff, 2004:889). It seems to be clear that environmental factors both add to and interact with genetic factors to produce the onset of symptoms (Lambert & Naber, 2009:118).

Repeated studies of families, twins and adopted individuals indicate that genetic factors are applicable in schizophrenia. Lifetime prevalence differs markedly between patients with relatives and those without relatives with schizophrenia. Lifetime prevalence for

those without relatives with schizophrenia was found as 0.2–2.0% and those with relatives with schizophrenia was 0.5-16.0% (Lambert & Naber, 2009:118).

The children of a parent diagnosed with schizophrenia have a 10-fold increased risk of developing the illness. Studies of twins suggest the importance of genetic factors, thereby indicating higher rates of occurrence of the disorder in monozygotic twins (44.3%) compared to the occurrence in dizygotic twins (12.1%). This is proved by consistent monozygotic to dizygotic ratios across the studies. Studies of adopted individuals provide further evidence for genetic vulnerability, demonstrating an association between biological relatives separated at birth. In addition, schizophrenia spectrum disorders have a significant familial relationship with schizophrenia (Lambert & Naber, 2009:118).

Overwhelming evidence indicates that patients with schizophrenia display abnormalities on computed tomography (CT), electroencephalography (EEG), magnetic resonance imaging (MRI), positron emission tomography (PET) scanning, neurological signs, cognitive impairment, eye tracking and psychophysiology. Unfortunately, the mechanisms of the association are not known. No single laboratory test or pathology is available to confirm the diagnosis of schizophrenia (Lambert & Naber, 2009:120).

2.2.2.1.4 Clinical presentation

Schizophrenia is probably one of the most complex psychiatric disorders and great variability occurs in clinical presentation (Dipiro *et al*., 2011:1149). Even in the first stages of the disorder (prodromal phase or first episode) many patients present with a variety of different symptoms, comorbid psychiatric and somatic disorders, and interrelated social and psychological dysfunctions (Lambert & Naber, 2009:123).

Patients normally present with positive, negative and disorganised symptoms as well as cognitive deficits (Lambert & Naber, 2009:123). Patients may have symptoms from one or all categories. These symptoms will be discussed briefly.

According to the DSM-IV-TR classification system there are two categories into which the symptoms of schizophrenia can be classified, namely positive and negative.

Recently emphasis has been placed on a third symptom category, namely cognitive deficits (Dipiro *et al*., 2011:1150).

2.2.2.1.4.1 Positive symptoms

Positive symptoms are perceptual or cognitive features that “normal” individuals usually do not experience (Schatzberg & Nemeroff, 2004:886). Generally positive symptoms tend to respond to treatment with antipsychotic agents. Traditionally they have been the focus of treatment with these medications (Schatzberg & Nemeroff, 2004:886). Positive symptoms appear to be related to increased dopaminergic (D_2) activity in the mesolimbic region (McPhee *et al*., 2012:1025; Wells *et al*., 2012:894).

Positive symptoms include hallucinations and delusions as well as disorganised thinking (Lambert & Naber, 2009:123, McPhee *et al*., 2012:1025; Stahl, 2008:250).

The following table summarizes the positive symptoms associated with psychosis and schizophrenia (adapted from Stahl, 2008:251).

Table 2.12 Positive symptoms of psychosis and schizophrenia

Positive symptoms
• Delusions • Hallucinations • Disorganised speech • Disorganised behaviour • Distortions or exaggerations in language and communication • Catatonic behaviour • Agitation

2.2.2.1.4.2 Negative symptoms

Negative symptoms represent a “loss” of functions or abilities that individuals without schizophrenia normally possess (Schatzberg & Nemeroff, 2004:887).

Negative symptoms are believed to be relatively treatment-resistant and may tend to become increasingly prominent as the illness progresses (Schatzberg & Nemeroff, 2004:889). Negative symptoms appear to be related to decreased D_2 dopamine activity in the mesocortical system (McPhee *et al.,* 2012:1025; Wells *et al*., 2012:894).

The following table summarizes the negative symptoms associated with schizophrenia (adapted from Stahl, 2008:251).

Table 2.13 Negative symptoms of schizophrenia

Negative symptoms
• Blunted affect • Alogia • Avolition • Anhedonia • Emotional withdrawal • Poor rapport • Passivity • Lack of spontaneity • Apathetic social withdrawal • Difficulty in abstract thinking • Stereotyped thinking • Attentional impairment

Negative symptoms are usually associated with intellectual and neurocognitive impairment, and they are better predictors of long-term functional outcome and psychosocial functioning of schizophrenia patients than are positive symptoms (Schatzberg & Nemeroff, 2004:887).

People with schizophrenia often display negative symptoms long before the first positive symptoms emerge (Lambert & Naber, 2009:123; Stahl, 2008:251). Thus negative symptoms may have developed long before the actual onset of illness, which is usually defined as the onset of psychosis (Schatzberg & Nemeroff, 2004:887).

Extrapyramidal symptoms produced by antipsychotic agents can sometimes resemble negative symptoms of schizophrenia (Schatzberg & Nemeroff, 2004:887). Negative symptoms can further be subdivided into primary and secondary negative symptoms (Schatzberg & Nemeroff, 2004:887). Primary negative symptoms represent the core negative symptoms reflecting the schizophrenia disease process. Secondary negative symptoms may resemble primary negative symptoms, but they are caused by or are secondary to positive symptoms of psychosis or the antipsychotic medications themselves (Schatzberg & Nemeroff, 2004:887).

It is important that primary negative symptoms are distinguished correctly from secondary negative symptoms, since it has important treatment implications. For example: a reduction in medication dosage may alleviate some secondary negative symptoms, but this strategy is unlikely to have a beneficial effect on primary negative symptoms (Schatzberg & Nemeroff, 2004:887).

2.2.2.1.4.3 Disorganised symptoms

These include disorganised thought, speech and behaviour (Porter & Kaplan, 2011:1560).

Speech can range from mildly disorganised to incoherent and incomprehensible. Bizarre behaviour may include agitation, childlike silliness, and inappropriate appearance, hygiene or conduct. Catatonia is an extreme behaviour that can include maintaining a rigid posture and resisting efforts to be moved or engaging in purposeless and unstimulated motor activity (Porter & Kaplan, 2011:1560).

There is some controversy over whether the disorganised symptoms are a separate set of symptoms of schizophrenia or whether, as they are seen in other clinical presentations (e.g. manic phase of bipolar disorder), they should not be considered diagnostic of schizophrenia on their own (Lambert & Naber, 2009:123).

Currently, schizophrenia is mostly defined by the presence of positive symptoms. However, there are those who see it as more of a cognitive disorder with the presence

of neurocognitive deficits being a marked feature of the presentation of many individuals with schizophrenia (Lambert & Naber, 2009:123).

2.2.2.1.4.4 Cognitive deficits

Cognitive deficits are mainly associated with impairment in attention, processing speed, working memory, abstract thinking, problem solving, and understanding of social interactions (Porter & Kaplan, 2011:1560).

The person's thinking might be inflexible, and the ability to solve problems, learn from experience, and understand the viewpoints of other people may be diminished. The symptoms of schizophrenia usually impair the ability to function and often noticeably interfere with work, social relations, and self-care (Porter & Kaplan, 2011:1560). It is important to recognize and monitor cognitive symptoms of schizophrenia because they are the single strongest correlate of real-world functioning and the severity of cognitive impairment is thus a major determinant of overall disability (Stahl, 2008:257).

The following table summarizes the cognitive symptoms associated with schizophrenia (adapted from Stahl, 2008:259).

Table 2.14 Cognitive symptoms of schizophrenia

Cognitive symptoms
• Problems focusing attention • Problems representing and maintaining goals • Problems prioritizing • Problems allocating attentional resources • Problems sustaining attention • Problems evaluating functions • Problems monitoring performance • Problems modulating behaviour based upon social cues • Problems with serial learning • Impaired verbal fluency • Difficulty with problem solving

2.2.2.1.5 Diagnosis of schizophrenia

2.2.2.1.5.1 Introduction

Until the early 1970s, the diagnosis of schizophrenia was one of the most contentious and fraught issues in the whole of psychiatry. Since then a massive international effort has been put in motion out of which explicit diagnostic criteria emerged (Gelder *et al.*, 2009:534).

There is no laboratory test/method available for confirming the diagnosis of schizophrenia (McPhee *et al*., 2012:1025). The diagnosis is based on a comprehensive assessment of history, symptoms, and signs. Collateral information sources such as family members, friends, co-workers and teachers are often important (Porter & Kaplan, 2011:1561).

2.2.2.1.5.2 DSM-IV-TR and ICD-10

The diagnosis of schizophrenia should be made using operationalized diagnostic systems, such as International Classification of Diseases (ICD) or the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Gelder *et al.,* 2009:534, 541; Jablensky, 2010:277; Lambert & Naber, 2009:131; Wells *et al.*, 2012:895). The versions of the DSM and ICD systems currently being used are the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) and ICD-10 (Sadock *et al.*, 2009:1435). Both systems require exactly defined criteria to be met before a diagnosis of schizophrenia can be made (Lambert & Naber, 2009:131).

In spite of some differences, both systems are consistent in terms of the definition of schizophrenia. Both systems reflect a clear narrowing of the diagnosis of schizophrenia compared to previous diagnostic practices, especially in the United States. The main differences between both systems are in the longitudinal course criteria (Sadock *et al.*, 2009:1435).

The following table summarizes the differences in defining the course of schizophrenia in the DSM-IV and ICD-10 classifications (adapted from Gelder *et al*., 2009:536).

Table 2.15 Terminology used to describe the course of schizophrenia in the DSM-IV and ICD-10 classification

DSM-IV	ICD-10
Continuous	Continuous
Episodic with residual symptoms	Episodic with stable deficit
Episodic with no interepisode symptoms	Episodic remittent
Single episode in partial remission	Incomplete remission
Single episode in full remission	Complete remission
Other	Other Episodic with progressive deficit

The ICD-10 that was published in 1992, is a diagnostic nomenclature maintained by the WHO. ICD-10 requires duration of symptoms for only one month and also makes a clear distinction between primary and secondary negative symptoms. The ICD-10 does not require deterioration in social and occupational function for the diagnosis of schizophrenia in contrast to the DSM-IV-TR. In addition, the ICD-10 continues to include a category of simple schizophrenia that does not require the presence of psychotic symptoms for the diagnosis. This subtype is not included in the DSM-IV-TR (Jablensky, 2010:278; Sadock *et al.*, 2009:761).

A few changes were made to the DSM-IV-TR and the latest version the DSM-V was released on 18 May 2013 by the American Psychiatric Association (Allgulander, 2013:321). Currently, psychiatrists are still receiving training on the use of DSM-V before it will be implemented in clinical practice. The development of the ICD-11 to be released in 2015 is being closely coordinated with the DSM-V (Allgulander, 2013:321). Therefore for the purpose of this study DSM-IV-TR criteria were used.

DSM-IV-TR which was released in 2000, is the most widely accepted and most important diagnostic reference used in the care of the mentally ill (Dipiro *et al.,* 2011:1077). It provides a common language for practitioners to describe and diagnose psychiatric conditions.

The DSM-IV-TR makes use of a multiaxial patient evaluation when performing a patient assessment (Dipiro *et al.,* 2011:1078).

Axis I lists the principal psychiatric disorder (e.g. schizophrenia), developmental disorders, or provisional diagnoses present in the patient. Mental retardation and personality disorders (e.g. antisocial) are listed on axis II. Axis III lists existing physical disorders or conditions. Axis IV lists the severity of psychosocial stressors that might have contributed to a new or recurrent mental disorder or exacerbation of an existing condition. Stressors are rated on a scale of 1 (none) to 6 (catastrophic) and can be acute (lasting less than 6 months) or enduring (lasting more than 6 months). Examples of stressors include difficulties with interpersonal relationships, living circumstances and finances. Axis V describes the global assessment of functioning (GAF) rated on a scale from 1 (persistent danger to self or others) to 90 (minimal or absent symptoms). A GAF rating is made based on the current level of functioning and can be used to describe the highest level of functioning achieved prior to the current evaluation. By documenting the baseline level of functioning, the GAF helps evaluate progress toward a patient's therapeutic goals (Dipiro *et al.,* 2011:1078).

According to the DSM-IV-TR, to make a diagnosis of schizophrenia there must be evidence of continuous symptomatic disturbance for at least 6 months accompanied by a decline from the premorbid level of functioning. This 6-month period can include functional deterioration occurring during the prodromal phase before the onset of overt psychosis (Jablensky, 2010:278; Schatzberg & Nemeroff, 2004:887).

Within the 6-month period, the patient must have two or more of the following symptoms for at least one month: hallucinations, delusions, disorganised speech, grossly disorganised or catatonic behaviour, and negative symptoms. If the duration of psychotic symptoms is less than one month because of successful treatment with antipsychotic medication, a diagnosis of schizophrenia can still be made. However,

before the diagnosis of schizophrenia can be made, other medical or psychiatric conditions need to be considered and ruled out (Schatzberg & Nemeroff, 2004: 887).

Other mental disorders with similar symptoms to schizophrenia include: brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, and delusional disorder. Mood disorders can also cause psychosis in some patients. Certain personality disorders (especially schizotypal) cause symptoms similar to those of schizophrenia, although they are usually milder and do not involve psychosis (Porter & Kaplan, 2011:1561).

As schizophrenia is a heterogeneous disorder, generally subtypes are differentiated. These are not disorders themselves, but rather descriptions of predominant psychopathology. The subtypes of schizophrenia differ from each other according to the predominant psychopathology and certain time criteria. The subtype encountered most often is the paranoid subtype, but a change of subtypes in the course of illness as a result of changing psychopathology is often diagnostically possible (Lambert & Naber, 2009:131).

2.2.2.1.5.3 Diagnostic subtypes of schizophrenia

There are five subtypes of schizophrenia namely; paranoid, disorganised, catatonic, undifferentiated and residual (Porter & Kaplan, 2011:1560).

- **Paranoid schizophrenia**

The Dorland's *Illustrated Medical Dictionary* (2012:1676) defines paranoid schizophrenia as "a type of schizophrenia characterised by preoccupation with one or more systematized delusions or with frequent auditory hallucinations but without disorganised speech, disorganised or catatonic behaviour, or flat or inappropriate affect".

Paranoid schizophrenia includes marked grandiose delusions often constant with hallucinations of similar content and with less marked disorganisation of speech and behaviour (McPhee *et al.*, 2012:1025). In DSM-IV-TR the diagnosis of the paranoid

subtype is largely made by excluding the other subtypes. Since some of the worst prognostic features are excluded, this subtype has a relatively favourable prognosis (Sadock *et al.*, 2009:1436).

- **Disorganised schizophrenia**

The Dorland's *Illustrated Medical Dictionary* (2012:1676) defines disorganised schizophrenia as: "a type of schizophrenia characterised by frequent incoherence, marked loosening of associations, or grossly disorganised behaviour, and flat or grossly inappropriate affect and that does not meet the criteria for catatonic type; associated features include extreme social withdrawal, grimacing, mannerisms, mirror gazing, inappropriate giggling, and other unusual behaviour."

Disorganised schizophrenia is characterised by marked incoherence and an incongruous or silly affect (McPhee *et al.*, 2012:1025). The distinctive feature of this subtype is thought disorder, although in DSM-IV-TR disorganised behaviour and flat or inappropriate affect are also required to make the diagnosis. Poor premorbid functioning, an insidious onset, a continuous course, and a poor prognosis are characteristics of this subtype (Sadock *et al.*, 2009:1437).

- **Catatonic schizophrenia**

The Dorland's *Illustrated Medical Dictionary* (2012:1676) defines catatonic schizophrenia as "a type of schizophrenia characterised by marked psychomotor disturbance, including some combination of motoric immobility (stupor, catalepsy), excessive motor activity, extreme negativism, mutism, echolalia, echopraxia and peculiarities of voluntary movement such as posturing, mannerisms, grimacing, or stereotyped behaviours".

Catatonic schizophrenia is distinguished by marked psychomotor disturbance of either excitement (purposeless and stereotyped) or rigidity with mutism. Infrequently, there may be rapid alteration between excitement and stupor (McPhee *et al.*, 2012:1025). In developed countries, catatonia is seen now much less frequently than in the past,

perhaps due to the widespread use of medical treatments early in the course of psychosis (Sadock *et al.*, 2009:1437).

- **Undifferentiated schizophrenia**

The Dorland's *Illustrated Medical Dictionary* (2012:1676) defines undifferentiated schizophrenia as "a type of schizophrenia characterised by the presence of prominent psychotic symptoms but not classifiable as catatonic, disorganised or paranoid".

Undifferentiated schizophrenia denotes a category in which symptoms are not specific enough to warrant inclusion of the illness in the other subtypes (McPhee *et al.*, 2012:1025). The diagnosis of undifferentiated schizophrenia is through the exclusion of the other subtypes. When patients with schizophrenia are carefully diagnosed, a large number of patients are found to meet criteria for this subtype (Sadock *et al.*, 2009:1437).

- **Residual schizophrenia**

The Dorland's *Illustrated Medical Dictionary* (2012:1676) defines residual schizophrenia as "a type of schizophrenia characterised by a history of one or more episodes of schizophrenia with prominent psychotic symptoms, current lack of symptoms, but continuing presence of other schizophrenic symptoms, such as blunted or inappropriate affect, social withdrawal, eccentric behaviour, illogical thinking, or loosening of associations".

Residual schizophrenia is a classification that includes persons who have clearly had an episode warranting a diagnosis of schizophrenia but who at present have no overt psychotic symptoms, although they show milder signs such as social withdrawal, flat affect, and eccentric behaviours (McPhee *et al.*, 2012:1025). This condition can be chronic or may be a transition to a complete remission of the illness (Sadock *et al*., 2009:1437).

Alternatively, some experts classify schizophrenia into deficit and non-deficit subtypes based on the presence and severity of negative symptoms, such as blunted affect, lack

of motivation, and diminished sense of purpose (Porter & Kaplan, 2011:1560). Patients with the deficit subtype have prominent negative symptoms unaccounted for by other factors (e.g. drug adverse effects, anxiety, depression or an under stimulating environment).

Those patients with the non-deficit subtype may have hallucinations, delusions and thought disorders but relatively do not experience any negative symptoms. The deficit and non-deficit subtypes do not differ in age at onset and length of illness, which argues against a progression leading from non-deficit to deficit schizophrenia (Jablensky, 2010:275; Porter & Kaplan, 2011:1560).

2.2.2.1.6 Morbidity and mortality

Lately, the impact of medical morbidity and mortality in patients with schizophrenia has received increasing interest (Sadock *et al*., 2009:1573).

Recent literature indicates that the average life expectancy for patients with schizophrenia is from 10 to more than 30 years shorter than that of the general population (Sadock *et al.*, 2009:1573).

The smaller estimates of the extent of this problem generally arise from exclusively inpatient samples where access to medical care may be greater compared to the access of care for outpatient samples (Sadock *et al.*, 2009:1573).

When compared to the general population, it seems that patients with schizophrenia are at higher risk for the development of various medical conditions, are less likely to receive and benefit from appropriate medical treatment, are more likely to experience poor clinical outcomes, and therefore have a greater chance of dying prematurely (Sadock *et al.*, 2009:1573).

In Taiwan, data collected over a 15-year period indicate that of all mental disorders followed up, schizophrenia was associated with the highest mortality, representing an 80% increase over the mortality of the general population (Sadock *et al.*, 2009:1460).

Patients with schizophrenia have, on average, a shorter life expectancy compared to the rest of the population (Stilo & Murray, 2010:306).

Standardized mortality ratios can be a useful way to quantify the additional mortality risk associated with a condition like schizophrenia, relative to the general population, although caution is warranted when interpreting this metric (Sadock *et al*., 2009:1573). SMRs are calculated as the ratio of observed to expected deaths within a specified sample or given age range (Sadock *et al*., 2009:1573).

According to McGrath *et al*. (cited by Stilo & Murray, 2010:306), who carried out a systematic review of mortality studies, reported that the SMR was 2.6, with suicide and cardiovascular disease the major contributors. It is alarming that they found that the SMR had been rising over recent decades

In a study conducted in 2006 in the United States in which the life expectancy of patients with a major mental illness such as major depression, bipolar disorder, schizophrenia and schizoaffective disorder were compared with that of the general population; it was found that the leading cause of early deaths in patients with mental disorders was coronary heart disease. The study also showed that cardiovascular disease including coronary heart disease, cerebrovascular disease and peripheral vascular disease was responsible for more than approximately 35% of deaths amongst patients suffering from mental illness (Sadock *et al.*, 2009:1573).

Unnatural causes of death, in both developed and developing countries, apart from schizophrenia are associated with excess mortality from respiratory, cardiovascular and gastrointestinal diseases, which are likely to be caused or exacerbated by poor self-care, inadequate nutrition, heavy smoking, and medical neglect. At least part of this excess mortality is preventable (Sadock *et al.*, 2009:1460).

2.2.2.1.7 Co-morbidity

Co-morbid physical disease occurs more commonly in patients with schizophrenia than in the general population (Schatzberg & Nemeroff, 2004:894).

Physical disease in patients with schizophrenia tends to be seriously undetected and underdiagnosed. About 46-80% of inpatients with schizophrenia and 20-43% of outpatients have been found to have concurrent medical illnesses (Sadock *et al*., 2009:1459). Patients with schizophrenia are at high risk for premature death from their comorbid medical conditions (Schatzberg & Nemeroff, 2004:894).

Individuals with schizophrenia, and especially those who are homeless or injection drug users are at increased risk for potentially life-threatening communicable diseases, such as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis and hepatitis B and C (Sadock *et al*., 2009:1459).

Epilepsy, osteoporosis, psychogenic polydipsia, diabetes mellitus, hypertension, arteriosclerosis and ischaemic heart disease are highly prevalent in schizophrenic patients (Schatzberg & Nemeroff, 2004: 894). Obesity and the concomitant metabolic syndrome involving insulin resistance are becoming increasingly common problems in patients with schizophrenia (Sadock *et al*., 2009:1459).

Since patients with schizophrenia often wait to report medical problems until they have reached an acute or advanced phase, medical practitioners need to take a proactive role in assessing comorbid medical conditions (Schatzberg & Nemeroff, 2004:895). Clinicians who treat patients with schizophrenia should understand the important barriers that may prevent patients from receiving adequate health care: limited access to medical care, stigmatization by health care professionals and poor communication skills or organisational skills in the patients. Patients may have difficulty scheduling a medical appointment, keeping an appointment, and following through with prescribed treatments (Schatzberg & Nemeroff, 2004:894). Mental health care practitioners should regularly evaluate the general medical health of patients and facilitate their access to medical care as needed (Schatzberg & Nemeroff, 2004:894).

Co-occurring substance use disorders, often termed dual diagnosis or comorbidity are also a serious and common issue among patients with schizophrenia, but frequently remain under-recognised and poorly addressed (Lambert & Naber, 2009:15; Sadock *et al*., 2009:1459).

Up to 90% of individuals with schizophrenia smoke cigarettes, whereas between 40% and 60% use other substances (Lambert & Naber, 2009:15, Schatzberg & Nemeroff, 2004:895). Co-occurring substance use disorders (excluding tobacco smoking) appear to be more prevalent (up to 75%) among young people with first episode psychosis as well as among those who are homeless or have come to the attention of the criminal justice system (Lambert & Naber, 2009:15; Sadock *et al*., 2009:1460).

The most frequently abused substances are cannabis, alcohol, nicotine and psychostimulants; although polysubstance abuse is relatively common. Generally, men with schizophrenia are overwhelmingly more likely to abuse these substances than are women (Schatzberg & Nemeroff, 2004:895).

Persistent substance abuse affects medication adherence, service engagement, health care costs and housing stability, and substantially increases the burden on patients, their families and the health care system (Lambert & Naber, 2009:19).

Patients with schizophrenia and co-morbid substance abuse require specialised treatment for both disorders, optimally in rehabilitation programmes that provide integrated mental health and substance abuse treatment, as well as medication management (Schatzberg & Nemeroff, 2004:899).

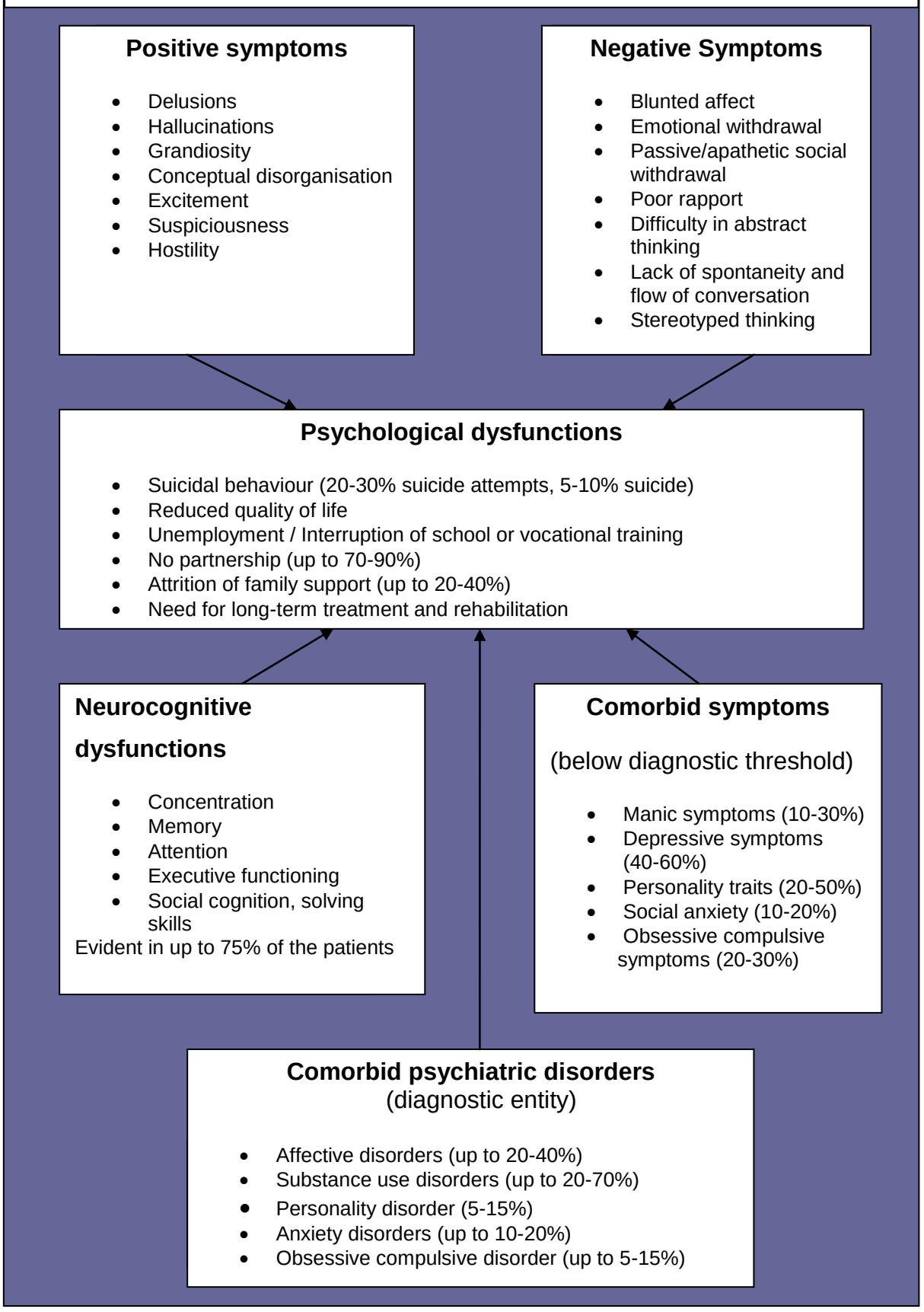
Cigarette smoking, substance abuse, poor nutrition, and lack of exercise are lifestyle factors related to the increased medical comorbidity in patients with schizophrenia. Providing patient education about lifestyle choices as well as regular clinical assessment for medication side effects may lead to long-term improvement in health status. Certainly, optimal pharmacotherapy must take into account the overall medical status of the patient and the potential role that medication side effects may have in worsening pre-existing medical conditions (Schatzberg & Nemeroff, 2004:895).

The following figure summarizes the symptoms, comorbid psychiatric symptoms and disorders, and resulting psychosocial dysfunctions in patients with schizophrenia (adapted from Lambert & Naber, 2009:124).

Figure 2.1 Symptoms, comorbid psychiatric symptoms and disorders, and resulting psychosocial dysfunctions in patients with schizophrenia

(See next page)

Symptoms, comorbid psychiatric symptoms and disorders, and resulting psychosocial dysfunctions in patients with schizophrenia



2.2.2.2 OTHER PRIMARY PSYCHOTIC DISORDERS

Both ICD-10 and DSM-IV-TR describe a number of disorders which show significant overlap with schizophrenia. It is currently unclear whether these disorders represent distinct disorders, or (more likely) they share some degree of common aetiology with schizophrenia (Semple & Smyth, 2009:210).

2.2.2.2.1 Delusional disorder

Delusional disorder is characterised by false beliefs that persist for at least 1 month, without other symptoms of schizophrenia (Porter & Kaplan, 2011:1557). The social and marital functioning of patients with delusional disorder is markedly affected whereas intellectual and occupational functioning is usually minimally affected (McPhee *et al.,* 2012:1025). Delusional disorder is relatively uncommon, but not rare. The prevalence of delusional disorder is estimated at 0.025-0.03% with a mean age of onset of 40-49 years (Semple & Smyth, 2009:213).

2.2.2.2.2 Brief psychotic disorder

Brief psychotic disorder has a sudden onset with variable presentation of hallucinations, delusions or other psychotic symptoms that lasts for at least 1 day but less than 1 month, with eventual return to previous functioning. Those under severe psychological stress are more susceptible and life events such as bereavement, unemployment and imprisonment may precipitate brief psychotic disorder (McPhee *et al.,* 2012:1025; Porter & Kaplan, 2011:1557). Brief psychotic disorder is generally more common in women, is associated with certain personality types (e.g. paranoid, borderline) and is more prevalent in developing nations where there is a strong emphasis on traditional values (Semple & Smyth, 2009:218). The prognosis of brief psychotic disorder is better than for schizophrenia (Semple & Smyth, 2009:218).

2.2.2.2.3 Schizoaffective disorder

Schizoaffective disorder is characterised by significant mood symptoms, psychosis and other symptoms of schizophrenia. Schizoaffective disorder can be differentiated from schizophrenia by the occurrence of one or more episodes of depressive or manic symptoms. The prognosis of schizoaffective disorder is better than that for schizophrenia but worse than that for mood disorders (McPhee *et al.,* 2012:1025; Porter & Kaplan, 2011:1558). The lifetime prevalence for schizoaffective disorder is 0.5-0.8% with limited data available on gender and age differences (Semple & Smyth, 2009:210).

2.2.2.2.4 Schizophreniform disorder

Schizophreniform disorder is characterised by symptoms identical to those of schizophrenia except that the symptoms should last for at least one month but not more than 6 months (McPhee *et al.,* 2012:1025; Porter & Kaplan, 2011:1567). Schizophreniform disorder is most common in adolescence and young adults and is much less common than schizophrenia with a lifetime prevalence of 0.2% (Semple & Smyth, 2009:211). Patients return to baseline functioning once the disorder has resolved. Progression to schizophrenia is estimated to be between 60-80%. Some patients have two or three recurrent episodes (Semple & Smyth, 2009:211).

2.2.2.2.5 Psychotic disorder not otherwise specified

Psychosis not otherwise specified (NOS) refers to a variety of clinical presentations that do not fit within current diagnostic structures. According to DSM-IV-TR psychosis NOS includes “psychotic symptomatology about which there is inadequate information to make a specific diagnosis or about which there is contradictory information, or disorders with psychotic symptoms that do not meet the criteria for any specific psychotic disorder” (Sadock & Sadock, 2007:518).

2.2.2.2.6 Shared delusional disorder

Also known as 'folie á deux', this disorder was recognised and described as early as 1651 (Semple & Smyth, 2009:220). Shared delusional disorder is rare and occurs when two individuals in close proximity share the delusion (McCarron *et al*., 2009:83). The delusion is similar in content (American Psychiatric Association, 2000:162). Patients with shared delusional disorder should be screened for recent stressors as well as anxiety, mood, and disorders related to substance abuse (McCarron *et al*., 2009:83).

2.2.3 SECONDARY PSYCHOTIC DISORDERS

Secondary psychotic disorders are clinical conditions in which psychosis is a complicating symptom of a general medical condition or a medication (e.g. encephalitis or the use of high-dose steroids), substance induced psychotic disorders (e.g. cannabis-induced psychosis) or mood disorders (e.g. bipolar disorder with psychotic features) (McCarron *et al*., 2009:81).

2.2.3.1 Substance induced psychotic disorders

Psychotic symptoms such as delusions and hallucinations can result from a wide variety of substances e.g. alcohol, amphetamines, cannabis, cocaine, hallucinogens, inhalants, opioids, and certain sedatives and anxiolytics. The diagnosis of substance induced psychotic disorder is made when the onset of symptoms occurs during or less than one month after intoxication with or withdrawal from the implicated substance. The diagnosis can only be made after the possibility of other psychotic disorders was ruled out (Porter & Kaplan, 2011:1567). Substance-induced illnesses will be associated in time with episodes of substance misuse and may have atypical clinical features (e.g. late first presentation with psychosis, prominence of non-auditory hallucinations) (Semple & Smyth, 2009:488).

2.2.3.2 Psychotic disorders due to a general medical condition

When evaluating a patient with a psychotic disorder consideration should be given to the possibility that the psychotic symptoms could result from a general medical condition (GMC) such as a brain tumour. The diagnosis of psychotic disorder due to GMC is defined in DSM-IV-TR by specifying the predominant symptoms. When the diagnosis is given, the medical condition, along with the predominant symptom pattern, should be included in the diagnosis e.g. psychotic disorder due to a brain tumour, with delusions (Sadock & Sadock, 2007:520).

2.2.3.3 Mood disorders

Bipolar mood disorder is one of the most common, severe, and persistent psychiatric illnesses. In the public mind it is associated with notions of 'creative madness', and indeed it has affected many creative people - both past and present (Semple & Smyth, 2009:280).

The Dorland's *Illustrated Medical Dictionary* (2012:220) defines bipolar disorder as: "a psychiatric disorder in which both major depressive episodes and manic or hypomanic episodes occur".

Chameleon-like in its presentation, the symptoms may vary from one patient to the next and from one episode to the next within the same patient (Semple & Smyth, 2009:280). Hence, bipolar disorder is a complex disorder that requires accurate diagnosis and effective clinical management (Rodseth, 2013:23). More than with other psychiatric disorders, the clinician needs to pay special attention to the life history of the patient and to collateral information from family and friends (Semple & Smyth, 2009:280).

In bipolar disorder periods of prolonged and profound depression usually alternate with periods of excessively elevated and/or irritable mood (known as mania). The symptoms of mania characteristically include a decreased need for sleep, pressured speech, increased libido, reckless behaviour without regard for consequences, and grandiosity. In severe cases there may be severe thought disturbances and even psychotic symptoms. Between these highs and lows, patients usually experience periods of full

remission (Semple & Smyth, 2009:280). Psychotic symptoms may occur during either depressive or manic episodes and usually remit upon treatment of the mood abnormality (McCarron *et al*., 2009:90).

According to the DSM-IV-TR classification system there are two main subtypes of bipolar disorder, namely bipolar I disorder and bipolar II disorder (American Psychiatric Association, 2000:179).

Bipolar I disorder has a lifetime prevalence of 1.0% and the mean reported age of the first mood episode is 18.2 years. For bipolar II disorder the lifetime prevalence is 1.1% and the mean reported age of the first mood episode is 20.3 years. Bipolar I disorder affects men and women equally, while bipolar II disorder is more common in women (Merikangas *et al*., 2007:543).

First-degree relatives have a seven-fold risk to develop the condition over the general population (i.e. 10.0-15.0% risk) (Semple & Smyth, 2009:290). Children of a parent with bipolar disorder have a 50.0% chance of developing a psychiatric disorder. Genetic liability thus appears shared for schizophrenia, schizoaffective, and bipolar disorder (Semple & Smyth, 2009:290).

The description of bipolar I disorder is synonymous with what was formerly known as bipolar disorder – a syndrome in which a complete set of mania symptoms occurs during the course of the disorder (Sadock & Sadock, 2007:536). According to the DSM-IV-TR classification system, bipolar I disorder is characterised by the occurrence of one or more manic episodes or mixed episodes, with or without a history of one or more depressive episodes (American Psychiatric Association, 2000:180). The diagnostic criteria for bipolar II disorder are characterised by one or more depressive episodes accompanied by at least one hypomanic episode during the course of the disorder, but the episodes of manic-like symptoms do not quite meet the diagnostic criteria for a full manic syndrome (American Psychiatric Association, 2000:187; Sadock & Sadock, 2007:536).

DSM-IV-TR defines criteria that can be used to describe the severity, psychotic and remission specifiers of various mood disorders (Sadock & Sadock, 2007:537). Some

patients may present with psychotic features (Semple & Smyth, 2009:280). Psychotic symptoms themselves are often characterised as either mood congruent, that is, in concordance with the mood disorder or mood incongruent, not in concordance with the mood disorder. Patients with mood disorder with mood congruent psychoses have a psychotic type of mood disorder; however, patients with mood disorder with mood-incongruent psychotic symptoms may have schizoaffective disorder or schizophrenia (Sadock & Sadock, 2007:538).

Although at present there is no cure for bipolar disorder, for most cases effective treatment is possible that can substantially decrease the associated morbidity and mortality (Semple & Smyth, 2009:280).

However, medical comorbidities such as cardiovascular disease, diabetes mellitus, obesity and thyroid disease have a significant impact on the presentation and management of bipolar disorders (Kupfer, 2005:2528). According to a study conducted by Osby *et al.* (2001) the most frequent cause of death in bipolar disorder was found to be cardiovascular disease (31.0%), followed by suicide (19.0%) and cancer (14.0%).

Treatment usually involves pharmacotherapy with combinations of different classes of medications and frequent medication revisions (Colin, 2013:164). In general, however, the specific aims of treatment are to decrease the frequency, severity, and psychosocial consequences of episodes and to improve psychosocial functioning between episodes (Semple & Smyth, 2009:280).

Patients with bipolar I disorder have a poorer prognosis than do patients with major depressive disorder (Sadock & Sadock, 2007:550). Within the first 2 years of the first episode 40.0-50.0% of patients experience another manic episode. Often, the cycling between depression and mania accelerates with age (Semple & Smyth, 2009:291).

2.2.4 TREATMENT OPTIONS FOR PSYCHOTIC DISORDERS

The management of psychosis in primary and secondary psychotic disorders is very similar to the management of schizophrenia, i.e. psychosis is treated with antipsychotic medication (Semple & Smyth, 2009:188). The treatment options for schizophrenia will be discussed below. Some of the treatment approaches will also be applicable for other psychotic disorders.

In general, symptomatic treatment of psychosis should include the use of an antipsychotic agent concomitantly with treatment for the underlying aetiology (McCarron *et al*., 2009:90).

However, when treating psychosis associated with a general medical condition, the treatment of the primary medical problem is essential e.g. masking a patient's psychotic symptoms and behavioural agitation in delirium solely with antipsychotic medication may delay the detection of an impending medical emergency such as septic shock from failure to detect a respiratory infection (McCarron *et al*., 2009:91).

It is of utmost importance that medical practitioners consider a comprehensive treatment plan for patients with chronic psychosis. This treatment plan should include facilitation and referral to psychological support and social services (McCarron *et al*., 2009:91).

There are three major treatment approaches used in patients with schizophrenia (Porter & Kaplan, 2011:1562):

1. **Antipsychotic medication**
2. **Rehabilitation, including community support services**
3. **Psychotherapy**

General goals are to reduce severity of psychotic symptoms, prevent recurrences of symptomatic episodes and associated deterioration of functioning, as well as assisting

patients to function at the highest level possible. Antipsychotics, rehabilitation with community support services, and psychotherapy are the most important components of treatment. Teaching patients illness self-management skills is a significant overall goal, since schizophrenia is a long-term and recurrent illness (Porter & Kaplan, 2011:1562).

Hospitalisation of a patient is often required, particularly if the patient's behaviour shows marked disorganisation. Each case needs to be judged individually, since the presence of competent family members lessens the need for hospitalisation. The major considerations include providing the patient's basic needs as well as preventing self-inflicted harm or harm to others (McPhee *et al*., 2012:1027).

2.2.4.1 ANTIPSYCHOTICS

Antipsychotic medication is considered the treatment of choice (McPhee *et al*., 2012:1027). Patients that are treated early during the course of schizophrenia, tend to respond more quickly and fully to medication. Without ongoing use of antipsychotics after the first episode of schizophrenia, 70 to 80% of patients have a subsequent episode within 12 months. The continuous use of antipsychotics can reduce the one year relapse rate to about 30% (Porter & Kaplan, 2011:1562).

Antipsychotic drugs are divided into two classes (Porter & Kaplan, 2011:1562):

1. **Conventional antipsychotics**
2. **Second generation antipsychotics (SGAs)**

Conventional antipsychotics are also known as first generation antipsychotics (FGAs) or "typical" antipsychotics and SGAs are also called "atypical" antipsychotics (Sadock *et al*., 2009:1549).

The classification of antipsychotics is based on their specific neurotransmitter receptor affinity and activity (McPhee *et al*., 2012:1027; Porter & Kaplan, 2011:1562).

Clozapine, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone and paliperidone are classified as SGAs and agents such as haloperidol, chlorpromazine and zuclopenthixol are classified as FGAs (Rossiter, 2012:470).

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study conducted between 2001 and 2004 in the United States compared the use of "typical" and "atypical" antipsychotics with each other (Lieberman *et al*., 2005:1209). The aim of the study was to determine which medications provide the best treatment option for schizophrenia. Symptom relief using any of four SGAs (e.g. olanzapine, risperidone, quetiapine and ziprasidone) was no greater than that with perphenazine (not registered in South Africa), a conventional antipsychotic. Although the results were not definitive, it suggested similar antipsychotic efficacy for both classes of antipsychotics and a tendency for the SGAs to be better tolerated and therefore associated with enhanced compliance (Lieberman *et al*., 2005:1209; McPhee *et al*., 2012:1027).

The selection of an antipsychotic should be based on the following (Wells *et al.*, 2012:896):

1. The need to avoid certain side effects
2. Concurrent medical or psychiatric disorders
3. Patient or family history of response

2.2.4.1.1 Conventional antipsychotics

These agents act primarily by blocking the D_2 dopamine receptor (Dipiro *et al*., 2011:1157). Conventional antipsychotics can be classified into three groups according to their potency. They are either of high, intermediate or low potency. High potency antipsychotics have a higher affinity for dopamine receptors and less for α-adrenergic and muscarinic receptors. Low-potency antipsychotics, which are rarely used, have less affinity for dopamine receptors and relatively more affinity for α-adrenergic, muscarinic and histaminic receptors (Porter & Kaplan, 2011:1562).

Antipsychotics are available in tablet, liquid, and short- and long-acting intramuscular formulations. A specific antipsychotic is selected primarily based on adverse effect

profile, required route of administration, and the patient's previous response to the drug (Porter & Kaplan, 2011:1562)

Conventional antipsychotics have several adverse effects, such as sedation, dystonia, muscle stiffness, tremors, cognitive impairment, elevated prolactin levels, and weight gain (Taylor et *al*., 2012:39). Akathisia (motor restlessness) is particularly unpleasant and may lead to medication non-adherence (McCarron *et al*., 2009:92).

Conventional antipsychotics may also cause tardive dyskinesia, an involuntary movement disorder most often characterised by non-rhythmic, quick, choreoathetoid movements of the face, trunk, and extremities (McCarron *et al*., 2009:94). The incidence of tardive dyskinesia among patients taking conventional antipsychotics is about 3% to 5% per year of drug exposure (Sadock *et al*., 2009:1552). Tardive dyskinesia is sometimes irreversible and can persist indefinitely in some patients even after the offending drug is discontinued (Porter & Kaplan, 2011:1562).

As mentioned previously about 30% of patients with schizophrenia do not respond to conventional antipsychotics. However, they may respond to clozapine, an SGA (McPhee *et al*., 2012:1029; Porter & Kaplan, 2011:1564).

2.2.4.1.2 Second generation antipsychotics

SGAs block dopamine receptors more selectively than conventional antipsychotics, decreasing the likelihood of extrapyramidal side effects (EPS) (Dipiro *et al*., 2011:1157). Although greater binding to serotonergic receptors was initially thought to contribute to the efficacy of SGAs, recent evidence suggests this binding is unrelated to efficacy or side effect profile (Porter & Kaplan, 2011, 1564).

The following characteristics are associated with SGAs (Porter & Kaplan, 2011:1564; Wells *et al*., 2012:895):

- Tend to alleviate positive symptoms
- May lessen negative symptoms to a greater extent than do conventional antipsychotics (controversial)

- May cause less cognitive impairment
- Are less likely to have EPS
- Have a lower risk of causing tardive dyskinesia
- Increase prolactin slightly or not at all (except for risperidone)
- Increased risk for metabolic adverse effects such as weight gain, diabetes mellitus and hyperlipidaemia

Clozapine is the only SGA that fulfils all these criteria (Wells *et al.*, 2012:895). Clozapine the first SGA is the only atypical agent shown to be effective in up to 60% of patients resistant to conventional antipsychotics (Wells *et al*., 2012:902).

Newer SGAs such as olanzapine and risperidone are very similar to each other in efficacy but differ in adverse effects, so drug choice is based on individual response and on other drug characteristics. These newer SGAs provide some of the benefits of clozapine without the risk of agranulocytosis and are generally preferable to conventional antipsychotics for treatment of an acute episode and for prevention of recurrence (Porter & Kaplan, 2011:1564).

The major adverse effects of SGAs include: weight gain, hyperlipidaemia, and elevated risk of type 2 diabetes mellitus collectively known as metabolic syndrome (Dipiro *et al*., 2011:1158). It is therefore important that a patient should be screened for risk factors, such as personal or family history of diabetes, weight, waist circumference, blood pressure, fasting plasma glucose and lipid profile before initiating treatment with an SGA (McPhee *et al*., 2012:1032).

Those patients found to have or to be at high risk of metabolic syndrome should rather be treated with SGAs with a low risk of metabolic side effects such as ziprasidone or aripiprazole (Porter & Kaplan, 2011:1565).

The following table summarizes the criteria used to diagnose metabolic syndrome (adapted from American Heart Association, 2011; International Diabetes Federation, 2006).

Table 2.16 Definition of metabolic syndrome

Definition of metabolic syndrome	
Parameter	***Pathological range***
Fasting triglyceride level	≥ 1,7 mmol/L
Fasting high density lipoprotein (HDL) level	< 1,03 mmol/L for men and < 1,29 mmol/L for women
Fasting plasma glucose level	≥ 5,6 mmol/L
Blood pressure	≥ 130/85 mmHg
Waist circumference	> 102 cm for men and > 88 cm for women

Metabolic syndrome is the development of a cluster of metabolic abnormalities associated with raised fasting triglyceride levels and low high density lipoprotein (HDL) cholesterol levels, elevated fasting plasma glucose, high blood pressure and weight gain (American Heart Association, 2011; Wells *et al*., 2012:908). The elements that compose the metabolic syndrome are major risk factors for type 2 diabetes mellitus and cardiovascular disease (Sadock *et al*., 2009:1578).

Adults with serious mental illness, treated with SGAs have up to two-times greater prevalence of type 2 diabetes, dyslipidaemia, hypertension and obesity (Morrato *et al*., 2009:1037). In the United States of America patients who are of African American, Native American, Latino and Asian American origin carry higher risks for developing diabetes mellitus (Ghosh *et al*., 2010:353). Smokers have higher rates of diabetes and metabolic syndrome compared to non-smokers and smokers tend to be unable to manage diabetes as well as non-smokers and therefore often have more diabetes-related complications (NAMI, 2010).

There is an elevated risk of developing diabetes mellitus particularly in patients taking clozapine and olanzapine (McPhee *et al*., 2012:1032).

Following concerns about medication-related metabolic risks associated with SGAs the Food and Drug Administration (FDA) in the United States mandated class warnings in 2004 describing increased risk for severe hyperglycaemia and diabetes and required all

drug manufacturers to mail 'Dear Doctor' letters about the warning (Morrato *et al*., 2009:1037). This was done in an attempt to increase awareness of the signs and symptoms of diabetes and promote earlier detection and treatment (Morrato *et al*., 2009:1037).

According to the FDA (cited by McPhee *et al*., 2012:1032) the risk of hyperglycaemia and new-onset diabetes associated with the use of SGAs is not related to weight gain. Another hypothesis suggests that the link between SGAs and the increased incidence of type 2 diabetes mellitus is thought to be caused by an increase in body weight or the direct effects of the antipsychotic agents on glucose transportation, elevation of serum leptin and antagonism of 5-HT_{1A} serotonin receptors decreasing pancreatic β-cell responsiveness (Usher *et al*., 2009:178).

Significant weight gain is the most noticeable sign of metabolic syndrome (Taylor *et al*., 2012:126). The weight gain associated with SGAs usually occurs during the first 4-12 weeks of treatment. After the initial period the weight gain continues at a lower level or may even stabilise, except in the case of clozapine and olanzapine where the weight gain tends to continue over a prolonged period of time (Usher *et al*., 2009:177). The weight gain associated with SGAs is a concern since patients with schizophrenia are known to have a 20% shorter life expectancy than the rest of the general population (Tirupati & Chua, 2007:470; Usher *et al*., 2009:177).

Patient and family education regarding signs and symptoms of diabetes mellitus, including polyuria, polydipsia, weight loss, and diabetic ketoacidosis should be provided. In addition, nutritional and physical activity counselling should be provided to all patients initiated on an SGA (NAMI, 2010). All patients taking an SGA require periodic monitoring of weight, body mass index (BMI), lipid profile and fasting plasma glucose and should be referred to a specialist for evaluation if they develop hyperlipidaemia or type 2 diabetes mellitus (McPhee *et al*., 2012:1032).

In February 2004 the American Diabetes Association published an expert consensus statement on antipsychotic drugs and diabetes and obesity with the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity. The consensus statement

recommend that patients initiated on SGAs agents should be screened for symptoms of metabolic syndrome (Morrato *et al*., 2009:1037). These screening tests involve measuring body weight at baseline, weeks 4, 8 and 12, then 3 monthly and thereafter annually. BMI, waist circumference, blood pressure, fasting plasma glucose, and fasting lipid profile should be monitored at the end of 3 months and then annually (Dipiro *et al*., 2011:1081; Wells *et al*., 2012:910). The American Diabetes consensus statement recognised that clozapine has the highest potential of all the antipsychotics to lead to diabetes (American Diabetes Association, 2004).

According to Mackin (cited by Dipiro *et al*., 2011:1081), more than 50% of patients on antipsychotics were not being monitored for signs and symptoms of diabetes mellitus and hyperlipidaemia. Blood glucose and lipid monitoring continues to be underutilised for patients taking antipsychotic medication. Although fasting serum results are preferred over random serum or capillary blood specimens, this should not be a barrier to adequate monitoring. The clinician can employ random glucose, HDL, or glycosylated HbA_{1c} if there is a problem in obtaining fasting serum levels.

2.2.4.1.3 Polypharmacy

According to the Dorland's *Illustrated Medical Dictionary* (2012:1492) polypharmacy can be defined as "the administration of many drugs together" or "the administration of excessive medication".

Polypharmacy has serious implications with regard to the use of antipsychotic medication. Polypharmacy in psychiatry means the use of two or more antipsychotics simultaneously, especially for the treatment of schizophrenia with the goal of increasing the overall efficacy of treatment (Usher *et al*., 2009:179).

The rationale for antipsychotic polypharmacy includes concern over an initial poor response rate with an antipsychotic, the use of a combination while 'switching' to another medication, the combination of an FGA with an SGA when the FGA is used as the lead-in while the SGA takes effect, and where an FGA is used as a 'top up' for an SGA when symptoms worsen in order to prevent a full exacerbation of psychiatric symptoms (Kane & Correll, 2010:351; Usher *et al*., 2009:179).

The disadvantages of polypharmacy are serious and include the following: potential to experience more frequent or severe adverse effects, increased risk of developing toxicity, non-adherence, and lack of understanding of the contribution of each agent towards any noticed improvement (Usher *et al*., 2009:179).

There are several reports indicating a high prevalence of antipsychotic polypharmacy in recent clinical practice (Kane & Correll, 2010:351). This suggests that clinical judgement sometimes overrides pharmacological guidelines even though there is no evidence to support the combination of antipsychotic drugs (Usher *et al.,* 2009:180).

2.2.4.1.4 Non-adherence to therapy

The Dorland's *Illustrated Medical Dictionary* (2012:31) defines adherence as "the act or condition of sticking to something". Other definitions for adherence include: "the extent to which a person's behaviour coincides with the medical advice that he or she has received" (Lambert & Naber, 2009:11) or "the extent to which patients follow the instructions they are given for prescribed treatments" (O'Donohue & Levensky, 2006:4).

Recently, the term adherence has begun to be used in place of the more traditionally used term compliance. The reason for the shift in terminology was the belief of researchers and clinicians that the term compliance suggests passivity and obedience on the part of patients, whereas the term adherence implies patient-provider collaboration and an active role of patients in their treatment (O'Donohue & Levensky, 2006:4).

In patients with schizophrenia, non-adherence can take a number of forms including: not taking the prescribed medication, not attending or coming late for appointments or terminating the treatment prematurely. Non-adherence to the complete treatment regimen is also possible (Lambert & Naber, 2009:11).

Adherence to drug therapy is a significant issue in the clinical management of psychiatric conditions (Lang *et al*., 2010:1239).

Early treatment discontinuation in patients with schizophrenia or schizophrenia-like disorders is very common, with about 50% of patients being non-adherent to treatment (Kazadi *et al*., 2008:52).

Discontinuing antipsychotic treatment is associated with relapse, increased hospitalisation, symptom exacerbation, poor long-term course of illness, and higher economic costs of treatment (Lang *et al*., 2010:1240; Novick *et al.*, 2010:112; Perkins, 2002:1122). Reasons for poor adherence are complex, but several studies suggest that it could be related to a hidden burden of adverse effects as well as poor illness insight (Moritz *et al*., 2013:918).

According to O'Donohue and Levensky (2006:4), the consequences of non-adherence also include a greater financial burden on the service provider for additional services and treatments for the patient as well as reduced quality of life and work productivity of the patient.

Understanding the reasons for and causes of non-adherence in schizophrenia is a logical step towards improving management of this vast problem. However, there is a range of theories and concepts of non-adherence, a variety of relevant risk factors, and the known problem that professionals, carers and patients do not have shared understanding of which of these factors are important in patients' behaviour with respect to therapy (Lambert & Naber, 2009:13).

The literature describes numerous risk factors that contribute to non-adherence. Some of the risk factors associated with non-adherence are listed in Table 2.17 (adapted from Lambert & Naber, 2009:14).

Table 2.17: Risk factors related to non-adherence

Risk factors related to non-adherence
Consistently associated with non-adherence
Negative attitudes towards medication and treatment in general
No development of insight during treatment
No development of a positive therapeutic alliance during treatment
Persistent comorbid substance use disorder during treatment
Poor subjective wellbeing under pharmacological treatment
Poor aftercare planning and environment
Mixed findings or not consistently associated with non-adherence
Medication regimen complexity
Age, gender, ethnicity, marital status, education level
Type and route of medication
Cognitive impairment
Family involvement
Higher antipsychotic dose
Severity of symptoms

These categories are helpful in providing an overview of the most relevant adherence factors. However, in clinical practice most patients fulfil several of these factors, the factors themselves fluctuate over time and they interfere with each other (Lambert & Naber, 2009:13).

It is of vital importance to focus on improving adherence by providing psychoeducation to the patient as well as his/her family and to discuss with the patient the reasons for non-adherence. Depot medication should be considered if non-adherence to oral medication persists e.g. risperidone long-acting injection, zuclopenthixol decanoate or fluphenazine decanoate (Schatzberg & Nemeroff, 2004:890). In patients previously unexposed to the drug, an oral test dose of the medication is recommended before long-acting antipsychotics are given (Wells *et al.*, 2012:902).

However, the NICE (2008:12) guidelines recommends that as long as the patient has capacity to consent, their right not to take medication should be respected. If according

to the prescriber this might have a negative impact on the patient's overall well-being, the reasons for the patient's decision not take medication and the prescriber's concerns should be recorded in the patient's file.

2.2.4.2 REHABILITATION AND COMMUNITY SUPPORT

Pharmacotherapy is the mainstay of treatment in schizophrenia and it is impossible in most patients to implement effective psychosocial rehabilitation programmes without adequate antipsychotic treatment (Dipiro *et al*., 2011:1150).

However, psychosocial rehabilitation programmes orientated toward improving a patient's adaptive functioning are the mainstay of non-pharmacological treatment for schizophrenia. Psychosocial skill training and vocational rehabilitation programmes help many patients work, shop, and care for themselves; manage a household; get along with others; and work with mental health care practitioners. Supported employment, in which patients are placed in a competitive work setting and provided with an on-site job coach to promote adaptation to work, may be particularly valuable (Porter & Kaplan, 2011:1565).

Support services enable many patients with schizophrenia to reside in the community (McCarron *et al.*, 2009:97). Although most can live independently, some require supervised apartments where a staff member is present to ensure drug adherence. Programmes provide a graded level of supervision in different residential settings, ranging from 24 hour support to periodic home visits. These programmes help promote patient autonomy while providing sufficient care to minimise the likelihood of relapse and need for inpatient hospitalisation (Porter & Kaplan, 2011:1565).

An intensive model of case management, termed Assertive Community Treatment (ACT) programmes makes use of a multidisciplinary team that provide services in the patient's home or other residence and are based on high staff-to-patient ratios; treatment teams directly provide all or nearly all required treatment services (McCarron *et al*., 2009:98). It is therefore clear that pharmacotherapy alone cannot be successful without proper attention to these aspects of care (Dipiro *et al*., 2011:1151).

Hospitalisation or crisis care in a hospital alternative may be required during severe relapses, and involuntary hospitalisation may be necessary if patients pose a danger to themselves or others. Despite the best rehabilitation and community support services, a small percentage of patients, particularly those with severe cognitive deficits and those poorly responsive to drug therapy, require long-term institutional or other supportive care (Porter & Kaplan, 2011:1566).

2.2.4.3 PSYCHOTHERAPY

The need for psychotherapy varies according to the patient's current status and history (McPhee *et al*., 2012:1034).

The goal of psychotherapy is to develop a therapeutic relationship between the patient, family members, and physician so that patients can learn to understand and manage their illness, take drugs as prescribed and handle stress more effectively (Sadock & Sadock, 2007:492).

Although individual psychotherapy plus drug therapy is a common approach, few empirical guidelines are available. Psychotherapy that begins by addressing the patient's basic social service needs, provides support and education regarding nature of the illness, promotes adaptive activities, and is based on empathy and a sound dynamic understanding of schizophrenia is likely to be most effective. Many patients need empathic psychological support in order to cope with their illness, since schizophrenia can substantially limit normal functioning (Porter & Kaplan, 2011:1567). The approach to the duration of psychotherapy for a patient with schizophrenia should be in terms of decades, rather than sessions, months, or even years (Sadock & Sadock, 2007:495).

Research suggests that cognitive behavioural therapy in combination with pharmacological treatment may have some efficacy in the treatment of symptoms of schizophrenia. Cognitive behavioural therapy for schizophrenia involves helping the individual to challenge psychotic thinking, reduce distractibility, alter response to hallucinations and correct errors in judgement (McPhee *et al*., 2012:1034; Sadock & Sadock, 2007:492).

Patients who would benefit from cognitive behavioural therapy generally have some insight into their illness (Sadock & Sadock, 2007:492). Cognitive remediation therapy is another promising approach that can be used as treatment, by helping patients to become more able to focus their disorganised thinking (McPhee *et al*., 2012:1034).

For patients who live with their families, psycho-educational family interventions can help alleviate the patient's stress and assist relatives in coping with the patient; and ultimately reduce the rate of relapse (McPhee *et al*., 2012:1034). Support and advocacy groups, such as the Schizophrenia and Bipolar Disorders Alliance (SABDA) are often helpful to families. SABDA, a South African based support group, was established in 1991 to assist patients with schizophrenia and bipolar disorders as well as their caregivers (SABDA, 2012).

2.3 DRUG UTILISATION REVIEW

2.3.1 INTRODUCTION

Drug utilisation studies in pharmacoepidemiology have become of greater significance since they are closely linked to other areas such as public health, pharmacovigilance, pharmacoeconomics and pharmacogenetics (Sachdeva & Patel, 2011:11).

Pharmacoepidemiology can be defined as: "The study of the use and effects/side effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population thereby improving health outcomes" (WHO, 2003:8).

Drug utilisation research forms an essential part of pharmacoepidemiology as it describes the extent, nature and determinants of drug exposure. However, while drug utilisation studies often employ various sources of information focusing on drugs, e.g., aggregate data from wholesale and prescription registers, the term epidemiology implies defined populations and that the drug use in the populations under study can be expressed in terms of incidence and prevalence (WHO, 2003:8).

2.3.2 DEFINITIONS AND OVERVIEW OF DRUG UTILISATION AND RATIONAL USE OF MEDICINE

One of the first definitions of drug utilisation was by the World Health Organization (WHO) in 1977 which defined it as “the marketing, distribution, prescription, and use of drugs in society, with special emphasis on the resulting medical, social, and economic consequences” (WHO, 2003:8). Another definition for drug utilisation is the study of “the prescribing, dispensing, administering, and ingesting of drugs” (Serradell *et al*., 1987:994).

Drug use is a complex process. The complexity of drug use means that optimal benefits of drug therapy in patient care may not be reached because of overuse, underuse or misuse of drugs. Inappropriate drug use may also lead to a rise in medical care costs, antimicrobial resistance, adverse effects and patient mortality (Sachdeva & Patel, 2011:11).

Therefore, in recent years studies on drug utilisation have become a potential tool to be used in the evaluation of health systems. The interest in drug utilisation studies began in the early 1960s as a result of growing concerns about undesired drug effects as well as the high cost of drugs (Hartzema *et al*., 2008:159). This can be associated with the fact that more drugs are being released on the market and there is a greater need for the marketing of drugs. Other possible reasons include the wide variation in the pattern of drug prescribing and consumption, greater concern about delayed adverse effects and the growing concern about the cost of drugs (Sachdeva & Patel, 2011:11).

It is important to differentiate between a *drug utilisation review (DUR) study* and a *drug utilisation review (DUR) programme*. According to Kreling and Mott (cited by Truter *et al*., 2011:61), a *DUR study* only identifies areas of inappropriate drug use without initiating efforts to correct it, since it is normally performed retrospectively whereas a *DUR programme* will strive to correct the problem areas by performing an intervention. A *DUR programme* would thus be more advantageous compared to a *DUR study*.

“Drug utilisation review is the process by which the quality of drug prescribing is measured against explicitly determined criteria and standards. It is a dynamic process aimed firstly at rational prescribing and the consequent improvement of the quality of care, and secondly, at minimizing expenditures” (Truter, 2008:95). DUR programmes have been employed to try and to improve prescribing practices in both institutional and ambulatory care settings throughout the world. “It provides the mechanism for developing standards, assessing current therapy, and implementing a specific intervention followed by reassessment of drug utilisation” (Truter, 2008:96).

“Drug utilisation studies explore what drugs are used, in what quantity, by whom, how they are used, and the context in which they are used” (Hartzema *et al.*, 1998:145).

Drug utilisation studies have focused on several areas of research to include the following (Hartzema *et al.*, 1998:146):

- Drug use in specific populations
- Drug use in specific disease conditions
- Drug use patterns, both over time and cross-sectionally
- Identification of adverse outcomes
- Drug use across countries
- The effects of demographics on drug use

The following concepts can form part of a DUR study (Truter *et al.*, 2011:61):

- A system that consists of drug use and prescribing processes
- It can include cost aspects
- It can include treatment guidelines and drug utilisation standards which form an important part of the evaluation system
- It can be therapy outcome orientated

Coupled to drug utilisation studies is the question of what constitutes rational drug use. When viewed together, they assist in improving drug therapy decisions by offering objective, quantifiable methods and techniques for evaluating and selecting drugs and optimizing drug therapy decisions (Truter, 2001:44).

The rational use of medicine can be defined as when “patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community” (WHO, 1987).

According to Crane (cited by Truter, 2001:43), the following steps can be employed to ensure the rational use of medicine:

- Identify the underlying problem

- Identify the alternative solutions to solve or relieve the problem

- Identify the costs and outcomes of each of the alternatives

- Measure the costs and outcomes

- Place a value on the costs and outcomes with respect to time

- Examine the sensitivity of the results

- Select the best alternative or alternatives.

World Health Organization (WHO_b, 2013) supports 12 key interventions that can be utilised to promote the more rational use of medicines:

- A multidisciplinary national body should be established to coordinate policies on medicine use.
- Clinical guidelines should be used.
- Compiling and use of national essential medicines list.
- Forming drug and therapeutic committees in districts and hospitals.
- Problem-based pharmacotherapy should form part of the training of undergraduate students.
- Continual professional development of health care professionals should be a requirement.
- Exercise successful supervision, audit and feedback.
- Independent information should be used in enquiries about medication.
- The public should be educated about medicines.
- Financial incentives should be avoided as far as possible.
- Utilisation of appropriate and enforced regulations.
- Sufficient government funding should be made available to ensure the proper supply of medication as well as health care staff.

The rational use of drugs can only be achieved when it is widely appreciated that the use of drugs in medicine is a social process that is influenced by a number of factors, only one of which is the desire to improve health care by reasoned pharmacologic intervention (Truter, 2001:45).

Ultimately, drug utilisation studies aim to facilitate the more rational use and prescribing of drugs in populations.

2.3.3 CLASSIFICATION OF DRUG UTILISATION REVIEWS

DUR studies can be classified as either quantitative or qualitative (Strom & Kimmel, 2006:400).

Quantitative studies are aimed at drug consumption and provide overall statistics, commonly with a detailed breakdown, or specific data in a given situation. Quantitative studies focus on the cost of therapy and the resulting social and economic consequences. These studies can be used to identify, for instance, areas of over- and under-prescribing, to estimate the misuse of medication and to identify the number of adverse drug reactions that occurred. Data obtained from these studies are generally considered suggestive, and not conclusive with respect to quality of drug use (Sachdeva & Patel, 2011:13; Truter *et al.*, 2011:62).

Qualitative studies on the other hand focus on the appropriateness of drug use/selection based on the availability of the diagnosis of the patient. These studies can be utilised for example to determine the appropriateness of the daily dose and to identify potential drug interactions. Qualitative studies usually investigate the use of specific drugs or specific conditions through applying predetermined criteria (Sachdeva & Patel, 2011:13; Truter *et al.*, 2011:62).

It is possible to combine both qualitative and quantitative drug utilisation studies, which will provide information about quality of drug use as well as pattern and amount of drug use (Sachdeva & Patel, 2011:13).

2.3.4 TYPES OF DRUG UTILISATION REVIEWS

Three types of DUR studies can be performed, depending on the timing of data collection, namely:

- retrospective studies
- concurrent reviews
- prospective reviews

In retrospective studies data are collected after the drug has been prescribed, dispensed and used by the patient. The data are obtained from patient files/records. The data are thus archival in nature. The advantage of using a retrospective study is

that future problems can be prevented by performing an intervention on prescribing behaviour in order to enhance appropriate drug use/selection by prescribers (Sachdeva & Patel, 2011:15; Truter, 2008:95).

Concurrent review involves the pharmacist reviewing the prescription before it is dispensed. If a problem is encountered the doctor is informed and the prescription is corrected. This aims to prevent the incorrect/inappropriate prescribing of drugs by medical practitioners. This type of utilisation review is more expensive than retrospective reviews and is also more time consuming. The benefits are, however, much greater since problems are identified before the prescription is dispensed. This can only be optimally used if the databases of the various pharmacies from which the patient obtains medication are merged (Sachdeva & Patel, 2011:15; Truter, 2008:95).

Prospective reviews are based upon the retrospective review of information from interviews and past medical history of the patient, in order to decide on the appropriate treatment for the present medical condition of the patient. This is done by making use of computer software that will display the past medical history of the patient when the doctor enters the prescription into the computer (Sachdeva & Patel, 2011:14; Truter, 2008:95).

Ideally, an integration of both retrospective and prospective drug utilisation reviews would result in optimal prescribing practices.

2.3.5 THE NEED FOR DRUG UTILISATION REVIEW

The need for DUR studies originated from the idea that the prescribing of medication and subsequent consumption by patients may be irrational. Another reason is the fact that medicine prices are constantly increasing.

DUR can be employed as a powerful tool to aid drugs in becoming more effective and safe. DUR can be used to analyse the appropriateness of drugs prescribed by doctors. DUR should be viewed by prescribers as an ongoing educational process that will aid them to provide improved quality of care to their patients and not as a tool used to

punish them every time a prescription does not meet the set criteria (Truter *et al.*, 2011:66).

2.3.6 PURPOSE OF DRUG UTILISATION REVIEWS

The aim of a DUR programme is to improve the quality of care provided by health care providers and to reduce the cost associated with treatment. Through improving the quality of care the probability of obtaining favourable health outcomes will be enhanced (Truter *et al.*, 2011:64).

However, the co-operation of all the health care professionals involved in the study is needed in order for the drug utilisation review programme to be successful.

2.3.7 APPLICATIONS OF DRUG UTILISATION REVIEWS

DUR studies have the following important applications (Truter *et al.,* 2011:71):

- *Side effects*
  A DUR programme can be utilised to identify side effects and to determine their severity and frequency if a drug control system is in place.
- *Economic value*
  DUR data are also of economic value, since some countries are requesting cost-effectiveness data in order to justify the (high) cost of the drug. However, it is important not to sacrifice quality of care due to economic constraints. Increased hospitalisations and decreased quality of life of patients may result due to suboptimal treatment received due to cost containment.
- *Quality assurance*
  DUR provides valuable information on the level of health care provided by institutions and how to monitor and measure quality of care provided.

- *Clinical research*

  DUR programmes are also useful in clinical research, since drugs can be monitored both for therapeutic efficacy and unpredicted side effects which were not discovered during the clinical trial of the drug.
- *Manufacturers*

  Manufacturers can find DUR useful in order to determine drug usage and the distribution of drug consumption in a specific geographical area(s).
- *Outcomes*

  DUR is also helpful in monitoring and measuring the clinical outcomes of therapy.
- *Appropriateness of therapy*

  Drug utilisation can also be a useful tool to evaluate/ analyse the appropriateness of drugs prescribed by medical practitioners and problem areas can be addressed through interventions to avoid future prescription errors.
- *Medical aids*

  Medical aids can use DUR information in order to manage or contain costs associated both with patients (high cost users) and prescribers. Second opinions in the case of surgery could also be considered by medical aids as a cost saving method.

2.3.8 LIMITATIONS OF DRUG UTILISATION REVIEWS

There are also some limitations to DUR studies which can include amongst others the following:

- Drug utilisation studies seem can be sporadic, unstructured and time-consuming.
- Most DUR programmes only concentrate on the shortcomings of therapies and can thus create a negative perception of DUR. This is seen as one of the limitations of DUR, because instead of it aiming to educate and assist health workers to perform their duties it only points out their mistakes.
- Often the diagnosis of a patient is not available to the pharmacist which makes it difficult to evaluate the treatment prescribed by the medical practitioner. Adequate interventions can therefore not take place (Truter *et al.*, 2011:74).

Another factor that needs to be considered is the fact that DUR programmes should never replace the role of the health care professional, but should provide them with extra information and knowledge in order to improve the quality of health care provided to patients (Truter *et al.*, 2011:74).

2.3.9 PUBLISHED LITERATURE AVAILABLE ON DRUG UTILISATION REVIEWS ON CLOZAPINE

The following information was found on DUR studies conducted on clozapine.

The aim of a DUR study conducted in 2004 by Latimer *et al*. (2013) was to describe the patterns of clozapine use in schizophrenic patients in the province of Québec, Canada. In order to determine whether the use of clozapine was cost-effective in Québec, the study compared the number of days hospitalised between patients taking clozapine and those not taking clozapine. The investigators found that only 6.7% of the 29155 schizophrenic patients that were included in the study received clozapine for six months or longer in 2004. Utilisation rates ranged from 3.9 to 9.0% among regions with 1000 or more people with schizophrenia. Over 8.0% of the 61 hospitals included in the study did not prescribe clozapine at all. They also found that people with schizophrenia taking clozapine experienced 3.4 fewer days of hospitalisation per year than those not taking clozapine, representing a cost saving of about $1 800.00 per year. This study clearly indicates both the clinical and economic advantages of using clozapine in patients with schizophrenia (Latimer *et al*., 2013:33).

Another retrospective DUR study (n=353) conducted by McKean *et al.* during 2008 in New Zealand, aimed to identify the pattern of clozapine usage in Christchurch. The study included investigations of daily dose, indication and use of drug concentration monitoring. The study findings revealed that the mean daily dose of clozapine was 325 mg. The study reported an age-related decline in dose, probably due to different indications, with many of the elderly patients receiving clozapine for Parkinsonian related symptoms. In this study clozapine was often used for unlicensed indications, and a clear majority of psychiatrists used drug concentration monitoring (McKean *et al*., 2008:263).

Hempill *et al*. (1975) conducted the first South African study on clozapine in 1974. The study setting was Valkenberg Hospital and included 52 patients that received clozapine for acute and chronic schizophrenia and gross behavioural disorders. All patients were followed-up for six months after clozapine therapy was initiated. The study found that 75.0% of acute cases recovered with full capacity and 66.0% of chronic cases improved markedly, whereas antisocial behaviour improved in 92.0% of the behaviour-disordered cases. The response to clozapine appeared to be specific and relapses occurred when maintenance therapy was stopped. The study showed that maximum improvement may only be reached after 8 weeks of continued clozapine therapy. The observed dosages, adverse effects and precautions were also discussed in the study (Hempill *et al*., 1975:2121).

However, the study by Hempill and colleagues was conducted before clozapine was voluntarily withdrawn from the market in 1975. No specific South African study on the use of clozapine in either the public or private health care sector after clozapine's return in 1989 could be found in the published literature. It is clear that limited data are available on the use of clozapine in South Africa.

2.4 CHAPTER SUMMARY

This concludes the literature review chapter. Various literature sources were utilised to provide an in-depth overview of clozapine, psychotic disorders and drug utilisation reviews. In the following chapter the exact research methodology employed in this study will be discussed.

CHAPTER 3

EMPIRICAL STUDY

3.1 INTRODUCTION

This chapter will describe the research method employed to conduct this pharmacoepidemiological investigation. The ethical considerations will be discussed as well as the shortcomings and limitations of the research method.

In this study, the group of patients under review were inpatients at Elizabeth Donkin Hospital that were initiated on clozapine therapy after admission.

The purpose of this study was to assess the usage of clozapine for the treatment of psychiatric conditions at the hospital. The main focus of the study, however; was to determine whether clozapine is initiated and monitored adequately in the public sector of the Nelson Mandela Metropole.

The prescription charts of the study sample as well as laboratory test results were investigated to determine the extent of compliance with the recommended guidelines, for both the metabolic and white cell count monitoring of clozapine. The initiation of clozapine therapy was also investigated with special emphasis on who initiated clozapine, i.e. a medical officer or psychiatrist, and at what dosages.

The data obtained were evaluated against predetermined and acceptable international and local guidelines and protocols, thereby allowing for the identification of possible discrepancies in current monitoring and prescribing practices. After discharge, follow-up investigations were performed at the clinics as well as at the long-term care facilities to which the patients were discharged.

This chapter provides an overview of the methods utilised to achieve the study objectives. The methodology comprised the following subsections: research design; setting; study population; data source; development of research instruments; implementation plan; and statistical analysis as well as ethical considerations.

3.2 AIM AND RESEARCH OBJECTIVES OF THE EMPIRICAL STUDY

3.2.1 General aim

This study aimed to investigate the prescribing and monitoring patterns of clozapine at Elizabeth Donkin Hospital in the Nelson Mandela Metropole.

3.2.2 Specific research objectives of the empirical study

The specific research objectives included the following:

- To determine the general prescribing patterns of clozapine at Elizabeth Donkin Hospital.
- To determine compliance with the recommended guidelines for the initiation of clozapine therapy.
- To investigate the presence and severity of any adverse reactions that could be associated with clozapine therapy.
- To identify possible drug interaction(s) when clozapine is used in combination with other agents.
- To assess the extent of compliance with the recommended guidelines for haematological and metabolic monitoring of clozapine both at Elizabeth Donkin Hospital as well as the community psychiatric clinics and long-term care centres after discharge from hospital.
- To determine the total monetary costs involved when admitting a patient and initiating the patient on clozapine therapy.
- To determine the percentage of patients still on clozapine three months as well as six months after discharge from Elizabeth Donkin Hospital.

3.3 RESEARCH DESIGN

An observational pharmacoepidemiological investigation in the form of a descriptive cross-sectional study was performed. Methodological concepts of a drug utilisation review study were also employed.

The following information was found in the literature pertaining to observational study designs:

Observational study designs in pharmacoepidemiology produce data and information about disease patterns or identify the occurrence of drug use problems. Researchers in observational studies may plan and identify variables to be measured, but human intervention is not part of the process (Waning & Montagne, 2001:45).

Descriptive studies generally attempt to uncover and portray the occurrence of the condition or problem and provide insight, data, and information about the course or patterns of disease or drug use problems in a population or group without manipulating the study environment (Waning & Montagne, 2001:46).

A cross-sectional study is a prevalence study – a basic descriptive study that examines relationships between a disease or drug use problem and other characteristics of people in a population at one point in time (Waning & Montagne, 2001:46). Such studies are useful in obtaining an overall 'picture' as it stands at the time of the study (Kumar, 2011:107).

3.3.1 Classification of drug utilisation review study

The drug utilisation review study was quantitative in nature. According to Sachdeva and Patel (2011:13), quantitative studies are aimed at drug consumption and provide overall statistics, commonly with a detailed breakdown, or specific data in a given situation.

3.3.2 Type of drug utilisation review study

A retrospective drug utilisation review was performed on the use of clozapine in a public sector psychiatric hospital in the Nelson Mandela Metropole. According to Kumar (2011:111), retrospective studies investigate a phenomenon, situation problem or issue that has happened in the past.

Secondary data sources were utilised, i.e. existing patient files from which retrospective data were collected. As part of the study, follow-up investigations, through the use of questionnaires were performed at the clinics and long-term care facilities to which the patients were discharged. Primary data were collected from the questionnaires.

3.4 SETTING

The setting where most of the data for the study were collected was Elizabeth Donkin Hospital.

Elizabeth Donkin Hospital is a public sector acute psychiatric hospital. This 196 bed hospital is situated in Port Elizabeth in the Nelson Mandela Metropole in the province of the Eastern Cape, South Africa.

Specialised medication is sent from Elizabeth Donkin Hospital Pharmacy to 11 community psychiatric clinics in the Nelson Mandela Metropole, as part of their outreach programme.

Data for the follow-up questionnaires were collected at the 11 community psychiatric clinics in the Nelson Mandela Metro as well as at the two long-term care centres to which patients were sent after discharge from Elizabeth Donkin Hospital (see lists attached below).

The following list provides the names of clinics to which patients in the study sample were discharged:

List of community psychiatric clinics situated in the Nelson Mandela Metropole to which patients were discharged:
1. Bloempark Clinic
2. Clarkson Clinic
3. Dora C-Block Clinic
4. Empilweni Clinic
5. Korsten Community Health Centre (CHC)
6. Kwazakhele Clinic
7. Laetitia Bam CHC
8. Motherwell CHC
9. P.E. Provincial Hospital Clinic
10. Stow Road Clinic
11. West End CHC

The following list provides the names of the two long-term care centres to which patients in the study sample were transferred after discharge from Elizabeth Donkin Hospital:

List of long-term care centres to which patients were transferred after discharge:
1. Life Esidimeni - Kirkwood Care Centre in Kirkwood
2. Tower Hospital in Fort Beaufort

3.5 STUDY POPULATION

In February 2011 there were approximately 475 patients that received clozapine therapy at Elizabeth Donkin Hospital and the surrounding community psychiatric clinics, in the public sector of the Nelson Mandela Metropole. A specified period of 15 months was identified, i.e. 1 December 2010 to 29 February 2012, and a total number of 65 patients were included in the study sample.

Patients were identified through the collection of all the discharge summaries received by the pharmacy department during the above-mentioned period. Since the size of the study population was limited, non-random sampling was performed and hence all the patients discharged on clozapine were eligible for the study and thus independently included.

Patients were not excluded based on their diagnosis. All the patients that were discharged on clozapine during the study period were included. Both male and female patients of various age groups and from different ethnic backgrounds were included. Only data from the first initiation of clozapine for the admission were included in the study. Data were only collected from the last admission of the patient in hospital. Data from the second and third initiation of clozapine during the admission were excluded.

3.6 DATA SOURCE

The first set of data was collected from the existing files of all patients who were initiated on clozapine at Elizabeth Donkin Hospital; and who were then subsequently discharged on clozapine. The second set of data was collected from the clinics and long-term care centres.

3.6.1 Patients discharged from Elizabeth Donkin Hospital

The medical files of these patients were studied to determine the prescribing and monitoring patterns followed at Elizabeth Donkin Hospital when a patient is initiated on clozapine therapy.

All the prescriptions, doctor's notes, laboratory test results and other treatment notes in the patient's file were assessed. These records allowed the researcher to obtain a complete consultation and treatment history of the patient.

3.6.2 Patients attending community psychiatric clinics and long-term care centres

Follow-up investigations were performed at these facilities, both three months and six months after discharge of the patient from Elizabeth Donkin Hospital. All patients that formed part of the study sample were followed to the clinic/long-term care centre to which they had been discharged.

These follow-up investigations were in the form of two questionnaires that were sent to the particular facility to which the patient had been discharged

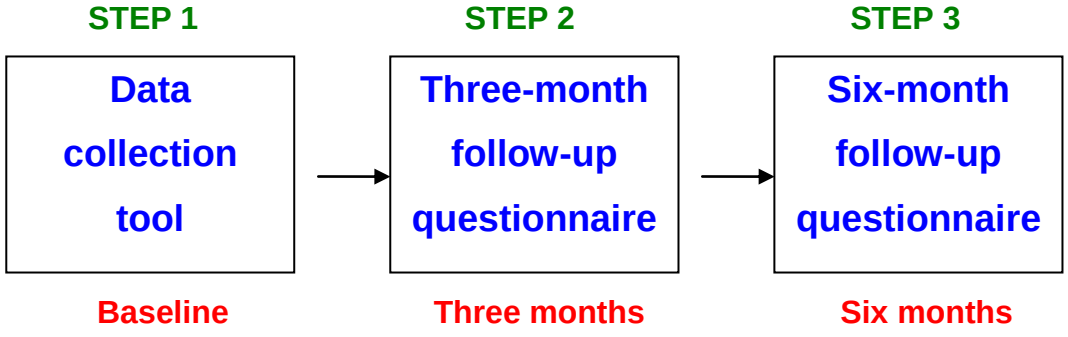
3.7 DEVELOPMENT OF RESEARCH INSTRUMENTS

The research instruments developed for this study included the following:

- Data collection tool (refer Appendix B)
- Three-month follow-up questionnaire (refer Appendix C)
- Six-month follow-up questionnaire (refer Appendix D)

Below is a diagrammatic presentation indicating the stepwise approach followed for the development of research instruments used in this study.

Figure 3.1 Development of research instruments



A stepwise approach was followed for the development of research instruments in this study. The study initiated at Elizabeth Donkin Hospital where the patient sample was identified and then continued at the clinics and long-term care centres where follow-up investigations were performed at both three and six-month intervals.

3.7.1 Data collection tool

A data collection tool was developed that would serve as a survey form, on which the relevant information from the patients' files was recorded.

3.7.1.1 Testing of data collection tool

The initial data collection tool was used to obtain information from 5 patient files at Elizabeth Donkin Hospital. The files were randomly selected on 2 July 2012 from several wards in Elizabeth Donkin Hospital.

The patient sample that was chosen to be used in the testing of the data collection tool was not part of the study sample. These patients were discharged on clozapine after the cut-off date of 29 February 2012.

After a careful investigation was performed a few changes were made to the design of the initial data collection tool. Thereafter the final data collection tool was developed that would be used to obtain information from patient files at Elizabeth Donkin Hospital.

A copy of the initial data collection tool utilised in the 'test run' is attached as ***Appendix A.***

3.7.2 Structuring of data collection tool

The criteria that were identified to investigate the use of clozapine as well as the prescribing and monitoring patterns followed at the hospital are discussed below.

3.7.2.1 Demographics

The data collection tool was designed to obtain the required information from existing patient files at Elizabeth Donkin Hospital.

3.7.2.1.1 Patient identification number

Each patient was assigned a unique patient number, since no patient name or patient surname was used on any documentation. Each patient in the study sample was assigned a number between 1 and 65.

3.7.2.1.2 Age

The age of each patient was obtained from his/her medical file. In some cases the patient's age had to be calculated, since only the date of birth was available in the file. The age of the patient at the time of his/her last admission in hospital was then calculated. The patient's age was then recorded on the data collection tool.

The ages recorded on the data collection tool were divided into the following categories to assist in the final analysis of data:

Age	
13 and < 18 yrs	Adolescents
≥ 18 and < 31 yrs	Young adults
≥ 31 and < 51 yrs	Middle aged adults
≥ 51 and < 65 yrs	Mature adults
≥ 65 yrs	Elderly

The age categories were chosen, since the age of patients in the study sample varied from 16 years to 64 years of age. It was decided not to divide the age categories into exact intervals of 10 years e.g. 10 to 20 years and 21 to 31 years, but rather to express the patient's age by referring to the age group within which the patient falls into. A

literature search was performed, but no specific categories could be identified for classifying psychiatric patients into groups according to their age.

Although there were no elderly patients in the study sample, it was also considered important to include this age category. Clozapine treatment in the elderly requires a careful geriatric assessment and its use is strongly limited by the possibility of onset of severe adverse effects such as agranulocytosis, myocarditis as well as metabolic adverse effects (Gareri *et al.*, 2008:525). In 2005 the United States FDA (Food and Drug Administration) issued a black box warning stating that the treatment of behavioural disorders in elderly patients with dementia with SGAs (including clozapine) is associated with increased mortality (FDA, 2005).

3.7.2.1.3 Gender

The gender of the patient was determined from the information in the patient's file. There were two categories to choose from on the data collection tool.

Gender	
1	Male
2	Female

3.7.2.1.4 Race

The race of the patient was determined from the information in the patient's file. Categories provided to choose from included the following:

Race	
1	White
2	African
3	Coloured
4	Indian
5	Other

The above-mentioned demographic indicators were included on the data collection tool to determine the demographic composition of the study sample.

3.7.2.2. Admission History

3.7.2.2.1 Admission date

The date of admission was recorded for the last admission of the patient. This date was obtained from the admission document filled in by the doctor that admitted the patient. The date of admission was recorded to calculate the duration of the admission in hospital as well as the length of stay in hospital after initiation of clozapine.

3.7.2.2.2 Number of previous admissions

The number of previous admissions for the patient, at Elizabeth Donkin Hospital, was obtained from the information available in the file about the past admissions of the patient. Categories available to choose from included:

Number of previous admissions	
1	No previous admissions
2	One previous admissions
3	Two previous admissions
4	Three previous admissions
5	> Three previous admissions

3.7.2.2.3 Date of discharge

The date of discharge as stated on the discharge summary for the last admission of the patient was recorded on the data collection tool. The date of discharge was used to calculate the duration of the admission in hospital as well as the length of stay in hospital after initiation of clozapine.

3.7.2.3. Social History

3.7.2.3.1 Smoking status

The patient's smoking status was indicated through selecting one of the applicable options. The patient's smoking status was obtained from the social history provided in the patient's file. The categories to choose from included:

Smoking status	
1	Non-smoker
2	Smoker
3	No information

The smoking status of the patient had to be established, since clozapine is metabolised faster in smokers compared to non-smokers and thus a higher dosage of clozapine was required in smokers (Taylor *et al.*, 2012:15).

3.7.2.3.2 Drug abuse

A list of drugs of abuse was provided on the data collection tool. Co-morbid substance abuse with alcohol, cannabis, cocaine, and other drugs is highly prevalent among patients with schizophrenia (Sadock *et al*., 2009:1578).

The drug(s), if any, used by the patient were indicated on the data collection tool. The information about past drug abuse was obtained from the social history provided in the patient's file.

The options to choose from included the following:

Drug abuse	
0	None
1	Alcohol
2	Cannabis
3	Methamphetamine
4	No information
5	Other

3.7.2.4. Medical History

3.7.2.4.1 Family history

The family history of chronic diseases of the patient was obtained from the medical history, if any, provided in the patient's file. Categories to choose from included:

Family history	
0	None
1	Type 2 Diabetes mellitus
2	Obesity
3	Hypercholesterolemia
4	No information
5	Other

Metabolic adverse effects such as weight gain, hyperlipidaemia and type 2 diabetes mellitus are associated with the use of clozapine (Usher *et al*., 2009:177). Metabolic syndrome is the development of a cluster of metabolic abnormalities associated with raised fasting triglyceride levels and low high density lipoprotein (HDL) cholesterol levels, elevated fasting plasma glucose, high blood pressure and weight gain (American Heart Association, 2011; Wells *et al*., 2012:908).

The elements that compose the metabolic syndrome are major risk factors for type 2 diabetes mellitus and cardiovascular disease (Sadock *et al*., 2009:1578).

The above-mentioned categories were included on the data collection tool to determine whether the patient had a family history of type 2 diabetes mellitus, obesity or hypercholesterolemia. According to studies performed in the United States, India and Europe it seems reasonable to argue that family history of type 2 diabetes mellitus, obesity and coronary heart disease could be useful as a predictive tool for early diagnosis and prevention of metabolic syndrome, since metabolic syndrome aggregates in families, suggesting that behavioural and genetic factors affect its development (Dallongeville *et al*., 2006:722; Das *et al*., 2012:104; Ghosh *et al*., 2010:353).

3.7.2.4.2 Co-morbid disease states

Information about a current co-morbid condition of the patient was obtained from the medical history in the patient's file. The discharge summary of the patient was also reviewed to obtain information about the presence of any co-morbid disease state. Categories on the data collection tool to choose from included:

Co-morbid disease states	
0	None
1	Hypertension
2	Type 2 Diabetes mellitus
3	Hypercholesterolemia
4	Epilepsy
5	Other

These categories were included on the data collection tool, since clozapine has quite a severe side effect profile. Some of the common adverse effects associated with clozapine therapy include: agranulocytosis, weight gain, diabetes mellitus type 2, hypercholesterolemia, hypertension and seizures (Rossiter, 2012:475; Taylor *et al*., 2012:76). Hence, co-morbidities that might be associated with the clozapine therapy that the patient received could therefore be identified.

3.7.2.4.3 Surgical History

Any surgery that the patient underwent that was mentioned in the patient's medical history was recorded on the data collection tool. The following categories were provided on the data collection tool:

Surgical history	
1	Yes
2	No
3	No information

If the patient had any surgery in the past, information about the type of surgery was mentioned on the space provided.

This indicator was included on the data collection tool to screen for any female patients in the study sample that underwent sterilisation or a hysterectomy. This information would later be used to determine whether female patients of childbearing age were on contraception or had been sterilized or had a hysterectomy, since there is a category B risk when using clozapine during pregnancy (Rossiter, 2012:475).

3.7.2.4.4 Date of first diagnosis of a mental disorder

The date when the patient was diagnosed with a mental disorder, by a medical practitioner for the first time, was recorded on the data collection tool. This information was obtained from the medical history available in the patient's file.

3.7.2.4.4.1 Number of years passed since first diagnosis

The date of first diagnosis of a mental disorder, as recorded on the data collection tool, was used to determine how many years had passed since the first diagnosis of a mental disorder was made.

The answer obtained for each calculation was then divided into one of the following categories and coded as such:

Number of years passed since first diagnosis	
1	< 1 year ago
2	≥ 1 and ≤ 5 years ago
3	> 5 and ≤ 10 years ago
4	> 10 and ≤ 15 years ago
5	> 15 and ≤ 20 years ago
6	> 20 years ago
7	No information available

3.7.2.4.5 Diagnosis

The diagnosis was obtained from the discharge form for the latest admission of the patient at Elizabeth Donkin Hospital.

The main indications of clozapine are treatment-resistant schizophrenia as well as the reduction of risk of suicide in patients with schizophrenia or schizoaffective disorder (Novartis, 2006). However, clozapine can also be used off-label in resistant mania associated with bipolar disorder (Kant *et al.,* 2004:57).

Thus it was decided to include the following categories to indicate the diagnoses on the data collection tool:

Diagnosis	
1	Schizophrenia
2	Bipolar disorder
3	Schizoaffective disorder
4	Other

3.7.2.4.6 Positive and negative symptoms

Schizophrenia is associated with both positive and negative symptoms and therefore these indicators, i.e. positive and negative symptoms experienced by the patient, were included on the data collection tool to establish which symptoms were predominantly

experienced by the study sample. Clozapine has shown superior efficacy, for both the positive and negative symptoms of schizophrenia, over conventional antipsychotics (Chandrasekaran, 2008:96).

The positive symptoms of schizophrenia include symptoms such as hallucinations (a sense of perception without a source in the external world) and delusions (false beliefs) (Dipiro *et al*., 2011:1150).

It was indicated on the data collection tool whether it could be elicited from the medical officers' notes in the patient's file if the patient had experienced any positive symptoms during his/her current admission in hospital:

Positive symptoms	
0	None
1	Hallucinations
2	Delusions
3	Other

The negative symptoms of schizophrenia include symptoms such as blunting of affect (restrictions in the range and intensity of emotional expression) and avolition (reduced desire, motivation or persistence) (Dipiro *et al*., 2011:1150).

It was indicated on the data collection tool whether it could be elicited from the information provided in the doctors' notes in the patient's file if any negative symptoms were observed during the current admission of the patient:

Negative symptoms	
0	None
1	Blunting of affect
2	Avolition
3	Other

3.7.2.5. Clozapine usage

3.7.2.5.1 Was the patient on clozapine before?

Information was obtained from the past prescriptions as well as medication history provided in the patient's file on whether or not the patient had been on clozapine before. It was then indicated on the data collection tool whether or not clozapine was prescribed and administered to the patient in the past.

The following categories were provided:

Patient on clozapine in the past	
1	Yes
2	No
3	No information available

3.7.2.5.2 Is the date available for the first initiation of clozapine?

Information was obtained from the past prescriptions as well as medication history provided in the patient's file to determine whether the date of first initiation of clozapine was available. It was then noted as such on the data collection tool.

The following categories were provided on the data collection form:

Is the date of first initiation available?	
1	Yes
2	No
3	No information available

If yes, state the date of the first initiation of clozapine:

The date was supplied, if available, in the space provided on the data collection tool. The date of first initiation of clozapine was used to calculate how long the patient had been on clozapine.

3.7.2.5.3 Number of years passed since first initiation of clozapine

The date of first initiation of clozapine, as recorded on the data collection tool, was used to calculate the number of years passed since the first initiation of clozapine. The following categories were used to aid in the analysis of data. The answer obtained for each calculation was classified into one of the following categories and coded as such:

Number of years passed since first initiation of clozapine	
1	< 1 year
2	≥ 1 and ≤ 5 yrs
3	> 5 and ≤ 10 yrs
4	> 10 yrs
5	No information available

3.7.2.5.4 Supply the date on which clozapine was started in hospital for this admission

The date was supplied, if available, in the space provided. The date of initiation of clozapine was used to calculate the length of stay in hospital after initiation of clozapine.

3.7.2.5.5 Length of stay in hospital after clozapine was initiated

The length of stay in hospital was determined by calculating the number of days from the date of initiation of clozapine for the last admission of the patient up until the date of discharge of the patient. The number of days was recorded on the data collection tool.

Data obtained were analysed and then classified into one of the following categories and coded as such:

Length of stay in hospital after initiation of clozapine (in months)	
1	< 1 month
2	≥1 and ≤ 3 months
3	> 3 and ≤ 6 months
4	> 6 and ≤ 9 months
5	> 9 and ≤ 12 months
6	> 12 months
7	No information available

3.7.2.6 Other drugs

3.7.2.6.1 Are the names of previous antipsychotics used available?

It was indicated on the data collection tool whether or not any previous antipsychotics were used. This information was obtained from the past prescriptions as well as medication history available in the patient's file.

The following categories were provided on the data collection tool:

Names of previous antipsychotics	
1	Yes
2	No
3	No information available

3.7.2.6.2 If yes, supply the names of the antipsychotics:

The names of previous antipsychotics (if any) that were used in the past were recorded on the data collection tool. This information was obtained from the past prescriptions as well as medication history available in the patient's file.

3.7.2.6.3 Trials of previous antipsychotics used before initiating clozapine

The answer provided for the previous question was analysed to determine which antipsychotics had been used by the patient in the past. The answer was then further analysed to determine which classes of antipsychotics had been used by the patient in the past. The information obtained was then categorized into one of the following categories:

Trials of previous antipsychotics used before initiating clozapine	
1	Two previous antipsychotics prescribed of which one is a second generation antipsychotic (SGA)
2	Two previous antipsychotics prescribed of which both are SGAs
3	Two previous antipsychotics prescribed of which both are conventional antipsychotics
4	One previous antipsychotic prescribed which is an SGA
5	One previous antipsychotic prescribed which is a conventional antipsychotic
6	Clozapine was the first antipsychotic prescribed
7	No information available

3.7.2.6.4 Compliance with the recommended guidelines for the initiation of clozapine

The answer provided for the question regarding the trials of previous antipsychotics used was analysed to determine the extent of compliance with the National Institute for Health and Clinical Excellence (NICE) guidelines for the initiation of clozapine.

The NICE guidelines suggest that before a patient is initiated on clozapine treatment, at least two other antipsychotics, at adequate doses, should be tried. At least one of these two drugs should be a non-clozapine second generation antipsychotic (NICE, 2009:10). The following categories were provided to indicate the extent of compliance with the guidelines:

Compliance with the guidelines with regard to the trials of previous antipsychotics used before initiating clozapine	
1	Fully compliant
2	Non-compliant
3	No information available

3.7.2.6.5 Use of contraceptives by female patients

It was noted on the data collection tool whether or not the patient was prescribed a contraceptive while in hospital or upon discharge.

This indicator was included on the data collection tool, since there is a category B risk with administering clozapine during pregnancy and hence contraception is advised if the patent is a female of childbearing age (Rossiter, 2012:475).

The categories to choose from included the following:

Use of contraceptives by females	
1	Yes
2	No
3	No information available
4	Not applicable, since it is a male patient

3.7.2.6.6 Supply the name of the contraceptive

If the answer for the previous question was 'yes', indicating that the patient was indeed on contraception, the name of the oral or injectable contraceptive that the patient received was recorded on the data collection tool.

Data obtained from the data collection tool were analysed and the following categories were identified into which the data were then classified:

Which contraceptive is the patient taking?	
1	Medroxyprogesterone acetate (e.g. Depo-Provera®)
2	Norethisterone enanthate (e.g. Nur-Isterate®)
3	Triphasic tablet (e.g. Triphasil®)
4	Monophasic tablet (e.g. Nordette®)
5	Other form of contraception (e.g. sterilization)

3.7.2.6.7 Supply the possible reason for not being on contraception

If the answer for the question regarding the use of contraception was 'no' indicating that the patient was not on contraception, the patient's file was screened to elicit a possible reason for not being on a contraceptive. It was decided not to include categories on the data collection tool for this question, but rather an open-ended question was posed. The answer was then recorded on the data collection tool.

The following categories were identified from the answers provided for not being on a contraceptive. These categories were implemented in the analysis of data for this question.

The third category i.e. age related was included, since according to the literature one can assume that a female patient older than 45 years of age is already in menopause and hence contraception is no longer a priority (Beksinska *et al.*, 2011:133).

Possible reason for not using contraception	
1	Patient received counselling but refused contraception
2	No explanation available and no information available that counselling was provided on the use of contraception
3	Age related (patient might be in menopause, since over 45 years of age)
4	Infertility/ Sterilisation/Hysterectomy

3.7.2.7 Current medication

Information about the drugs that were used during the last admission of the patient was recorded on the data collection tool.

The following information was obtained from the prescriptions for the last admission of the patient at Elizabeth Donkin Hospital:

- Drug name
- Dose
- Frequency
- Start date
- Discontinuation date

3.7.2.8 Drug interactions

Because the cytochrome P450 (CYP) mitochondrial system is involved in the metabolism of clozapine, interactions with drugs that inhibit or stimulate this system will affect clozapine plasma concentrations (Sadock *et al*., 2009:3214)

3.7.2.8.1 Presence of any drug interactions

The data collected from the above question regarding the current medication of the patient, especially the drugs used concomitantly with clozapine, were further analysed to identify any possible drug interactions between clozapine and these agents.

The following categories were included on the data collection tool:

Presence of any drug interaction(s)?	
1	Yes
2	No
3	No information available

3.7.2.8.2 Supply information about the identified drug interactions

The data supplied from the question about the current medication of the patient were further analysed to establish the following:

- the number of interactions present
- names of the drugs that interact with clozapine
- the severity level of the interactions

The above information was recorded on the data collection tool.

The data recorded on the data collection form were then further analysed to determine the severity level of the identified drug interaction.

The following categories were used to express the severity level of the interaction between clozapine and the 'other' drug and is outlined in Table 3.1 (adapted from Tatro, 2011:2043).

Table 3.1 Severity level of clozapine drug interactions

Severity level of interaction	
0	Severity level of interaction not available in the reference source used to assess the severity level of the identified drug interactions.
1	Interaction is potentially severe or life-threatening and its occurrence has been suspected, established or probable in well controlled studies.
2	Interaction may cause deterioration in a patient's clinical status, and its occurrence has been suspected, established, or probable in well controlled studies.
3	Interaction causes minor effects, and its occurrence has been suspected, established, or probable in well controlled studies.
4	Interaction may cause moderate-to-major effects, but data are very limited.
5	Interaction may cause minor-to-moderate effects, but the occurrence of an interaction is unlikely or there is no good evidence of an altered clinical effect.

One possible example of the presence of a drug interaction is when clozapine and a selective serotonin-reuptake inhibitor such as citalopram are co-administered, resulting in raised clozapine levels and hence an increased risk for clozapine toxicity. According to Tatro (2011:478), this interaction is classified as a level 1 interaction, which is potentially severe or life-threatening and may require hospitalisation and close clinical monitoring of the patient.

3.7.2.9 Clozapine dosage titration

3.7.2.9.1. Was dosage titration performed from initiation?

Firstly, it was determined whether dosage titration had been performed from initiation. The necessary information was obtained from the prescription chart in the patient's file.

The following categories were provided:

Was dosage titration performed from initiation?	
1	Yes
2	No
3	No information available

3.7.2.9.2 Dosage on day one

The dosage titration performed from initiation was described through obtaining information from the prescription chart pertaining to the initial dosage used, as well as the increments with which the dosage was adjusted.

The following dosages were included on the data collection tool, since it is recommended that clozapine should be initiated using a dosage of 12.5 mg to 25 mg on the first day (Novartis, 2006).

Categories to choose from for the initial dosage used included the following:

Dosage on day 1	
1	12,5 mg
2	25 mg
3	37,5 mg
4	Other
5	No information

3.7.2.9.3 Dosage on day two

The dosage used on the second day, after initiation of clozapine, was recorded on the data collection tool.

The following dosages were included on the data collection tool, since according to recommendations the dosage of clozapine on the second day should be 25 mg to 50 mg (Novartis, 2006).

Categories to choose from for the dosage on day two included the following:

Dosage on day 2	
1	25 mg
2	50 mg
3	75 mg
4	Other
5	No information available

3.7.2.9.4 How was the titration performed within the first 2-3 weeks of initiation?

The necessary information was obtained from the prescription(s) in the patient's file with regard to the various dosages used during the upward titration of clozapine during the patient's last admission at Elizabeth Donkin Hospital.

According to the package insert, if the initial dosage is well tolerated, the daily dose may be increased slowly in increments of 25 mg to 50 mg in order to achieve a dose level of up to 300 mg per day within 2 to 3 weeks (Novartis, 2006).

Consideration was given to the above information in formulating the following categories that were included on the data collection tool:

How was the titration performed within the first 2-3 weeks?	
1	Increments < 50 mg/day
2	Increments of 50 mg/day
3	Increments of > 50 mg/day
4	No information

3.7.2.9.5 Maintenance dose and maximum dose

Information about the maintenance as well as the maximum dosage used was recorded. This information was used to determine the prescribed daily dose as well as the average maintenance and maximum dosage used for the patients in the study sample.

3.7.2.9.6 Record actual titration performed from initiation

Lastly, the actual titration of clozapine for the patient's last admission was reviewed. The following information was obtained from the prescriptions in the patient's file and was recorded on the data collection tool:

- Day within the titration period
- Date
- Dose
- Dosing frequency

The information recorded on the data collection tool to indicate how the actual titration of clozapine was performed, was used to answer the questions regarding the dosages as well as the amount of tablets administered to the patient.

From the above information the maximum/highest dosage used as well as the minimum/lowest dosage used could be determined.

3.7.2.9.7 Calculate the number of tablets administered

The numbers of both 25 mg and 100 mg tablets dispensed during the admission were calculated and recorded on the data collection tool. This information was used to calculate the cost of clozapine therapy received at Elizabeth Donkin Hospital during the patient's admission.

3.7.2.10 Costs for the admission of the patient

Due to the long-term nature of mental disorders the most evident economic burden is that of direct treatment costs (Gelder *et al*., 2009:11). The main goal of a mental health budget should be to provide comprehensive outpatient services oriented toward maintaining remission and improving psychosocial functioning and not for crisis prevention and hospitalisation. There is contradictory evidence in the literature on whether clozapine therapy will result in lower mental health care costs when compared to other antipsychotics (Dipiro *et al*., 2011:1168).

3.7.2.10.1 Cost of clozapine therapy while in hospital

The monetary cost of the clozapine therapy that the patient received during the admission was calculated and recorded.

The cost of the clozapine therapy that each patient received was calculated separately. The patients that were included in the study sample were admitted from 1 December 2010 to 29 February 2012. Therefore, the prices of both 25 mg and 100 mg tablets for each year, i.e. 2010, 2011 and 2012, had to be determined.

After careful consideration, it was decided that the actual prices paid for clozapine tablets ordered from the pharmaceutical depot would be used to calculate the cost of clozapine therapy for each patient. These prices were obtained from the invoices received from the depot for stock delivered to Elizabeth Donkin Hospital Pharmacy.

The following procedure was performed to determine the cost of clozapine tablets:

- Clozapine tablets are available in two strengths, namely, 25 mg and 100 mg.
- Both the 25 mg and 100 mg clozapine tablets are supplied in containers of 100s.
- Six invoices were obtained to identify the price paid each year for both strengths of clozapine.

- One invoice for each year for both tablet strengths of clozapine was obtained, i.e. 2010, 2011 and 2012 price per container of 25 mg tablets, as well as 2010, 2011 and 2012 price per container of 100 mg tablets.

The following table summarises the prices for each strength of clozapine tablet as obtained from the invoices:

Table 3.2 Price of clozapine tablets (100s)

Year	Price of clozapine 25 mg (100s)	Price of clozapine 100 mg (100s)
2010	R 57.56	R125.76
2011	R 36.52	R 112.78
2012	R 36.55	R 113.33

Since the tablets come in containers of 100 the price per individual tablet had to be calculated.

The price per 25 mg as well as per 100 mg tablet was calculated as follows:
e.g. R 57.56 ÷ 100 = R 0.58 per 25 mg tablet

Table 3.3 below indicates the price per 25 mg and per 100 mg tablet for each of the years included in the analysis.

Table 3.3 Price per clozapine tablet

Year	Clozapine 25 mg price per tablet	Clozapine 100 mg price per tablet
2010	R 0.58	R 1.23
2011	R 0.37	R 1.13
2012	R 0.37	R 1.13

The prices supplied in the table above were used to calculate the cost of clozapine therapy for each individual patient, through multiplying the cost per tablet by the amount of each tablet dispensed.

The price used to calculate the cost of therapy depended on the year in which the patient was admitted at Elizabeth Donkin Hospital, i.e. 2010/ 2011/ 2012.

The total cost of clozapine therapy also included the cost of tablets dispensed to the patient upon discharge from Elizabeth Donkin Hospital.

An example is provided below of how the cost was calculated:
e.g. **Patient 16** was admitted in 2011

24 x 25mg tablets as well as 45.5 x 100 mg tablets were dispensed during the admission of the patient.

A: Cost of 25 mg tablets dispensed = Number of tablets x Price/tablet
= 24 x R0.37
= R 8.88

B: Cost of 100 mg tablets dispensed = 45.5 x R 1.13
= R 51.42

C: Cost of clozapine tablets dispensed during admission = **A** + **B**
= R 8.88 + R51.42
= R60.30

Two week treatment taken out (TTO) medication dispensed which included 28 x 100 mg tablets

D: Cost of TTO dispensed upon discharge = Number of tablets x price/tablet
= 28 x R1.13
= R31.64

Total cost of clozapine therapy = **C** + **D**
= R60.30 + R31.64
= R91.94

Thus the total cost of clozapine therapy for this patient was R 91.94.

The same formula was used to calculate the cost of clozapine therapy received for the other patients in the study sample.

3.7.2.10.2 Cost of hospital stay for this admission

The finance office at Elizabeth Donkin Hospital was contacted to obtain an estimate price for the patient per day expenditure for 2010, 2011 and 2012.

The following table summarises the cost of admission per patient per day for each of the years included in the analysis.

Table 3.4 Cost per patient per day

2010	R 1268.33/day
2011	R 1159.08/day
2012	R1732.97/day

The monetary cost of the hospital stay for every individual patient was calculated by multiplying the cost per day by the number of days that the patient spent in hospital.

An example is provided below of how the cost was calculated:

e.g. **Patient 16** was admitted for 50 days in 2011

= 50 x R 1159.08

= R 57 954.00

Thus the total cost for the hospital stay for this patient was R 57 954.00.

The same formula was used to calculate the cost of a hospital stay for the other patients in the study sample.

3.7.2.10.3 Cost of laboratory investigations performed

The monetary cost of the laboratory investigations performed during the admission of the patient was calculated as follow:

- The cost of performing a white blood cell count, fasting plasma glucose, total cholesterol, triglycerides and high-density lipoprotein (HDL) laboratory test during 2010, 2011 and 2012 respectively, was obtained from the National Health Laboratory Service (NHLS, 2012).

- These are the prices that medical aid companies would pay.
- The tender prices that government hospitals would pay could not be disclosed to the researcher.

Table 3.5 below summarises the prices charged for laboratory investigations performed for each of the years that were included in the analysis.

Table 3.5 Prices charged for laboratory investigations

	2010	**2011**	**2012**
White blood cell count (WBC)	R 17.40	R 17.00	R 18.00
Fasting plasma glucose	R 34.90	R 33.00	R 36.40
Cholesterol (total)	R 51.40	R 49.00	R 53.60
Triglycerides	R 76.30	R 73.00	R79.50
HDL-cholesterol	R 66.50	R 70.40	R 69.10

The monetary cost of the laboratory tests performed for every individual patient was calculated by multiplying the cost per test by the number of tests performed while the patient was in hospital.

An example is provided below of how the cost was calculated:
e.g. **Patient 16** was admitted in 2011
The following laboratory investigations were performed:

4 x WBC while on clozapine
= 4 x R17.00
= R 68.00

Thus the total cost for laboratory investigations performed for this patient during his/her admission in hospital was R68.00.

The same formula was used to calculate the cost of laboratory tests performed for the other patients in the study sample.

3.7.2.10.4 Total cost of this admission in hospital

The total monetary cost of the admission of the patient in hospital was calculated as the sum of the other three mentioned costs.

An example is provided below of how the total cost of admission was calculated:

Total cost of admission for **patient 16**

= Cost of clozapine therapy + Cost of hospital stay + Cost of laboratory investigations

= R91.94 + R 57 954.00 + R 68.00

= R 58 113.94

3.7.2.11 Prescriber

3.7.2.11.1 Who prescribed clozapine?

Information was gathered from the patient's file to determine whether clozapine was initiated by a psychiatrist or by a medical officer.

This was included on the data collection tool, since according to the Standard Treatment guidelines: Hospital Level Adults (Department of Health, 2012:298) a psychiatrist should initiate clozapine.

The following categories were provided on the data collection form:

Prescriber	
1	Medical Officer
2	Psychiatrist
3	Unknown

3.7.2.11.2 If prescribed by a medical officer, did he/she consult with a psychiatrist?

If clozapine was initiated by a medical officer, it was determined from evidence within the patient's file, whether a psychiatrist was consulted before clozapine was prescribed.

Was a psychiatrist consulted?	
1	Yes
2	No
3	No information available

3.7.2.12 Adverse effects

The adverse effects of clozapine make it one of the most challenging medications to prescribe (Schatzberg & Nemeroff, 2004:448).

3.7.2.12.1 Adverse effects reported

Information was obtained from the doctor's notes in the patient's file to establish whether the patient experienced any side effects that may be attributed to clozapine.

The following categories were included on the data collection tool:

Adverse effects reported	
1	Yes
2	No
3	No information

3.7.2.12.2 Which adverse effects were reported?

Since clozapine is known to have quite a severe side effect profile, the following categories were included on the data collection tool (Novartis, 2006; Rossiter, 2012:475; Taylor *et al*., 2012:76).

If the patient experienced any side effects, it was indicated on the list provided, which ones was applicable in the particular patient's case.

Which adverse effects were reported?	
1	Agranulocytosis
2	Hypersalivation
3	Constipation
4	Hypertension
5	Weight gain
6	Nausea
7	Fever
8	Hypotension
9	Seizures
10	Tachycardia
11	Not applicable
12	Other

3.7.2.12.3 Were the adverse effects treated and how were they treated?

It was determined whether the patient received any treatment for the adverse effects that he/she experienced. Information was also gained from the patient's file on how these adverse effect(s) were treated.

These categories were included on the data collection tool:

Was the adverse effect treated and how was it treated?	
1	Yes
2	No
3	Not applicable
4	No information available

If ‘yes’ specify how the adverse effects were treated:

Information was provided on the data collection tool on the treatment prescribed for adverse effects experienced by the patient as a result of clozapine therapy.

3.7.2.13 Baseline monitoring

3.7.2.13.1 Haematological monitoring

It was determined from the laboratory results in the patient’s file whether screening was performed to determine the baseline white blood cell count (WBC).

The date on which the test was performed as well as the result obtained was recorded on the data collection tool.

3.7.2.13.2 Metabolic monitoring

It was determined from the laboratory results in the patient’s file whether screening was performed to establish the levels of the following baseline metabolic markers:

- fasting plasma glucose
- fasting lipogram, including:
    - total cholesterol
    - low-density lipoprotein (LDL)
    - high-density lipoprotein (HDL)
    - triglycerides

The date and the result obtained from the laboratory investigation performed were recorded.

It was also determined whether the patient’s baseline weight, height, waist circumference and BMI (body mass index) were calculated. The date when the measurement was performed as well as the findings was recorded on the data collection tool.

3.7.2.14 Follow-up monitoring

3.7.2.14.1 Haematological monitoring

According to the package insert and the Maudsley Prescribing Guidelines in Psychiatry after a patient was initiated on clozapine the WBC count need to be monitored weekly for the first eighteen weeks of therapy thereafter twice weekly for the remainder of the year. From the second year onwards the WBC count should be monitored every four weeks if the patient is still on clozapine therapy (Novartis, 2006; Taylor *et al*., 2012:93).

It was determined whether follow-up haematological monitoring was performed. This was done through reviewing the results of WBC count tests that were performed. The date on which the test was performed as well as the result obtained was recorded on the data collection tool.

3.7.2.14.2 Metabolic monitoring

It was determined whether follow-up metabolic monitoring was performed. The date on which a laboratory investigation for a particular metabolic marker was performed, as well as the result obtained, was recorded on the data collection tool. The dates and results obtained from measurements performed (e.g. weight and waist circumference) were also recorded.

3.7.2.15 Extent of compliance with the guidelines for WBC count monitoring

3.7.2.15.1 Baseline monitoring

According to the package insert and National Health Service (NHS) Foundation Trust guidelines, baseline WBC count monitoring should be performed not more than 10 days prior to the initiation of clozapine (Novartis, 2006; Riley, 2011:54).

Therefore, if the results of baseline investigations performed were older than 10 days than the date on which clozapine was initiated, it was considered as if no baseline investigation(s) had been performed. This would mean that even though baseline white

cell count monitoring was performed, it did not comply with the recommended guidelines for haematological monitoring of clozapine. The actual baseline monitoring performed, if any, was compared with the recommended guidelines for the haematological monitoring of clozapine, to determine the level of compliance with the guidelines.

The following categories were available to choose from:

Compliance with the recommended guidelines for baseline WBC count monitoring	
1	Fully compliant
2	Non-compliant
3	No information available

3.7.2.15.2 Follow-up monitoring

The dates on which the follow-up WBC count was performed were evaluated against the mandatory guidelines for follow-up haematological monitoring of clozapine. The compliance with the recommended guidelines was established and recorded as such on the data collection tool.

A grace period of 1 day before or 1 day after the actual date on which the laboratory investigation should have been performed, was granted and applied as such in the process of determining the level of compliance with the guidelines.

It was also taken into consideration when there was a break in the monitoring period, due to a patient being absent from hospital.

Reasons for being absent included the following:

- if a patient went out on weekend leave for a few days or
- if a patient was transferred to another hospital for a short period of time to receive specialised medical care that could not be provided at Elizabeth Donkin Hospital or
- if a patient absconded and had to be brought back to hospital.

The following categories were available on the data collection tool to describe the extent of compliance with the recommended guidelines:

Compliance with the recommended guidelines for follow-up WBC count monitoring	
1	No information available
2	Fully compliant
3	Non-compliant
4	Not applicable, since patient was admitted in hospital for less than one week

3.7.2.16 Extent of compliance with the guidelines for metabolic monitoring

3.7.2.16.1 Baseline monitoring

Currently, there is no guideline available with regard to the time frame in which baseline metabolic investigations need to be performed, but it is of clinical opinion that baseline results older than 10 days cannot be considered when a patient is initiated on clozapine (Esterhuysen, 2011).

The actual baseline monitoring performed, if any, was compared to the recommended guidelines for the metabolic monitoring of clozapine to determine the level of compliance with the guidelines.

The following categories were available to choose from:

Compliance with the recommended guidelines for baseline metabolic monitoring	
1	Fully compliant
2	Non-compliant
3	No information available

3.7.2.16.2 Follow-up monitoring

The actual follow-up monitoring performed, if any, was compared with the recommended guidelines for the metabolic monitoring of clozapine to determine the level of compliance with the guidelines.

A grace period of one day before or one day after the actual date on which the laboratory investigation should have been performed, was granted and applied as such in the process of determining the level of compliance with the guidelines.

The following categories were provided on the data collection tool:

Compliance with the recommended guidelines for follow-up metabolic monitoring	
1	No information available
2	Fully compliant
3	Non-compliant
4	Not applicable, since patient was admitted in hospital for less than one week

3.7.2.17 Follow-up care after discharge

The name of the clinic where the patient was sent for follow-up visits, or the name of the long-term care facility where the patient was sent to receive further treatment was obtained from his/her discharge note and recorded on the data collection tool.

Patients at Elizabeth Donkin Hospital are either discharged to a community psychiatric clinic for follow-up visits or in cases where additional therapy is required, they are transferred to a long-term care institution after discharge.

There are 11 clinics in the Nelson Mandela Metropole to which patients are discharged. At the moment there are two long-term care facilities to which patients can be transferred, i.e. Kirkwood Care Centre and Tower Hospital.

For the purpose of this study both the 11 community psychiatric clinics and the two long-term care centres will be referred to as ‘facilities’ to which the patients were discharged.

3.7.2.18 Point of monitoring upon discharge

From the discharge note of the patient it was determined whether it was communicated to the facility, to which the patient was discharged, where in the process the WBC monitoring currently is, so that the follow-up monitoring could be continued correctly.

The following categories were provided on the data collection tool:

Was it indicated on the discharge note where in the process the WBC count monitoring currently is?	
1	Yes
2	No

A copy of the data collection tool that was used is attached as ***Appendix B****.*

3.7.3 Questionnaires

Two questionnaires were designed, a three-month follow-up questionnaire as well as a six-month follow-up questionnaire. The questionnaires were developed to gather information on how the follow-up haematological and metabolic monitoring of clozapine is managed after discharge of the patient. The questionnaires were aimed at the nursing staff working in the clinics and long-term care centres. It was decided to obtain first-hand information directly from them, rather than to develop another data collection tool for the researcher to gather data for the follow-up investigation.

3.7.3.1 Testing of questionnaires

The initial three-month and six-month follow-up questionnaires were used to establish whether any discrepancies could be detected with any of the questions that appeared in the questionnaires. Testing of questionnaires may reveal that the reading level is not appropriate for the intended target group, that some questions are unclear or that some of the instructions are unclear (Dawson & Trapp, 2004:289).

A large sample is not required to test the measuring instruments to be used in the study but it is more important to choose people who will provide feedback after completing the questionnaire (Dawson & Trapp, 2004:289).

Both initial versions of the three-month and six-month questionnaires were administered to five nursing sisters working at Elizabeth Donkin Hospital. Testing of the initial questionnaires was specifically aimed at the nursing staff working at the hospital, since the questionnaires were intended for nursing staff working at the community psychiatric clinics as well as long-term care centres.

None of the nursing staff members at Elizabeth Donkin Hospital participated in the final research study. Overwhelmingly positive feedback was received from the five nurses that completed the initial questionnaires and no major changes had to be made to any of the questions that appeared in both questionnaires.

3.7.3.2 Three-month follow-up questionnaire

The first questionnaire, hereafter referred to as the *three-month follow-up questionnaire*, was developed to determine the level of monitoring performed during a three-month interval after discharge from hospital.

After approval was obtained to conduct research in the clinics and long-term care facilities, the matron in charge at each facility was contacted. Appointments were arranged and the researcher then visited each facility. Collective administration was the chosen method used for administering the questionnaires.

At each facility a group of registered nurses who were willing to participate in the completion of the questionnaires was selected. Each registered nurse had to fill in at least one questionnaire. In most cases the questionnaire was either completed by a nursing sister working in the ward of the long-term care centre in which the patient was admitted, or if the patient was discharged to a clinic, by a registered nurse that usually examined the patient when he/she attended the clinic for follow-up visits. Only one three-month follow-up questionnaire had to be filled in for each patient.

The researcher went through the questions in the questionnaires with the nurses to clarify any uncertainties. The nurses then filled in the questionnaires and had to return them to the matron's office.

Each patient was assigned a unique patient identification number. The identity of the patient was only disclosed to the nurse who filled in the particular patient's questionnaire. Only the patient identification number appeared on the questionnaire and thus no patient names or surnames was recorded on the questionnaire.

Mostly closed-ended questions were asked, since categories were provided after each question from which an answer had to be selected. When conducting questionnaire-based research, it is generally found that respondents prefer shorter surveys above longer surveys (Dawson & Trapp, 2004:285). Therefore only six questions were included in the three-month follow-up questionnaire.

The following criteria were identified and included as questions in the three-month follow-up questionnaire.

Table 3.6 Three-month follow-up questionnaire

Three-month follow-up questionnaire		
Question	**Categories**	**Motivation for inclusion**
Question 1		
Is the above mentioned patient still on clozapine three months after discharge from Elizabeth Donkin Hospital?	1 = Yes 2 = No 3 = No information	This question was included to determine how many patients are still on clozapine three months after discharge from hospital. Thus, a default rate three months after discharge could be calculated.
Question 2		
If answered no, why is the patient no longer on clozapine?	1 = Adverse effects 2 = Non-compliance 3 = No information 4 = Other	Various categories were included in the questionnaire to choose from. From the answers provided in the questionnaires it could then be determined why clozapine therapy had been stopped.
Question 3		
If the patient is still on clozapine what is the current dosage?	This was an open ended question and no categories were provided.	The dosage was recorded on the questionnaire. From these dosages recorded the mean, minimum and maximum dosage used, three months after discharge could be determined. A calculation could also be performed to determine whether the patient is still on the same dosage as which he/she was discharged or whether the dosage increased or decreased.
Question 4		
Did the hospital inform you upon discharge where in the process	1 = Yes 2 = No	It is important that the hospital inform the clinic or long-term care

the patient's WBC count monitoring is?	3 = No information	facility to which the patient was sent, where in the process the monitoring is, so that they can continue with the monitoring correctly.
Question 5		
Currently, how is the follow-up WBC count monitoring performed?	1 = Weekly 2 = Two weekly 3 = Monthly 4 = Other	This question was included in the questionnaire to determine how the haematological monitoring is performed three months after discharge from Elizabeth Donkin Hospital. This information was then used to compare current practice with the guidelines to determine the extent of compliance with the guidelines, for the haematological monitoring performed at the clinics and long-term care centres.
Question 6		
Currently, how is the follow-up metabolic monitoring performed?	1 = Monthly 2 = Two monthly 3 = Three monthly 4 = Other	This question was included in the questionnaire to determine how the metabolic monitoring is performed three months after discharge from Elizabeth Donkin Hospital. This information was then used to determine the extent of compliance with the guidelines, for the metabolic monitoring performed at the clinics and long-term care centres.

The data obtained from questions 5 and 6 of the three-month follow-up questionnaires were then further analysed to determine the following:

Extent of compliance with the recommended guidelines for follow-up haematological monitoring

The data obtained from question 5 were analysed and the following categories were used to express the extent of compliance with the recommended guidelines:

Compliance with the recommended guidelines for follow-up WBC count monitoring	
1	Fully compliant
2	Non-compliant
3	No information available

Extent of compliance with the recommended guidelines for follow-up metabolic monitoring

The data obtained from question 6 were analysed and the following categories were used to express the extent of compliance with the recommended guidelines:

Compliance with the recommended guidelines for follow-up metabolic monitoring	
1	Fully compliant
2	Non-compliant
3	No information available

A copy of the three-month follow-up questionnaire is attached as ***Appendix C.***

3.7.3.3 Six-month follow-up questionnaire

The second questionnaire, hereafter referred to as the *six-month follow-up questionnaire*, was developed to determine the level of monitoring performed during a six-month interval after discharge from hospital.

The same procedure was followed as for the three-month follow-up questionnaire. However, the researcher could not visit the facilities again due to time and cost

constraints. Therefore the researcher contacted the matron at each facility again to request assistance with the completion of the six-month follow-up questionnaires.

The researcher informed the matron about the procedure that had to be followed when completing the questionnaires. The questions asked in the six-month follow-up questionnaire were almost the same as the questions asked in the three-month follow-up questionnaire.

The six-month follow-up questionnaires were then sent to the matron in charge at each facility. A list with the names of the patients that were discharged to the particular facility was also sent to the matron. A sealed envelope was used to ensure patient confidentiality. On the list next to the patient's name a corresponding unique patient identification number was provided that had to be used on the six-month follow-up questionnaire. This was the only method that could be used to identify which questionnaire had to be filled in for which patient. Only the matron and the registered nurse that had to fill in the questionnaire knew the identity of the patient.

The matron then distributed the questionnaires to the registered nurses that voluntarily wanted to participate in the completion of the questionnaires. Only one six-month follow-up questionnaire had to be filled in for each patient. It was not always the same nurse that filled in both the three-month and six-month follow-up questionnaire for a particular patient. At each facility the completed questionnaires had to be returned to the matron's office.

E-mail reminders were sent to the matrons at the facilities and the researcher also performed telephonic follow-ups in an attempt to improve the response rate to the questionnaires.

The completed questionnaires were sent back to the researcher in a sealed envelope. The response rate achieved was 82.0% (n=53).

The following criteria were identified and included as questions in the six-month follow-up questionnaire. Four out of the five questions asked were closed-ended questions,

since categories were provided after each question from which an answer had to be selected.

Table 3.7 Six-month follow-up questionnaire

Six-month follow-up questionnaire		
Question	**Categories**	**Motivation for inclusion**
Question 1		
Is the above-mentioned patient still on clozapine six months after discharge from Elizabeth Donkin Hospital?	1 = Yes 2 = No 3 = No information	This question was included to determine how many patients are still on clozapine six months after discharge from hospital. Thus a default rate six months after discharge could be calculated.
Question 2		
If answered no, why is the patient no longer on clozapine?	1 = Adverse effects 2 = Non-compliance 3 = No information 4 = Other	See question 2 for three-month follow-up questionnaire.
Question 3		
If the patient is still on clozapine what is the current dosage?	This was an open ended question and no categories were provided.	See question 3 for three-month follow-up questionnaire.
Question 4		
Currently, how is the follow-up WBC count monitoring performed?	1 = Weekly 2 = Two weekly 3 = Monthly 4 = Other	This question was included in the questionnaire to determine how the haematological monitoring is performed six months after discharge from Elizabeth Donkin Hospital. The data obtained were then compared with the guidelines to determine the extent of

		compliance with the guidelines for haematological monitoring.
Question 5		
Currently, how is the follow-up metabolic monitoring performed?	1 = Monthly 2 = Two monthly 3 = Three monthly 4 = Other	This question was included in the questionnaire to determine how the metabolic monitoring is performed six months after discharge from Elizabeth Donkin Hospital. This information was then used to compare current practice with the guidelines to determine the extent of compliance with the guidelines for metabolic monitoring.

The data obtained from questions 4 and 5 of the six-month follow-up questionnaires were then further analysed to determine the following:

Extent of compliance with the recommended guidelines for follow-up haematological monitoring

Answers obtained from question 4 were analysed and grouped into one of the following categories to express the extent of compliance with the guidelines.

Compliance with the recommended guidelines for follow-up WBC count monitoring	
1	Fully compliant
2	Non-compliant
3	No information available

Extent of compliance with the recommended guidelines for follow-up metabolic monitoring

Answers obtained from question 5 were analysed and grouped into one of the following categories to express the extent of compliance with the guidelines.

Compliance with the recommended guidelines for follow-up metabolic monitoring	
1	Fully compliant
2	Non-compliant
3	No information available

*A copy of the six-month follow-up questionnaire is attached as **Appendix D**.*

3.7.4 Study variables and study measurements

A summary is provided below of the study variables and study measurements applied in the study.

Table 3.8 Summary of study variables and measurements applied in the study

Study variables	Study measurements
• Age • Gender • Race • Family history • Smoking history • Drug abuse • Surgical history	• Co-morbid disease states • Diagnosis • Positive and negative symptoms • Clozapine dosages • Drug interactions • Cost • Adverse effects • Compliance with the recommended guidelines

3.7.5 Levels of measurement

Different variables in a research study can be at different levels of measurement (Rubin, 2013:23). Generally there are four levels of measurement, namely: nominal, ordinal, interval and ratio. Each level of measurement will be discussed briefly.

3.7.5.1 Nominal measures

According to Rubin (2013:23), nominal-level variables are variables that can be measured only in terms of frequencies. An example of a nominal-level variable is gender. Patients are either male or female and there are not different levels of male or female. Nominal variables vary only in categories that are qualitative in nature.

Examples of nominal variables used in this study include; gender, race as well as diagnosis.

3.7.5.2 Ordinal measures

Ordinal-level variables are variables whose categories can be rank-ordered according to degree, meaning they can be ranked according to how much of that variable they are (Rubin, 2013:24).

An example of an ordinal-level variable found in this study is the number of years past since the first diagnosis of a psychiatric condition was made. The number of years passed since a patient was diagnosed for the first time was grouped under one of the following categories: <1 year ago, ≥ 1 and ≤ 5 years ago, > 5 and ≤ 10 years ago, > 10 and ≥ 15 years ago, > 15 and ≤ 20 years ago and > 20 years ago.

3.7.5.3 Interval measures

The concept of variables at the interval level of measurement refers to variables with differences between different levels but with the same meanings, e.g. the difference in IQ scores of 95 and 100 is considered to be to the same extent as the difference between 100 and 105. Standardized scales, such as the Likert scale, have had norms developed based on very large samples and are about the only type of interval measures that health care practitioners may encounter (Rubin, 2013:25).

In this study the interval level of measurement was not used to measure any variables.

3.7.5.4 Ratio measures

According to Rubin (2013:25), ratio-level variables have the same attributes as interval measures, but in addition have a true zero point.

An example of such a variable is the number of days a patient is hospitalised. Because there is a true zero point we know that the person who has been hospitalised for 36 days has stayed in hospital for twice the number of days compared to a patient who was only hospitalised for 18 days. If one were examining the precise number of days each patient was hospitalised, the number of days hospitalised would be a ratio-level variable.

Regardless of a variable's level of measurement, the method used to measure it should be both reliable and valid (Rubin, 2013:27).

3.7.6 Reliability and validity of the research instruments

Regardless of a variable's level of measurement, the procedure used to measure it should be both reliable and valid (Rubin, 2013:27). Reliability and validity of the research instruments used in this study will be briefly discussed.

3.7.6.1 Reliability

Reliability determines the ability of a measurement instrument to reproduce the same results on repeated administrations (Dawson & Trapp, 2004:285; Sadock *et al*., 2009:759). Hence, reliability refers to the degree to which a measure or result can be replicated (Kumar, 2011:181; Waning & Montagne, 2001:123).

In addition, the reliability of a measurement instrument is demonstrated with more ease when the individuals assessed are clear cases for inclusion in the study (Sadock *et al*., 2009:759).

The following factors may influence the reliability of a research instrument:

- The wording of questions

The reliability of a research instrument can be affected by a slight ambiguity in the wording of questions or statements as the questions may be interpreted differently at different times, resulting in different responses (Kumar, 2011:182).

- The physical setting

Where a research instrument is used during an interview, any change in the physical setting at the time of the repeat interview may affect the responses given by a respondent, which in turn may affect the reliability of the instrument (Kumar, 2011:182).

- The respondent's mood

A change in a respondent's mood when providing answers to a questionnaire may occur and can affect the reliability of the research instrument (Kumar, 2011:182).

The following methods were used to increase the reliability of questions in the questionnaires:

- Special attention was given to ensure that each measure or question indicates only one concept.
- Attention was also given to measuring constructs at the most precise level possible.
- Multiple question items were used for the same constructs in the questionnaires. Different aspects of the construct could therefore be measured, each with its own indicator.
- Different preliminary versions of the questionnaires were drawn up and evaluated by various persons before the final version was compiled.

It is important to note that reliability is not a guarantee of validity (Waning & Montagne, 2001:123). A research instrument can be reliable without being valid. However, it cannot be valid if it is unreliable (Kumar, 2011:181).

3.7.6.2 Validity

Validity refers to the degree to which a measuring instrument measures what it is designed to measure (Dawson & Trapp, 2004:288; Kumar, 2011:177; Sadock *et al*., 2009:760; Waning & Montagne, 2001:123).

There are three types of validity (Kumar, 2011:179):

- Content and face validity
- Criterion validity
- Construct validity

In this study only criterion validity and content and face validity were employed and are therefore discussed below.

- Content and face validity

Content validity is concerned with how well a measurement instrument covers the areas being assessed (Kumar, 2011:180; Sadock *et al*., 2009:760). Content validity depends on the population that the instrument was designed for as well as the chosen method for data collection (Sadock *et al*., 2009:760). Content validity cannot be empirically measured, but should be assessed by expert consensus after careful investigation of the characteristics of the construct that is being measured as well as by comparing the measurement instrument with other instruments that may be available (Sadock *et al*., 2009:760).

The judgement that a research instrument is measuring what it is supposed to is primarily based upon the logical link between the questions and the objectives of the study (Kumar, 2011:179). Each question or area under investigation on the research instrument must have a logical connection with at least one of the objectives of the study. Face validity refers to the establishment of this link (Kumar, 2011:180).

Content validity therefore indicates the degree to which the items on the data collection tool and in the questionnaires are representative of the knowledge being tested or the

characteristic being investigated. The questionnaires or survey form should thus include questions related to the issue under investigation.

In this study both exploratory and semi-structured interviews were held with different experts in the fields of psychiatry and pharmacy.

Formal interviews were conducted with two of the psychiatrists employed at Elizabeth Donkin Hospital to establish whether the relevant questions were included on the data collection tool with regard to the medical history of the patient. The study was retrospective in design, and therefore this would not have any influence on the results obtained.

Informal interviews were also held with different role-players in the public health care sector of South Africa. They were pharmacists and nursing staff employed at other government institutions in the area. These institutions were not included in the research study and therefore had no influence on the results obtained.

The contents of the questionnaires and data collection tool were also evaluated by various persons with experience in pharmaceutical research. These included the supervisors and co-supervisors of the study.

A number of people were consulted during the development phase to judge the face-validity of the questionnaires and data collection tool. These included a statistician as well as the supervisor and co-supervisors of the study currently employed at North-West University.

- Criterion validity

"Criterion validity assesses the measurement instrument in relationship to a factor that is external to the measurement, known as the criterion" (Sadock *et al*., 2009:760).
In certain circumstances where a scale is developed as an indicator of some observable criterion, the scale's validity can be investigated by seeing how good an indicator it is (Kumar, 2011:180).

The result of certain questions is validated with some criterion external to the study. Certain questions which relate to statistics regarding the gender of patients as well as the costs associated with psychiatric treatment were compared with 'gold standards' available in the literature. Compliance with the recommended clinical guidelines was measured through allowing a 10-day grace period in which baseline observations had to be performed before the initiation of clozapine (Esterhuysen, 2011; Novartis, 2006; Riley, 2011:54). If baseline monitoring was performed more than 10 days prior to the initiation of clozapine, it was stated that the baseline monitoring was non-compliant with the recommended guidelines.

The actual follow-up monitoring performed, if any, was compared with the recommended guidelines for the metabolic monitoring of clozapine to determine the level of compliance with the guidelines. Compliance with the recommended clinical guidelines was measured through granting a grace period of 1 day before or 1 day after the actual date on which the laboratory investigation should have been performed (Esterhuysen, 2011).

3.7.6.3 Methods employed to ensure reliability and validity of the research instruments

Specific methods were used to ensure the reliability and validity of the surveys used in this study. One of the most important disadvantages of using questionnaires is the possibility of ambiguity in the phrasing of questions and thus that respondents can interpret questions in ways not intended by the researcher (Kumar, 2011:182).
Although specific methods were implemented to make sure that questions and terms used in questionnaires would be understood by the target group, it is important to remember this disadvantage during the interpretation of the results. Persons of different backgrounds were used to review the preliminary versions of the two questionnaires, namely pharmacists in practice (4), pharmacists at academic institutions (3), psychiatrists (2), nursing staff (4) and a statistician. These persons were specifically asked to review the physical layout of the questionnaires, the content of questionnaires, phrasing of questions, and completeness of the questionnaires. They were also asked to give comments and recommendations on the construction of the questionnaires. The shortcomings identified by the reviewers were rectified in the final questionnaires.

3.8 IMPLEMENTATION PLAN

Firstly, the researcher had to determine whether a register is kept at Elizabeth Donkin Hospital that contains the details of all the patients that were initiated and treated on clozapine. It was found that in fact no register was kept and therefore discharge forms had to be collected for the determined study period to identify the patients to be included in the study sample.

Secondly, an investigation had to be performed to determine whether a set protocol is available for the initiation and monitoring of clozapine at Elizabeth Donkin Hospital. It was found that no specific guidelines or protocols are used for the initiation and monitoring of clozapine at the hospital. Most prescribers used international guidelines which are not specifically adapted for the South African setting. The possible presence of insufficient monitoring practice was identified and had to be investigated in the study.

Hence, the data collection tool and questionnaires that were designed were implemented and used in the collection of data for the study.

3.8.1 Data collection methods

Data were collected as previously mentioned and described through the use of data collection forms and questionnaires. The data collection forms were used to obtain information from patient files at Elizabeth Donkin Hospital. The questionnaires completed by nurses in the community psychiatric clinics and long-term care centres were used to obtain information about the patient after discharge from hospital. Details about the procedure used and the criteria applied in the data collection process are outlined in the research method section.

Before any data were collected, a letter requesting permission to collect data at the particular facility was sent to the facility manager. The exact process followed to obtain approval to collect patient data at the various facilities was discussed in the section on data requisition. Data could only be collected after approval was granted by the facility managers.

The recording of information on the data collection form was done by the primary investigator of the study. The data collection process first started after ethical approval had been received. Data were collected from 8 May to 31 August 2012 from the files of patients at Elizabeth Donkin Hospital.

The three-month follow-up questionnaires were distributed to the clinics from 1 July until 7 July 2012. The questionnaires were also taken to Kirkwood Care Centre on 11 July 2012 and to Tower Hospital on 12 July 2012. All the completed questionnaires were returned to the researcher by 31 July 2012. The researcher received one completed three-month questionnaire for each patient.

The six-month follow-up questionnaires were distributed to the clinics from 1 September 2012 to 15 September 2012. The questionnaires were also sent to Kirkwood Care Centre on 20 September 2012 and to Tower Hospital on 21 September 2012. All the completed six-month questionnaires were returned to the researcher by 10 October 2012. One completed six-month questionnaire per patient was received.

3.8.2 Data capturing and data editing

3.8.2.1 Data collection tool

The data recorded on the data collection forms were captured in an Excel spreadsheet using the programme Microsoft Office Excel® 2007.

Columns were included in the Excel spreadsheet for every criterion investigated on the data collection form. The data obtained from the data collection tool were then captured in the corresponding column on the Excel spreadsheet.

Data were captured from 1 September 2012 up to 30 September 2012. The data in the Excel spreadsheet were then exported to the computer programme SAS® 2012 version 9.3 for statistical analyses (SAS, 2012).

3.8.2.2 Three-month and six-month follow-up questionnaires

The same procedure was followed for data obtained from the three-month and six-month follow-up questionnaires. However, data from the two questionnaires were captured in separate Excel spreadsheets.

Data were captured from 16 September 2012 up to 15 October 2012. Then once again, the data in the Excel spreadsheet were exported to the computer programme SAS® 2012 version 9.3 for statistical analyses (SAS, 2012).

3.8.3 Data coding

Data coding can be defined as "converting data to a machine-readable format by assigning a code number or a code letter to each category of a variable" (Rubin, 2013:330). A numerical classification system was used to code the data and a codebook was developed. A codebook can be defined as "a document that identifies the location of each variable in a data file and the codes that apply to each attribute for each variable" (Rubin, 2013:330). Thus, numerical values were assigned to the categories provided as possible answers to the questions that appeared on the data collection form and in questionnaires.

Not all the possible answers could be provided as categories to choose from on the data collection tool and questionnaires. If an answer was provided that did not appear as a category on the data collection tool or questionnaires, it was also given a numerical value and hence coded. These answers were mostly supplied under the category "other" that was provided as an option to choose from when supplying answers for a criterion being investigated.

Data coding was used as an aid in the analysis of data. An example is provided below of how the data coding procedure was performed.

The following was extracted from the data collection form as an example:

Race	White	African	Coloured	Indian	Other:

The data recorded on the data collection form were coded as follow, before it were captured on an Excel spreadsheet:

Categories provided	**Data Code**
White	1
African	2
Coloured	3
Indian	4
Other	5

3.9 STATISTICAL ANALYSIS

Descriptive statistics were used to provide a description of the data obtained from both the data collection tool as well as the three-month and six-month follow-up questionnaires.

Descriptive statistics can be defined as “statistics that organise, summarize, and display the data collected in a particular study without trying to develop inferences beyond the sample or trying to rule out sampling error in hypothesis testing” (Rubin, 2013:331).

The programme SAS® 2012 version 9.3 was used to perform the data analyses (SAS, 2012). Frequency distributions, measures of central tendency (e.g. mean and median), confidence intervals and standard deviations were calculated to summarise the ordinal and ratio data. Nominal data were summarised using frequency distributions and cross-tabulations. In each of the cross-tabulations the row percentage and column percentage were calculated.

In some cases the extreme values, i.e. outliers, could be identified through assessing the frequency distributions of the measured variables. The trimmed mean could then be used to summarise the data. The trimmed mean is the calculation of the mean without taking the outliers at both the high and low ends of the distribution into consideration, when those outliers make up a very small percentage of the distribution (Rubin, 2013:338). The frequency distributions were used to perform data cleaning. Data cleaning is the process of identifying and correcting data entry errors.

The chi-square test, a non-parametric statistical test, was performed to draw conclusions from the nominal data. The chi-square test assesses the probability that sampling error explains the relationships we observe between nominal-level variables displayed in cross-tabulation tables (Rubin, 2013:190).

According to Rowe (2007:85), a result can be said to be statistically significant when the probability is that the observed relationship or a difference in a sample occurred by pure chance and that in the population from which the sample was drawn, no such relationship or difference exists. In essence, statistical significance indicates the degree to which the result being analysed is an accurate representation of the population.

SAS® was also used to calculate the *p*-value (SAS, 2012). The *p*-value of an analysis is calculated in order to determine whether a result is statistically significant. The *p*-value can thus be used as a measure of the strength of the evidence obtained, the lower the *p*-value, the more unlikely it is that the results would arise by sheer chance and so the stronger the evidence (Rowe, 2007:84).

When the *p*-value of an analysis is 0.05 it is indicative that there is a 5.00% probability that the relation between the variables being assessed in the sample happened by chance and the analysis is considered to be borderline statistically significant (Rowe, 2007:85). A result is said to be significant when $p < 0.05$ and highly significant when $p < 0.001$ (Rowe, 2007:131). Results are classified as being non-significant when there is insufficient evidence to require any change (Rowe, 2007:131).

Cramér's V is based on the chi-square statistic and was calculated in order to ascertain whether a particular finding was of practical significance. The Cramér's V value is an

effect size measure and is defined as “a non-parametric correlation statistic used when both variables are nominal and at least one has more than two categories” (Rubin, 2013:330).

The following table illustrates the different Cramér’s V values and their interpretation (adapted from Parker & Rea, 2005:255).

Table 3.9 Cramér’s V value and interpretation

CRAMÉR’S V VALUE	**INTERPRETATION**
0.00 – 0.09	Negligible association
0.10 – 0.19	Weak association
0.20 – 0.39	Moderate association
0.40 – 0.59	Relatively strong association
0.60 – 0.79	Strong association
0.80 – 1.00	Very strong association

The *p*- and Cramér’s V values and interpretations were used during the analysis and discussion of the results of the study. The study findings are described and discussed in Chapter Four.

3.10 ETHICAL CONSIDERATIONS

The research proposal was submitted to the Research Ethics Committee of the North-West University and approval was granted on 4 May 2012 under ethics number: NWU-0003-12-A2. The final letter of approval is attached as ***Appendix E***. The project title and proposal were accepted on 14 October 2011 by the Faculty of Health Sciences at North-West University.

The research proposal was submitted to the Elizabeth Donkin Hospital Research Committee on 2 August 2011 in order to conduct research at the hospital. The research proposal was approved by the committee on 8 May 2012, following ethical approval.

An application was also submitted to the Eastern Cape Department of Health Research Committee on 22 June 2012. See letter attached as ***Appendix F.***

Approval was received from the Deputy Director of Epidemiological Research and Surveillance Management on 29 June 2012. Approval letter attached as ***Appendix G***.

3.10.1 Data requisition letters sent to facilities

- A letter of intention to conduct research on the use of clozapine at Elizabeth Donkin Hospital was submitted on 21 July 2011 to the chairperson of the research committee at the hospital.
  *See **Appendix H** attached.*

- The researcher was then requested to perform a presentation on the research proposal for the proposed study at a research committee meeting held on 2 August 2011. Preliminary approval was granted provided that ethical approval would be obtained. Final approval was granted on 8 May 2012, following ethical approval.
  *See **Appendix I** attached.*

- A letter requesting permission to conduct research on the monitoring of clozapine performed at the clinics was sent to the District Manager of the Nelson Mandela Bay Health District on 12 May 2012.
  *See **Appendix J** attached.*

- On 17 May 2012 approval was received from the District Manager to collect data at the community psychiatric clinics in the Nelson Mandela Metropole.
  *See **Appendix K** attached.*

- Letters were also sent to the Hospital Managers at the two long-term care centres i.e. Tower Hospital and Life Esidimeni.
  *See **Appendix L** and **Appendix M** attached.*

- Approval was received on 3 July 2012 to conduct research at Life Esidimeni – Kirkwood care centre, a private care institution situated in Kirkwood.
  *See **Appendix N** attached*.

- Approval was also received on 11 July 2012 to collect data at Tower Hospital, a public sector long-term psychiatric hospital situated in Fort Beaufort.
  *See **Appendix O** attached.*

3.10.2 Confidentiality

The main ethical consideration of the study was patient as well as prescriber confidentiality. Patient confidentiality was maintained at all times and no patient name or file number was used on any documentation. Each patient was assigned a unique patient identification number which was used on documentation. No patients were contacted or interviewed for the purpose of research. The collection of data from the patients' files was done by the primary investigator of the study. The primary investigator is an employee at the hospital at which the study was conducted. No field workers were used at any stage of the data collection process.

It was determined that informed consent was not necessary, since the patients included in this study was not contacted or interviewed and no changes were made to the patients' current treatment. This study also had no advantages or disadvantages for the patient, although services in the future may change after an educational intervention has taken place.

No prescribers were contacted or identified during the study. Therefore, the identity of the patients and prescribers in the study has been protected and will also remain protected after the completion of the study.

The data collected for this study will be kept for a period of five years. The survey forms are locked in a cupboard and only the primary investigator has access to the data.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association, 2008).

3.11 CHAPTER SUMMARY

This concludes the methodology chapter. The exact methodology employed in performing this study was outlined fully in this chapter. The ethical considerations as well as patient confidentiality were discussed in detail. In the following chapter the results of the study will be reported.

CHAPTER 4

RESULTS AND DISCUSSION

4.1 INTRODUCTION

In this chapter the results of the study are reported. This include the results obtained from the data collection tool, three-month and six-month follow-up questionnaires.

The results will be analysed under two subdivisions namely, data collection tool (refer Appendix B) and questionnaires (refer Appendix C and D).

Please note that the results displayed as percentages in the tables below were rounded off to two decimal places. The results displayed as percentages in the graphs were rounded off to the nearest integer.

4.2 DATA COLLECTION TOOL

The data collection tool was used as a survey form to gather the necessary data from the 65 patients included in this study.

An analysis was carried out to investigate the prescribing and monitoring patterns of clozapine at Elizabeth Donkin Hospital in the Nelson Mandela Metropole and the results of the investigation are reported below.

4.2.1 Demographics

The first set of results outlined the demographical configuration of the study sample.

4.2.1.1 Age

The following table indicates the age distribution of the study sample. Age categories were used to simplify the interpretation of the results.

Table 4.1 Age distribution of the study sample (N=65)

Age categories	n	Percent (%)
13 and < 18 yrs	3	4.62
≥ 18 and < 31 yrs	25	38.46
≥ 31 and < 51 yrs	26	40.00
≥ 51 and < 65 yrs	11	16.92
≥ 65 yrs	0	0
Total	**65**	**100**

From the results it is clear that most patients in the study sample were between 31 and 50 years of age (n=26, 40.00%). The results showed that the mean age of the study sample was 35.22 ± 12.94 years.

The youngest patient was 16 years old and the oldest was 64 years of age. Emphasis needs to be placed on the fact that there was no patient older than 65 years of age discharged on clozapine.

4.2.1.2 Gender

The following figure indicates the results for the gender distribution of the study sample.

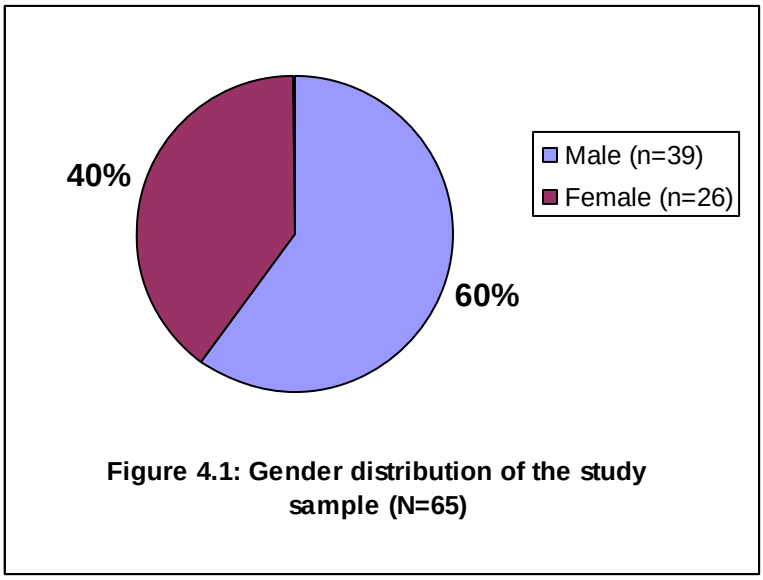


Figure 4.1: Gender distribution of the study sample (N=65)

From the results it is clear that most patients included in the study were in fact males (n=39, 60.00%).

4.2.1.3 Age by gender

The following table summarises the age by gender distribution for the study sample.

Table 4.2 Age by gender (N=65)

Age categories	Gender		Total (n)
	Male (n)	Female (n)	
13 and < 18 yrs	2 (66.67%)	1 (33.33%)	3 (100.00%)
≥ 18 and < 31 yrs	20 (80.00%)	5 (20.00%)	25 (100.00%)
≥ 31 and < 51 yrs	13 (50.00%)	13 (50.00%)	26 (100.00%)
≥ 51 and < 65 yrs	4 (36.36%)	7 (63.64%)	11 (100.00%)
Total	39 (100.00%)	26 (100.00%)	65 (100.00%)

From the results it is clear that most male patients were in the age group 18 to 30 years (n=20, 51,28%) of age and most female patients were in the age group 31 to 50 years of age (n=13, 50.00%).

The statistical analysis performed through the chi-square test revealed that the results obtained were in fact significant (p=0.0489) and Cramer's V value (0.3479) showed that there is a moderate association between age and gender in patients using clozapine. The results of the statistical analysis are summarised in Table 4.3.

Table 4.3 Statistical analysis for age by gender (n=65)

Statistic	Value	Probability
Chi-Square	7.8662	0.0489
Cramer's V	0.3479	

4.2.1.4 Race distribution

The following table summarises the results for the race distribution of the study sample.

Table 4.4 Race distribution of the study sample (N=65)

Race	n	%
White	9	13.85
African	39	60.00
Coloured	17	26.15
Indian	0	0
Total	**65**	**100**

The results indicate that most patients included in the study were African (n=39, 60.00%). No Indian patients participated in the study.

4.2.1.5 Age by race

The following table summarises the age by race distribution for the study sample.

Table 4.5 Age by race (N=65)

Age categories	Race			Total (n)
	White (n)	African (n)	Coloured (n)	
13 and < 18 yrs	0 (0.00)	3 (100.00%)	0 (0.00)	3 (100.00%)
≥ 18 and < 31 yrs	1 (4.00%)	20 (80.00%)	4 (16.00%)	25 (100.00%)
≥ 31 and < 51 yrs	5 (19.23%)	11 (42.31%)	10 (38.46%)	26 (100.00%)
≥ 51 and < 65 yrs	3 (27.27%)	5 (45.46%)	3 (27.27%)	11 (100.00%)
Total	9 (100.00%)	39 (100.00%)	17 (100.00%)	65 (100.00%)

From the results it is clear that most African patients were in the age group 18 to 30 years (n=20, 51.28%) of age and most White patients (n=5, 55.56%) as well as Coloured patients (n=10, 58.82%) were in the age group 31 to 50 years of age.

The statistical analysis represented by Cramer's V value (0.2765) indicates that there is a moderate association between age and race in patients on clozapine treatment. The results of the statistical analysis are summarised in Table 4.6.

Table 4.6 Statistical analysis for age by race

Statistic	Value	Probability
Chi-Square	14.9109	0.2463
Cramer's V	0.2765	

4.2.2 Admission history

4.2.2.1 Number of previous admissions

The following figure represents the results for the number of previous admissions for the patients in the study sample.

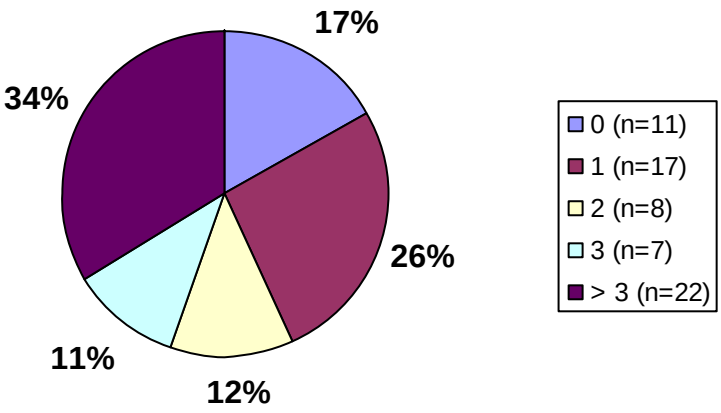


Figure 4.2: Number of previous admissions (N=65)

From the results it is clear that most patients included in the study had more than three previous admissions (n=22, 34.00%) in a psychiatric hospital.

4.2.2.2 Number of previous admissions by age

The following table summarises the number of previous admissions by age distribution for the patients included in the study.

Table 4.7 Number of previous admissions by age (N=65)

Age categories	Number of previous admissions					Total (n)
	0 (n)	1 (n)	2 (n)	3 (n)	> 3 (n)	
13 and < 18 yrs	2 (66.67%)	1 (33.33%)	0 (0.00)	0 (0.00)	0 (0.00)	**3** (100.00%)
≥ 18 and < 31 yrs	4 (16.00%)	6 (24.00%)	4 (16.00%)	3 (12.00%)	8 (32.00%)	**25** (100.00%)
≥ 31 and < 51 yrs	4 (15.38%)	8 (30.77%)	4 (15.38%)	3 (11.54%)	7 (26.92%)	**26** (100.00%)
≥ 51 and < 65 yrs	1 (9.09%)	2 (18.18%)	0 (0.00)	1 (9.09%)	7 (63.64%)	**11** (100.00%)
Total	**11** (100.00%)	**17** (100.00%)	**8** (100.00%)	**7** (100.00%)	**22** (100.00%)	**65** (100.00%)

The results indicate that patients in the age group 31 to 50 years had the most previous admissions (n=22, 40.74%) whereas patients in the age group 13 to 17 years had the least number of previous admissions (n=1, 1.85%).

* Please note that category “0” indicates no previous admissions.

The statistical analysis represented by Cramer’s V value (0.2513) indicates that there is a moderate association between number of previous admissions and age in patients on clozapine treatment. The results of the statistical analysis are summarised in Table 4.8.

Table 4.8 Statistical analysis of number of previous admissions by age

Statistic	Value	Probability
Chi-Square	12.3110	0.4210
Cramer's V	0.2513	

4.2.3 Social history

4.2.3.1 Smoking status

The following table summarises results for the smoking status of the study sample.

Table 4.9 Smoking status of the study sample (N=65)

Smoking status	n	%
Non-smoker	17	26.15
Smoker	39	60.00
No information	9	13.85
Total	**65**	**100**

From the results it is clear that most patients were smokers (n=39, 60.00%).

4.2.3.2 Drug abuse

The following table summarises the results obtained with regard to history of drug abuse amongst the study sample.

Table 4.10 History of drug abuse (N=65)

Illicit drug	n	%
None	13	20.00
Alcohol	16	24.62
Cannabis	2	3.08
Methamphetamine	1	1.54
No information	7	10.77
Alcohol and cannabis	17	26.15
Cannabis and methaqualone	2	3.08
Alcohol, cannabis and methaqualone	5	7.69
Alcohol, cannabis, methamphetamine and methaqualone	2	3.08
Total	**65**	**100**

The results indicate that most patients abused alcohol (n=40, 61.53%) followed by cannabis (n=28, 43.08%) and then methaqualone which is also known as mandrax (n=9, 13.85%).

4.2.4 Medical history

4.2.4.1 Family history

The table below summarises the results obtained for family history of any disease state(s).

Table 4.11 Family history of disease state(s) (N=65)

Disease state	n	%
None	12	18.46
Hypercholesterolemia	1	1.54
No information	24	36.92
Mental disorder	25	38.46
Breast cancer	1	1.54
Mental disorder and hypertension	1	1.54
Mental disorder and epilepsy	1	1.54
Total	**65**	**100**

From the results it is clear that most patients included in the study had a family history of a mental disorder (n=27, 41.54%). However it was not possible to distinguish between the various types of mental disorders, since limited data were available in the patients' files.

4.2.4.2 Co-morbid disease states

The table below summarises the results obtained for the co-morbid disease states that the patients suffered from.

Table 4.12 Co-morbid disease states (N=65)

Disease state	n	%
None	41	63.08
Hypertension	4	6.15
Hypercholesterolemia	1	1.54
Retroviral disease positive	3	4.62
Pulmonary Tuberculosis	1	1.54
Tuberculosis Meningitis	1	1.54
Anorexia Nervosa	1	1.54
Mental retardation	1	1.54
Organo-axia volvulus	1	1.54
Hypertension and Hypercholesterolemia	1	1.54
Hypertension and Retroviral disease positive	3	4.62
Hypertension and Hypothyroidism	1	1.54
Hypertension and Asthma	1	1.54
Hypertension and Pulmonary Tuberculosis	1	1.54
Retroviral disease positive and Asthma	1	1.54
Retroviral disease positive and obesity	1	1.54
Hypothyroidism and Iron-deficiency anaemia	1	1.54
Hypertension, Hypercholesterolemia and Obesity	1	1.54
Total	**65**	**100**

The results indicate that most patients had a primary diagnosis of a psychiatric condition without any reported co-morbidities (n=41, 63.08%). Please note that category “none” represents no co-morbid disease state.

4.2.4.3 Surgical history

The following table summarises the surgical history of patients included in the study sample.

Table 4.13 Surgical history (N=65)

Surgery performed	n	%
Yes	3	4.62
No	48	73.85
No information	14	21.54
Total	**65**	**100**

The surgical procedures (n=3, 4.62%) noted from the files of patients that participated in the study included: one female patient that had had a hysterectomy and two other females that had undergone sterilization (tubal ligation).

4.2.4.4 Number of years passed since first diagnosis

The following table displays the results for the number of years passed since the first diagnosis of a mental disorder.

Table 4.14 Number of years passed since first diagnosis (N=65)

Number of years ago	n	%
< 1 year ago	5	7.69
≥ 1 and ≤ 5 years ago	11	16.92
> 5 and ≤ 10 years ago	17	26.15
> 10 and ≤ 15 years ago	9	13.85
> 15 and ≤ 20 years ago	5	7.69
> 20 years ago	9	13.85
No information available	9	13.85
Total	**65**	**100**

From the results it is clear that most patients (n=17, 26.15%) were already diagnosed with a mental disorder between six and ten years ago whereas five patients were only diagnosed recently (n=5, 7.69%).

4.2.4.5 Diagnosis

The following table summarises the results for the different diagnoses for the patients included in the study sample.

Table 4.15 Diagnoses distribution of the study sample (N=65)

Diagnosis	n	%
Schizophrenia without subtype mentioned	23	35.38
Bipolar disorder	6	9.23
Schizoaffective disorder	4	6.15
Schizophrenia, disorganised type	11	16.92
Schizophrenia, catatonic type	3	4.62
Schizophrenia, paranoid type	2	3.08
Psychosis due to general medical condition (GMC)	3	4.62
Psychosis not otherwise specified (NOS)	2	3.08
Schizophreniform	1	1.54
Schizophrenia and psychosis due to GMC	2	3.08
Schizophrenia and co-morbid cannabis abuse	2	3.08
Schizophrenia and co-morbid alcohol abuse	2	3.08
Schizophrenia and co-morbid polysubstance abuse	2	3.08

Schizophrenia (disorganised type) and co-morbid polysubstance abuse	1	1.54
Schizophrenia (paranoid type) and co-morbid cannabis abuse	1	1.54
Total	**65**	**100**

The results indicate that most patients had a diagnosis of schizophrenia (n=49, 75.39%) followed by bipolar disorder (n=6, 9.23%) and schizoaffective disorder (n=4, 6.15%).

4.2.4.6 Positive and negative symptoms

The following tables summarise the distribution of positive and negative symptoms amongst the study sample.

Table 4.16 Positive symptoms experienced (N=65)

Symptom	**n**	**%**
None	2	3.08
Hallucinations	9	13.85
Delusions	5	7.69
Hallucinations and delusions	49	75.38
Total	**65**	**100**

From the results it is clear that most patients experienced hallucinations (n=58, 89.23%) followed by delusions (n=54, 83.08%).

Table 4.17 Negative symptoms experienced (N=65)

Symptom	n	%
None	19	29.23
Blunting of affect	18	27.69
Avolition	1	1.54
Other	11	16.92
Blunting of affect and avolition	9	13.85
Blunting of affect and other	2	3.08
Blunting of affect, avolition and other	3	4.62
Avolition and other	2	3.08
Total	**65**	**100**

From the results it is clear that most patients experienced blunting of affect (n=32, 49.23%) followed by avolition (n=15, 23.08%).

4.2.5 Clozapine usage

4.2.5.1 Previous trial of clozapine therapy

The following figure represents the results for the number of patients that received clozapine therapy in the past.

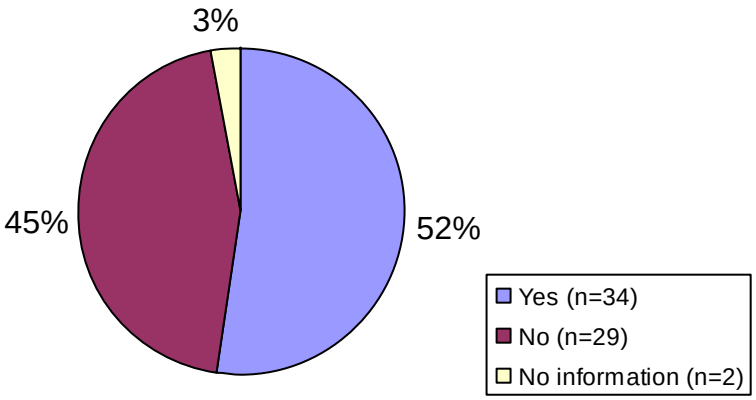


Figure 4.3: Number of patients that previously received clozapine therapy (N=65)

The results indicate that most patients (n=34, 52.30%) received a trial of clozapine prior to current therapy.

4.2.5.2 Availability of the date of first initiation

The following table displays the results obtained regarding the availability of the date of first initiation of clozapine.

Table 4.18 Availability of the date of first initiation (N=65)

Date available	n	%
Yes	56	86.15
No	7	10.77
No information available	2	3.08
Total	**65**	**100**

From the results it is clear that for most patients (n=56, 86.15%) the date of first initiation of clozapine could be found.

4.2.5.3 Number of years passed since first initiation of clozapine

The following table displays the results for the number of years passed since the first initiation of clozapine for the patients.

Table 4.19 Number of years passed since the first initiation of clozapine (N=65)

Number of years	n	%
< 1 year	30	46.15
≥ 1 and ≤ 5 yrs	7	10.77
> 5 and ≤ 10 yrs	11	16.92
> 10 yrs	9	13.85
No information available	8	12.31
Total	**65**	**100**

In most cases (n=30, 46.15%) clozapine therapy was started fairly recently. In only a few cases (n=9, 13.85%) clozapine was initiated more than 10 years ago.

4.2.5.4 Length of stay in hospital after initiation of clozapine

The following table summarises the results for the number of months that the patients received clozapine therapy before being discharged from hospital.

Table 4.20 Length of stay in hospital after initiation of clozapine (N=65)

Length of stay in months	n	%
< 1 month	19	29.23
≥1 and ≤ 3 months	36	55.38
> 3 and ≤ 6 months	5	7.69
> 6 and ≤ 9 months	3	4.62
> 9 and ≤ 12 months	0	0
> 12 months	0	0
No information available	2	3.08
Total	**65**	**100**

From the results it is clear that most patients (n=36, 55.38%) stayed in hospital for a period of one to three months before being discharged from hospital. The average length of stay in hospital was found to be 60.60 ± 50.99 days.

4.2.6 Other drugs

4.2.6.1 Availability of the names of previous antipsychotics

The following table summarises the results regarding the availability of the names of previous antipsychotics.

Table 4.21 Availability of the names of previous antipsychotics (N=65)

Names of previous antipsychotics available	n	%
Yes	64	98.46
No	0	0
No information available	1	1.54
Total	**65**	**100**

The results indicate that for almost all patients (n=64, 98.46%) the names of previous antipsychotics used were available.

4.2.6.2 Previous antipsychotic therapy received

The following table provides the names of other antipsychotics that patients received prior to clozapine therapy.

Table 4.22 Names of previous antipsychotics used (N=65)

Antipsychotics	n	%
No information available	1	1.54
Haloperidol	2	3.08
Haloperidol and Chlorpromazine	1	1.54
Haloperidol and Risperidone	5	7.69
Clozapine and Risperidone	2	3.08
Haloperidol, Chlorpromazine and Risperidone	2	3.08
Haloperidol, Zuclopenthixol decanoate and Risperidone	3	4.62

Haloperidol, Risperidone and Olanzapine	2	3.08
Haloperidol, Fluphenazine decanoate and Risperidone	1	1.54
Haloperidol, Sulpiride and Risperidone	1	1.54
Haloperidol, Zuclopenthixol decanoate and Clozapine	1	1.54
Haloperidol, Chlorpromazine and Zuclopenthixol decanoate	1	1.54
Zuclopenthixol decanoate, Clozapine and Risperidone	1	1.54
Haloperidol, Chlorpromazine, Fluphenazine decanoate and Risperidone	1	1.54
Haloperidol, Sulpiride, Flupenthixol decanoate and Clozapine	1	1.54
Haloperidol, Chlorpromazine, Zuclopenthixol decanoate and Risperidone	1	1.54
Haloperidol, Chlorpromazine, Fluphenazine decanoate and Clozapine	1	1.54
Haloperidol, Zuclopenthixol decanoate, Flupenthixol decanoate and Risperidone	1	1.54
Haloperidol, Chlorpromazine, Sulpiride and Risperidone	1	1.54
Haloperidol, Chlorpromazine, Zuclopenthixol decanoate and Olanzapine	1	1.54
Haloperidol, Chlorpromazine, Fluphenazine decanoate and Zuclopenthixol decanoate	1	1.54
Haloperidol, Zuclopenthixol	1	1.54

decanoate, Clozapine and Risperidone		
Haloperidol, Chlorpromazine, Zuclopenthixol decanoate, Clozapine and Risperidone	4	6.15
Haloperidol, Chlorpromazine, Fluphenazine decanoate, Clozapine and Olanzapine	1	1.54
Haloperidol, Chlorpromazine, Fluphenazine decanoate, Zuclopenthixol decanoate and Risperidone	2	3.08
Haloperidol, Chlorpromazine, Fluphenazine decanoate, Zuclopenthixol decanoate and *Thioridazine	1	1.54
Haloperidol, Chlorpromazine, Fluphenazine decanoate, Clozapine and Clothiapine	1	1.54
Haloperidol, Chlorpromazine, Fluphenazine decanoate, Zuclopenthixol decanoate and Trifluoperazine	1	1.54
Haloperidol, Sulpiride, Fluphenazine decanoate, Risperidone and Olanzapine	1	1.54
Haloperidol, Chlorpromazine, Sulpiride, Zuclopenthixol decanoate and Risperidone	1	1.54
Haloperidol, Chlorpromazine, Fluphenazine decanoate, Zuclopenthixol decanoate and Clozapine	3	4.62
Haloperidol, Chlorpromazine, Zuclopenthixol decanoate, Risperidone and Olanzapine	1	1.54

Haloperidol, Chlorpromazine, Zuclopenthixol decanoate, Clozapine and Clothiapine	1	1.54
Chlorpromazine, Fluphenazine decanoate, Zuclopenthixol decanoate, Clozapine and Trifluoperazine	1	1.54
Zuclopenthixol decanoate, Clozapine, Risperidone, Prochlorperazine and Trifluoperazine	2	3.08
Haloperidol, Chlorpromazine, Sulpiride, Clozapine, Risperidone and Aripiprazole	1	1.54
Haloperidol, Chlorpromazine, Zuclopenthixol decanoate, Flupenthixol decanoate, Risperidone and Olanzapine	1	1.54
Haloperidol, Chlorpromazine, Zuclopenthixol decanoate, Clozapine, Risperidone and Olanzapine	2	3.08
Haloperidol, Zuclopenthixol decanoate, Flupenthixol decanoate, Clozapine, Risperidone and Olanzapine	1	1.54
Haloperidol, Chlorpromazine, Fluphenazine decanoate, Zuclopenthixol decanoate, Clozapine and *Thioridazine	1	1.54
Haloperidol, Chlorpromazine, Fluphenazine decanoate, Zuclopenthixol decanoate, Flupenthixol decanoate and Trifluoperazine	1	1.54
Haloperidol, Chlorpromazine,	2	3.08

Fluphenazine decanoate, Zuclopenthixol decanoate, Clozapine, Clothiapine and Trifluoperazine		
Haloperidol, Chlorpromazine, Zuclopenthixol decanoate, Clozapine, Olanzapine, Clothiapine and Trifluoperazine	1	1.54
Haloperidol, Chlorpromazine, Fluphenazine decanoate, Zuclopenthixol decanoate, Clozapine, Clothiapine, *Thioridazine and Trifluoperazine	1	1.54
Haloperidol, Chlorpromazine, Fluphenazine decanoate, Zuclopenthixol decanoate, Clozapine, Risperidone, Olanzapine and Clothiapine	1	1.54
Haloperidol, Chlorpromazine, Fluphenazine decanoate, Zuclopenthixol decanoate, Clozapine, Risperidone, Olanzapine, Clothiapine and *Thioridazine	1	1.54
Total	**65**	**100**

The results clearly show that haloperidol (n=58, 89.23%) was the most widely used first generation antipsychotic (FGA) and risperidone (n=40, 61.54%) was the most widely used second generation antipsychotic (SGA) prior to clozapine therapy.

* Please note: Thioridazine is no longer available on the market in South Africa.

4.2.6.3 Trials of previous antipsychotics used before initiating clozapine

The following table summarises the results obtained for the trials of previous antipsychotics used prior to the initiation of clozapine therapy.

Table 4.23 Trials of previous antipsychotics prior to clozapine (N=65)

Trials of previous antipsychotics	n	%
Two previous antipsychotics prescribed of which one is an SGA	41	63.08
Two previous antipsychotics prescribed of which both are SGAs	2	3.08
Two previous antipsychotics prescribed of which both are conventional antipsychotics	19	29.23
One previous antipsychotic prescribed - a conventional antipsychotic	2	3.08
No information available	1	1.54
Total	**65**	**100**

The results indicate that most patients (n=41, 63.08%) did receive trials of both an FGA and an SGA before clozapine was initiated.

4.2.6.4 Compliance with the recommended guidelines for the initiation of clozapine

The following figure displays the results for the extent of compliance with the National Institute for Health and Clinical Excellence (NICE) guidelines for the initiation of clozapine (NICE, 2009).

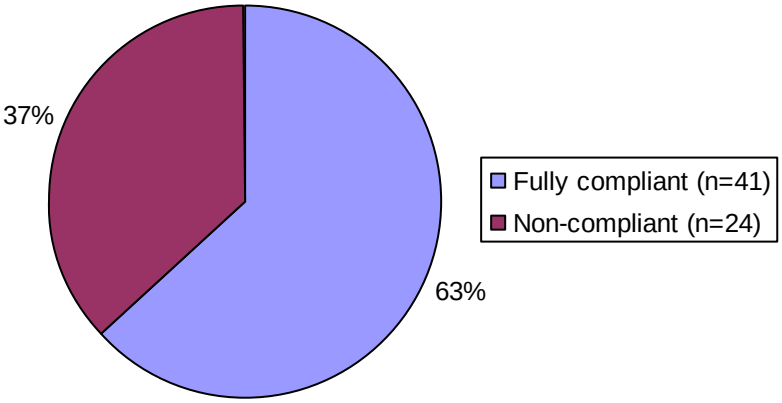


Figure 4.4: Compliance with the recommended guidelines for the initiation of clozapine (N=65)

From the results it is clear that in most cases the initiation of clozapine was compliant with the recommended NICE (2009) guidelines (n=41, 63.10%).

4.2.6.5 Use of contraceptives by female patients

The following table displays the results obtained for the use of contraceptives amongst female patients in the study.

Table 4.24 Use of contraceptives by female patients (N=26)

Oral or injectable contraceptives	n	%
Yes	5	19.23
No	21	80.77
Total	**26**	**100**

The results indicate that only five females (n=5, 19.23%) were on oral or injectable contraceptives while receiving clozapine therapy.

4.2.6.6 Supply the name of the contraceptive

The following table shows the results for the names of contraceptives/ alternative forms of contraception used by the patients in the study.

Table 4.25 Name of contraceptive (N=5)

Name of contraceptive	n	%
Medroxyprogesterone acetate (e.g. Depo-Provera®)	2	40.00
Low dose monophasic combined oral contraceptive (e.g. Nordette®)	1	20.00
Other form of contraception (e.g. sterilization)	2	40.00
Total	**5**	**100**

From the results it is clear that two patients were on injectable contraception (n=2, 40.00%) and one patient was on oral contraception (n=1, 20.00%).

4.2.6.7 Supply the possible reason for not being on contraception

The following table summarises the possible reasons why some of the female patients were not on contraception.

Table 4.26 Reason for not being on contraception (N=21)

Reason	n	%
Patient received counselling but refused contraception	4	19.05
No explanation available and no information in the patient's file indicating that counseling was provided	6	28.57
Age related (> 45 yrs) patient might be in menopause	11	52.38
Total	**21**	**100**

The results indicate the most possible reason for a female patient not being on contraception could be age related, since the patient might already be in menopause (n=11, 52.38%). However, no apparent reason could be found why six of the patients were not on contraception (n=11, 52.38%).

4.2.7 Drug interactions

4.2.7.1 Presence of any drug interactions

The following table indicates whether any drug interactions could be identified between clozapine and other drugs that the patients received during their admission in hospital.

Table 4.27 Presence of any drug interactions (N=65)

Drug interaction	n	%
Yes	55	84.62
No	8	12.31
No information available	2	3.08
Total	**65**	**100**

The results clearly show that in most cases (n=55, 84.62%) drug interactions with clozapine were identified.

4.2.7.2 Number of drug interactions identified

The following table summarises the results for the number of drug interactions that could be identified.

Table 4.28 Number of interactions identified (N=55)

Number of interactions	n	%
One interaction	17	30.91
Two interactions	22	40.00
Three interactions	10	18.18
Four interactions	3	5.45
Five interactions	3	5.45
Total	**55**	**100**

According to the results amongst the 55 patients in which drug interactions could be identified, only one drug interaction was identified between clozapine and other drugs in 17 patients (30.91%). Whereas in 22 patients (40.00%) two drug interactions with clozapine could be identified, leading to a total number of 44 drug interactions. In 10

patients (18.18%) three drug interactions with clozapine could be identified, leading to 30 drug interactions. In three patients (5.45%) four drug interactions with clozapine could be identified, leading to 12 drug interactions. In three patients (5.45%) five drug interactions with clozapine could be identified, leading to 15 drug interactions.

Therefore, a total number of 118 drug interactions were identified in the 55 patients that were receiving clozapine concomitantly with other drugs. The results indicate that in most patients (n=22, 40.00%) two possible drug interactions with clozapine could be identified per patient.

4.2.7.3 Identified drug interactions

4.2.7.3.1 Drug interaction *1

Please note: Drug interaction *1 refers to the first drug interaction that was identified in a patient.

The following table summarises the results obtained for all the possible combinations of drug interactions with clozapine for the first drug interaction that was identified.

Table 4.29 Drug interaction *1 (N=55)

Interaction (1)	Severity level	n	%
Haloperidol	4	21	38.18
Sodium valproate	4	4	7.27
Valproic acid	4	9	16.36
Risperidone	4	7	12.73
Zuclopenthixol decanoate	0	4	7.27
Fluphenazine decanoate	0	1	1.82
Lithium carbonate	4	4	7.27
Lorazepam	1	4	7.27
Chloramphenicol	0	1	1.82
Total		**55**	**100**

The following table summarises the severity level of the drug interactions identified in Table 4.29.

Table 4.30 Severity level of interaction *1 (N=55)

Severity level	n	%
Level 0 = Severity level of interaction not available in reference source used to assess the level of the drug interaction.	6	10.91
Level 1 = Interaction is potentially severe or life-threatening and its occurrence has been suspected, established or is probable in well-controlled studies.	4	7.27
Level 4 = Interaction may cause moderate-to-major effects, but data are very limited.	45	81.82
Total	**55**	**100**

4.2.7.3.2 Drug interaction *2

Please note: Drug interaction *2 refers to the second drug interaction that was identified in a patient.

The following table summarises the results obtained for all the possible combinations of drug interactions with clozapine for the second drug interaction that was identified.

Table 4.31 Drug interaction *2 (N=38)

Interaction 2	Severity Level	n	%
Valproic acid	4	5	13.16
Risperidone	4	3	7.89
Olanzapine	0	3	7.89
Zuclopenthixol decanoate	0	7	18.42
Lithium carbonate	4	5	13.16

Lorazepam	1	6	15.79
Co-trimoxazole	0	3	7.89
Chloramphenicol	0	1	2.63
Atenolol	0	1	2.63
Rifampicin	4	2	5.26
Ciprofloxacin	2	1	2.63
Combined oral contraceptive (Nordette®)	4	1	2.63
Total		**38**	**100**

The following table summarises the severity level of the drug interactions identified in Table 4.31.

Table 4.32 Severity level of interaction *2 (N=38)

Severity level	n	%
Level 0 = Severity level of interaction not available in reference source used to assess the level of the drug interaction.	15	39.47
Level 1 = Interaction is potentially severe or life-threatening and its occurrence has been suspected, established or is probable in well-controlled studies.	6	15.79
Level 2 = Interaction may cause a deterioration in a patient's clinical status, and its occurrence has been suspected, established, or is probable in well-controlled studies.	1	2.63
Level 4 = Interaction may cause moderate-to-major effects, but data are very limited.	16	42.11
Total	**38**	**100**

4.2.7.3.3 Drug interaction *3

Please note: Drug interaction *3 refers to the third drug interaction that was identified in a patient.

The following table summarises the results obtained for all the possible combinations of drug interactions with clozapine for the third drug interaction that was identified.

Table 4.33 Drug interaction *3 (N=16)

Interaction 3	Severity level	n	%
Olanzapine	0	1	6.25
Zuclopenthixol decanoate	0	3	18.75
Flupenthixol decanoate	0	1	6.25
Lithium carbonate	4	3	18.75
Citalopram	1	1	6.25
Lorazepam	1	4	25.00
Co-trimoxazole	0	1	6.25
Atenolol	0	2	12.50
Total		**16**	**100**

The following table summarises the severity level of the drug interactions identified in Table 4.33.

Table 4.34 Severity level of interaction *3 (N=16)

Severity level	n	%
Level 0 = Severity level of interaction not available in reference source used to assess the level of the drug interaction.	8	50.00
Level 1 = Interaction is potentially severe or life-threatening and its occurrence has been suspected, established or is probable in well-controlled studies.	5	31.25

Level 4 = Interaction may cause moderate-to-major effects, but data are very limited.	3	18.75
Total	**16**	**100**

4.2.7.3.4 Drug interaction *4

Please note: Drug interaction *4 refers to the fourth drug interaction that was identified in a patient.

The following table summarises the results obtained for all the possible combinations of drug interactions with clozapine for the fourth drug interaction that was identified.

Table 4.35 Drug interaction *4 (N=6)

Interaction 4	Severity level	n	%
Zuclopenthixol decanoate	0	1	16.67
Lithium carbonate	4	1	16.67
Citalopram	1	1	16.67
Diazepam	1	1	16.67
Propranolol	0	2	33.33
Total		**6**	**100**

The following table summarises the severity level of the drug interactions identified in Table 4.35.

Table 4.36 Severity level of interaction *4 (N=6)

Severity level	n	%
Level 0 = Severity level of interaction not available in reference source used to assess the level of the drug interaction.	3	50.00
Level 1 = Interaction is potentially severe or life-threatening and its occurrence has been suspected, established or is probable in well-controlled studies.	2	33.33
Level 4 = Interaction may cause moderate-to-major effects, but data are very limited.	1	16.67
Total	**6**	**100**

4.2.7.3.5 Drug interaction *5

Please note: Drug interaction *5 refers to the fifth drug interaction that was identified in a patient.

The following table summarises the results obtained for all the possible combinations of drug interactions with clozapine for the fifth drug interaction that was identified.

Table 4.37 Drug interaction *5 (N=3)

Interaction 5	Severity level	n	%
Lorazepam	1	3	100.00
Total		**3**	**100**

The following table summarises the severity level of the drug interactions identified in Table 4.37.

Table 4.38 Severity level of interaction *5 (N=3)

Severity level	n	%
Level 1 = Interaction is potentially severe or life-threatening and its occurrence has been suspected, established or is probable in well-controlled studies.	3	100.00
Total	**3**	**100**

From the results it is clear that most of the observed drug interactions were level 4 interactions which could cause moderate-to-major effects (n=65, 55.09%). However, emphasis need to be placed on the fact that 20 of the drug interactions were level one interactions (n=20, 16.95%). These drug interactions could have been severe or life-threatening to the patient.

4.2.8 Clozapine dosage titration

The results for the actual dosage titration performed will now be reported.

4.2.8.1 Dosage titration performed from initiation

The following figure displays the results for the number of cases in which clozapine titration was performed from initiation.

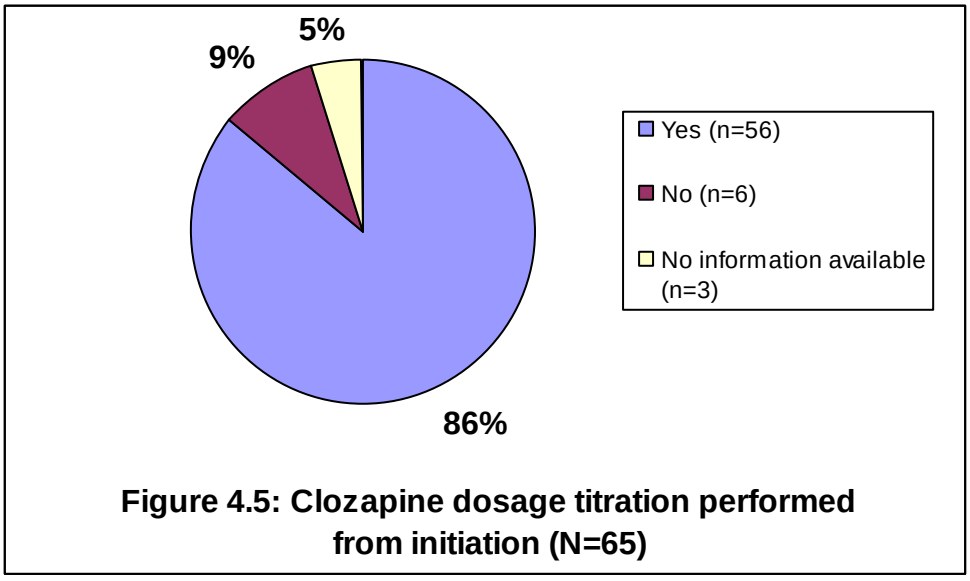


Figure 4.5: Clozapine dosage titration performed from initiation (N=65)

From the results it is clear that in most cases (n=56, 86.00%) dosage titration was performed.

4.2.8.2 Dosage on day one

The following table summarises the results obtained for the dosage administered on the first day.

Table 4.39 Dosage on day 1 (N=62)

Dosage	n	%
12.5 mg	18	29.03
25 mg	33	53.22
37.5 mg	6	9.68
> 37.5 mg	5	8.07
Total	**62 ***	**100**

* For the purpose of this analysis only 62 cases were included because in three patients the dosage was unknown (N=62).

From the results it is clear that most patients (n=33, 53.22%) received a dosage of 25 mg on the first day.

4.2.8.3 Dosage on day two

The following table summarises the results obtained for the dosage administered on the second day.

Table 4.40 Dosage on day 2 (N=62)

Dosage	n	%
< 25 mg	6	9.68
25 mg	40	64.51
50 mg	9	14.52
75 mg	2	3.23
> 75 mg	5	8.06
Total	**62 ***	**100**

* For the purpose of this analysis only 62 cases were included because in three patients the dosage was unknown (N=62).

From the results it is clear that most patients (n=40, 64.51%) received a dosage of 25 mg on the second day.

4.2.8.4 Titration performed within the first two to three weeks of initiation

The following table shows the results obtained for the dosage increments used during the titration period.

Table 4.41 Dosage increments used during titration (N=62)

Dosage increment	n	%
Increments of < 50 mg/day	45	72.58
Increments of 50 mg/day	16	25.81
Increments of > 50 mg/day	1	1.61
Total	**62 ***	**100**

* For the purpose of this analysis only 62 cases were included because in three patients the dosages used were unknown (N=62).

The results indicate that mostly increments of < 50mg/day was used during the titration period (n=45, 72.58%). It should however be noted that one patient was discharged from hospital while the dosage of clozapine was still being tapered upwards.

4.2.8.5 Mean dosages

The following table summarises the results obtained for the mean dosages on day one and day two as well as the mean maintenance and maximum dosage. The mean dosage upon discharge was also calculated and was found to be the same as the maintenance dosage.

Table 4.42 Mean dosages (N=62)*

Dosage criteria	Mean dosage
Day one	41.50 mg ± 35.21 mg
Day two	49.60 mg ± 35.69 mg
Maintenance	315.00 mg ± 140.44 mg
Maximum	349.23 mg ± 146.11 mg
Dosage upon discharge	315.0 g ± 140.44 mg

* For the purpose of this analysis only 62 cases were included because in three patients the dosages used were unknown (N=62).

Most male patients received a maintenance dose of 400 mg (n=15, 38.46%) and most female patients received a maintenance dose of 200 mg (n=9, 34.62%). Only 10 (25.64%) of the patients who were smokers received dosages > 450 mg/day.

4.2.9 Total number of days spent in hospital

The following table summarises the total number of days each patient spent in hospital during the admission under investigation.

Table 4.43 Number of days spent in hospital (N=62)

Number of days	n	%
1 and ≤ 100 days	37	59.68
> 100 and ≤ 200 days	18	29.03
> 200 and ≤ 300 days	6	9.68
> 300 and ≤ 400 days	1	1.61
Total	**62 ***	**100**

* For the purpose of this analysis only 62 cases were included because in three patients the necessary documentation was not available (N=62).

The results indicate that most patients stayed in hospital for 100 days or less (n=37, 59.68%). The longest hospital stay was 325 days and the shortest stay was 3 days. The average length of stay in hospital was 99.42 ± 78.3 days.

4.2.10 Costs for admission in hospital

The results for the various costs associated with admission will now be reported.

4.2.10.1 Cost of clozapine therapy while in hospital

The following table summarises the results for the cost of clozapine therapy that the patients received while in hospital.

Table 4.44 Cost of clozapine therapy (N=62)

Cost (in Rand)	n	%
39.10	1	1.61
49.48	1	1.61
52.70	1	1.61
78.02	1	1.61
83.09	1	1.61
83.69	1	1.61
91.94	1	1.61
92.34	1	1.61
97.74	1	1.61
102.59	1	1.61
111.28	1	1.61
112.68	1	1.61
114.40	1	1.61
118.10	1	1.61
120.35	1	1.61
123.96	1	1.61
128.58	1	1.61
130.95	1	1.61
137.49	1	1.61
142.18	1	1.61
148.84	1	1.61
154.22	1	1.61
160.63	1	1.61
160.65	1	1.61
167.47	1	1.61
168.26	1	1.61
171.60	1	1.61
175.01	1	1.61
194.53	1	1.61
204.37	1	1.61
228.26	1	1.61
234.53	1	1.61
239.11	1	1.61

241.05	1	1.61
243.96	1	1.61
255.98	1	1.61
264.13	1	1.61
284.44	1	1.61
311.21	1	1.61
315.65	1	1.61
320.52	1	1.61
327.17	1	1.61
334.98	1	1.61
339.50	1	1.61
370.39	1	1.61
419.75	1	1.61
420.99	1	1.61
434.17	1	1.61
441.32	1	1.61
450.34	1	1.61
450.88	1	1.61
459.46	1	1.61
468.18	1	1.61
473.76	1	1.61
501.25	1	1.61
717.68	1	1.61
790.61	1	1.61
794.95	1	1.61
797.50	1	1.61
980.91	1	1.61
1 003.12	1	1.61
1 490.76	1	1.61
Total	**62 ***	**100**

* For the purpose of this analysis only 62 cases were included because in three patients the dosage of clozapine was unknown and hence the cost of clozapine therapy could not be calculated (N=62).

From the results it is clear that the minimum cost spent on clozapine therapy was R39.10 and the maximum cost was R 1490.76. The average cost of clozapine therapy received per patient was R 294.20 ± R 273.95.

4.2.10.2 Cost of hospital stay for this admission

The following table summarises the results for the cost of hospital stay for the patients.

Table 4.45 Cost of hospital stay (N=63)

Cost (in Rand)	n	%
5 198.91	1	1.59
22 528.61	1	1.59
26 658.84	1	1.59
28 977.00	1	1.59
32 454.24	1	1.59
33 983.74	1	1.59
34 659.40	1	1.59
35 931.48	1	1.59
41 726.88	1	1.59
42 885.96	1	1.59
44 045.04	1	1.59
47 522.28	1	1.59
48 681.36	1	1.59
53 317.68	1	1.59
57 954.00	1	1.59
59 113.08	1	1.59
60 272.16	1	1.59
62 590.32	1	1.59
66 067.56	1	1.59
73 022.04	1	1.59
74 117.76	1	1.59
74 181.12	1	1.59
75 340.20	1	1.59
78 532.36	1	1.59
80 301.81	1	1.59
80 437.41	1	1.59
82 294.68	1	1.59
90 408.24	2	3.18
96 203.64	1	1.59
102 313.03	1	1.59
105 476.28	1	1.59

107 794.44	1	1.59
108 716.22	1	1.59
109 385.37	1	1.59
113 341.24	1	1.59
115 228.59	1	1.59
115 908.00	1	1.59
121 703.40	1	1.59
129 816.96	1	1.59
130 291.48	1	1.59
139 089.60	1	1.59
140 467.18	1	1.59
140 808.54	1	1.59
145 198.99	1	1.59
155 316.72	1	1.59
157 521.88	1	1.59
161 392.21	1	1.59
165 748.44	1	1.59
181 186.97	1	1.59
194 054.49	1	1.59
197 043.60	2	3.18
216 747.96	1	1.59
218 879.01	1	1.59
223 497.55	1	1.59
260 793.00	1	1.59
265 429.32	1	1.59
307 697.30	1	1.59
312 951.60	1	1.59
339 610.44	1	1.59
368 561.69	1	1.59
412 207.25	1	1.59
Total	**63 ***	**100**

* For the purpose of this analysis only 63 cases were included because in two patients the duration of admission was unknown (N=63).

From the results it is clear that the minimum cost of hospital stay was R 5 198.91 and the maximum cost was R 412 207.25. The average cost of hospital stay per patient was R 120 939.05 ± R 91 351.80.

4.2.10.3 Cost of laboratory investigations performed

The following table summarises the results for the cost of laboratory investigations performed for the patients.

Table 4.46 Cost of laboratory investigations (N=60)

Cost (in Rand)	n	%
17.00	5	8.33
34.00	2	3.33
36.00	1	1.67
51.00	8	13.33
54.00	1	1.67
68.00	3	5.00
68.80	1	1.67
85.00	2	3.33
85.40	1	1.67
89.00	1	1.67
90.00	1	1.67
102.00	5	8.33
102.80	1	1.67
119.00	4	6.67
120.60	1	1.67
122.00	1	1.67
126.00	1	1.67
136.00	2	3.33
153.00	1	1.67
170.00	1	1.67
209.40	1	1.67
221.00	1	1.67
226.40	2	3.33
237.00	1	1.67
243.40	1	1.67
260.40	1	1.67
278.00	1	1.67
279.00	1	1.67
311.40	1	1.67
323.00	1	1.67
344.40	1	1.67
354.00	1	1.67
382.80	1	1.67

700.80	1	1.67
740.80	1	1.67
952.20	1	1.67
Total	**60 ***	**100**

* For the purpose of this analysis only 60 cases were included because in five patients' files no data could be found on any laboratory investigations performed (N=60).

From the results it is clear that the minimum cost for laboratory investigations performed was R 17.00 and the maximum cost was R 952.20. The average cost for laboratory investigations performed per patient was R 149.25 ± R 175.14.

4.2.10.4 Total cost of the admission in hospital

The following table summarises the results for the cost of admission for the patients.

Table 4.47 Cost of admission (N=63)

Cost (in Rand)	n	%
5 251.61	1	1.59
22 614.09	1	1.59
26 731.94	1	1.59
29 131.49	1	1.59
32 568.98	1	1.59
34 407.06	1	1.59
34 787.98	1	1.59
36 233.22	1	1.59
41 909.28	1	1.59
43 543.35	1	1.59
44 346.48	1	1.59
47 749.46	1	1.59
48 815.45	1	1.59
53 469.37	1	1.59
58 113.94	1	1.59
59 591.01	1	1.59
60 477.38	1	1.59
62 815.33	1	1.59
66 412.77	1	1.59
73 492.79	1	1.59
74 627.29	1	1.59
74 738.01	1	1.59
75 503.88	1	1.59
79 153.24	1	1.59
80 454.41	1	1.59
80 552.46	1	1.59
82 994.84	1	1.59
90 754.20	1	1.59
90 944.41	1	1.59
96 365.92	1	1.59
102 469.62	1	1.59
105 645.38	1	1.59
108 388.76	1	1.59

109 069.35	1	1.59
109 840.95	1	1.59
113 691.50	1	1.59
115 899.86	1	1.59
116 372.75	1	1.59
122 063.45	1	1.59
130 208.94	1	1.59
130 747.27	1	1.59
139 218.62	1	1.59
140 712.81	1	1.59
141 081.71	1	1.59
145 640.64	1	1.59
155 838.98	1	1.59
158 589.83	1	1.59
162 388.89	1	1.59
165 897.28	1	1.59
181 915.31	1	1.59
195 418.20	1	1.59
197 218.56	1	1.59
197 814.46	1	1.59
216 980.91	1	1.59
219 169.61	1	1.59
223 709.08	1	1.59
262 017.12	1	1.59
266 960.73	1	1.59
308 138.80	1	1.59
314 072.10	1	1.59
339 985.55	1	1.59
369 730.67	1	1.59
414 650.21	1	1.59
Total	**63 ***	**100**

* For the purpose of this analysis only 63 cases were included because in two patients both the dosage of clozapine as well as the duration of admission were unknown (N=63).

From the results it is clear that the minimum cost of admission was R 5 251.61 and the maximum cost was R 414 650.21. The average cost of admission per patient was R 121 386.15 ± R 91 636.36.

4.2.11 Prescriber

4.2.11.1 Prescriber who initiated clozapine

The following figure displays the results indicating which group of practitioners initiated clozapine therapy.

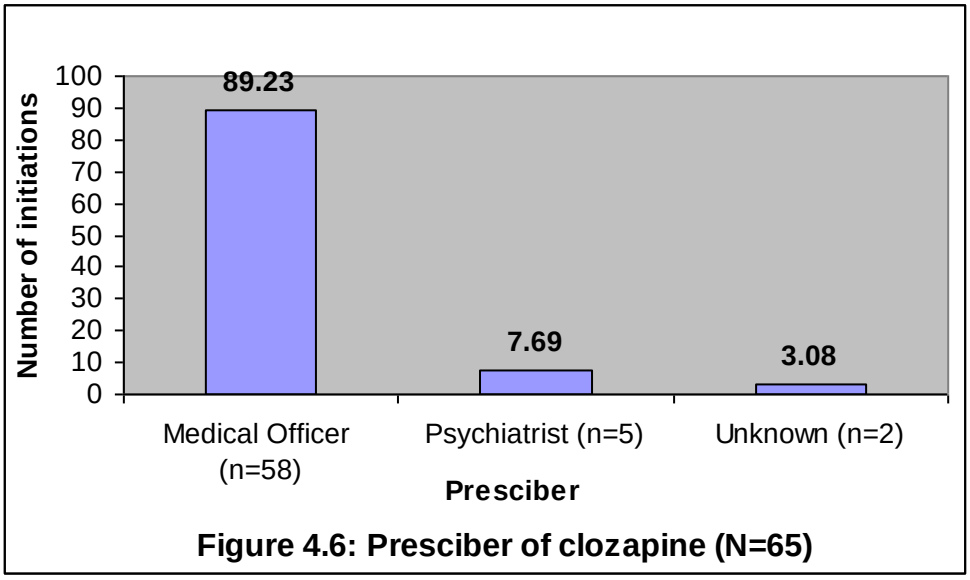


Figure 4.6: Presciber of clozapine (N=65)

The results indicate that most of the clozapine prescriptions were written by a medical officer (n=58, 89.23%).

4.2.11.2 Involvement of a psychiatrist in the initiation of clozapine

The following figure indicates the results of whether a medical officer consulted with a psychiatrist prior to the initiation of clozapine.

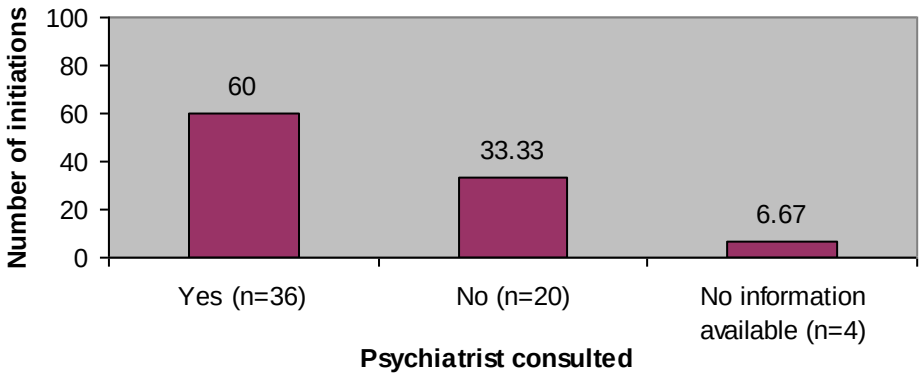


Figure 4.7: Involvement of a psychiatrist in the initiation of clozapine (N=60)

* For the purpose of this analysis only 60 cases were included because as seen in Figure 4.6 clozapine were initiated by a psychiatrist in five patients (N=60).

The results clearly indicate that in most cases (n=36, 60.00%) a psychiatrist was consulted before clozapine was initiated.

4.2.11.3 Compliance with the recommended guideline for the prescribing of clozapine by a psychiatrist

The following table indicates the results for the analysis of whether clozapine was initiated by a psychiatrist or by a medical officer (after consultation with a psychiatrist).

Table 4.48 Compliance with the recommended guideline for the initiation of clozapine by a psychiatrist (N=65)

Compliance	n	%
Fully compliant	41	63.08
Non-compliant	20	30.77
No information available	4	6.15
Total	**65**	**100**

The results clearly show that a psychiatrist was only involved in the decision making process to initiate clozapine in 41 cases (63.08%).

4.2.12 Adverse effects

4.2.12.1 Adverse effects reported

The following figure displays the results for the number of adverse effects reported for patients receiving clozapine.

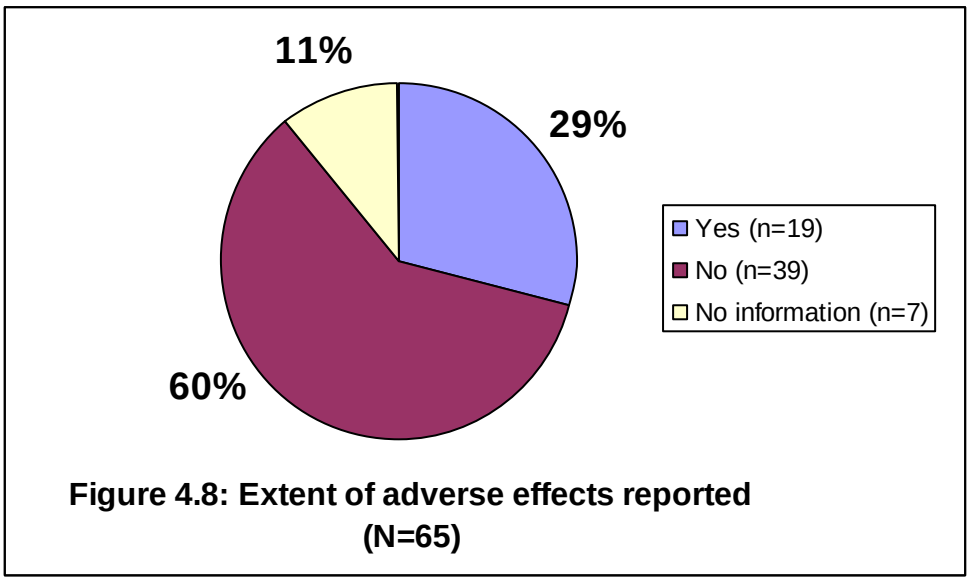


Figure 4.8: Extent of adverse effects reported (N=65)

From the results it is clear that only a few patients experienced adverse effects while on clozapine therapy (n=19, 29.00%).

4.2.12.2 Which adverse effects were reported?

The following table summarises the results obtained for the adverse effects experienced by the study sample.

Table 4.49 Adverse effects reported (N=19)

Adverse effect	n	%
Hypersalivation	3	15.79
Constipation	2	10.53
Nausea	1	5.26
Fever	1	5.26
Hypotension	1	5.26

Sedation	5	26.32
Urinary incontinence	1	5.26
Hypersalivation and sedation	1	5.26
Constipation and tachycardia	1	5.26
Hypersalivation, hypertension and weight gain	1	5.26
Hypersalivation, constipation and fasculation of facial muscles	1	5.26
Hypersalivation, sedation and urinary incontinence	1	5.26
Total	**19 ***	**100**

* For the purpose of this analysis, 19 cases were included because only 19 patients experienced adverse effects while on clozapine therapy (N=19).

According to the results sedation was the most common adverse effect experienced by patients (n=5, 26.32%).

During the study period one patient developed agranulocytosis while being an inpatient at the hospital and another patient developed neutropenia while receiving clozapine therapy as an outpatient at one of the community psychiatric clinics. However these patients did not form part of the initial study sample and therefore this information were not reported with the rest of the results above.

4.2.12.3 Adverse effects treated

The following table summarises the results for whether the adverse effects were treated.

Table 4.50 Adverse effects treated (N=19)

Treatment received	n	%
Yes	17	89.47
No	2	10.53
Total	**19 ***	**100**

* For the purpose of this analysis only 19 cases were included because only 19 patients experienced adverse effects (N=19).

The results indicate that only 17 of those patients that experienced adverse effects did in fact receive treatment for it (n=17, 89.47%).

4.2.13 Monitoring

The results obtained for baseline and follow-up monitoring will now be reported.

4.2.13.1 Extent of compliance with the guidelines for baseline monitoring

Haematological and metabolic monitoring was measured.

4.2.13.1.1 Haematological monitoring

The following figure displays the results obtained for baseline haematological monitoring performed.

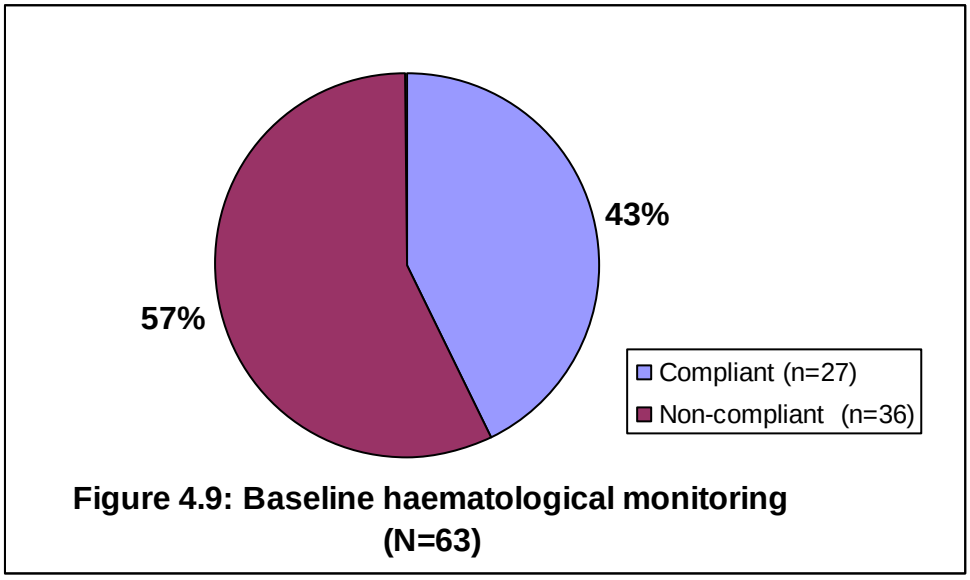


Figure 4.9: Baseline haematological monitoring (N=63)

* For the purpose of this analysis, only 63 cases were included because two of the patient files lacked some of the required data (N=63).

The results indicate that in the majority of cases mandatory baseline haematological monitoring performed was non-compliant with the recommended guidelines (n=36, 57.00%).

4.2.13.1.2 Metabolic monitoring

The following figure displays the results for baseline metabolic monitoring performed.

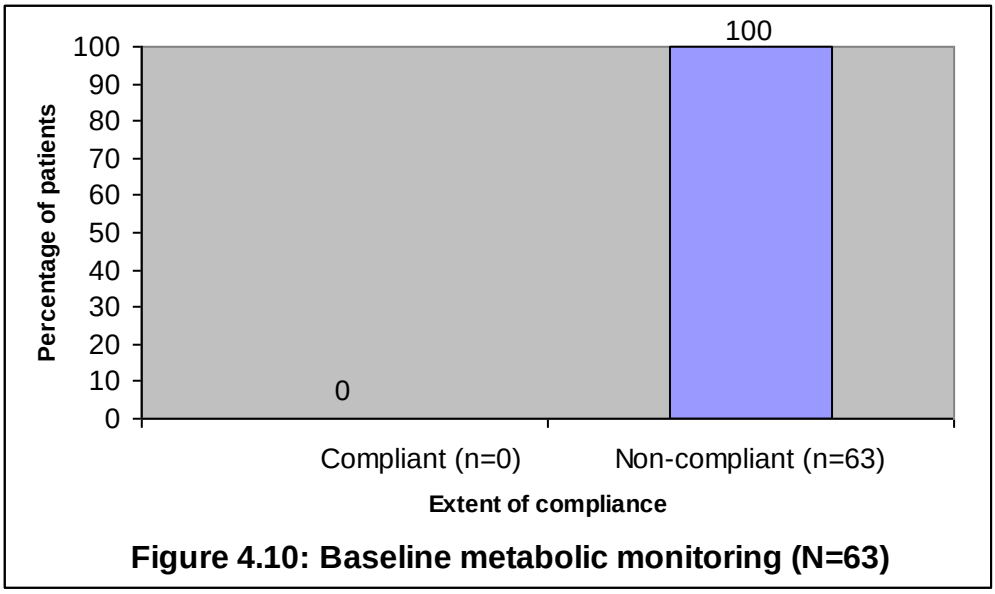


Figure 4.10: Baseline metabolic monitoring (N=63)

* For the purpose of this analysis, only 63 cases were included because two of the patient files lacked some of the required data (N=63).

From the results it is clear that no baseline metabolic monitoring was performed (n=63, 100%).

4.2.13.2 Extent of compliance with the guidelines for follow-up monitoring

Haematological and metabolic monitoring was once again measured.

4.2.13.2.1 Haematological monitoring

The following figure indicates the results for the follow-up haematological monitoring performed.

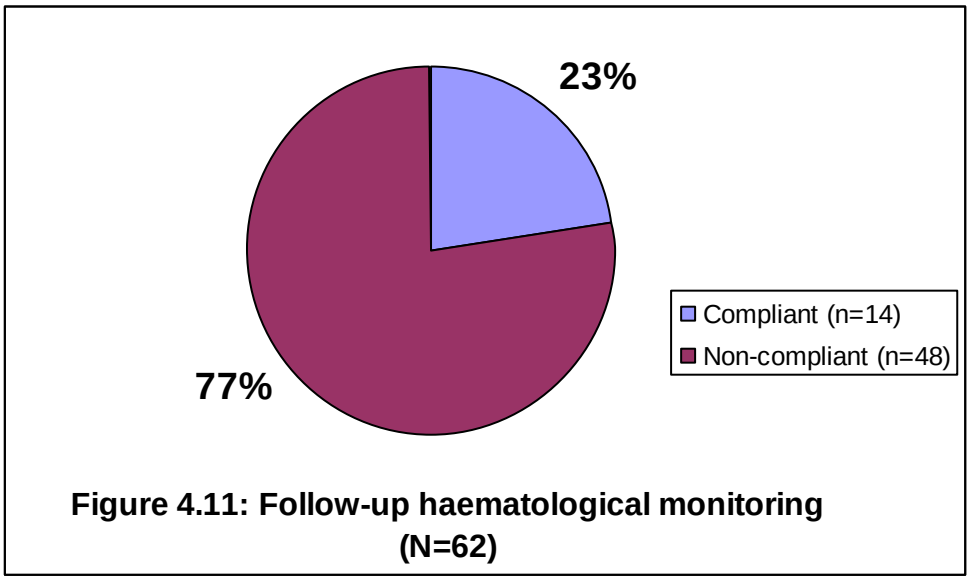


Figure 4.11: Follow-up haematological monitoring (N=62)

* For the purpose of this analysis, only 62 cases were included because three of the patient files lacked some of the required data (N=62).

The results indicate that in the majority of cases follow-up haematological monitoring was non-compliant with the recommended guidelines (n=48, 77.00%).

4.2.13.2.2 Metabolic monitoring

The following figure shows the results for the follow-up metabolic monitoring performed.

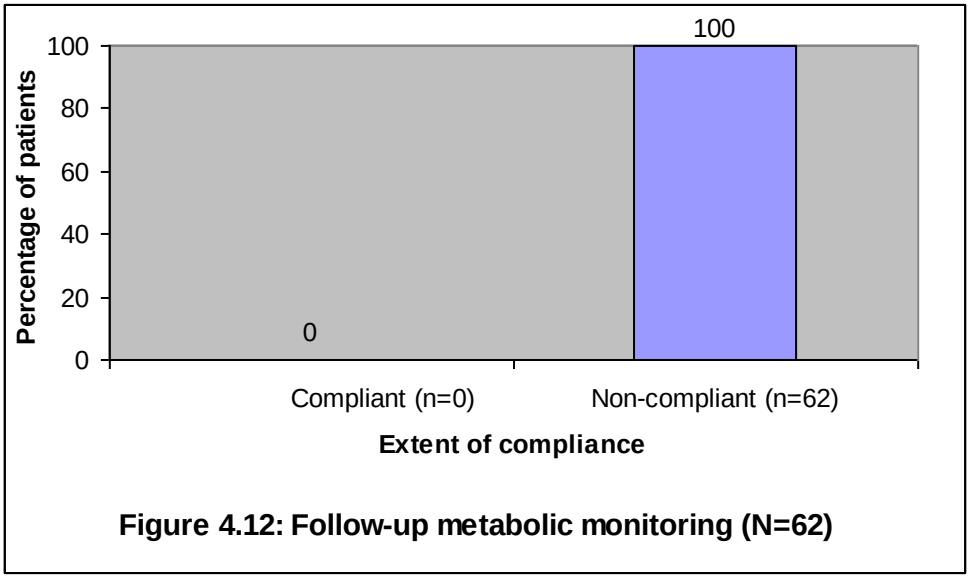


Figure 4.12: Follow-up metabolic monitoring (N=62)

* For the purpose of this analysis, only 62 cases were included because three of the patient files lacked some of the required data (N=62).

From the results it is clear in all the cases under investigation the follow-up metabolic monitoring did not comply with the recommended guidelines (n=62, 100%).

4.2.14 Follow-up care after discharge

The following table shows the results regarding the facilities to which the patients were sent after discharge from Elizabeth Donkin Hospital.

Table 4.51 Follow-up care after discharge (N=65)

Facility	n	%
Bloempark clinic	4	6.15
West End clinic	5	7.69
Kwazakhele clinic	3	4.62
Motherwell clinic	8	12.31
Empilweni clinic	7	10.77
Stow Road clinic	7	10.77
Laetitia Bam clinic	2	3.08
Clarkson clinic	1	1.54
Provincial clinic	5	7.69
Dora C-Block clinic	3	4.62
Korsten clinic	1	1.54
Kirkwood Care Centre	13	20.00
Tower Hospital	6	9.23
Total	**65**	**100**

According to the results most patients attended clinics after discharge (n=46, 70.77%) whereas a smaller proportion of patients were discharged/transferred to long-term care centres (n=19, 29.23%).

4.2.15 Point of monitoring upon discharge

The following figure displays the results regarding the point of monitoring upon discharge from Elizabeth Donkin Hospital.

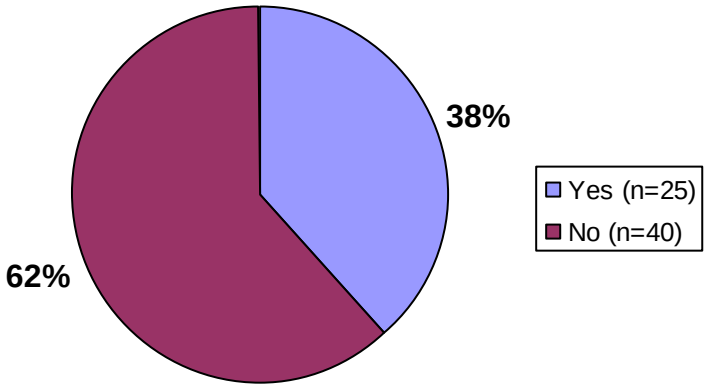


Figure 4.13: Facilities notified where in the process the haematological monitoring was upon discharge of the patient (N=65)

From the results it is clear that most facilities were not notified where in the process the white blood cell (WBC) count monitoring was upon discharge of the patient from hospital (n=40, 62.00%).

4.3 QUESTIONNAIRES

Two sets of questionnaires were used to gather data on the use of clozapine by patients after discharge from Elizabeth Donkin Hospital.

4.3.1 Three-month follow-up questionnaire

The results obtained from the three-month follow-up questionnaire will now be reported.

4.3.1.1 Number of patients still on clozapine after three months

The following figure displays the results for the number of patients still on clozapine therapy three months after discharge from Elizabeth Donkin Hospital.

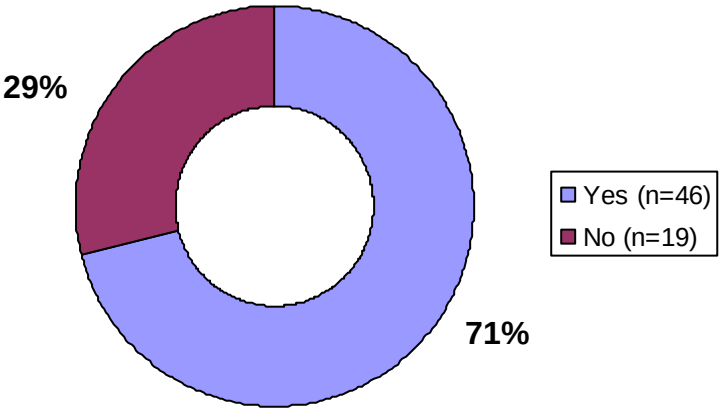


Figure 4.14: Number of patients still on clozapine three months after discharge (N=65)

From the results it is clear that a discontinuation rate of 29.00% was observed three months after discharge from hospital (n=19, 29.00%).

4.3.1.2 Reason(s) for no longer being on clozapine

The following table summarises the results of the reason(s) for discontinuation of clozapine therapy.

Table 4.52 Reason(s) for discontinuation of clozapine after three months (N=19)

Reason	n	%
Adverse effects	1	5.26
Non-compliance	5	26.32
Patient never reported to clinic after discharge	10	52.63
Patient not known to clinic/ hospital	2	10.53
No information available on why clozapine was stopped	1	5.26
Total	**19**	**100**

* For the purpose of this analysis only 19 cases were included since clozapine was discontinued in 19 patients (N=19).

The results indicate that the main reason for discontinuation of clozapine therapy was lost to follow-up, since most patients did not seek treatment after discharge (n=12, 63.16%).

4.3.1.3 Dosage of clozapine three months after discharge

The following table summarises the results for clozapine dosages three months after discharge from hospital.

Table 4.53 Clozapine dosage three months after discharge (N=46)

Dosage	n	%
< 300 mg	16	34.78
≥ 300 and ≤ 600 mg	30	65.22
> 600 mg	0	0
Total	**46**	**100**

* For the purpose of this analysis only 46 cases were included because clozapine therapy was continued in 46 patients (N=46).

From the results it is clear that most patients received a dosage between 300 mg and 600 mg/day (n=30, 65.22%). The lowest dosage was 100 mg and the highest dosage was 600 mg. The mean dosage three months after discharge was 346.67 mg ± 122.43 mg.

4.3.1.4 Notification regarding point of WBC count monitoring upon discharge from Elizabeth Donkin Hospital

The following table summarises the results for the notification of the clinics or long-term care centres regarding the point of WBC count monitoring upon discharge from Elizabeth Donkin Hospital.

Table 4.54 Notification about point of WBC count monitoring (N=65)

Informed	n	%
Yes	23	35.38
No	27	41.54
No information available	3	4.62

Patient never reported to clinic after discharge	10	15.38
Patient not known to clinic/ hospital	2	3.08
Total	**65**	**100**

The results indicate that most clinics and long-term care centres (n=27, 41.54%) did not receive any form of communication (e.g written/ verbal) with regard to the point of monitoring of WBC counts upon discharge of patients from Elizabeth Donkin Hospital.

4.3.1.5 Extent of compliance with the recommended guidelines for follow-up haematological monitoring

The following figure represents the results for the follow-up haematological monitoring performed at the clinics and long-term care centres three months after discharge from Elizabeth Donkin Hospital.

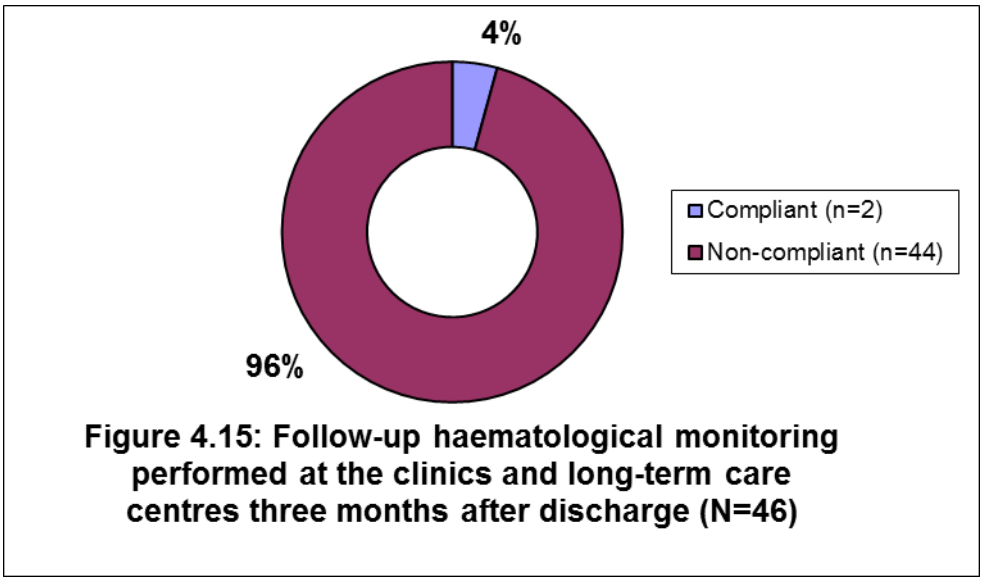


Figure 4.15: Follow-up haematological monitoring performed at the clinics and long-term care centres three months after discharge (N=46)

* For the purpose of this analysis only 46 cases were included because clozapine was continued in 46 patients (N=46).

The results indicate that in 96.00% (n=44) of the cases the haematological monitoring performed at the clinics and long-term care centres was non-complaint with the recommended guidelines.

4.3.1.6 Extent of compliance with the recommended guidelines for follow-up metabolic monitoring

The following figure represents the results for the follow-up metabolic monitoring performed at the clinics and long-term care centres three months after discharge from Elizabeth Donkin Hospital.

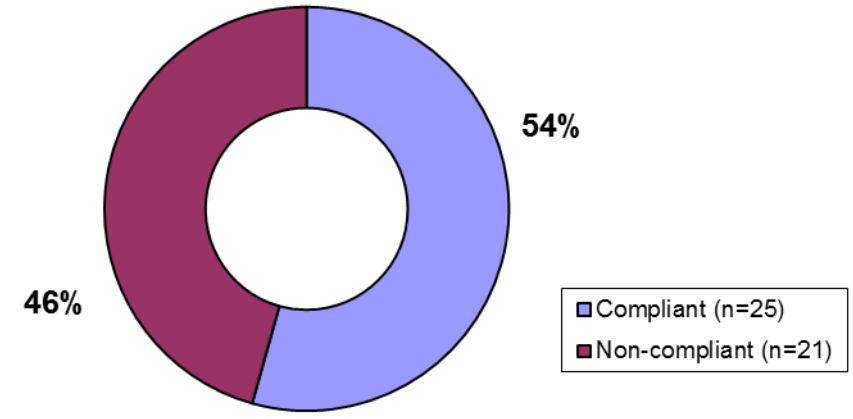


Figure 4.16: Follow-up metabolic monitoring performed at the clinics and long-term care centres three months after discharge (N=46)

* For the purpose of this analysis only 46 cases were included because clozapine was continued in 46 patients (N=46).

From the results it is clear that in only 54.00% (n=25) of the cases the follow-up metabolic monitoring was compliant with the recommended guidelines.

4.3.2 Six-month follow-up questionnaire

The results obtained from the six-month follow-up questionnaire will now be reported.

4.3.2.1 Number of patients still on clozapine after six months

The following figure displays the results for the number of patients still on clozapine six months after discharge from Elizabeth Donkin Hospital.

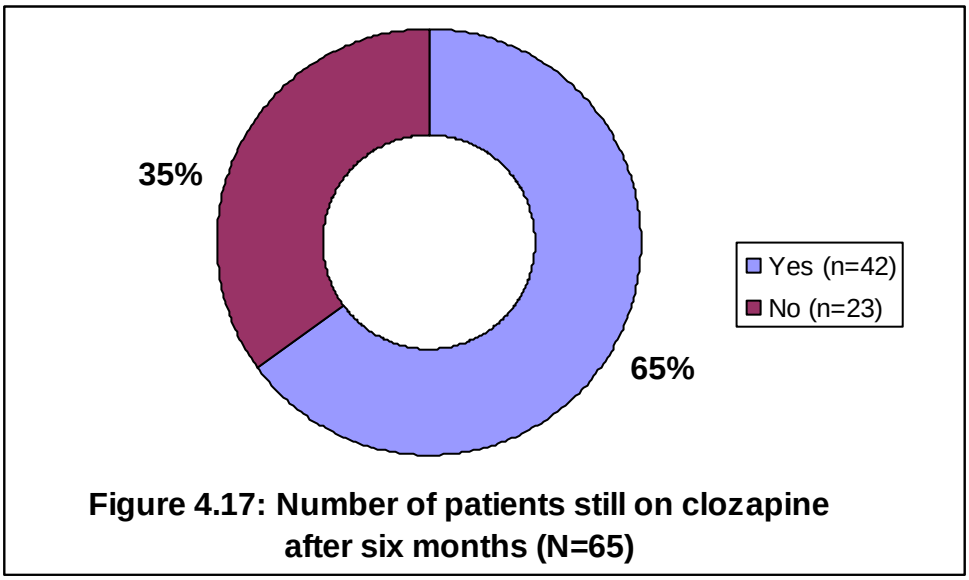


Figure 4.17: Number of patients still on clozapine after six months (N=65)

From the results it is clear that a discontinuation rate of 35.00% was observed six months after discharge from hospital (n=23, 35.00%).

4.3.2.2 Reason(s) for no longer being on clozapine

The following table summarises the results of the reason(s) for discontinuation of clozapine therapy in some patients six months after discharge from hospital.

Table 4.55 Reason(s) for discontinuation of clozapine after six months (N=23)

Reason	n	%
Adverse effects	1	4.35
Non-compliance	9	39.13
No information available, since patient's file was transferred to another clinic	2	8.70
Patient never reported to clinic after discharge	8	34.78
Patient not known to clinic/ hospital	2	8.69
No information available on why clozapine was stopped	1	4.35
Total	**23**	**100**

* For the purpose of this analysis only 23 cases were included since clozapine was discontinued in 23 patients (N=23).

From the results it is clear that in most cases clozapine was discontinued due to non-compliance (n=9, 39.13%) and a number of patients were lost to follow-up (n=10, 43.48%).

4.3.2.3 Dosage of clozapine six months after discharge

The following table summarises the results for clozapine dosages six months after discharge from hospital.

Table 4.56 Clozapine dosage six months after discharge (N=42)

Dosage	n	%
< 300 mg	12	28.57
≥ 300 and ≤ 600 mg	30	71.43
> 600 mg	0	0
Total	**42**	**100**

* For the purpose of this analysis only 42 cases were included because clozapine therapy was continued in 42 patients (N=42).

The results indicate that most patients remained on a dosage between 300 mg and 600 mg/day six months after discharge from hospital (n=30, 71.43%). The lowest dosage was 100 mg and the highest dosage was 600 mg. The mean dosage six months after discharge was 370.37 mg ± 117.06 mg.

4.3.2.4 Extent of compliance with the recommended guidelines for follow-up haematological monitoring

The following figure represents the results for the follow-up haematological monitoring performed at the clinics and long-term care centres six months after discharge from Elizabeth Donkin Hospital.

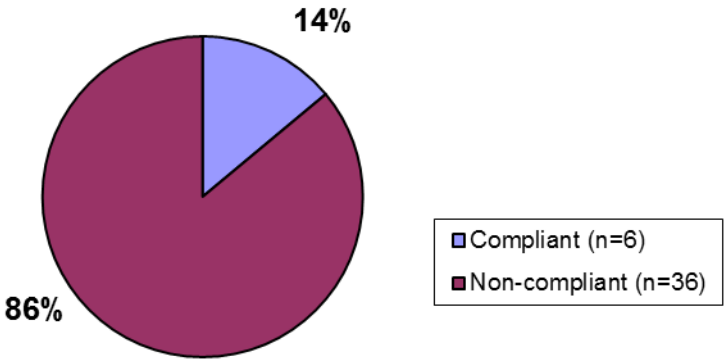


Figure 4.18: Follow-up haematological monitoring performed at the clinics and long-term care centres six months after discharge (N=42)

* For the purpose of this analysis only 42 cases were included because clozapine was continued in 42 patients (N=42).

The results indicate that in 86.00% (n=36) of the cases the haematological monitoring performed at the clinics and long-term care centres was non-complaint with the recommended guidelines.

4.3.2.5 Extent of compliance with the recommended guidelines for follow-up metabolic monitoring

The following figure represents the results for the follow-up metabolic monitoring performed at the clinics and long-term care centres six months after discharge from Elizabeth Donkin Hospital.

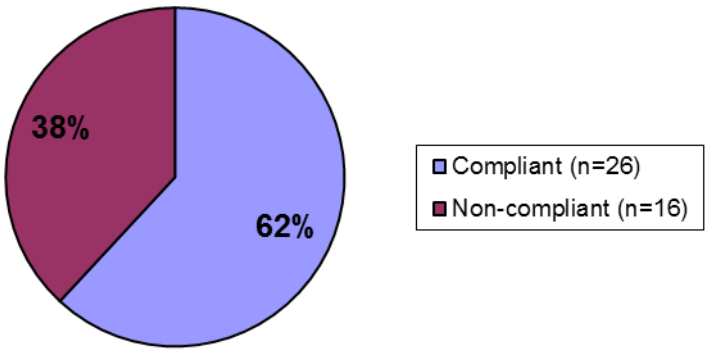


Figure 4.19: Follow-up metabolic monitoring performed at the clinics and long-term care centres six months after discharge (N=42)

* For the purpose of this analysis only 42 cases were included because clozapine was continued in 42 patients (N=42).

From the results it is clear that in only 62.00% (n=26) of the cases the follow-up metabolic monitoring was compliant with the recommended guidelines.

4.4 CHAPTER SUMMARY

In this chapter the results of the empirical study were reported. Results were reported for each of the three research instruments used in the study (refer Chapter 3). In the following chapter the conclusions drawn from the results will be discussed. The limitations of the study as well as the recommendations for future studies will be also discussed.

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

5.1 INTRODUCTION

In this chapter the conclusions and limitations of this research study are discussed, and recommendations are made.

5.2 CONCLUSIONS

The conclusions in this research study will be discussed according to the specific research objectives mentioned in Chapter 1.

The aim of the study was to investigate the prescribing and monitoring patterns of clozapine at Elizabeth Donkin Hospital in the Nelson Mandela Metropole. An extensive drug utilisation review was performed to establish the compliance with the recommended guidelines for the initiation and monitoring of clozapine. The study showed that current practice of clozapine initiation and monitoring may be clinically improved.

The general objective of the study was to determine whether clozapine is rationally prescribed, for the treatment of psychotic disorders at Elizabeth Donkin Hospital. The results obtained indicated that all the patients included in the study suffered from either a primary or secondary psychotic disorder. Clozapine was therefore correctly indicated in all patients (n=65) that participated in the study. However, not all the patients qualified for a trial of clozapine therapy. Only 63.00% (n=41) of the patients received trials of two other antipsychotics of which one was a second generation antipsychotic (SGA). In light of the above it was found that in most cases clozapine were rationally used but current practice needs to be addressed in order to improve clinical outcomes in future.

5.2.1 Literature review

The following conclusions were found from the literature study (refer Chapter 2). Each of the specific objectives for the literature review will now be discussed.

The first specific research objective was to obtain information from the literature on the use of clozapine in patients with schizophrenia and other psychotic disorders.

- It was found that clozapine was the first SGA agent released on the market.
- Clozapine provides significant help for at least 60.00% of patients not responding to conventional antipsychotics.
- Clozapine shows superior efficacy for both the positive and negative symptoms of schizophrenia over conventional antipsychotics.
- Clozapine is mostly considered as a treatment of last resort, since it is mainly used for treatment-resistant cases.
- Clozapine decreases suicidality in patients with schizophrenia and schizoaffective disorder.
- Clozapine has quite a severe side effect profile.
- Agranulocytosis is a serious adverse effect associated with the use of clozapine and affects about 1-2% of patients receiving clozapine therapy.
- Metabolic syndrome is generally associated with the use of SGAs including clozapine. About one in every two patients may develop metabolic syndrome while on clozapine therapy.
- Regular haematological and metabolic monitoring is required when patients receive clozapine therapy to assist in the early detection of agranulocytosis and any metabolic abnormalities.
- Upon initiation of clozapine a slow upward dosage titration is recommended, since many of the adverse effects associated with clozapine are dose-dependent.
- There are a number of drug interactions that can occur between clozapine and other agents.
- Patients receiving clozapine therapy generally have fewer admissions and reduced hospital stays which in turn decreases the financial burden on the health care system.
- The underuse of clozapine could be related to the mixed picture of increased efficacy with sometimes severe adverse effects that could contribute to clinicians being hesitant to prescribe clozapine.

- The suboptimal use of clozapine is a serious concern that needs to be addressed. Optimising the use of clozapine therapy would enhance patient outcomes.
- Clozapine should not be considered a treatment of last resort but drug of first choice as soon as non-responsiveness to established first-line treatments is evident.

The second specific research objective was to gain knowledge from the available literature on psychotic disorders including schizophrenia, where clozapine therapy can be considered as a treatment option.

- Psychotic disorders generally affect 3% of the population (Perälä *et al.*, 2007: 19).
- Psychotic disorders can be divided into two groups, namely primary and secondary psychotic disorders. This classification is based on diagnosis.
- It was found that schizophrenia is a primary psychotic disorder that causes marked morbidity, reduced quality of life and productivity.
- Schizoaffective disorder is a primary psychotic disorder characterised by significant mood symptoms, psychosis and other symptoms of schizophrenia.
- Bipolar mood disorder is classified as a secondary psychotic disorder and can also present with psychotic symptoms as found in schizophrenia. The psychotic symptoms may occur during manic or depressive episodes.
- The treatment choices for schizophrenia and other psychotic disorders include antipsychotic medication, rehabilitation and community support as well as psychotherapy.
- Clozapine therapy is mainly indicated in refractory schizophrenia and occasionally in other severe forms of psychosis under special circumstances.
- As schizophrenia often renders patients disabled, therapy that can reduce the extent of disability like clozapine remains a valid treatment option despite its severe side effect profile.

The third specific research objective was to conceptualise drug utilisation review, its purpose and applications.

- It was found that drug utilisation is a complex process.
- Drug utilisation studies tend to determine what drugs are used, in which quantity, by whom, how they are used and the circumstances surrounding their use.
- Three types of drug utilisation reviews can be performed, namely retrospective, concurrent and prospective reviews.
- The aim of a drug utilisation review is to improve the quality of care provided by health care providers and to reduce the cost associated with treatment.
- A drug utilisation review can be utilised to identify side effects and to determine their severity as well as to monitor and measure the clinical outcomes of drug therapy.
- Drug utilisation review programmes should never replace the role of the practitioner, pharmacist or nurse in the multidisciplinary team but in fact it should be utilised as an aid to assist them in carrying out their daily duties in order to improve the quality of health care provided to patients.
- Only one previous drug utilisation review on clozapine in South Africa could be found while conducting the literature review.
- Therefore, limited data are available on the use of clozapine in South Africa.

5.2.2 Empirical study

The following conclusions were drawn from the empirical study (refer Chapter 4). Each specific objective of the empirical study will be discussed briefly. The specific objectives were achieved through performing an extensive drug utilisation review through auditing the files of all the patients (n=65) included in the study sample, as well as through the use of follow-up questionnaires completed at clinic level.

The first specific objective for the empirical study was to determine the general prescribing patterns of clozapine at Elizabeth Donkin Hospital.

- According to the demographics of the study sample, most of the patients were males. Of the 65 patients included in the study 60.00% (n=39) were found to be males and 40.00% (n=26) were females.
- According to the literature the lifetime risk for schizophrenia seems to be equal in both males and females.
- The results indicated that 38.00% (n=25) of the patients in the study sample were between the age of 18 and 30 years and 40.00% (n=26) of the patients were between the age of 31 and 50 years.
- Most males were between the age of 18 and 30 years (n=20, 51,28%) and most females were between the age 31 and 50 years (n=13, 50.00%).
- The results obtained in this study are suggestive that most of the patients in the study sample were in fact those which are supposed to be active in the work place.
- These results are similar to the results provided in the World Health Report that indicated that mental disorders accounted for 6 of the 20 leading causes of disability worldwide for people between the ages of 15 and 44 years – the most productive section of the population.
- Most patients in the study sample were of African origin. Of the patients 14.00% (n=9) were white, 60.00% (n=39) were African and 26.00% (n=17) were coloured.
- The incidence of schizophrenia and other psychotic disorders, as well as the symptoms, course, and outcomes for people so diagnosed, seems to vary across cultural contexts (Myers, 2011:305). This problem is especially apparent in South Africa with its cultural diversity.
- On the other hand, ethnicity can be strongly tied to refractory schizophrenia (Teo *et al*., 2013:167).
- White European patients with schizophrenia are at greater risk for being treatment-resistant compared to other ethnicities. This Canadian study by Teo *et al*. indicated that neither gender nor a positive family history for psychiatric disorders was significantly associated with treatment resistance. One of the

reasons stated by the researchers was that because African-American patients are prescribed higher doses and given depot medications they have a lower chance of developing resistance as compared to white Europeans (Teo *et al*., 2013:168).

- About one third of the patients included in the study had more than three admissions to a psychiatric hospital (n=22, 34.00%). Most patients were diagnosed with a mental illness between six and ten years ago (n=17, 26.15%). This indicates that most patients suffered from chronic illness.
- The indications for which clozapine is mainly prescribed at the hospital were also established. It was found that all the patients included in the study had a diagnosis of either a primary or secondary psychotic disorder, with three out of four patients having a diagnosis of schizophrenia (n=49, 75.39%).
- Most patients included in the study were smokers (n=39, 60.00%). Adjustments should have been made to their clozapine dosage, since smokers require higher clozapine dosages compared to non-smokers. Only 10 (25.64%) of the patients who are known smokers received dosages ≥ 450 mg/day. No evidence in the patients' files could be found that their smoking status was taken into consideration when deciding on what clozapine dosage to use. According to the literature smokers generally require dosages in the range of 450-550 mg/day (Taylor *et al*., 2012:65).
- Positive symptoms were more prevalent than negative symptoms amongst the patients included in the study. About 97.00% (n=63) of the patients experienced at least one positive symptom of schizophrenia whereas only 71.00% (n=46) experienced at least one negative symptom.
- About one in two patients (n=34) received a prior trial of clozapine with 41.54% (n=27) of patients receiving clozapine for longer than one year.
- The average length of stay in hospital after clozapine therapy was initiated was 60.60 days compared to 50.99 days as the average hospital stay. This indicates that after clozapine therapy was initiated most patients' condition improved to such an extent that they could be discharged from hospital at a faster rate.
- The dosages used at initiation of clozapine and the maintenance and maximum dosages were established.

- The mean dosage used on day one was 41.5 mg compared to 49.6 mg on day two.
- In most cases titration during the first three weeks was performed using a dosage increment of less than 50 mg/ day (n=45, 72.58%).
- Most male patients received a maintenance dose of 400 mg (n=15, 38.46%) and most female patients received a maintenance dose of 200 mg (n=9, 34.62%). The results indicate that lower dosages were used in female patients than in male patients. These results are supported by the literature indicating that females require lower dosages of clozapine than males.
- The mean maintenance dose observed in hospital was 315.00 mg ± 140.44 mg. The maximum dosage used in an individual patient was 600 mg/day and the minimum dosage was 100 mg/day. The average maintenance dosage of 315 mg/day falls well within the recommended dosage range of 300-600 mg/day.
- However, the dosage used at initiation in some cases exceeded the recommended starting dose, therefore leading to an increased risk of side effects.

The second specific research objective for the empirical study was to determine compliance with the recommended guidelines for the initiation of clozapine therapy.

- According to the results haloperidol (n=58, 89.23%) was the most widely used first generation antipsychotic (FGA) and risperidone (n=40, 61.54%) was the most widely used SGA prior to clozapine therapy.
- In most cases the initiation of clozapine was compliant with the recommended NICE guidelines (n=41, 63.08%). This indicates that most patients received trials of both an FGA and an SGA before clozapine was initiated.
- It was found that in most cases dosage titration was performed from initiation (n=56, 86.00%).
- Generally a dosage of 25 mg was used both on the first (n=33, 53.22%) and second day (n=40, 64.51%) of clozapine initiation.
- Increments of < 50 mg/day were used mostly during the titration period (n=45, 72.58%).

- Clozapine was mainly initiated by medical officers (n=58, 89.23%) while psychiatrists only initiated clozapine in 8.00% (n=5) of cases. In 60.00% (n=36) of the cases a psychiatrist was consulted before clozapine was prescribed by a medical officer. Therefore a psychiatrist was only involved in the decision making process to initiate clozapine in 41 cases (n=41, 63.08%).
- Overall, it can be concluded that both the initiation and prescribing of clozapine was not fully compliant with the recommended guidelines. More emphasis should thus be placed on the correct initiation of clozapine and psychiatrists should become more involved in the decision making process.

The third specific research objective for the empirical study was to investigate the presence and severity of any adverse reactions that could be associated with clozapine therapy.

- Only 19 patients (29.00%) experienced adverse effects while on clozapine therapy.
- The most common adverse effect was sedation (n=5, 26.32%) followed by hypersalivation (n=3, 15.79%).
- During the study period it was brought to the primary investigator's attention that one patient developed agranulocytosis while an inpatient at the hospital and another patient developed neutropenia while receiving clozapine therapy as an outpatient at one of the community psychiatric clinics.
- Only 17 of the patients that experienced adverse effects did receive treatment (89.47%).
- Therefore almost one in three patients experienced adverse effects. Thus more attention should be paid to the detection and treatment of adverse effects amongst patients receiving clozapine therapy.

The fourth specific research objective for the empirical study was to identify possible drug interaction(s) when clozapine is used in combination with other agents.

- The presence of drug interactions was identified in most cases (n=55, 84.62%).
- In the 55 patients included in the analysis a total number of 118 drug interactions were identified between clozapine and other drugs.
- In 22 patients (40.00%) two possible drug interactions with clozapine could be identified.
- In three patients (5.45%) five interactions between clozapine and other drugs could be identified.
- Most of the drug interactions were level 4 interactions which could cause moderate-to-major effects (n=65, 55.09%).
- Twenty of the drug interactions were level one interactions (16.95%). These drug interactions could have been severe or life-threatening to the patient.
- In most cases haloperidol interacted with clozapine (n=21, 38.18%). These were level 4 interactions which could cause moderate-to-major effects.
- In 17 cases lorazepam interacted with clozapine (30.91%). In two cases citalopram interacted with clozapine (3.64%). These were level 1 interactions that could have had severe or life-threatening effects.
- It is a cause of concern that so many drug interactions could be identified between clozapine and other agents. Special care needs to be taken when clozapine is prescribed concomitantly with agents such as citalopram and lorazepam that have a potential to cause level 1 interactions.

The fifth specific research objective for the empirical study was to assess the extent of compliance with the recommended guidelines for haematological and metabolic monitoring of clozapine both at Elizabeth Donkin Hospital as well as the community psychiatric clinics and long-term care centres after discharge from hospital.

- In the majority of cases mandatory baseline haematological monitoring was not performed at the hospital (n=36, 57.00%).

- Baseline metabolic monitoring performed at inpatient level was found non-compliant in all the observed cases (n=63, 100%).
- In most cases follow-up haematological monitoring performed at the hospital was non-compliant with the recommended guidelines (n=48, 77.00%).
- In all of the observed cases follow-up metabolic monitoring performed at the hospital did not comply with the recommended guidelines (n=62, 100%).
- After discharge from Elizabeth Donkin Hospital most patients attended clinics (n=46, 70.77%) whereas a smaller proportion of patients were transferred to long-term care centres (n=19, 29.23%). Most facilities were poorly informed whether the white blood cell (WBC) count monitoring should be continued at weekly, two weekly or monthly intervals upon discharge of the patient from hospital (n=40, 62.00%).
- According to information obtained from the clinics and long-term care centres most of them did not receive any form of communication (e.g. written/ verbal) with regard to the point of monitoring of WBC counts upon discharge of patients from the hospital (n=27, 41.54%). A discrepancy therefore exists between the results obtained at the hospital and the clinics/long-term care centres. This could be due to poor communication between the facilities.
- In 96.00% (n=44) of the cases the haematological monitoring performed at the clinics and long-term care centres three months after discharge from hospital was non-complaint with the recommended guidelines.
- In only 54.00% (n=25) of the cases the follow-up metabolic monitoring performed three months after discharge from hospital was compliant with the recommended guidelines.
- In 86.00% (n=36) of the cases the haematological monitoring performed at the clinics and long-term care centres six months after discharge from hospital was non-complaint with the recommended guidelines.
- In only 62.00% (n=26) of the cases the follow-up metabolic monitoring performed six months after discharge from hospital was compliant with the recommended guidelines.
- Therefore, both the haematological and metabolic monitoring performed was found to be inadequate.

- A cause of concern is that the metabolic monitoring was poorly performed both at inpatient and at outpatient level.
- One of the possible reasons for the observed poor compliance with the guidelines for metabolic and haematological monitoring could be that the focus of clinicians is on the improvement of the patient's mental state, which in turn can result in the haematological and metabolic monitoring of clozapine being overlooked.

The sixth specific research objective for the empirical study was to determine the total monetary costs involved when admitting a patient and initiating the patient on clozapine therapy.

- The average cost of clozapine therapy received per patient was R 294.20 ± R273.95.
- The average cost of hospital stay per patient was R 120 939.05 ± R 91 351.80.
- For one patient the cost of hospitalisation was R412 207.25. However, this patient was admitted for 325 days.
- The average cost for laboratory investigations performed per patient was R 149.25 ± R 175.14.
- The minimum cost of admission was R 5 251.61 and the maximum cost was R 414 650.21. The average cost of admission per patient was R 121 386.15 ± R 91 636.36.
- The sum of the costs of admissions for all the patients included in this study was R 15 779 961.68. However, this indicates the high costs associated with admitting patients to hospital. Efforts therefore need to be made to try and reduce the need for hospitalisation of patients.
- In an attempt to cut costs it is advised that clozapine should be initiated earlier on during the course of treatment. According to Taylor *et al*. (2002:21), the use of clozapine provides overall savings in health care costs, mainly through reductions in admissions and hospital stay.

The seventh specific research objective for the empirical study was to determine the percentage of patients still on clozapine three months as well as six months after discharge from Elizabeth Donkin Hospital.

- A higher clozapine discontinuation rate was observed 6 months (n=23, 35.00%) after discharge compared to 3 months (n=19, 29.00%) after discharge.
- The discontinuation rates observed in this study were lower than the discontinuation rate observed in international literature such as the Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) study.
- This is however remarkable, since CATIE was conducted in a developed country whereas this study was conducted in a developing country with limited health care resources.

5.3 RECOMMENDATIONS

This pharmacoepidemiological evaluation has yielded useful information pertaining to the research topic and therefore the following recommendations can be made:

- Health care professionals need to be educated on the use of existing treatment guidelines to promote the rational use of clozapine.
- The implementation of an ongoing drug utilisation review (DUR) programme at Elizabeth Donkin Hospital will assist in identifying problems with the use of clozapine in order to improve the rational use of clozapine.
- The role of the psychiatrist in the initiation of clozapine needs to be re-emphasized. Clozapine should only be initiated by a psychiatrist. However, at inpatient level a medical officer could initiate clozapine after he/she consulted with the treating psychiatrist in the ward.
- The primary investigator of the study developed a guidance document for the initiation and monitoring of clozapine. The guidance document should be included in patients' files to assist with the safe and effective monitoring of clozapine. Presentations aimed at the medical officers and psychiatrists employed at Elizabeth Donkin Hospital should be performed to explain their role

in the initiation and monitoring of clozapine and the proposed guidance document must be presented to them. A presentation should also be arranged for the nursing staff employed at the hospital. The aim of the presentation should be to inform them about their role in the monitoring of a patient receiving clozapine therapy (See Appendix P attached).

- The date on which clozapine therapy was started in hospital as well as the last white blood cell (WBC) count result should be included on the discharge form. On the discharge summary the medical officer or psychiatrist should provide instructions on how the monitoring of the WBC count should be continued at the community psychiatric clinic or long-term care centres after discharge, i.e. monitored weekly, two weekly or monitored monthly. A separate document can be developed on which the medical officer or psychiatrist can provide the necessary instructions on the monitoring requirements regarding the patient's clozapine therapy. However, there will be a risk associated with this in that the clinic/long-term care centre might not receive the additional form that should accompany the discharge summary. Therefore it is suggested that the information should be included on the existing discharge summary to facilitate the process.
- A multi-disciplinary team approach is required with regard to the management of patients receiving clozapine therapy. Workshops should be organised in which nurses, pharmacists and doctors could learn to communicate and provide assistance to each other in order to optimise a patient's clozapine therapy.
- While conducting the analysis the primary investigator observed that one patient was discharged from hospital while the dosage of clozapine was still being tapered upwards. Education thus need to be provided to medical officers that it is advisable that clozapine titration should first be completed to achieve maintenance level before a patient should be discharged from hospital. The main reason why cautious titration is preferred is since it reduces the risks for orthostatic hypotension, bradycardia, syncope and seizures (Sadock *et al*., 2009: 3207).
- Education needs to be provided to health care practitioners on the metabolic markers and WBC count monitoring requirements of clozapine.
- Health care professionals need to be educated on the fact that when clozapine therapy is stopped for more than two days, then clozapine needs to be

reintroduced by titrating upwards slowly. Patients should not just be continued on the maintenance dose that they received prior to the discontinuation of clozapine since this may result in toxicity.

- Education needs to be provided to medical practitioners regarding the dosage of clozapine in smokers. Higher clozapine dosages are required in smokers compared to non-smokers, since nicotine reduces clozapine plasma levels by up to 50% due to increased hepatic metabolism (CYP1A2).
- Education needs to be provided to patients to enable them to recognise the signs and symptoms of agranulocytosis associated with clozapine therapy. Patients need to be encouraged to inform their clinician immediately as soon as they develop a sore throat, fever, painful mouth ulcers, anal ulcers or flu-like symptoms while taking clozapine therapy. The pharmacist can play an active role in educating patients on the signs and symptoms of agranulocytosis.
- Family interventions can be performed in an attempt to improve adherence to medication. A session can be arranged with a patient's family to inform them that their relative is receiving clozapine therapy. During the session the family should be educated on the possible adverse effects of clozapine with which the patient may present and the importance of performing regular haematological and metabolic monitoring while the patient is receiving clozapine. This session can be arranged between the pharmacist and the patient's relatives.
- Pamphlets can be designed for health care professionals and patients that provide information on the use of clozapine, e.g. dosages, side effects and monitoring requirements.
- The implementation of a computer programme or an evaluation system would help to identify interactions between clozapine and other drugs.
- Patients with schizophrenia and other psychotic disorders already have a decreased life expectancy compared to the general population. The risk of developing metabolic syndrome associated with the use of clozapine may reduce the patient's life expectancy even further (Sadock *et al*., 2009:1573). Further investigations need to be performed to determine what can be done to limit the occurrence of metabolic syndrome amongst patients receiving clozapine to the minimum.

- Specific guidelines are required for both the haematological and metabolic monitoring of clozapine. Limited health care resources are available and the costs of laboratory investigations are expensive. Therefore, it is recommended that the WBC count be monitored weekly for the first eighteen weeks and thereafter monthly. It is also difficult for the patients attending community psychiatric clinics for follow-up visits to travel there twice a month since most of them are from a lower income group.
- The Standard treatment guidelines: Hospital Level for adults (2012) need to be reviewed to incorporate the National Institute for Health and Clinical Excellence (NICE) guidelines for the initiation of clozapine. According to the NICE guidelines clozapine should be offered to a patient after a trial of a FGA as well as a trial of a non-clozapine SGA was found to be unsuccessful (NICE, 2009:10).
- A specific guideline needs to be developed for the baseline as well as follow-up metabolic monitoring of patients initiated on clozapine that is suitable for the South African setting.
- When clozapine is correctly indicated for a patient with treatment-resistant schizophrenia and the patient is responding well to clozapine, the psychiatrist might be reluctant to discontinue clozapine therapy although the patient might show signs of metabolic syndrome. If clozapine is the only option therapy might need to be continued. In these situations the benefits of clozapine therapy need to be weighed against the possible risks associated with metabolic syndrome (e.g. cardiovascular disease and diabetes mellitus).
- The pharmaceutical companies manufacturing clozapine in South Africa should establish a clozapine patient monitoring system similar to those in first world countries such as the United Kingdom and United States that serve as a central monitoring system for patients initiated and maintained on clozapine. The system should however be developed in such a way as to incorporate the special needs for the monitoring of clozapine in the South African setting. This will ensure that the monitoring of clozapine is uniformly performed in both the public and private health care sectors of South Africa. Especially now with the introduction of the National Health Insurance (NHI) it might be the ideal opportunity to introduce a special monitoring system for clozapine in South Africa.

- A more holistic approach is needed in the management of patients with psychiatric conditions to facilitate early detection and reporting of signs of metabolic syndrome that can be associated with the use of SGAs. Psychiatrists and medical officers at clinic level should interact to carry out efficient monitoring of all relevant parameters so that early interventions to reduce the risk of cardiovascular disease and type 2 diabetes are possible. A shared care agreement is a possible way to enhance care of patients receiving clozapine therapy. This agreement can address responsibilities for prescribing between the psychiatrist and medical officer (Gumber *et al*., 2010:394).
- Under ideal circumstances designated metabolic clinics can be established in the community health centres in the Nelson Mandela Metropole to assist in the monitoring of metabolic side effects in patients receiving clozapine and other SGAs. Consultant psychiatrists can then refer their patients to these metabolic clinics. The results of the metabolic parameters investigated at each visit can be recorded on a standard form and included in the patient's clinic file. However, due to the availability of limited health care resources this might be considered as a challenge at present.
- Awareness needs to be created on the use of contraception in female patients receiving clozapine who have not yet reached menopause. Clozapine has a category B risk in pregnancy and hence the benefit needs to be weighed against the possible risk of harm to the foetus when clozapine is administered to women of child-bearing potential (Rossiter, 2012:475).
- Investigations need to be performed to establish the reason(s) for clozapine discontinuation at both inpatient and outpatient level.
- The earlier use of clozapine in adequate dosages represents a neglected therapeutic opportunity in this age of stagnated antipsychotic innovation.
- Treatment with clozapine should not be considered as a last resort. Clozapine therapy should be initiated as soon as a trial of both an FGA and a non-clozapine SGA was found to be unsuccessful.

The following are recommendations for future studies:

- To implement drug utilisation reviews and similar studies on clozapine in other provinces in the country to determine a general overview of clozapine usage in South Africa as well as to identify national trends in the use of clozapine.
- Future research projects can be performed to determine whether specific monitoring guidelines for clozapine are required for the South African setting.
- A future study can be performed to establish the prevalence of agranulocytosis and metabolic syndrome associated with the use of clozapine in the South African population.
- To perform a similar study in which two groups of patients are evaluated to determine whether clozapine is in fact superior to a conventional antipsychotic in the South African setting. The one treatment group can be placed on clozapine and the other group on haloperidol. The aim of the study should be to compare the efficacy of clozapine to that of haloperidol in the South African population.
- Future studies can be conducted to determine the role of the pharmacist in the provision of clozapine therapy to patients.
- In future, this study could be expanded to include a patient-questionnaire component to address patient concerns about the use of clozapine.
- A follow-up study can be conducted to see how many patients are still on clozapine 18 months after discharge from hospital to determine the 18-month discontinuation rate.

5.4 LIMITATIONS OF THE STUDY

The following were limitations of the study:

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- Caution needs to be exercised when generalising the results, since the data were collected at one psychiatric hospital in the Eastern Cape and can thus not be reflective of the situation throughout South Africa.

- The results of this study may not be representative of the trends and patterns in the population of the Eastern Cape as they reflect patterns in public practice only; without considering the private sector trends in the Eastern Cape.
- No South African guidelines are currently available for the initiation of clozapine and therefore international guidelines had to be considered.
- No South African guidelines are currently available for the metabolic monitoring of clozapine and thus international guidelines had to be considered which are not specifically adapted for the South African setting.
- Limited literature was available because of little research on clozapine usage in both the private and public health care sectors in South Africa.
- Some patient's medical records lacked information and therefore had to be excluded from some of the analyses performed.
- A diagnosis of 'treatment-resistant schizophrenia' or 'refractory schizophrenia' could not be found in any of the patient files that were included in this study. It seems that usually only 'schizophrenia' was stated on axis I of the DSM-IV-TR multiaxial patient evaluation.
- Patients that experienced serious adverse effects on clozapine and whose treatment was stopped were not included in the study, since only patients discharged on clozapine were included. Hence, this study does not reflect those patients that experienced life-threatening adverse effects such as agranulocytosis.
- It was inevitable that recall inaccuracy and bias could not be avoided with regard to the completion of questionnaires by the nursing staff at the clinics and long-term care centres.
- Some patients did not attend clinics after discharge and some could not be traced since they moved during the course of the study. These patients had to be omitted from the follow-up questionnaire analyses.
- Due to time and budget constraints the second questionnaire i.e. the six-month follow-up questionnaire had to be sent to the facilities, since the principal investigator could not personally visit the facilities again as she is employed full-time.

- The study focused on the initiation of clozapine at inpatient level only and did not consider the initiation of clozapine in outpatients attending community psychiatric clinics.
- Due to time and budget constraints an intervention could not be performed to facilitate the more effective monitoring of clozapine in the public health sector of the Nelson Mandela Metropole. However, the aim of the study was only to investigate current monitoring practices.

5.5 CHAPTER SUMMARY

It is hereby concluded that all the objectives of the study have been achieved. The recommendations and limitations of the study were discussed in this chapter.

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APPENDIXES

Appendix A

Appendix B

Appendix C

Appendix D

Appendix E

.

Appendix F

Appendix G

Appendix H

Appendix I

Appendix J

Appendix K

Appendix L

Appendix M

Appendix N

Appendix O

Appendix P

Appendix Q

Appendix R

Appendix S

Appendix T

Appendix U

Appendix V

Glossary

5-HT	Serotonin
ACE	Angiotensin-Converting Enzyme
ACT	Assertive Community Treatment
AIDS	Acquired Immunodeficiency Syndrome
ANC	Absolute Neutrophil Count
BMI	Body Mass Index
BP	Blood Pressure
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CHC	Community Health Centre
CIOMS	Council for International Organisations of Medical Sciences
CK	Creatine Kinase
cm	Centimetre
CPMS	Clozaril Patient Monitoring System
CT	Computed Tomography
CYP	Cytochrome P450
D	Dopamine
DSM	Diagnostic and Statistical Manual of Mental Disorders
DUR	Drug Utilisation Review
ECT	Electroconvulsive Therapy
EEG	Electroencephalography
EPS	Extrapyramidal Side Effects
FBC	Full Blood Count
FDA	Food and Drug Administration
FGA	First Generation Antipsychotic
GAF	Global Assessment of Functioning
GMC	General Medical Condition
HDL	High-Density-Lipoproteins
HIV	Human Immunodeficiency Virus
ICD	International Classification of Diseases

InterSept	International Prevention of Suicide
IPAP	International Psychopharmacology Algorithm Project
kg	Kilogram
LDL	Low-Density-Lipoproteins
LFTs	Liver Function Tests
m	Metre
MCC	Medicines Control Council
mg	Milligram
MO	Medical Officer
MRI	Magnetic Resonance Imaging
NAMI	National Alliance on Mental Illness
NHI	National Health Insurance
NHLS	National Health Laboratory Service
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMS	Neuroleptic Malignant Syndrome
NOS	Not Otherwise Specified
PET	Positron Emission Tomography
R	Rand
SABDA	Schizophrenia and Bipolar Disorders Alliance
SASH	South African Stress and Health
SGA	Second Generation Antipsychotic
SMR	Standardised Mortality Ratio
SSRI	Selective Serotonin Re-uptake Inhibitors
TD	Tardive Dyskinesia
TTO	Treatment Taken Out
US	United States
UK	United Kingdom
WBC	White Blood Cell
WHO	World Health Organization
yrs	Years

Initial Data Collection Tool

1. Demographics

(✓ appropriate option and supply information requested)

Patient identification no:					
Admission date:					
Number of previous admissions:	**0**	**1**	**2**	**3**	**> 3**
Diagnosis:	**Schizophrenia**	**Bipolar disorder**	**Schizoaffective disorder**		**Other:**
Age:	**< 20 yrs**	**20-30 yrs**	**30-40 yrs**	**40-50 yrs**	**> 50 yrs**
Gender:	**Male**		**Female**		
Race:	**White**	**African**	**Coloured**	**Indian**	**Other:**
Family history:	**Diabetes mellitus**	**Hypercholesterolaemia**	**Obesity**	**Other:**	**No information**
Smoking status:	**Non-smoker**	**Smoker**	**No information**		
Drug abuse:	**Alcohol**	**Cannabis**	**Methamphetamine**	**Other:**	**No information**
Date of discharge:					

2. Medication history for current admission

(✓ appropriate option and name the antipsychotics already used)

Two previous antipsychotics prescribed of which one is an atypical antipsychotic:	
Two previous antipsychotics prescribed of which both are typical antipsychotics:	
Only one previous antipsychotic prescribed - an atypical antipsychotic:	
Only one previous antipsychotic prescribed - a typical antipsychotic:	
Clozapine was the first antipsychotic prescribed:	
Patient was on Clozapine in the past:	

3. Current medication

(Supply information requested)

Drug name	Dose	Frequency	Start date	Discontinuation date

4. Drug interactions

(Yes/No and specify)

Any possible drug interactions identified?	

5. Dosage titration

(Yes / No, ✓ appropriate option and supply information requested)

Clozapine dosage titration performed from initiation?		
Initial dosage used:		
Initial dose of 12,5mg on 1st day	Initial dose of 25mg on 1st day	Initial dose of > 25mg on 1st day
Dosage of 25 mg on the 2nd day	Dosage of 50mg on the 2nd day	Dosage of > 50 mg on the 2nd day
Titration performed within first 2 - 3 weeks:		

Increments < 50 mg/day	Increments of 50 mg/day		Increments > 50 mg/day
Maintenance dose:		**Maximum dose:**	

6. Prescriber (initiator)

(Supply information requested)

Medical officer (MO), Psychiatrist (P) or Unknown (U):	
If a MO initiated Clozapine, was a psychiatrist consulted before it was prescribed? Yes/ No/ No information in file	

7. Adverse effects

[✓ appropriate option(s)]

Any adverse effects reported? Yes/ No/ No information					
If yes, which adverse effects were experienced:		Agranulocytosis	Hypersalivation	Constipation	Hypertension
Weight gain	Nausea	Fever	Hypotension	Seizures	Tachycardia
Was the adverse effect(s) treated and how was it treated? Yes/No and specify:					

8. Baseline monitoring

(✓ in appropriate column and supply result if available)

Parameter:	**Yes:**	**No:**	**Result:**
White cell count (WCC):			
Weight (kg):			
Height (m):			
Waist circumference (cm):			
BMI (kg/m²):			
Fasting plasma glucose:			
Fasting Lipogram:			
Total Cholesterol:			
Triglycerides:			
LDL:			

9. Follow-up monitoring up untill discharge

(✓ in appropriate column)

Parameter:	**4 weeks**	**12 weeks**	**16 weeks**	**18 weeks**
White cell count (WCC):				
Weight (kg):				
Height (m):				
Waist circumference (cm):				
BMI (kg/m²):				
Fasting plasma glucose:				

Fasting Lipogram:				
Total Cholesterol:				
Triglycerides:				
LDL:				

10. Extent of compliance with guidelines for WCC monitoring

(Fully compliant, Partially compliant or Non-compliant)

Compliance with the recommended guidelines for baseline monitoring?	
Compliance with the recommended guidelines for follow-up monitoring?	

11. Extent of compliance with guidelines for Metabolic monitoring

(Fully compliant, Partially compliant or Non-compliant)

Compliance with the recommended guidelines for baseline monitoring?	
Compliance with the recommended guidelines for follow-up monitoring?	

12. Clinic follow-up

(Supply the information requested)

Name of clinic to which patient is discharged to:	

13. Point of monitoring upon discharge

(State Yes or No)

Was it indicated on the discharge note where in the process the WCC monitoring currently is?	

Data collection tool

1. Demographics **Tick (✓) the appropriate option and supply information where requested**					
Patient identification number:					
Date of birth:			**Age:**		
Gender:	Male		Female		
Race:	White	African	Coloured	Indian	Other:
2. Admission History **Tick (✓) the appropriate option and supply information where requested**					
Admission date:					
Number of previous admissions:	0	1	2	3	> 3
Date of discharge:					
3. Social History **Tick (✓) the appropriate option**					
Smoking status:	Non-smoker	Smoker	No information		
Drug abuse:	Alcohol	Cannabis	Methamphetamine	No information	Other:
4. Medical History **Tick (✓) the appropriate option and supply the information where requested**					
Family history:	Type 2 Diabetes mellitus	Obesity	Hypercholesterolaemia	No information	Other:
Co-morbid disease states:	Hypertension	Type 2 Diabetes mellitus	Hypercholesterolaemia	Epilepsy	Other:
Surgical history:	Yes	No	No information		
If yes, please specify:					
Date of first diagnosis of a mental disorder (if available):					
Diagnosis (current admission):	Schizophrenia	Bipolar disorder	Schizoaffective disorder		Other:

Positive Symptoms reported during current admission:		Hallucinations	Delusions	Other:
Negative Symptoms reported during current admission:		Blunting of affect	Avolition	Other:

5. Clozapine usage

*** Information about previous admissions from the patient's file**

Was the patient on clozapine before?	Yes	No	No information available	
Is the date available for the first initiation of clozapine?		Yes	No	No information
If yes, state the date of the first initiation of clozapine:				
Number of years passed since first initiation of clozapine:				
Supply the date on which clozapine was started in hospital for this admission:				
Length of stay in hospital (in terms of days) after clozapine was initiated:				

6. Other drugs

*** Information about previous admissions from the patient's file**

Are the names of previous antipsychotics used available?		Yes	No	No information
If yes, supply the names of the antipsychotics:				
Trials of previous antipsychotics used before initiating clozapine:				
Two previous antipsychotics prescribed of which one is an atypical antipsychotic			Yes	No
Two previous antipsychotics prescribed of which both are atypical antipsychotics			Yes	No
Two previous antipsychotics prescribed of which both are typical antipsychotics			Yes	No
One previous antipsychotic prescribed - an atypical antipsychotic			Yes	No
One previous antipsychotic prescribed - a typical antipsychotic			Yes	No
Clozapine was the first antipsychotic prescribed			Yes	No
Compliance with the guidelines for the initiation of clozapine		Fully compliant	Non-complaint	No information
Use of contraceptive(s) by female patients	Yes	No	No information available	
If yes, supply the name of the contraceptive:				
If no, what is the possible reason for not being on contraception:				

7. Current medication

*** Excluding clozapine**

Drug name	Dose	Frequency	Start date	Discontinuation date

8. Drug interactions

(Yes / No and specify)

Any possible drug interactions identified?	Yes	No	No information available
If yes, provide information about the drug interaction(s)			

9. Clozapine dosage titration

(Yes / No, Tick (✓) appropriate option and supply information where requested)

Was clozapine dosage titration performed from initiation?	Yes	No	No information

Tick (✓) from the list supplied the initial dosages used:

Initial dose of 12,5mg on 1st day	**Initial dose of 25mg on 1st day**	**Initial dose of 37,5mg on 1st day**	**Other:**
Dosage of 25 mg on the 2nd day	**Dosage of 50mg on the 2nd day**	**Dosage of 75 mg on the 2nd day**	**Other:**

Tick (✓) from the list supplied the increments with which the dosage was increased within the first 2-3 weeks of the titration period:

Increments < 50 mg/day	**Increments of 50 mg/day**	**Increments > 50 mg/day**
Maintenance dose:	**Maximum dose:**	

Record actual titration of clozapine from initiation

Day of titration period	Date	Dose	Frequency	Amount of 25 mg tabs	Amount of 100mg tabs

10. Costs for admission

*** Monetary costs supplied in South African Rand**

Cost of clozapine therapy while in hospital:	
Cost of hospital stay for this admission:	
Cost of laboratory investigations performed:	
Total cost of this admission in hospital:	

11. Prescriber (initiator)

(Supply information requested)					
Who prescribed clozapine?			Medical officer (MO)	Psychiatrist (P)	Unknown (U)
If prescribed by a MO, did he/she consult with a psychiatrist?			Yes	No	No information

12. Adverse effects

[✓ appropriate option(s)]

Any adverse effects reported?		Yes	No	No information available	
If yes, which adverse effects were experienced:		Agranulocytosis	Hypersalivation	Constipation	Hypertension
Weight gain	Nausea	Fever	Hypotension	Seizures	Tachycardia
Other:					Not applicable
Was the adverse effect(s) treated?		Yes	No	No information	Not applicable
If yes, specify how the adverse effects were treated					

13. Baseline monitoring

(✓ in appropriate column and supply result if available)

Parameter:	Yes:	No:	Date performed:	Result:
Haematological monitoring				
White blood cell count (WBC):				
Metabolic monitoring				
Weight (kg):				
Height (m):				
Waist circumference (cm):				
BMI (kg/m²):				
Blood pressure (mmHg):				
Fasting plasma glucose (mmol/l):				
Fasting Lipogram:				
Total Cholesterol (mmol/l):				
Triglycerides (mmol/l):				
LDL (mmol/l):				

14. Follow-up monitoring up untill discharge

(Supply the requested information)		
Parameter:	**Date performed:**	**Result:**
Haematological monitoring		
White blood cell count (WBC):		
Metabolic monitoring		
Weight (kg):		
Waist circumference (cm):		
BMI (kg/m²):		
Fasting plasma glucose (mmol/L):		
Fasting Lipogram:		
Total Cholesterol (mmol/L):		
Triglycerides (mmol/L):		
LDL (mmol/L):		

15. Extent of compliance with guidelines for WBC count monitoring

(State whether fully compliant / non-compliant / no information available)

Compliance with the recommended guidelines for baseline monitoring?	Fully compliant	Non-compliant	No information
Compliance with the recommended guidelines for follow-up monitoring?	Fully compliant	Non-compliant	No information

16. Extent of compliance with guidelines for Metabolic monitoring

(State whether fully compliant / non-compliant / no information available)

Compliance with the recommended guidelines for baseline monitoring?	Fully compliant	Non-compliant	No information
Compliance with the recommended guidelines for follow-up monitoring?	Fully compliant	Non-compliant	No information

17. Follow-up after discharge

(Supply the information requested)

Name of clinic to which the patient was discharged to:	

18. Point of monitoring upon discharge

(State Yes or No)

Was it indicated on the discharge note where in the process the periodic WBC count monitoring was?	Yes	No

Questionnaire for nursing personnel at the clinics

*** Please answer the following questions.**
*** Tick (✓) the appropriate option or supply the necessary information where requested.**

Name of Community Psychiatric Clinic:	
Patient Identification Number:	

Question 1

Is the above mentioned patient still on clozapine 3 months after discharge from Elizabeth Donkin Hospital?

	Yes	**No**	**No information available**

Question 2

If answered no, why is the patient no longer on clozapine?

	Adverse effects	**Non-compliance**	**No information**	**Other:**

Question 3

If the patient is still on clozapine what is the current dosage?

Question 4

Did the hospital inform you upon discharge where in the process the patient's White Cell Count monitoring is ?

	Yes	**No**	**No information available**

Question 5

Currently, how is the follow-up White Cell Count monitoring performed?

	Weekly	**Two weekly**	**Monthly**	**Other:**

Question 6

Currently, how is the follow-up metabolic monitoring performed? (i.e. weight, lipids, blood glucose monitoring)

	Monthly	**Two Monthly**	**Three Monthly**	**Other:**

Date:	***Rank:***
Print Name & Surname:	***Signature:***

Questionnaire for nursing personnel at the clinics

*** Please answer the following questions.**
*** Tick (✓) the appropriate option or supply the necessary information where requested.**

Name of Community Psychiatric Clinic:	
Patient Identification Number:	

Question 1

Is the above mentioned patient still on clozapine 6 months after discharge from Elizabeth Donkin Hospital?

	Yes	**No**	**No information available**

Question 2

If answered no, why is the patient no longer on clozapine?

	Adverse effects	**Non-compliance**	**No information**	**Other:**

Question 3

If the patient is still on clozapine what is the current dosage?

Question 4

Currently, how is the follow-up White Blood Cell Count monitoring performed?

	Weekly	**Two weekly**	**Monthly**	**Other:**

Question 5

Currently, how is the follow-up Metabolic monitoring performed? (i.e. weight, lipids, blood glucose monitoring)

	Monthly	**Two Monthly**	**Three Monthly**	**Other:**

Date:	***Rank:***
Print Name & Surname:	***Signature:***

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ETHICS APPROVAL OF PROJECT

2012/07/31

The North-West University Ethics Committee (NWU-EC) hereby approves your project as indicated below. This implies that the NWU-EC grants its permission that, provided the special conditions specified below are met and pending any other authorisation that may be necessary, the project may be initiated, using the ethics number below.

Project title : Clozapine usage in a public sector psychiatric hospital in the Nelson Mandela Metropole

Project Leader: Prof JC Lamprecht

Ethics number:

N	W	U	-	0	0	0	0	3	-	12		-	A	2
Institution				Project Number						Year			Status	

Status: S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation

Approval date 2012/05/04 **Expiry date**:2017/05/03

Special conditions of the approval (if any): None

General conditions:

While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, please note the following:

- *The project leader (principle investigator) must report in the prescribed format to the NWU-EC:*
  - *annually (or as otherwise requested) on the progress of the project,*
  - *without any delay in case of any adverse event (or any matter that interrupts sound ethical principles) during the course of the project.*
- *The approval applies strictly to the protocol as stipulated in the application form. Would any changes to the protocol be deemed necessary during the course of the project, the project leader must apply for approval of these changes at the NWU-EC. Would there be deviated from the project protocol without the necessary approval of such changes, the ethics approval is immediately and automatically forfeited.*
- *The date of approval indicates the first date that the project may be started. Would the project have to continue after the expiry date, a new application must be made to the NWU-EC and new approval received before or on the expiry date.*
- *In the interest of ethical responsibility the NWU-EC retains the right to:*
  - *request access to any information or data at any time during the course or after completion of the project;*
  - *withdraw or postpone approval if:*
    - *any unethical principles or practices of the project are revealed or suspected,*
    - *it becomes apparent that any relevant information was withheld from the NWU-EC or that information has been false or misrepresented,*
    - *the required annual report and reporting of adverse events was not done timely and accurately,*
    - *new institutional rules, national legislation or international conventions deem it necessary.*

The Ethics Committee would like to remain at your service as scientist and researcher, and wishes you well with your project. Please do not hesitate to contact the Ethics Committee for any further enquiries or requests for assistance.

Yours sincerely

Prof Amanda Lourens
(chair NWU Ethics Committee)

In order to comply with ethical standards this document will be available from MUSA. Terms and conditions apply.

Enquiries can be sent to:

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Clozapine monitoring guide

Baseline results

Parameter	Date	Result
WBC count		
Fasting total cholesterol		
Fasting HDL		
Fasting LDL		
Fasting plasma glucose		
Weight		
Waist circumference		
BMI		
BP		
Pulse		
Temperature		

*** Notify the patient's doctor if results outside these limits occur***

Parameter	
White blood cell (WBC) count	< 3.0 x 10^9/L
Fasting total cholesterol	> 5 mmol/L
Fasting triglyceride level	≥ 1,7 mmol/L
Fasting high density lipoprotein	< 1,03 mmol/L (men)/ < 1,29 mmol/L (women)
Fasting plasma glucose level	≥ 5,6 mmol/L
Blood pressure (BP)	≥ 130/85 mmHg
Waist circumference	> 102 cm for men and > 88 cm for women
BMI	> 30 kg/m^2
Pulse	> 100 beats per minute
Temperature	> 38 °C

Follow-up haematological monitoring

WBC count need to be monitored as follow:

*** Weekly for the first 18 weeks**
*** Then 2 weekly for the remainder of the year**
*** Thereafter monthly**

Parameter	Week 1		Week 2		Week 3		Week 4		Week 5	
WBC count	Date	Result	Date	Result	Date	Result	Date	Result	Date	Result
	Week 6		Week 7		Week 8		Week 9		Week 10	
	Date	Result	Date	Result	Date	Result	Date	Result	Date	Result
	Week 11		Week 12		Week 13		Week 14		Week 15	
	Date	Result	Date	Result	Date	Result	Date	Result	Date	Result
	Week 16		Week 17		Week 18		Week 20		Week 22	
	Date	Result	Date	Result	Date	Result	Date	Result	Date	Result
	Week 24		Week 26		Week 28		Week 30		Week 32	
	Date	Result	Date	Result	Date	Result	Date	Result	Date	Result

Follow-up metabolic monitoring

Parameter	1 Month		3 Months		4 Months		6 Months		12 Months	
	Date	Result	Date	Result	Date	Result	Date	Result	Date	Result
Fasting total cholesterol										
Fasting HDL										
Fasting LDL										
Fasting plasma glucose										
Weight										
Waist circumference										
BMI										
Pulse										
Blood pressure										

Monitoring of Clozapine in a Public Sector Psychiatric Hospital and Associated Clinics

Moolman M, Esterhuysen W, Joubert R, Lamprecht JC, Lubbe MS
Medicine Usage in South Africa (MUSA), School of Pharmacy, North-West University, Potchefstroom Campus

Introduction

Clozapine has shown superior efficacy, for both the positive and negative symptoms of schizophrenia, over conventional antipsychotics. The reputation of clozapine lies mainly with its repeated proven efficacy in the treatment of refractory schizophrenia.

South Africa lacks uniform provincial or national guidelines regulating practices in the treatment of mental disorders. International guidelines may be considered, which are not specifically adapted for the South African setting. These guidelines recommend both the haematological and metabolic monitoring of clozapine. The Standard Treatment Guidelines, Hospital Level for Adults, suggest that a psychiatrist should initiate clozapine therapy and that haematological monitoring should be performed as is instructed on the package insert. At present there are no South African guidelines recommending the metabolic monitoring of clozapine.

The motivation for this study is to assess the safe and effective use of clozapine, through performing an investigation on the monitoring patterns followed in a tertiary hospital, using a public sector psychiatric hospital and community psychiatric clinics as a model.

Objectives

The objectives were to determine whether baseline and follow-up haematological and metabolic monitoring of clozapine was performed.

Methods

In this pharmacoepidemiological study a retrospective drug utilisation review of clozapine was performed. The study was observational in design and included both qualitative and quantitative data. Data were collected from the files of 65 patients discharged on clozapine between 1 December 2010 and 29 February 2012 from the hospital. Follow-up investigations were performed at the clinics.

Results

Non-compliance with the recommended guidelines for follow-up haematological monitoring occurred in 77,4% of patients in the hospital setting (n=48) as well as in 95,7% of patients during the 3 month follow-up at the clinics (n=44). Non-compliance with the guidelines for follow-up metabolic monitoring occurred in all the observed patients in the hospital setting (n=62) as well as in 45.7% of patients in the clinic setting (n=21).

Recommendations and Conclusion

It was found that clozapine was inadequately monitored. A proposed guidance document must be included in patients' files to assist in the safe and effective monitoring of clozapine.

Retrospective review of clozapine prescribing patterns

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Medicine Usage in South Africa (MUSA), School of Pharmacy, North-West University, Potchefstroom Campus, 2520

Background

About 30% of schizophrenic patients fail to respond to conventional antipsychotics. Clozapine has shown superior efficacy, for both the positive and negative symptoms of schizophrenia, over conventional antipsychotics. The reputation of clozapine lies mainly with its repeated proven efficacy in the treatment of refractory schizophrenia.

South Africa lacks uniform provincial or national guidelines regulating practices in the treatment of mental disorders. International guidelines may be considered, which are not specifically adapted for the South African setting. The Standard Treatment guidelines: Hospital level for Adults suggests that a psychiatrist should initiate clozapine therapy. The National Institute for Health and Clinical Excellence (NICE) clinical guideline for schizophrenia suggests that before clozapine therapy is initiated, at least two other antipsychotics, at adequate doses, should be tried. At least one of these should be a non-clozapine second generation antipsychotic.

The motivation for this study was to assess the prescribing patterns of clozapine in a tertiary hospital, using a public sector psychiatric hospital and community psychiatric clinics as a model.

Methods

A quantitative retrospective drug utilisation review of clozapine was performed in a public sector psychiatric hospital. Data were collected from the files of 65 patients discharged on clozapine between 1 December 2010 and 29 February 2012. Follow-up investigations were performed, at the clinics, both three and six months after discharge from hospital.

Results

Compliance with the NICE guideline for the appropriate initiation of clozapine was 63,1% (n=41). Compliance with the Standard Treatment guidelines for the initiation of clozapine by a psychiatrist was 63,1% (n=41). In 86.0% (n=56) of the cases dosage titration was performed from initiation. Six months after discharge 64,6 % (n=42) of the patients were still on clozapine.

Conclusion

It was found that in most cases the initiation of clozapine was compliant with the recommended guidelines. However, practitioners should be educated on the existing prescribing guidelines to promote the rational use of clozapine in the public health sector of South Africa.

Retrospective review of clozapine monitoring in a public sector psychiatric hospital and associated clinics

Moolman M[1], Esterhuysen W[2], Joubert R[1], Lamprecht JC[1], Lubbe MS[1]
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Format of presentation
Poster

Introduction

About 30% of schizophrenic patients fail to respond to conventional antipsychotics. Clozapine has shown superior efficacy, for both the positive and negative symptoms of schizophrenia, over conventional antipsychotics. The reputation of clozapine lies mainly with its repeated proven efficacy in the treatment of refractory schizophrenia.

South Africa lacks uniform provincial or national guidelines regulating practices in the treatment of mental disorders. International guidelines may be considered, which are not specifically adapted for the South African setting. These guidelines recommend both the haematological and metabolic monitoring of clozapine. The Standard Treatment Guidelines, Hospital Level for Adults, suggest that a psychiatrist should initiate clozapine therapy and that haematological monitoring should be performed as is instructed on the package insert. At present there are no South African guidelines recommending the metabolic monitoring of clozapine.

The motivation for this study is to assess the safe and effective use of clozapine, through performing an investigation on the monitoring patterns followed in a tertiary hospital, using a public sector psychiatric hospital and community psychiatric clinics as a model.

Methods

A quantitative retrospective drug utilisation review of clozapine was performed in a public sector psychiatric hospital. Data were collected from the files of 65 patients discharged on clozapine between 1 December 2010 and 29 February 2012. Haematological and metabolic monitoring of clozapine was compared to recommended national and international guidelines. Follow-up investigations were performed, at the clinics, both three and six months after discharge from hospital.

Results
Non-compliance with the recommended guidelines for follow-up haematological monitoring occurred in 77,4% (n=48) of patients in the hospital setting as well as in 95,7% (n=44) of patients during the three month follow-up at the clinics. Non-compliance with the recommended guidelines for follow-up metabolic monitoring occurred in all the observed patients (n=62) in the hospital setting as well as in 45.7% (n=21) of patients during the three month follow-up at the clinics.

Conclusion
It was found that clozapine was inadequately monitored. A guidance document should be developed and included in patients' files to assist in the safe and effective monitoring of clozapine in the public health sector of South Africa.

Clozapine discontinuation rates in a public health care setting

Moolman M[1], Esterhuysen W[2], Joubert R[1], Lamprecht JC[1], Lubbe MS[1]
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Introduction

Adherence to drug therapy is a significant issue in the clinical management of psychiatric conditions.[1] Early treatment discontinuation in patients with schizophrenia or schizophrenia-like disorders is very common, with about 50% of patients being non-adherent to treatment.[2]

According to results obtained from the 18-month Clinical Antipsychotic Trial for Intervention Effectiveness (CATIE) study, 74% of patients discontinued their antipsychotic medication, despite monthly monitoring. More specifically, the results indicated that clozapine was more effective than the other second generation antipsychotics. On average, patients stayed on clozapine for 10 months, while patients on any of the other antipsychotics stayed on therapy for only 3 months.

Discontinuing antipsychotic treatment is associated with relapse, increased hospitalization, symptom exacerbation, poor long-term course of illness, and higher economic costs of treatment. [1,3,4] Reasons for poor adherence are complex, but several studies suggest that it could be related to a hidden burden of adverse effects as well as poor illness insight.[5]

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[1] Lang K, Meyers JL, Korn JR *et al*. 2010. Medication adherence and hospitalization among patients with schizophrenia treated with antipsychotics. *Psychiatric services,* 61(1):1239–1247.

[2] Kazadi NJB, Moosa MYH, Jeenah FY. 2008. Factors associated with relapse in schizophrenia. *South African journal of psychiatry*, 14(1):52-62.

[3] Perkins D. 2002. Predictors of noncompliance in patients with schizophrenia. *Journal of clinical psychiatry.*, 63(1):1121-1128.

[4] Novick D, Haro JM, Suarez D *et al.* 2010. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. *Psychiatry research,* 176(1):109–113.

[5] Moritz S, Favrod J, Andreou C *et al*. 2013. Beyond the Usual Suspects: Positive attitudes towards positive symptoms is associated with medication noncompliance in psychosis. *Schizophrenia bulletin*, 39(4):917-922.

The aim for this study was to determine the observed discontinuation rates for clozapine, both three months and six months after discharge from hospital.

Methods
Data were collected from the files of 65 patients discharged on clozapine between 1 December 2010 and 29 February 2012, from a public sector psychiatric hospital. Follow-up investigations, after discharge, were performed at community psychiatric clinics at both three and six month intervals.

Results
About 34% (n=22) of patients had more than three previous admissions to a psychiatric hospital. In 52% (n=34) of the cases clozapine was previously prescribed. It was found that 71% (n=46) of patients were still on clozapine 3 months after discharge and 65% (n=42) were still on clozapine 6 months after discharge from hospital, resulting in discontinuation rates of 29% and 35% respectively.

Conclusion
The discontinuation rate observed for this study exceeded the results obtained in the CATIE study. This is however remarkable, since CATIE was conducted in a developed country whereas this study was conducted in a developing country with limited health care resources.

Investigations need to be performed to establish the reason(s) for clozapine discontinuation, since clozapine's main indication is treatment resistant schizophrenia.

Biological Psychiatry Congress 2013

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For the Biological Psychiatry Congress Best Poster Presentation

"Clozapine discontinuation rates in a public health care setting"

Seedat

Prof Soraya Seedat

On behalf of the Biological Psychiatry Organising Committee

Chairperson of the Biological Psychiatry Interest Group (SASOP)

31 August 2013