AN EVALUATION OF THE PRESCRIBING AND MONITORING OF CLOZAPINE AT A PUBLIC SECTOR PSYCHIATRIC HOSPITAL

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An evaluation of the prescribing and monitoring of clozapine at a public sector psychiatric hospital

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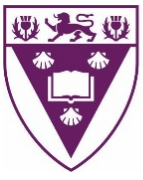

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DECLARATION

I, Ms Vimbisai Millicent Mukoko (Rhodes University Student Number G13M3002), hereby declare that all the experimental work, planning, literature search, data capturing and interpretation, as well as writing the initial version of this dissertation was conducted by myself. My supervisor (Prof Johannes Bodenstein) and co-supervisors (Mrs Mari-san Bodenstein and Prof Martie S. Lubbe) assisted in the interpretation of the results of the experimental work and proof read the dissertation in preparation for its final version. 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.

Signature	**Date**

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SUMMARY

An evaluation of the prescribing and monitoring of clozapine at a public sector psychiatric hospital

Key words: Clozapine, schizophrenia, schizoaffective disorder, drug utilisation review, prescribing patterns, monitoring patterns, psychiatric hospital

Introduction: Approximately one percent (1%) of the South African population suffers from schizophrenia. Clozapine has proven to be more effective than conventional antipsychotics in the treatment of schizophrenia, particularly in alleviating positive symptoms. Clozapine is primarily indicated for treatment-resistant schizophrenia due to its severe adverse effect profile. The prescribing guidelines recommend a trial of at least two different antipsychotic drugs before the initiation of clozapine. At least one should be a non-clozapine second generation antipsychotic.

Compared to other atypical antipsychotics, clozapine poses the greatest risk of causing a haematological event, such as neutropenia and agranulocytosis. Agranulocytosis (estimated prevalence of 1.3%) is a life-threatening adverse effect. Common adverse effects include weight gain and metabolic syndrome, hypersalivation and constipation. These can also predispose the patient to co-morbid diseases which further complicate their current diagnosis.

Haematological and metabolic monitoring is paramount throughout the duration of clozapine therapy. International (NICE guidelines, Clozapine REMS, and Maudsley prescribing guidelines) and national (South African STGs, SASOP treatment guidelines and the SAMF) guidelines recommend these monitoring patterns to assist with the prevention and management of the adverse effects of clozapine.

Aim and Objectives: The aim of the study was to conduct a drug utilisation review on the psycholeptic drug clozapine, by investigating its prescribing and monitoring patterns in outpatients at a public sector psychiatric hospital and compliance with the recommended treatment guidelines.

Methodology: A retrospective drug utilisation review was conducted. A descriptive, cross-sectional research approach was implemented to analyse the data and assess the adherence to national and international treatment guidelines for schizophrenia. A

data collection tool was used to document the data of 57 outpatients who were on clozapine therapy between 1 January 2017 and 31 December 2017.

Results and Discussion: Of the 57 patients, 78.95% (n=45) were on their first trial of clozapine. Compliance to the treatment guidelines (NICE and SASOP) for schizophrenia regarding previous trials of other antipsychotics were evident in only 22 cases (61.11%) of the 36 cases with available data. A total of 15 cases (26.32%) were compliant with the NICE guidelines for prescribing clozapine. Baseline haematological and metabolic monitoring was not evident in the majority of the patients. Only 23.81% (n=10) cases were fully compliant with the haematological monitoring guidelines. Metabolic monitoring was evident in 80.70% (n=46) cases. However, there were inconsistencies in complying with the recommended intervals of the metabolic monitoring tests. Metabolic or endocrine co-morbid disease states were common in 29.82% (n=17) of the patients.

Conclusion: Haematological monitoring is essential during clozapine use. The majority of the cases in the study were not fully compliant with the white blood cell count monitoring guidelines. Adherence to these guidelines should be emphasised to minimise the fatal outcomes of agranulocytosis. The intervals for the various metabolic monitoring tests should also be adhered to. This would prevent predisposing patients to co-morbid disease states and it would be useful in the management of adverse effects. The prescribing and monitoring guidelines of clozapine ensure the rational use of the drug. Health care professionals must endeavour to provide the most effective and safe therapeutic outcomes for the patient.

LIST OF ABBREVIATIONS

A

AMI	Any mental illness
AOS	Adult-onset schizophrenia
APA	American Psychiatric Association

B

BEN	Benign ethnic neutropenia
BMI	Body mass index

C

CBT	Cognitive behavioural therapy
COS	Childhood-onset schizophrenia
CNS	Central nervous system
CVD	Cardiovascular disease

D

DALY	Disability-adjusted life year
DMS	Delusional misidentification syndrome
DSM-5®	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
DUR	Drug utilisation review

E

ECT	Electro-convulsive therapy
EML	Essential Medicines List
EOS	Early-onset schizophrenia
EPSE	Extrapyramidal side effects

F

FDA Food and Drug Administration

I

ICD10 International Statistical Classification of Diseases and Related Health Problems 10th Revision

ICD11 International Statistical Classification of Diseases and Related Health Problems 11th Revision

M

MARTA Multi-acting receptor-targeted antipsychotics

MATRICS Measurement and Treatment Research to Improve Cognition in Schizophrenia

N

NICE The National Institute for Health and Care Excellence

NIMH National Institute of Mental Health

NHI National Health Insurance

NSA-16 Negative Symptom Assessment Scale

P

PANSS Positive and Negative Syndrome Scale

R

REMS Risk Evaluation and Mitigation Strategy

RVD Retroviral disease

S

SAMF South African Medicines Formulary

SANS Scale for the Assessment of Negative Symptoms

SAS Statistical Analysis System®

SASOP South African Society of Psychiatrics

SDA Serotonin-dopamine receptor antagonist

SDS Schedule for the Deficit Syndrome

SMD Spontaneous movement disorder

SMI Serious mental illness

W

WBC White blood cell

WHO World Health Organization

Y

YLD Years lived with disability

LIST OF DEFINITIONS

Affective blunting: This is categorised as a negative symptom of schizophrenia. The blunting of affect is the loss of the normal degree of emotional sensitivity and the lack of appropriate reactions to events (Semple & Smyth, 2013: 88).

Alogia: Campbell (2009: 41) describes alogia as speechlessness that is due to intellectual deficiency or confusion. It is also described as the lack of spontaneity and flow of conversation characteristic of the schizophrenic deficit state.

Agranulocytosis: A disorder in which there is a severe acute deficiency of certain blood cells (neutrophils) as a result of damage to the bone marrow by toxic drugs or chemicals. It is characterised by fever, with ulceration of the mouth and throat, and may lead rapidly to prostration and death (Martin, 2015).

Anhedonia: When literally translated, anhedonia means "without pleasure" (Fonseca-Pedrero *et al.*, 2014: 22). Anhedonia is the feeling of absence or the significant diminished enjoyment of previously pleasurable activities. It is categorised as a negative symptom (Semple & Smyth, 2013: 86).

Asociality: This is considered as a core negative symptom of schizophrenia. It is a state at which the patient has a loss of interest in the world and social interaction (Buck & Lysacker, 2014: 11).

Avolition: Avolition is a negative symptom of schizophrenia (Semple & Smyth, 2013: 187). A literal translation of avolition is "without will". It is defined as a person's inability to initiate and maintain a goal directed activity. Generally, the person has a lack of initiative to pursue any meaningful, life enriching activities (Preda *et al.*, 2011: 53).

Catatonia: The DSM-5® classifies catatonia as a psychotic symptom which is associated with many causes (Bhati, 2013: 5). The term is derived from the Greek "kata" (down) and "tonas" (tension or tone). Catatonia is a syndrome of motor dysregulation, whereby there is a dramatic reduction of psychomotor activity presenting as rigidity, waxy flexibility, mutism and negativism (Sanders, 2015; Wilcox & Duffy, 2015: 577).

Delusions: Semple and Smyth (2013: 90) define a delusion as an abnormal belief which is held with absolute certainty. This belief does not require external proof, it may be held in the face of contradictory evidence, and it has personal significance and importance to the individual concerned. Primary delusions are a direct result of psychopathology. Secondary delusions occur in response to other primary psychiatric conditions (Semple & Smyth, 2013: 90). There are many other forms of delusions (Campbell, 2009: 263).

Drug Utilisation Review: This is defined by the World Health Organization (World Health Organization, 2003a: 8) as the marketing, distribution, prescription, and the use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences.

Dyskinesia: A moderately fast, repetitive, frequent (this may vary), and often stereotypic movement. The diagnosis of dyskinesia is usually as an adverse effect of the medical management of Parkinson's disease, and as tardive dyskinesia associated with phenothiazines.

Dystonia: A neurologic syndrome dominated by involuntary, sustained muscle contractions frequently causing twisting and repetitive movements, or squeezing movements, or abnormal postures (Fuller *et al.*, 2011: 766). These may be present at rest, with changing posture, or when performing a specific motor activity (Samanta, 2006: 107).

Hypokinesia: Rodnitzky and Uc (2012: 292) defined hypokinesia as a decrease in the amount and amplitude of both volitional (voluntary) and automatic movements. This is almost always associated with bradykinesia (slowness of movement).

Neologism: A new word, usage, or expression. In the context of schizophrenia, this is a new word that is coined (invented) and is meaningless except to the coiner (inventor), and is typically a combination of two existing words or a shortening or distortion of an existing word (Merriam-Webster, 2019a).

Neutropenia: An abnormal decrease in the number of neutrophils in peripheral blood. Neutropenia results in an increased susceptibility to infections; if patients become

unwell due to infection, this can lead to neutropenic sepsis, which can be life-threatening (Martin, 2015).

Pharmacoepidemiology: A study of the use, and the effects, of drugs and other medical devices in large numbers of people (Strom *et al.*, 2013: 1990). The World Health Organization explains the purpose of this type of study is to support the rational and cost-effective use of drugs in the population, thereby improving health outcomes (World Health Organization, 2003a: 8).

Pharmacovigilance: The World Health Organization (2018a) defines this as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Polygenic: Relating to, or determined by polygenes. Polygenes are any group of nonallelic genes that collectively control the inheritance of a quantitative character or modify the expression of a qualitative character (Merriam-Webster, 2019b).

Psycholeptic: A substance that exhibits central nervous system depression by slowing the transmission of nerve impulses and body functions (Sergi & Napoletano, 2012: 352). Psychoactive drugs that have a depressant effect on mental activity, such as a sedative, tranquilliser, hypnotic, or anxiolytic is commonly given this designation (Oxford University Press, 2018).

Schizophrenia: This is defined as a severe mental illness characterised by disintegration of the processes of thinking, of contact with reality, and of emotional responsiveness. Both positive and negative symptoms are common, and diagnosis is only made if symptoms persist for at least one month (Martin, 2015).

Schizoaffective disorder: A chronic mental health condition characterised primarily by symptoms of schizophrenia, such as hallucinations or delusions, and symptoms of a mood disorder, such as mania and depression (National Alliance on Mental Illness, 2018).

Tardive dyskinesia: This occurs commonly as an adverse effect of certain medications used to treat mental illness. It presents as repetitive, jerking movements that occur in the face, neck and tongue (National Institute of Mental Health, 2017a).

Volition: The power of choosing or determining. It is also defined as the act of making a choice or a decision. The synonym that is commonly used is “will” (Merriam-Webster, 2019c).

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CHAPTER 1. INTRODUCTION AND PROBLEM STATEMENT

1.1 Introduction

A drug utilisation review entails a collection of descriptive and analytical methods for the quantification, the comprehension and evaluation of the prescribing, dispensing and use of medicines (World Health Organization, 2003a: 8). The benefits of this type of review include the ability to assay these interventions and provide valuable recommendations to improve the processes (Wettermark *et al.*, 2016: 3). The current study will entail a retrospective descriptive study analysing the prescribing and monitoring patterns of the psycholeptic drug clozapine at a public sector psychiatric hospital in the Eastern Cape Province of South Africa.

This chapter outlines the background to the study, the problem statement, aim, research objectives, research methods as well as layout of the chapters to follow in the dissertation.

1.2 Background to the study

A population-based study of common mental disorders in South Africa established that approximately 30.3% of all adults would have suffered from a form of mental disorder in their lifetime (Herman *et al.*, 2009: 3). In the study, the researchers found that the Eastern Cape had comparatively lower lifetime prevalence rates than the other provinces in South Africa, however, the general prevalence rates of some mental disorders in South Africa are significantly higher compared to other countries (Herman *et al.*, 2009: 3). Approximately one percent of the South African population suffers from schizophrenia (Trump & Hugo, 2006: 251).

The predominant ethnic group in the Eastern Cape is the Xhosa people. A study that focused on the "Antipsychotic prescription patterns in Xhosa patients with schizophrenia or schizoaffective disorder" revealed that there was an overall low rate of clozapine usage in only 10% of all patients with schizophrenia. An explanation of this occurrence was due to the decreased patient compliance and irregular follow-up patterns (Koen *et al*., 2008: 289). The severe adverse effects of clozapine also made it an undesirable drug to be prescribed by clinicians (Koen *et al*., 2008: 289).

Clozapine is used for the therapy of treatment-resistant schizophrenia. The National Institute for Health and Care Excellence (NICE) guidelines advise that clozapine is

offered after the failure of trials of at least two other antipsychotics (Taylor *et al.*, 2009: 19). Adverse effects include agranulocytosis, neutropenia and metabolic syndrome (Taylor *et al.*, 2009: 64). The risk of these adverse effects is much greater with clozapine than with any other antipsychotic drug (Rossiter, 2016: 474; 480).

A study concerning the "undiagnosed metabolic syndrome and other adverse effects among clozapine users of Xhosa descent" reveals that 44.8% of the population under study suffered from a metabolic adverse effect due to clozapine administration (Faasen *et al.*, 2014: 56). This is a significantly large number indicating the implications of clozapine on the health of the Xhosa patient.

A study was conducted at a public sector psychiatric hospital in the Nelson Mandela Metropole in 2013 in which clozapine usage was investigated. The perception that South Africa lacks regulating provincial or national guidelines for the treatment of mental disorders was explored. It was found that the initiation and the prescribing of clozapine was not completely compliant with the recommended guidelines (Moolman, 2013: 256).

The acute pharmacological treatment of schizophrenia follows a step-wise prescribing guideline, whereby clozapine monotherapy is considered the third-line treatment after a failed response or adherence problems with other antipsychotic drugs (Swingler, 2013: 154).

It is evident that clozapine has the potential to cause severe adverse effects that would require haematological monitoring upon initiation of therapy. It is important for prescribers and patients alike to be aware of the implications of the medication they are taking or being administered. Safety and efficacy are amongst the top priorities for the utilisation of medications. The United States Food and Drug Administration (FDA) is currently endorsing and modifying the Clozapine Shared Risk Evaluation and Mitigation strategy (REMS), which focuses on refining and managing patients with severe neutropenia in an effort to ensure safety amongst all patients (Clozapine REMS Program, 2015: 2; U.S Food and Drug Administration, 2019). This is a useful programme to potentially mitigate and manage the adverse effects of clozapine.

For the assurance of safety and efficacy, the utilisation of clozapine must follow the correct guidelines, including dosing and monitoring. Interventions similar to those

applied by the Australian Commission on Safety and Quality in Health Care (2019), whereby a National Inpatient Medication Chart (NIMC) for clozapine titration has been adopted, would be beneficial in the South African context. The objective of this type of documentation is to record the prescribing patterns and to monitor the administration of clozapine.

1.3 Motivation and problem statement

Approximately seven percent (7%) of the world population living with schizophrenia reside in Africa, however, only one out of two hundred (0.005%) of the world schizophrenia trials have been conducted in Africa and an even lesser one out of a thousand (0.001%) of the patients entered in the schizophrenia trials worldwide have been enrolled in Africa (Purgato *et al.*, 2012: 8). There is a major gap in knowledge in the African context pertaining to psychiatric studies and trials. Clozapine is the drug of choice for treatment-refractory schizophrenia as recommended by the NICE guidelines (Taylor *et al.*, 2018: 6). Similarly, there is minimal information regarding the use of clozapine in the public sector in South Africa.

In South Africa, limited evidence of protocols were found to monitor neutropenia or the metabolic side-effects of clozapine, yet research has shown the importance of metabolic monitoring strategies amongst the Xhosa community (Faasen *et al.*, 2014: 56). The Essential Medicines List (EML) Clinical Guide states the need for atypical antipsychotics to be regularly monitored for metabolic side-effects. The guidelines for white blood cell count (WBC) monitoring for patients using clozapine are also summarised in the EML Clinical Guidelines (Department of Health, 2014).

The South African Medicines Formulary (Rossiter, 2016: 481) recommends a specific protocol to ensure that this monitoring is accurately undertaken, which includes white blood cell counts prior to treatment as well as weekly monitoring after initiation for eighteen weeks. The monitoring is continued fortnightly for a year, and then finally monthly for the duration of the treatment. The Daily Drug Use also advises that white blood cell counts be monitored for at least four weeks after terminating the treatment (Turner *et al.*, 2010: 460). The South African Society of Psychiatrists (SASOP) treatment guidelines for psychiatric disorders are the most up to date guidelines in South Africa for the use of clozapine (Swingler, 2013: 154). These guidelines

recommend that white blood cell counts should be monitored at baseline, then weekly for the first 18 weeks after initiation. Following this period, WBC must be monitored monthly thereafter (Swingler, 2013: 154).

The motivation for this study was to review the current national and international guidelines concerning clozapine prescribing and monitoring. The South African Medicines Formulary (SAMF), the South African Standard Treatment Guidelines (STGs) and the South African Society of Psychiatrists (SASOP) Treatment Guidelines for Psychiatric Disorders are the national guidelines cited in this study. The SAMF includes the indications of clozapine therapy, the recommended white blood cell count monitoring and intervals, and also outlines the dosage-titration upon the initiation of treatment with clozapine (Rossiter, 2016: 481). The STGs briefly recommend the required metabolic monitoring and WBC count monitoring parameters required during clozapine therapy (Maartens *et al.*, 2015: 15.15). The SASOP treatment guidelines are the most current national guidelines for treatment of psychiatric conditions. They have recognised the need for locally applicable guidelines suited to the South African community. A major short-coming of the SASOP treatment guidelines is the recommended prescribing of some drugs that are not available in the local public sector healthcare institutions (Emsley & Seedat, 2013: 134). The prescribing and WBC count monitoring guidelines for clozapine are included in the SASOP treatment guidelines (Emsley & Seedat, 2013: 154).

The Maudsley prescribing guidelines (Taylor *et al.*, 2009: 63-122) and the National Institute for Health and Care Excellence (NICE) guidelines (National Institute for Health and Care Excellence, 2015: 24) were used as the international standards in this study. The Maudsley guidelines provided a comprehensive dosage initiation chart for clozapine, the pharmacological algorithms for the management of adverse effects and pharmacological augmentation strategies during therapy (Taylor *et al.*, 2009: 63-122). The NICE guidelines focused on the treatment of schizophrenia, the criteria for the prescribing of clozapine, recommendations for augmentation of clozapine therapy and dosage adjustments. These guidelines were used to evaluate the treatment with clozapine in a public sector psychiatric hospital. A literature survey has shown that there is minimal other information available regarding clozapine usage and monitoring in the public sector in South Africa (Emsley & Seedat, 2013: 134).

1.4 Primary aim and research objectives

This research project includes a general research aim alongside specific research objectives.

The aim of the current study was to conduct a drug utilisation review on the psycholeptic drug clozapine, by investigating its prescribing and monitoring patterns in outpatients at a public sector psychiatric hospital in Grahamstown (Cacadu District Municipality, Makana Local Municipality, Eastern Cape Province, South Africa).

In order to achieve the aim of the current study, the research project consisted of a literature survey and an empirical investigation at the psychiatric hospital. The specific objectives of the study are discussed in response to the research questions presented below.

1.4.1 Research questions

The project was designed to address the following research questions:

1. Which psychiatric disorders commonly occur in South Africa and what is the prevalence of such disorders?
2. What are psychotic disorders, such as schizoaffective disorders and schizophrenia, how do they occur and how are they treated?
3. What is the history, pharmacological and toxicological properties of clozapine?
4. What is a drug utilisation review and how can it be used to assess the prescribing and monitoring patterns of clozapine and provide recommendations for optimal treatment at a public sector psychiatric hospital?

Research questions 1-3 were answered by conducting a literature investigation and question 4 was answered by an empirical investigation.

1.4.2 Specific objectives for the literature review

The specific research objectives of the literature review for the current study included the following:

- To describe psychiatric disorders in general and their prevalence in South Africa.

- To discuss the pathophysiology (hypotheses) of schizoaffective disorders and schizophrenia.
- To determine the medicine treatment guidelines of schizoaffective disorders and schizophrenia.
- To describe the history of the development of clozapine.
- To discuss the pharmacological properties of clozapine (pharmacokinetics and pharmacodynamics) and compare it to other psycholeptics.
- To discuss the toxicological properties of clozapine (adverse effects, interactions, safety in pregnancy and lactation, use in specific patient populations) and compare it to other psycholeptics.
- To determine what constitutes a drug utilisation review and discuss the components thereof.
- To discuss drug utilisation reviews on psycholeptics in general and specifically on clozapine in the public and private sectors, locally and internationally.
- To conceptualise the most appropriate parameters to conduct a drug utilisation review on clozapine by investigating patient files.
- To explain statistical terminologies that will be used to analyse the data obtained from the empirical study.

1.4.3 Specific objectives for the empirical study

The specific research objectives of the empirical investigation for the current study included the following:

- To determine the prescribing patterns of clozapine (dosages and treatment period) and compliance with the recommended treatment guidelines (the pharmacoepidemiology component of this study).
- To identify medication problems (interactions and adverse effects) associated with the use of clozapine (the pharmacovigilance component of this study).

1.5 Research methodology

The research procedure of the current study consisted of a comprehensive literature review and an empirical investigation.

1.5.1 Literature review

The literature (books, articles, review and research journal articles, websites and dissertations) that was included in the literature survey was selected through an Internet search and the following process was followed:

- Appropriate data bases such as Google Scholar, PubMed, Science Direct, EBSCO Publication Finder and OPAC (The Online Catalogue) with the emphasis on medical and psychiatric journals were utilised.
- The following key words or combinations thereof were used in the Internet search to identify the literature related to the research objectives of the study:

  - "Psychiatric disorders".
  - "Definition of treatment-resistant schizophrenia".
  - "Pathophysiology of schizoaffective disorders and schizophrenia".
  - "Hypotheses of schizoaffective disorders and schizophrenia".
  - "Treatment of schizoaffective disorders and schizophrenia".
  - "Psycholeptic".
  - "Clozapine".
  - "History of clozapine".
  - "Pharmacology of clozapine".
  - "Toxicology of clozapine".
  - "Drug utilisation review".
  - "Pharmacoepidemiology".
  - "Pharmacovigilance".
  - "Prescribing and monitoring patterns".
  - "Public health sector".
  - "Makana local municipality".
  - "Cacadu district municipality".
  - "Eastern Cape province".
  - "Private health sector".
  - "Descriptive statistics".
  - "Inferential statistics".

1.5.2 Empirical study

A descriptive, cross-sectional research approach was implemented to analyse the retrospective data gathered from a structured data collection sheet. Cross-sectional research can be exploratory, descriptive or explanatory; however, a descriptive design is the most reliable (Neuman, 2014: 44). A cross-sectional study examines the data at one point in time and can be used to observe correlations between variables in the data set (LoBiondo-Wood & Haber, 2014: 205). A descriptive study design can be used to recognise current problems, justify current practice, make judgements or determine what other individuals in similar situations are doing, or to develop theories (Grove & Gray, 2019: 31). Therefore, a descriptive study can describe certain variables, such as medication prescribing and monitoring patterns, as well as therapeutic drug levels for example. In a retrospective study, data of interest that have already been documented will be used (Lyman Ott & Longnecker, 2016: 22). In this study, the retrospective data was collected from the documented data from patient files by using a structured data collection sheet.

1.5.2.1 Study setting

The research was conducted at Fort England Hospital in Grahamstown. Fort England Hospital was established in 1875 as the first dedicated mental health hospital in South Africa. It is a 313-bed tertiary specialist psychiatric hospital with multidisciplinary healthcare teams that cares for both in- and outpatients.

1.5.2.2 Study population

The target population were all outpatients (> 18 years) who met the set inclusion criteria and who were on treatment with clozapine for the study period 1 January 2017-31 December 2017.

1.5.2.3 Inclusion criteria

The following inclusion criteria was used:

All patients, both male and female, older than 18-years, who were diagnosed (previously or newly) with a psychiatric disorder between 1 January 2017-31

December 2017 and who were being treated with clozapine at the outpatient clinic of Fort England Hospital.

1.5.2.4 Exclusion criteria

There were no additional exclusion criteria besides patients who were younger than 18-years.

1.5.2.5 Research instrument

A data collection tool was developed to document data in line with the objectives for this study.

1.5.2.6 Data collection

The primary investigator of the study collected data from the patient files for a period of 3 months.

1.5.2.7 Data collection tool

The data collection tool consisted of a structured data collection form. The purpose of the data collection form was to record demographical and clinical information from the patient file. Refer to ANNEXURE A and B.

1.5.2.8 Data source

The data source for the study were the patient files of patients attending the study site during the study period. Data was collected retrospectively from the patient files.

1.5.2.9 Data analysis

Collected data was arranged, analysed, summarised and presented (graphs and tables) with the computer software Statistical Analysis System® (SAS Institute Inc.) and Microsoft® Excel.

Statistical significance was considered with a two-sided probability of $p < 0.05$. The practical/clinical significance of differences was explained when results were statistically significant.

Variables were explained using descriptive statistics. These include frequencies (n), percentages (%), means, medians and standard deviations.

Comparisons were explained using inferential statistics. The chi-square test was used to determine whether an association exists between proportions of two or more categorical variables. Cramér's V value was used to determine the relative strength of the correlation between two variables. The interpretation of the V values are explained in detail in Chapter 3.

1.5.2.10 Study variables

The study variables that were used in this study were prepared as part of a data collection form. In this clinical note, the subjective data encompassed demographical information. Patient age was recorded using the date of birth, and patients divided into age groups. The objective data focused on the medication and can be useful to identify, resolve and prevent potential and actual drug-related problems. This may contribute to the extent of quality care that psychiatric patients receive.

1.5.2.11 Study measurements

The study measurements involved in this study included: Differential diagnosis, co-morbid disease states, dosages and compliance with the recommended treatment and monitoring guidelines.

1.5.2.12 Ethical aspects

All clinical data for this research project was acquired retrospectively from the patient files. There was no communication with patients and the project was unobtrusive and non-invasive in nature. The researcher performed the study in an ethical and reliable manner throughout the course of the study. This extends from the formulation, research and development phase, through the execution and data collection phase, to the presenting of the results phase. Approval to conduct this study was obtained from the following institutions:

- Rhodes University Faculty of Pharmacy Higher Degrees Committee.
- Rhodes University Faculty of Pharmacy Research Ethics Committee (PHARM-2018-04).

- Fort England Hospital Research Committee (PHARM-2018-04).
- Eastern Cape Department of Health Research Committee (EC_201808_009).

1.6 Dissertation layout

The dissertation was written in South African English. An introduction and a summary will be provided at the beginning and end of each chapter respectively. References in the Harvard style were used with the assistance of Mendeley reference manager software (Mendeley Ltd) and listed in-between the last chapter and the annexures. The following traditional layout was employed:

- Chapter 1: Introduction and Problem Statement.
- Chapter 2: Literature Survey.
- Chapter 3: Methodology.
- Chapter 4: Results and discussion.
- Chapter 5: Summary, Conclusion, Limitations and Future directions.
- References
- Annexures

1.7 Chapter 1 summary

This chapter provided an overview of the study conducted. The research questions were listed; the aim and objectives described; and the research methodology and ethical aspects briefly discussed. The following chapter will introduce and discuss the literature concerning the research topic.

CHAPTER 2.
LITERATURE REVIEW

2.1 Introduction

This literature review focuses on an overview of psychiatric disorders, specifically on the clinical aspects of two psychotic disorders, schizophrenia and schizoaffective disorder; the pharmacodynamic and pharmacokinetic properties of the antipsychotic drug clozapine; and lastly a synopsis of drug utilisation reviews.

2.2 Psychiatric disorders

According to Campbell (2009: 799), psychiatry is the branch of medicine that is concerned with the examination, diagnosis, therapeutics and prevention of behaviour disorders. In comparison to other medical disorders, mental disorders have proved to be more difficult to diagnose due to a lack of the use of laboratory tests, scans or biopsies to give definitive diagnoses (Jacob, 2013: 1).

A mental disorder is defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5®) as *"a syndrome characterized by clinically significant disturbance in an individual's cognition, emotion regulation, or behaviour that reflects a dysfunction in the psychological, biological or developmental processes underlying mental functioning"*. The DSM-5® further explains that mental disorders are associated with significant distress or disability in social, occupational, or other important activities (American Psychiatric Association, 2013a: 20). Mental disorder is therefore the umbrella term given for conditions causing an upset in a person's psychological well-being. Unlike many other medical problems which are commonly referred to as 'diseases' or 'illnesses'; mental and behavioural problems are termed as 'disorders'. Disorder is not a precise term and implies that there is a wide range of symptoms and behaviours possibly accompanied by distress and interference of personal functions (World Health Organization, 1992: 5).

The International Statistical Classification of Diseases and Related Health Problems 10th Revision lists psychiatric disorders under mental and behavioural disorders. Some of these include mental retardation; neurotic, stress-related and somatoform disorders; and mood (affective) disorders to name a few (World Health Organization, 2016).

The severity of the mental illness can also be classified as either Any Mental Illness (AMI) or a Serious Mental Illness (SMI). The severity of a mental illness termed as an AMI varies according to the impact of the mental disorder, ranging from mild, moderate and severe impairment, whereas an SMI results in serious functional impairment, limiting one or major life activities (National Institute of Mental Health, 2017b).

The United Nations states that "Ensuring healthy lives and promoting the well-being for all at all ages" is the third goal of the seventeen Sustainable Development Goals (United Nations, 2018). Health needs to be prioritised globally, including mental health. In May 2013, the World Health Organization adopted the Mental Health Action Plan 2013-2020 after recognising the need to endorse, protect and promote the recovery of mental health (World Health Organization, 2013: 7). The WHO Mental Health Gap Programme (mhGAP) was also launched in an aid to assist with the necessary services for mental, neurological and substance abuse disorders for low and middle income countries (National Institute of Mental Health, 2017b).

In the global context, neuropsychiatric conditions are responsible for 13% of the total Disability-Adjusted Life-Years (DALYs) lost due to all diseases and injuries. In 2004 the total DALYs were predicted to increase to 15% by the year 2020 (World Health Organization, 2004: 13). A study by Whiteford *et al.* on the global burden of disease showed that where 10.4% of the cause of all DALYs was accounted for by mental, neurological and substance abuse disorders, whereby mental disorders contributed the most (56.7%) followed by neurological disorders (28.6%) (Whiteford *et al.*, 2015: 6). Mental disorders also account for a significant amount of disabilities. Schizophrenia is amongst one of the mental disorders that significantly contributes to the total DALYs for neuropsychiatric disorders. The WHO reported that schizophrenia accounts for 2.8% of the total 31.7% years lost due to disability (YLD) for neuropsychiatric disorders (Prince *et al.*, 2007: 859–860).

The lifetime prevalence of schizophrenia is stated to be approximately 0.3-0.7%, although this could be influenced by variables such as race or geographical location (American Psychiatric Association, 2013b: 102). Similarly, schizoaffective disorder has a lifetime prevalence of approximately 0.3%, yet it is recorded to occur less commonly compared to schizophrenia (American Psychiatric Association, 2013b: 107).

Research conducted by the South African Medical Research Council on the revised Disability-Adjusted Life-Year (DALY) estimates ranked mental and nervous system disorders (as a single neuropsychiatric category) as the third greatest burden of disease in South Africa, after HIV/AIDS and infectious diseases (Bradshaw *et al*, 2007: 438). The risk of the South African population acquiring a mental illness increased after 1992 due to the negative effects of apartheid on mental health (Williams *et al.*, 2008: 211).

A study on the lifetime prevalence of psychiatric disorders in South Africa portrayed the lack of availability of nationally representative data which would be essential in providing a suitable local mental health care strategy (Stein *et al.*, 2008: 112). The South African Stress and Health (SASH) study pioneered population-based research on common mental disorders. Herman *et al.* (2009: 341) portrayed that the lifetime prevalence of any mental disorder in South Africa was 30.3%. Respondents depicting two or more, and three or more lifetime disorders were significantly less, with a prevalence of 11.2% and 3.5% respectively. Anxiety disorders were the predominant class showing a lifetime prevalence of 15.8%, followed by substance disorders (13.3%) and mood disorders (9.8%) (Herman *et al.*, 2009: 341). The first study that explored the prevalence of mental disorders in a prison population in Durban, South Africa, highlighted the lack of mental healthcare in the facility due to a lack of resources and services. A total of 23.3% of the prison population had psychotic, bipolar, depressive or anxiety disorders (Naidoo & Mkize, 2012: 3).

Petersen and Lund suggested that future mental healthcare research should primarily focus on evidence-based interventions and economic evaluations that will impact at the community level of healthcare (Petersen & Lund, 2011: 756). There is evidently a gap in information regarding the prevalence of psychiatric disorders in South Africa. There have been no national studies that have explored this prevalence in children and adolescents, which is a cause for concern as many psychiatric disorders have an early onset (Mayosi *et al.*, 2009: 937).

2.3 Psychotic disorders

Psychosis is a mental disorder than causes a person to lose their capacity to distinguish reality and alters their ability to relate to others (SANE Australia, 2019). It

is defined by a group of clinically observable characteristics and is therefore characterised as a clinical syndrome (Gaebel & Zielasek, 2015: 9).

A narrow definition of psychosis states that it is the presence of hallucinations (without understanding of the causal effect), delusions, or both (Arciniegas, 2015: 716). A broader definition defines psychosis as the presence of delusions and/or hallucinations (with understanding of the nature of the hallucination) (Cardinal & Bullmore, 2011: 3). The exact definition of psychosis remains ambiguous and has since been summarised to include a selection of characteristics. The DSM-5® describes psychotic disorders to include one or more of the following five appearances (American Psychiatric Association, 2013b: 87):

- Delusions.
- Hallucinations.
- Disorganised thinking or speech.
- Grossly disorganised or abnormal motor behaviour (including catatonia).
- Negative symptoms.

Psychotic disorders may be classified, according to the diagnosis, as either primary or secondary psychosis (Freundenreich, 2016: 24). Secondary psychosis will be briefly discussed first, followed by primary psychosis with extensive focus on schizophrenia and schizoaffective disorder.

2.3.1 Secondary psychosis

Secondary psychoses may be described as clinical conditions whereby psychosis is the complicating symptom of a pre-existing disorder (Johnson *et al.*, 2009: 81). There are four conditions in which secondary psychosis can occur (Freundenreich, 2016: 25):

- Delirium.
- Dementia.
- Medical and neurological diseases.
- Substances.

2.3.1.1 Delirium

The impact of psychotic symptoms in delirium is still vague. They are principally present in hyperactive delirium (e.g. delirium tremens), and they can also be present in hypoactive delirium (Meagher *et al.*, 2007: 139). Symptoms of delirium that overlap with psychotic symptoms include visual hallucinations, thought and perceptual disturbances and impaired attention (Meagher, 2001: 435). Such symptoms may be present in 50% of delirium cases (Freundenreich, 2016: 25).

2.3.1.2 Dementia

A study on the behaviour disorders of dementia states that psychotic symptoms most commonly occur at the advanced stages of dementia, particularly as the patient becomes more dependent (or in need of assistance). Alongside the expected hallucinations and delusional features, delusional misidentifications also occur (Rayner *et al.*, 2006: 647). Delusional misidentification syndromes (DMSs) are complex psychotic phenomena comprising of signs and symptoms that are viewed in psychotic disorders, such as schizophrenia paranoid-type, affective disorders and organic brain disorders. Several syndromes are classified under the DMSs, these include Capgras syndrome and Fregoli syndrome, amongst others. Capgras syndrome is the most prevalent of the syndromes, and is described as a disorder where a person holds a delusion that an identical-looking imposter has replaced a friend or relation (Atta *et al.*, 2006: 57; Klein & Hirachan, 2014: 369-370).

2.3.1.3 Medical and neurological diseases

Psychotic symptoms are most prevalent in the elderly suffering from co-morbid medical illnesses and are more difficult to diagnose in younger patients. The atypical presentation of psychotic symptoms generally associates with an underlying medical condition. These symptoms resolve as the medical condition improves (Keshavan & Kaneko, 2013: 9). Some examples of these specific medical conditions include Alzheimer disease, Diffuse Lewy body disease, Huntington Disease and Parkinson Disease (Arciniegas, 2015: 727-730).

2.3.1.4 Substances

Psychosis may be induced by the use of a psychoactive substance and continues to occur even without the administration of the substance (Keshavan & Kaneko, 2013: 4). The World Health Organization (2019a) describes a psychoactive substance as one that can affect mental processes, such as cognition or affect . Examples of psychoactive substances include illicit drugs, such as stimulants (e.g. cocaine) and psychotomimetics (e.g. lysergic acid diethylamide, LSD) (Freundenreich, 2016: 26). Psychomimetic refers to the inducing of psychotic alteration of behaviour and personality (Merriam-Webster, 2019d).

2.3.2 Primary psychosis

Primary psychosis occurs when the psychotic symptoms are not directly caused by any other disorder (Johnson *et al.*, 2009: 80). The DSM-5 has classified these disorders as the Schizophrenia Spectrum and Other Psychotic Disorders. These specifically include schizotypal (personality) disorder, delusional disorder, brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder and other unspecified psychotic disorders (American Psychiatric Association, 2013b: xv).

2.3.3 Schizophrenia

2.3.3.1 Definition

The term schizophrenia is derived from two Greek words: “Schizo” meaning tear or split and “phren” meaning “the mind” or “the intellect” (Walker *et al.*, 2004: 402). It is a complex disorder which has various ambiguous definitions.

The WHO defines schizophrenia as *“a severe mental disorder, characterized by profound disruptions in thinking, affecting language, perception, and the sense of self. It often includes psychotic experiences, such as hearing voices or delusions. It can impair functioning through the loss of an acquired capability to earn a livelihood, or the disruption of studies”* (World Health Organization, 2018b).

An alternative definition by the British Medical Journal (BMJ) defines schizophrenia as *“an illness characterized by a co-occurrence of at least two of the following symptoms:*

delusions, hallucinations, disorganised speech, disorganised/catatonic behaviour, or negative symptoms occurring for a significant period of at least 1 month and associated with continuous problems over at least a 6-month period". At least one of the symptoms needs to be a positive symptom (British Medical Journal, 2018). Delusions, hallucinations and disorganised speech are categorised as the principal primary symptoms (Tandon *et al.*, 2013: 3).

2.3.3.2 Aetiology of schizophrenia

The aetiology of schizophrenia has been misunderstood in the past. It is now known to be multifactorial; it is dependent on both genetic and environmental factors. However, the mechanisms of how these factors cause schizophrenia remain unknown (Tandon *et al.*, 2008: 12). These factors may operate cohesively as causal factors for schizophrenia or they may not be the ultimate causal factors at all. Therefore, the distinction between the genetic and environmental factors is often unclear (Zammit *et al.*, 2003: 220).

The 'biopsychosocial model' is used to categorise the three dimensions that describe the aetiology of schizophrenia. These dimensions are listed below (Tsoi *et al.*, 2008: 405):

- Biological
- Psychological
- Social

A diagrammatic summary of the biopsychosocial model is illustrated in figure 2–1 (adapted from Tsoi *et al.*, 2008: 405):

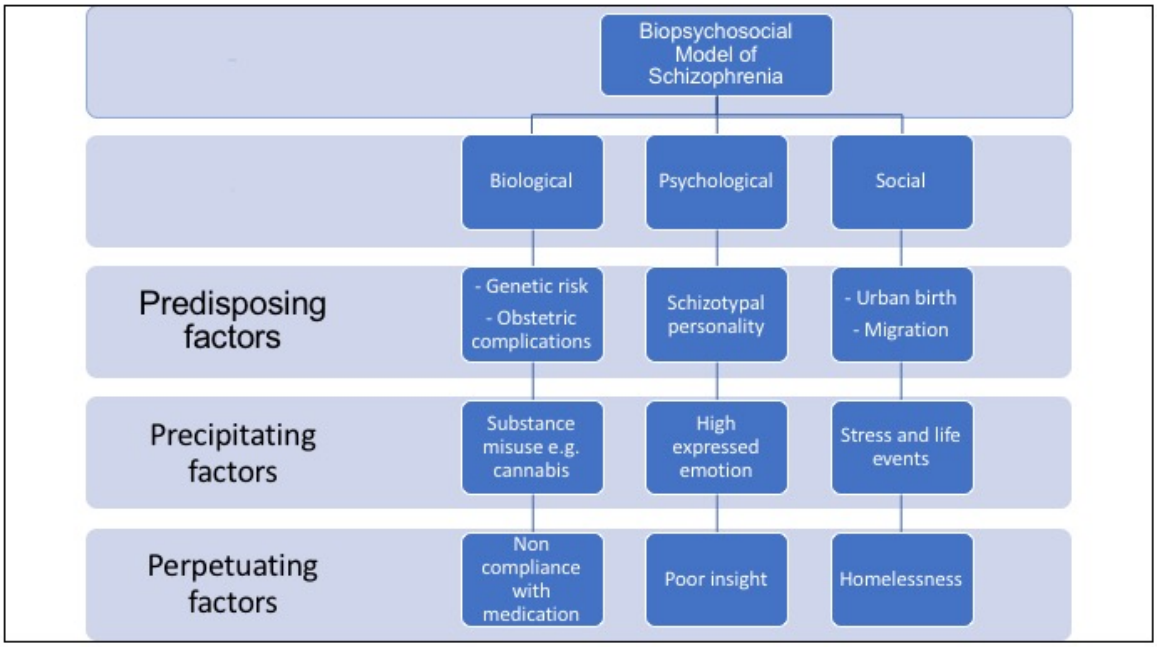

Figure 2–1. The biopsychosocial model of schizophrenia.

2.3.3.2.1 Biological factors

Genetic contribution is the most common risk factor currently known to cause schizophrenia. However, this does not occur discretely as environmental factors also affect genetic factors and the two are hypothesised to simultaneously cause schizophrenia (Castle and Buckley, 2014: 33). Specific genes have been found to be associated with schizophrenia, namely NRG1 (neuregulin-1), DTNBP1 (dysbindin), COMT (catechol-O-methyltransferase), DISC1 (disrupted in schizophrenia 1), RGS4 (regulator of G protein signalling 4), GRM3 (metabotropic glutamate receptor) and G7. However, only COMT has been presumed to have an allele with causative qualities (Jones *et al.*, 2006:45). Therefore, schizophrenia is also defined as polygenic because multiple genetic polymorphisms contribute a small effect to increase the disease susceptibility (Tandon *et al.*, 2008: 8).

There is also a risk of schizophrenia diagnosis if a family member is schizophrenic, due to the genetic relationship between an individual and the proband. A proband is defined as an individual who is the first subject (as part of a genetic character in a family lineage) in a study to be affected with a disorder. An investigation into the prevalence of the disorder in the rest of the family is initiated from the proband case (Nugent, 2013; Merriam-Webster, 2019e). The susceptibility of having schizophrenia

is graded on a gradient scale for genetic risk as indicated in figure 2–2 (adapted from Castle and Buckley, 2014: 34):

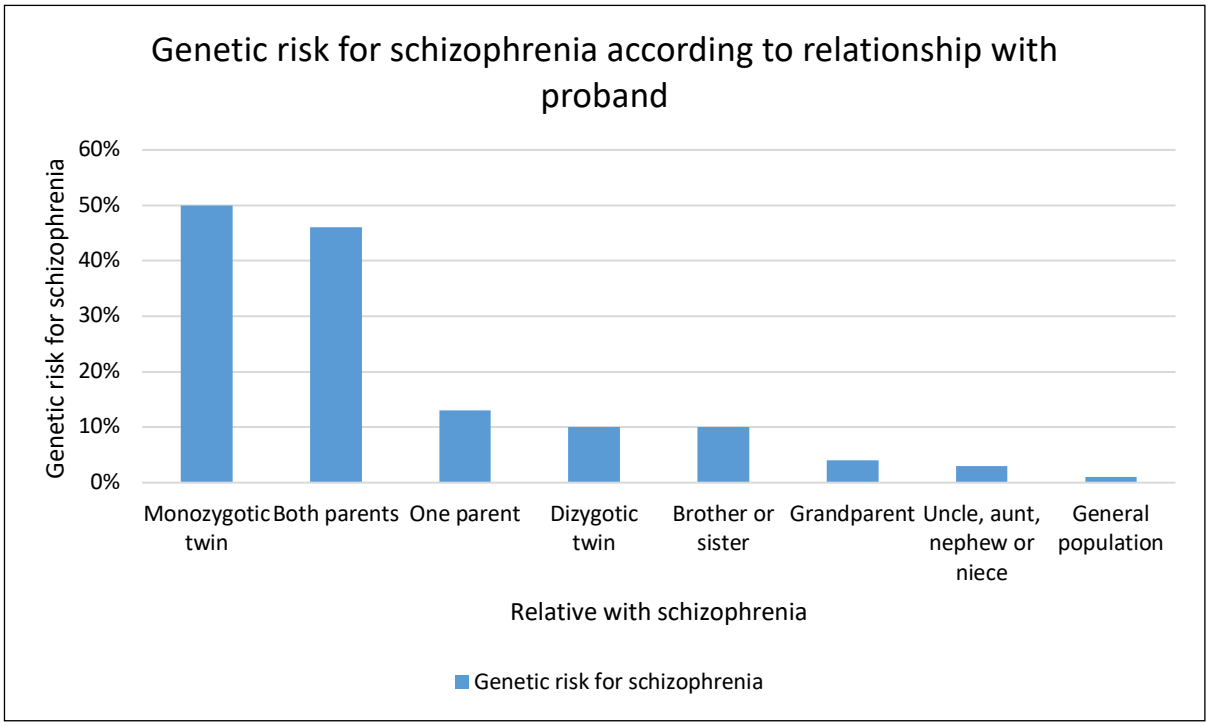

Figure 2–2. Genetic risk for schizophrenia according to the relationship with proband.

Neurochemistry describes the 'dopamine hypothesis' as an explanation for the cause of schizophrenia. It is postulated that the hyperactive dopamine transmission in mesolimbic areas and hypoactive dopamine transmission in the prefrontal cortex results in schizophrenic symptoms (Brisch *et al.*, 2014: 1).

Anatomical abnormalities in the brain of schizophrenic patients have also been a basis of neuroanatomical hypotheses for the causation of schizophrenia. These abnormalities often have a functional correlate which results in the exhibition of psychotic symptoms such as auditory hallucinations (Tsoi *et al.*, 2008: 406).

Obstetrical, labour and delivery complications in expecting mothers adversely contribute to the development of the foetal brain. This has been linked to the increased risk of schizophrenia in the adult offspring due to the significant stress (e.g. foetal oxygen deprivation) experienced during the complication (Walker *et al.*, 2004: 410).

2.3.3.2.2 Psychological factors

Cognitive impairment is considered a psychological risk factor contributing to the causes of schizophrenia. Tsoi *et al.* (2008: 406) suggested that the failure of selective attention to novel or unexpected stimuli leads to excessive stimulation of the sensorium. This excessive stimulation results in delusions as there is an attempt to form links between disparate items of information.

Certain schizotypal personality traits are indicative of increased vulnerability to schizophrenia. Pre-schizophrenic children portray abnormal social behaviours and motor development and lower intelligence or achievements relative to other children or siblings. However, they do not all develop into patients with schizophrenia (Walker *et al.*, 2004: 412).

2.3.3.2.3 Social factors

Patients with psychotic disorders commonly abuse nicotine, alcohol, cannabis (dagga) and cocaine. Psychiatric symptoms are aggravated by substance abuse, particularly the positive symptoms of schizophrenia (Margolese *et al.*, 2004: 158). The use of dagga in the adolescent phase has been associated with an increased risk of developing schizophrenia, although this cause-effect relationship is often disputed (Tandon *et al.*, 2008: 10).

Migration (in the context of the movement of people from one place to a new location with the intent of temporarily or permanently settling) has also been linked with the increased risk of developing schizophrenia, although the specific mediating factor is obscured (Tandon *et al.*, 2008: 2). Tandon *et al.* (2008: 2) also explains how the major contributing factors include social adversities, including discrimination and isolation.

Schizophrenia and psychotic symptoms are influenced by stressful life events. The development of schizophrenia can be a combination of vulnerability and stressful environments (Norman & Malla, 1993: 161).

The risk of suicide is another complicating factor in patients diagnosed with schizophrenia. The incidence of attempted suicide has been reported to occur at least twenty times more frequently in patients suffering from schizophrenia, and it is estimated to be completed in 10% of all sufferers (Siris, 2001: 127). Modes of suicide

in schizophrenic patients are often more violent and aggressive than those of people who do not suffer from this illness (Lippi *et al*., 2009: 56).

2.3.3.3 Onset of schizophrenia

The age of onset is of importance as it is indicative of the possible aetiology of schizophrenia (DeLisi, 1992: 209). It also bears significance on the outcome of schizophrenia. For example, higher levels of cognitive impairment may be present in patients with early onset schizophrenia (Kao & Liu, 2010: 63). Haffner *et al.* (1994: 30) depicts the gender difference relating to the age of onset for schizophrenia symptoms, and index episode and hospitalisation as a result of schizophrenia. This is summarised by figure 2–3 (adapted from Haffner *et al*., 1994: 30).

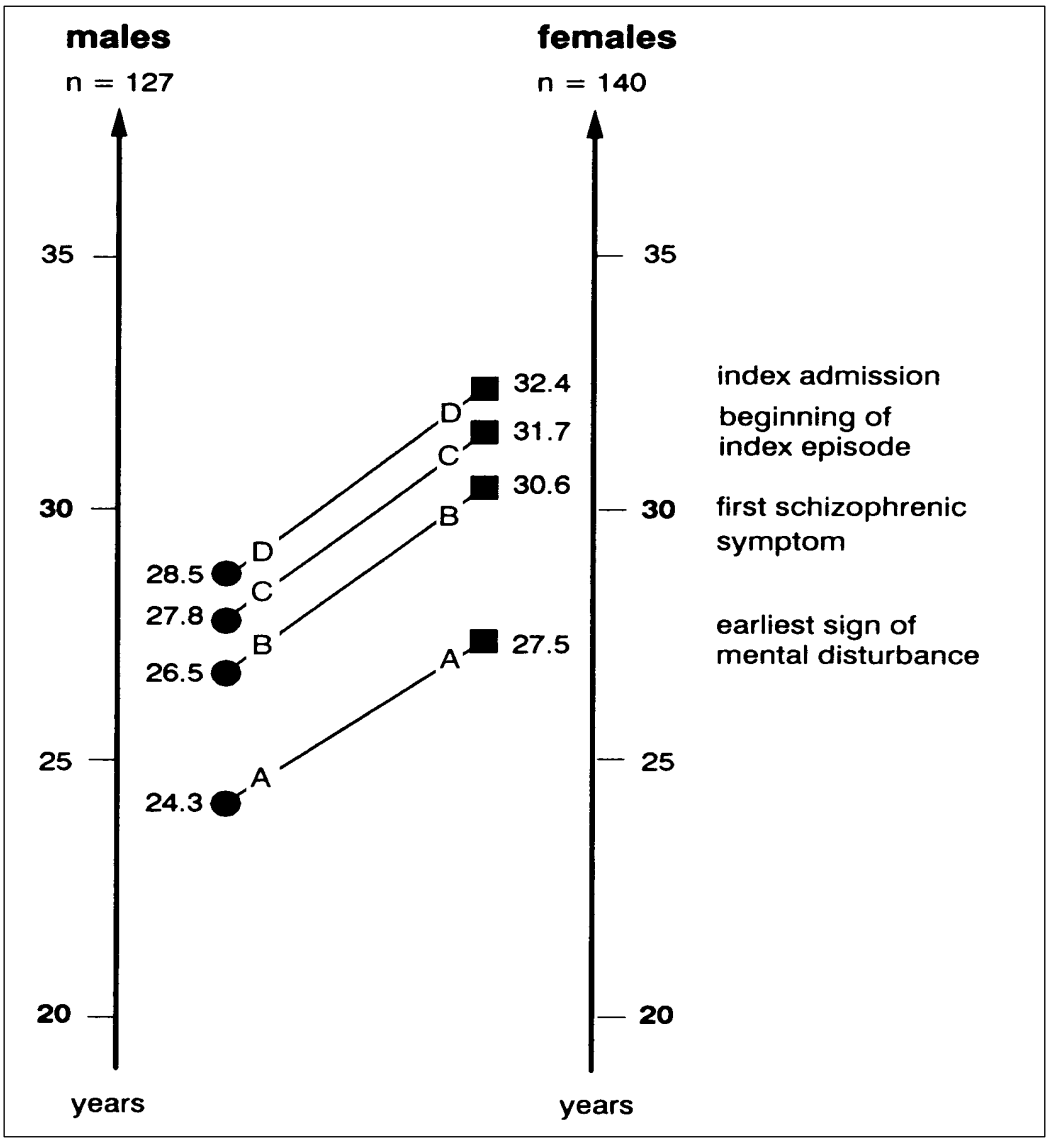

Figure 2–3. Mean age for four definitions of onset of schizophrenia: A, earliest sign of mental disturbance; B, first schizophrenic symptom; C, beginning of index episode; D, index admission.

Generally, the clinical signs and symptoms commence in the late teenage years and early twenties for males, whereas females begin to experience the same signs and symptoms in their mid-twenties to early thirties (World Health Organization, 2016).

Childhood-onset schizophrenia (COS) occurs by the age of 12 and remains a rare occurrence, despite the presentation of psychotic symptoms in up to 5% of healthy children (Driver *et al.*, 2013: 539). The diagnostic criteria also includes a premorbid intelligence quotient (IQ) of 70 or above and the absence of a significant neurological disorder (Gogtay, 2008: 30). Early-onset schizophrenia (EOS) is defined as symptoms occurring by the age of 18, however, symptoms presenting between the ages 13 to 18

are classified as adolescent-onset schizophrenia (AOS). Early-onset schizophrenia is deemed to result in the more severe form of schizophrenia (Kao & Liu, 2010: 64).

2.3.3.4 Clinical presentation

The first episode of schizophrenia often presents in the late teenage years or the early 20s (Frangou & Byrne, 2002: 522). This episode may be characterised by a manifold set of signs and symptoms which are expressed differently in patients along the course of their illness. These clinical symptoms are classified in their various clusters, namely positive, negative, cognitive, mood and neuromotor symptoms (Tandon *et al.*, 2009: 4). The clinical characteristics of schizophrenia are summarised in table 2–1 (adapted from Khamker, 2015: 30):

Table 2–1. A summary of the clinical symptoms of schizophrenia.

Positive	Negative	Cognitive	Mood	Neuromotor
Delusions	Affective blunting	Attention deficit	Depression	Catatonia
Hallucinations	Alogia	Memory deficit	Irritability	Stereotypic movements
Disorganised speech	Avolition	Executive functioning	Hopelessness	Dystonia
Disorganised behaviour	Anhedonia		Suicidality	Hypokinesia
	Social withdrawal		Anxiety	Dyskinesia
			Agitation	
			Hostility	

2.3.3.4.1 Positive symptoms

Historically, schizophrenia was divided into Type I and Type II syndromes. Type I is composed of positive symptoms such as delusions, hallucinations and disorganised thinking (Kay *et al.*, 1987: 261). Positive symptoms have since been amongst the most useful clinical guidelines in diagnosing schizophrenia according to Schneider's 'first rank symptoms' (Tsoi *et al.*, 2008: 407).

Crow's model postulates that positive symptoms are a result of problems in the dopaminergic neural transmission (Pogue-Geile & Harrow, 1984: 372). Crow also hypothesised that the pathology of positive symptoms is the increased levels of dopamine receptors (Crow, 1985: 473).

Delusions, hallucinations and disorganised speech are the primary positive symptoms that give high probability of an accurate diagnosis of schizophrenia (Tandon *et al.*, 2013: 3). The positive symptoms could be distributed into five factors as shown in table 2–2 (adapted from Kitamura *et al.*, 1998: 133):

Table 2–2. The five factors of positive symptoms of schizophrenia.

Factor	Symptom
Manic	Grandiose delusion
Depressive	Delusions of poverty and guilt
Negative	Incoherence and neologism
Catatonic	Catatonia
Discrete	All other delusions and hallucinations

2.3.3.4.2 Negative symptoms

Hughlings Jackson (cited by Pogue-Geile & Harrow, 1984: 371), the originator of the positive/negative symptom terminology, defined negative symptoms as losses of function that are a direct cause to some anatomical lesion. Similarly, Marks and Luchins (cited by Andreasen, 1990: 620) suggest there is a relationship between structural brain abnormalities and negative symptoms.

The negative symptoms are categorised as such when they represent a deficiency in interpersonal behaviour comparative to social norms (Pogue-Geile & Harrow, 1984: 372). Instruments such as the Scale for the Assessment of Negative Symptoms (SANS), the Positive and Negative Syndrome Scale (PANSS), the Schedule for the Deficit Syndrome (SDS) and the Negative Symptom Assessment Scale (NSA-16) may be used to evaluate and measure negative symptoms in schizophrenia (Blanchard & Cohen, 2006: 238; Daniel, 2013: 343). The National Institute of Mental Health (NIMH) initiated the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project which provided another scale to express the different domains of negative symptoms (Kirkpatrick *et al.*, 2006: 214). The different characteristics of negative symptoms are assessed by the instruments as shown in table 2–3 below (adapted from Daniel, 2013: 344):

Table 2–3. Characteristics of negative symptoms of schizophrenia according to their assessment instruments.

NIMH-MATRICS	SANS	NSA-16	PANSS
Blunted affect	Affective flattening or blunting	Emotional/affective dysfunction	Blunted affect
Alogia	Alogia	Communication dysfunction	Lack of spontaneity and conversation flow
Asociality	Anhedonia-asociality	Dysfunction in sociality	Passive apathetic social withdrawal, active social avoidance, poor rapport
Anhedonia			Emotional withdrawal
Avolition	Avolition apathy	Motivational dysfunction	
	Attention		
		Reduced psychomotor activity	Motor retardation

The presence of negative symptoms during the period of first-episode psychosis has negative connotations. Often these symptoms signify the possibility of an unfavourable outcome with respect to full recovery of the patient and decreased social functioning (Taylor *et al.*, 2018: 31).

2.3.3.4.3 Cognitive symptoms

Neurocognitive deficits are clinically significant in schizophrenia patients, including deficits in memory, attention, working memory, problem solving, processing speed and social cognition (Keefe & Fenton, 2007: 912). However, they are not classified as one of the diagnostic criteria for schizophrenia due to the lack of evidence sufficiently differentiating cognitive symptoms in schizophrenia from 'boundary' disorders (Tandon *et al.*, 2013: 4). These symptoms are not commonly resolved by medication, however

Cognitive Remediation Therapy (CRT) serves as an alternative therapy (Millan *et al.*, 2014: 646). Cognitive Remediation Therapy is described as a method based on behaviour training that sustainably and vastly improves cognitive activities, such as memory, attention and executive functioning (Fan *et al.*, 2017: 373).

2.3.3.4.4 Mood symptoms

Mood symptoms, such as depression and mania, are a domain of symptoms relevant to schizophrenia. This differs from major mood episodes observed in schizoaffective disorder (Carpenter & Tandon, 2013: 267). As stated in the DSM-V, significant mood symptoms must be present for the major part of the illness for the diagnosis of schizoaffective disorder instead of schizophrenia (Tandon *et al.*, 2013: 2). Mood symptoms may also be present in major depression and bipolar disorder. In both these conditions as well as schizophrenia, the depressed mood state can potentiate anhedonia and affect every day behaviours of the patient (Harvey, 2011: 17).

2.3.3.4.5 Neuromotor symptoms

Several characteristics fall under neuromotor symptoms, such as involuntary movement, neurological abnormalities, catatonic symptoms, parkinsonism, negative syndrome and psychomotor slowing (Walther & Strik, 2012: 77). Tardive dyskinesia is an example of involuntary movements that may occur due to a neuropsychiatric disorder such as schizophrenia (Waddington, 1989: 305).

Catatonia is a syndrome of abnormal motor behaviour, including diminished volition and affect. Frequently occurring catatonic symptoms in schizophrenia are mutism, posturing, stereotypies, and mannerisms (Walther & Strik, 2012: 80).

Parkinsonism is classified as a spontaneous movement disorder (SMD), with symptoms including rigidity, bradykinesia and tremor (Pappa & Dazzan, 2009: 1065). Extrapyramidal symptoms may present in neuroleptic-naïve schizophrenia patients, which could stipulate a disturbance of dopamine neurotransmission within the basal ganglia (Lohr & Caligiuri, 1997: 563).

Psychomotor symptoms may be present during the onset of psychosis (Khamker, 2015: 29). A common occurrence amongst schizophrenic patients is psychomotor slowing, also described as prolonged reaction times (Morrens *et al.*, 2007: 1038).

Jogems-Kosterman *et al.* observed that there was an overall psychomotor slowing in schizophrenia patients that was due to a retarded speed of basic psychobiological processes (Jogems-Kosterman *et al.*, 2001: 328).

2.3.3.5 Schizophrenia diagnosis using the DSM-V and ICD-11

The revised Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5®) is used globally and is considered for the effective clinical diagnoses for the multi-ethnic and multiracial community (Kupfer *et al.*, 2008: 2). The DSM-5® organises each disorder into three sections (Bhati, 2013: 3):

1. The diagnostic classification.
2. The diagnostic criteria sets.
3. The descriptive texts.

The DSM-5® and the 11th revision of the International Classification of Diseases (ICD-11) are the most current and reliable classification systems used for the diagnosis of mental disorders, including schizophrenia (Reed, 2010: 459; Bhati, 2013: 6). They were revised from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) and 10th revision of International Classification of Diseases (ICD-10) to allow for harmonisation of the diagnostic criteria, and to provide a global tool that will be useful in various multicultural settings (Kupfer *et al.*, 2008: 4; Bhati, 2013: 3). Harmonised changes in both of these revised versions include (Gaebel, 2012:264):

- No longer accentuating the first-rank symptoms in schizophrenia.
- Substituting the subtypes of schizophrenia with symptoms specifiers.
- Inclusion of cognitive impairments.
- Revised and harmonised course specifiers.

Symptom qualifiers include the presence of positive, negative, depressive, manic and psychomotor symptoms. Course qualifiers allow for distinction between first and multiple episode cases, between acute episode and partial/full remission, and between acute and insidious onset of (first) psychotic episodes. Cognitive impairments were

included due to their significant psychosocial and functional outcomes when they are treated in schizophrenia (Gaebel, 2012:897; Gaebel *et al.*, 2013:264).

According to the DSM-5®, at least two of the Criterion A symptoms (hallucinations, delusions or disorganised speech) must be present for the majority of the time, through a period of at least 1 month. Negative symptoms, grossly disorganised or catatonic behaviour may also be present (American Psychiatric Association, 2013a: 100). Similarly, the ICD-11 emphasises the same criteria for diagnosis, insisting that persistent delusions, persistent hallucinations, thought disorder and experiences of influence, unresponsiveness and control are measured as the primary symptoms (World Health Organization, 2018c: 6A20).

The DSM-5® and ICD-11 have classified the following illnesses under Schizophrenia or Other (Primary) Psychotic Disorders as summarised in table 2–4 (adapted from American Psychiatric Association, 2013b; World Health Organization, 2018c):

Table 2–4. Classification of psychotic disorders according to the DSM-5® and ICD-11.

DSM-5®	ICD-11
Schizophrenia	Schizophrenia
Schizoaffective Disorder	Schizoaffective Disorder
Schizotypal (Personality) Disorder	Schizotypal Disorder
Schizophreniform Disorder	Acute and Transient Psychotic Disorder
Brief Psychotic Disorder	Delusional Disorder
Delusional Disorder	Symptomatic Manifestations of Primary Psychotic Disorders
Substance/Medication-Induced Psychotic Disorder	Substance-Induced Psychotic Disorders
Other Specified Schizophrenia Spectrum and Other Psychotic Disorder	Other Specified Schizophrenia Spectrum and Other Primary Psychotic Disorder
Unspecified Schizophrenia Spectrum and Other Psychotic Disorder	Unspecified Schizophrenia Spectrum and Other Primary Psychotic Disorder

The Schizophrenia Spectrum Disorders differ in their severity. They can be comparatively analysed along a continuum of severity as depicted in figure 2–4 (adapted from Bhati, 2013: 3):

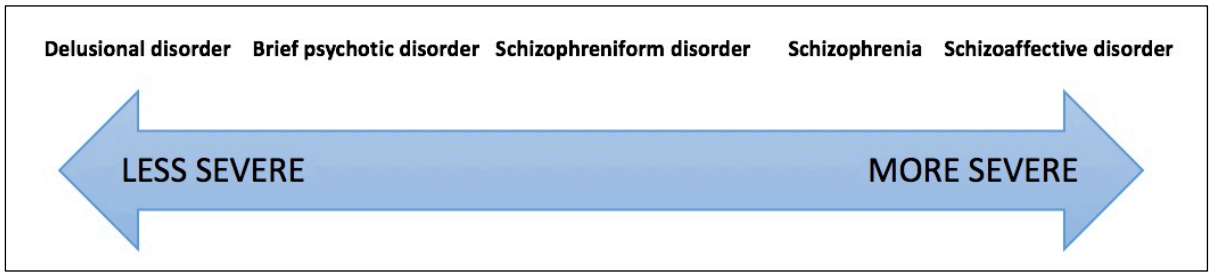

Figure 2–5. A continuum of severity of schizophrenia spectrum disorders.

2.3.4 Schizoaffective disorder

2.3.4.1 Definition

The differentiation of schizoaffective disorder from schizophrenia and major mood disorders continues to be a dilemma and a point of constant debate (Tandon *et al.*, 2009: 16). The terminology has been evolving in the DSM since 1962 as shown in table 2–5 (adapted from Malaspina *et al.*, 2013: 22):

Table 2–5. The evolution of terminologies in the DSM.

DSM	Year	Schizoaffective disorder diagnoses
DSM I	1962	Schizophrenic reaction Schizoaffective type
DSM II	1968	Schizophrenia, Schizoaffective type, excited Schizophrenia, Schizoaffective type, depressed
DSM III	1980	Schizoaffective Disorder
DSM III-R	1987	Schizoaffective Disorder Bipolar type Depressive Type (4 diagnostic criteria introduced)
DSM-IV	1994	Mixed subtype of Bipolar Type added
DSM-IV-TR	2000	No change in diagnostic criteria
DSM V	2013	Schizoaffective Disorder Bipolar type

		Depressive type With catatonia

The Research Diagnostic Criteria defines schizoaffective disorder as the acute co-occurrence of a full mood syndrome (depression and mania) and one of a set of "core-schizophrenic" symptoms, such as bizarre delusions, first-rank symptoms, or nearly continuous hallucinations (Levinson *et al.*, 1999: 1139). Similarly the 1993 ICD-10 Classification of Mental and Behavioural Disorders describes schizoaffective disorders as a combination of affective (manic and/or depressive) and schizophrenic symptoms (World Health Organization, 1993: 74). The DSM-V also classifies schizoaffective disorder as a distinct psychotic disorder, not under schizophrenia or mood disorders (Malaspina *et al.*, 2013: 23).

Schizoaffective disorder was first recognised by Jacob Kasanin in 1933 as the co-occurrence of symptoms of schizophrenia and mood or "affective" symptoms. He termed this as "schizoaffective psychosis" (Kasanin, 1994: 99). In contrast to the two former definitions, schizoaffective disorder has also been defined as an atypical form of schizophrenia presenting with affective symptoms (Cheniaux *et al.*, 2008: 210). The unique recognition of schizoaffective disorder in psychiatric nosology (the classification of diseases) is not certain (Abrams *et al.*, 2008: 1089).

2.3.4.2 Schizophrenia or schizoaffective disorder debate

Previously, researchers have explored the validity of the existence of schizoaffective disorder. The popular consensus in existing literature suggests that schizoaffective disorder is a heterogeneous illness that is closely related to schizophrenia, closely followed by the opinion that it is in fact a mood disorder. However, few studies do hypothesise that schizophrenia and schizoaffective disorder are the same illness, others postulate that schizoaffective disorder is a separate disease, and other studies are inconclusive on any of the previous claims (Lake & Hurwitz, 2006: 260). A literature review by Lake and Hurwitz (2006: 263) summarises these results in figure 2–5 (adapted from Lake & Hurwitz, 2006: 263):

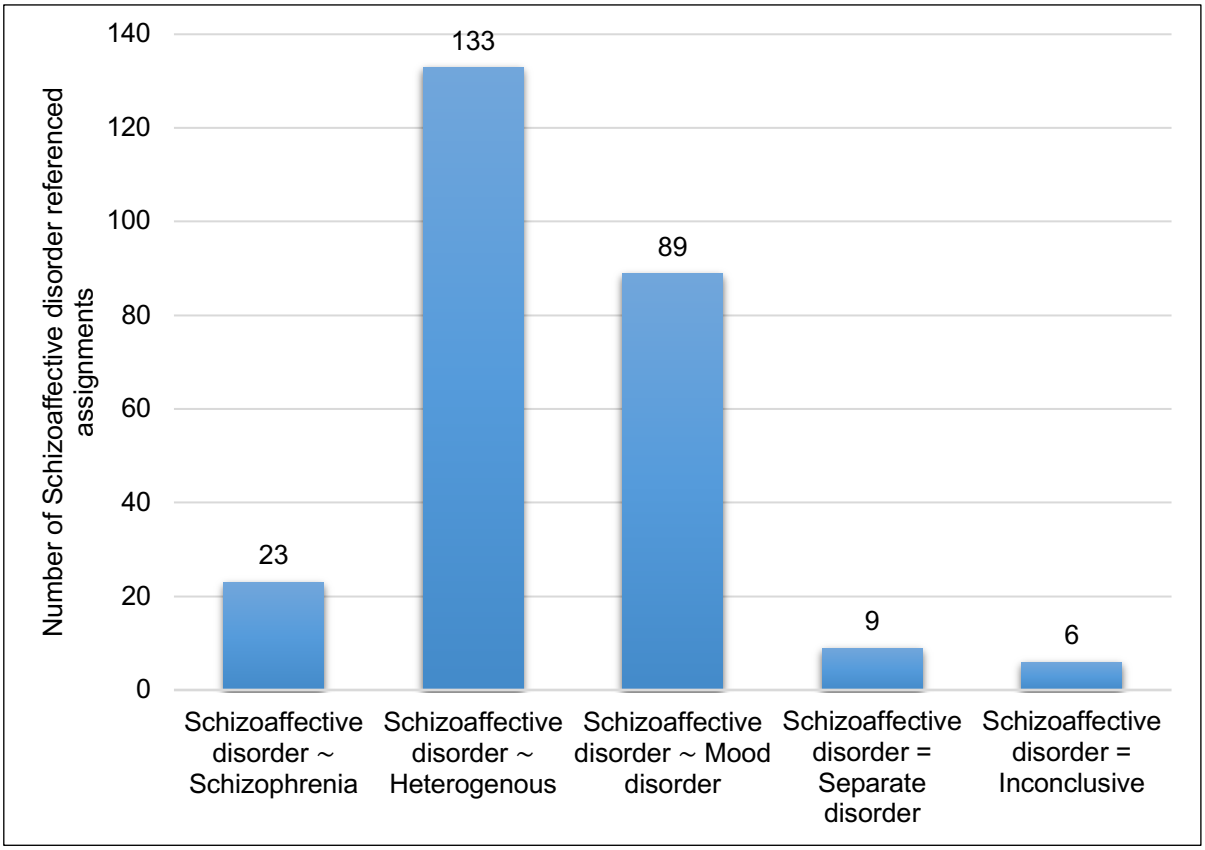

Figure 2–6. The definition of schizoaffective disorder in literature assignments.

However, the DSM-5® has organised schizoaffective disorder as a separate illness from schizophrenia and does not categorise it as a mood disorder but as one of the schizophrenia spectrum disorders (American Psychiatric Association, 2013b: xv). The mood symptoms experienced in schizoaffective disorder are not prominent enough to meet the criteria for a mood disorder diagnosis (Malaspina *et al.*, 2013: 24). Recent investigations in the literature also support these diagnostic criteria and consider schizoaffective disorder as a separate entity to schizophrenia and the other mood disorders such major depressive disorder and bipolar mood disorder (Cheniaux *et al.*, 2008: 214; Leposavić *et al.*, 2015: 395).

Inevitably the diagnoses of psychiatric disorders proves to be a challenge in many cases, as symptoms frequently overlap and a distinct and unconditional diagnosis is never assured (Abrams *et al.*, 2008: 1103).

2.3.4.3 Aetiology of schizoaffective disorder

The aetiology of schizoaffective disorder has not been extensively investigated and is usually clustered with schizophrenia or bipolar disorder studies. Molecular studies show that schizophrenia and manic episodes share similar genetic risk factors for the bipolar subtype of schizoaffective disorder (Cardno & Owen, 2014: 510). The DSM-5® also claims that among schizophrenia patients, there is an increased risk of the development of schizoaffective disorder in the first-degree relatives (a parent, sibling or child). Similarly, a first-degree relative with schizophrenia, bipolar disorder, or schizoaffective disorder increases the risk of the development of schizoaffective disorder in an individual (American Psychiatric Association, 2013b: 108). Supporting studies have shown that there is a prevalence of schizophrenia in the families of probands with schizoaffective disorder and bipolar disorder (Lake & Hurwitz, 2006: 269).

Lencz *et al.* (2009: 313) hypothesised that there could be molecular differentiation between schizophrenia and schizoaffective disorder. Distinction for the allele in the gene coding brain-derived neurotrophic factor (BDNF) was associated with schizoaffective disorder but not or schizophrenia (Lencz *et al.*, 2009: 316).

An association between the underrepresentation of a distinct haplotype from a region on the Disrupted-In-Schizophrenia-1 (DISC1) gene and schizoaffective disorder has been hypothesised by Hodgkinson *et al.* (2004: 863). A haplotype is defined as “a group of alleles of different genes on a single chromosome that are closely enough linked to be inherited usually as a unit” (Merriam-Webster, 2019f). Abnormalities of DISC1 poses as a genetic risk for acquiring schizoaffective disorder (Hodgkinson *et al.*, 2004: 863).

2.3.4.4 Onset of schizoaffective disorder

Studies have shown that the age of onset for schizoaffective disorder is estimated to be analogous to the age of onset for schizophrenia and major depressive disorder (Cheniaux *et al.*, 2008: 214). Earlier reviews in the 1990s approximated that the age of onset falls within a broad range from ages prior to 25 years up to ages over 35 years old, with an equal proportion of patients developing the illness between the ages of 25 to 35 years old (Abrams *et al.*, 2008: 1093). A small study in South Africa identified

that the mean age of onset in patients diagnosed with schizoaffective disorder was 25 years, which corresponds with the global literature reviews (Singh & Subramaney, 2016: 3).

Due to the challenges formerly faced in well-classified diagnostic criteria for schizoaffective disorder, the demographical profile (including age of onset) for schizoaffective disorder has not been fully explored and is often predicted to be the same as that of schizophrenia and bipolar mood disorder (Kao & Liu, 2010: 7; Pinna *et al.*, 2014: 47).

2.3.4.5 Schizoaffective disorder diagnosis using the DSM-V and ICD-11

The DSM-IV did not provide clear definitions of the boundary between schizophrenia and schizoaffective disorder. The issue of reliability and validity when defining schizoaffective disorder as a distinctive illness from mood disorders and schizophrenia has been interrogated (Malaspina *et al.*, 2013: 22; Pinna *et al.*, 2014: 47). The inquiry arose, yet again, as to whether schizoaffective disorder should be contemplated as a subtype of schizophrenia (Maj *et al.*, 2000: 96).

The ICD-11 requires that the concurrent incidence of schizophrenia symptoms (such as delusions, hallucinations) and mood disorder symptoms (depressive or manic episodes) be present or within a few days of each other for 4 weeks each (Gaebel, 2012: 264). The ICD-11 describes schizoaffective disorder to present with prominent symptoms of schizophrenia followed by the typical symptoms of a depressive or manic episode, or a mixed episode. These symptoms are not an indication of another medical condition, a substance or a medication (World Health Organization, 2018c: 6A21).

The revised DSM-5® specifies a more specific criteria for diagnosing schizoaffective disorder, such as the requirement of the presentation of a major mood episode for the majority of the extent of the illness, contrary to the previous criteria in the DSM-IV. This differentiates schizoaffective disorder from schizophrenia which requires the mood symptoms to be present for only a brief episode (American Psychiatric Association:2013b).

Alongside this diagnosis, other examinations have been recommended in the South African context by the South African Society of Psychiatrists, to support the exclusion of other biological causes of psychosis. This includes screening for HIV, syphilis and psychoactive substances (Swingler, 2013: 153).

2.3.5 Treatment guidelines

A broad multi-modal approach is typically employed for the treatment of schizophrenia, including pharmacological, psychosocial interventions, and often assistance with social and lifestyle maintenance (Tandon *et al.*, 2010:2). Treatment-resistant schizophrenia (TRS) is prevalent in about 30% of patients and it is portrayed when there is no clinical response to at least two different antipsychotics, excluding clozapine (Swingler, 2013: 154). The SASOP treatment guidelines specify that TRS is considered when at least two antipsychotics (one of which is a non-clozapine SGA) have failed to produce any symptomatic relief after a duration of 6 weeks of therapy (Emsley & Seedat, 2013: 155).

2.3.5.1 Acute pharmacological treatment

First episode psychosis is marked by the onset of obvious psychotic symptoms (positive and/or negative), such as hallucinations, delusions and disorganised thinking and behaviour (Khamker, 2015:29). Pharmacological and psychosocial treatment options are both viable. The primary goal of treatment is to restore rapid remission of the acute episode as it is proposed that patients are most responsive to treatment during their first episode (Frangou & Byrne, 2002: 522). However, these patients are also more vulnerable to the adverse effects of antipsychotic medication, therefore most of the antipsychotics are titrated up gradually until the optimal dosage is achieved (Khamker, 2015:32).

First episode psychosis is initially treated by haloperidol, a first generation or typical antipsychotic. This therapy alleviates symptoms, such as thought disorders, hallucinations and delusions and is preventative in relapse (World Health Organisation, 2008:455). In terms of efficacy, haloperidol produces outcomes similar to those produced by the second-generation antipsychotics (SGAs) (Zhu *et al.*, 2017:10). Alternatively, this condition may also be treated by a second generation or atypical antipsychotic such as risperidone or chlorpromazine (Maartens *et al.*,

2015:15.14). Although the clinical efficacy between typical and atypical antipsychotics in this instance is equivalent, the atypical antipsychotics are the preferred choice (excluding clozapine) due to the presentation of minimal adverse effects (Emsley *et al.*, 2013:154). The long term use of first-generation antipsychotics are more likely to cause extrapyramidal side effects and tardive dyskinesia (Khamker, 2015:32). In such cases, the first generation antipsychotic is substituted for a second generation antipsychotic (Maartens *et al.*, 2015:15.15).

The treatment algorithm for first-episode schizophrenia, illustrated in figure 2–6, was adapted from the Maudsley Prescribing Guideline for Psychiatry (adapted from Taylor *et al.*, 2018:40):

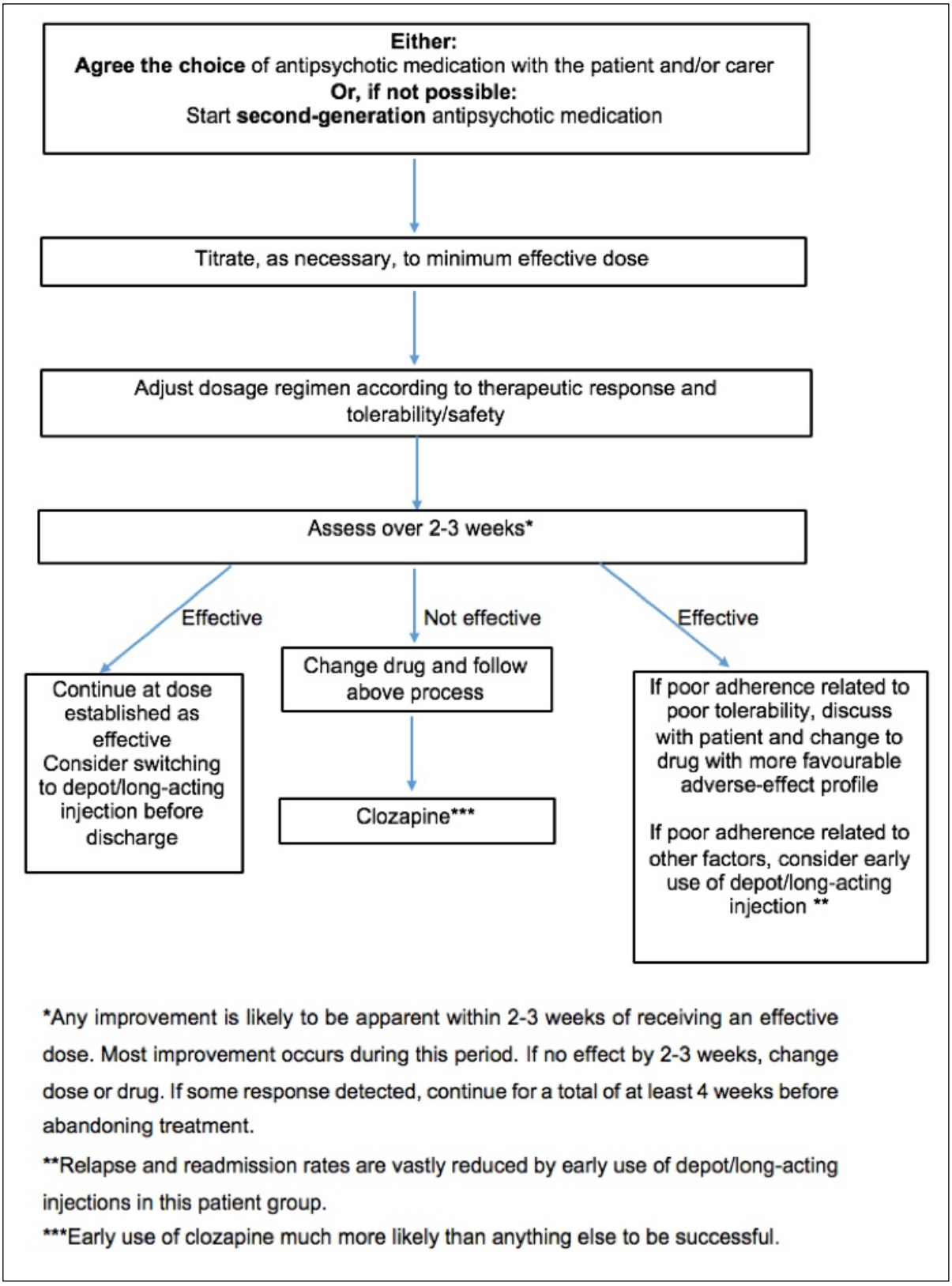

Figure 2–7. Treatment algorithm for first-episode schizophrenia.

A South African study by Khamker (2015: 32) confirmed that 50% to 70% of patients receiving antipsychotics during their first episode of psychosis attained positive

symptoms remission. This correlates with other studies that portray that 80% of patients will recover from the first episode psychosis (Frangou & Byrne, 2002: 523).

Depending on the initial antipsychotic drug used during treatment of the first episode psychosis, the drug of choice for multi-episodes or a case of relapse has to be more efficacious and more tolerable. Second-generation antipsychotics are still preferred, and a cross-titration, overlap-and-taper, or an abrupt change method is employed (Swingler, 2013: 154). A cross-titration, also referred to as cross-tapering, is a method whereby the dosage of the first drug is gradually decreased over the course of 2-4 weeks whilst the second drug is initiated simultaneously on a low dosage. The second drug dosage is gradually increased. The overlap-and-taper method maintains the first drug at the maintenance dose for 2-3 weeks whilst the second drug is initiated. The dosage is titrated to the optimal therapeutic dose. Once this is achieved, withdrawal of the first drug is commenced by decreasing the dosage gradually over 1-2 weeks. In the case of the abrupt change method, the first drug is stopped immediately, and the second drug is initiated at the initial recommended dosage followed by a gradual increase in dosage (Golebiewski, 2006: 1).

Non-compliance with their medication is one of the greatest predictors of patients' relapse, alongside other factors such as poor efficacy, adverse effects, and poor access to medicines (Khamker, 2015: 33). The South African Treatment Guidelines recommend that a long-acting intramuscular injectable antipsychotic that is administered every 4 weeks be prescribed, such as flupenthixol decanoate, fluphenazine decanoate or zuclopenthixol decanoate (Maartens *et al.*, 2015: 15.15). Long-acting injectable antipsychotics are also useful for long-term maintenance and could be the patient's most convenient choice (Swingler, 2013: 154).

2.3.5.2 Maintenance therapy

The South African Society for Psychiatrists (SASOP) treatment guidelines claim that the duration of treatment depends on the frequency of the psychotic episode and the period at which the patient has been free of symptoms as summarised in table 2–6 (adapted from Swingler, 2013: 154):

Table 2–6. Maintenance therapy depending on the psychotic episode.

Episode	Severity	Response to treatment	Minimum duration of symptom free treatment
First episode	Mild severity	Good response	1 year
First episode	Severe	Slow response	2 years
Second episode			2-5 years
Third episode			Indefinite

A maintenance treatment plan is dependent on the most effective treatment during the acute phase of the psychotic condition. Treatment with antipsychotics is individualised and dependent on patient responsivity and efficacy (Tandon *et al.*, 2010: 6). The pharmacological treatment is recommended to be continued and the early withdrawal of effective drugs is not desirable, instead a steady tapering down approach must be followed (Frangou & Byrne, 2002: 522; Swingler, 2013: 154). For schizophrenia diagnoses, the main therapeutic outcome is to induce the rapid remission of the acute psychotic episode using a tolerable antipsychotic drug (Frangou & Byrne, 2002: 522).

The lowest possible dosage of the most appropriate antipsychotic drug for the patient is prescribed as the maintenance therapy (World Health Organization, 2008: 455). Long-acting injectables or depot antipsychotic drugs are an advisable treatment option, particularly to prevent relapse and avoid non-compliance (Khamker, 2015: 33). In South Africa, the maintenance therapy must be initiated by a specialist, such as a psychiatrist, and a review of the therapy must be undertaken every 6 months (Maartens *et al.*, 2015: 15.15). Antipsychotic drugs are usually prescribed on a trial-and-error and risk-benefit basis, and the monitoring of clinical response and adverse effects is of paramount importance in choosing the most beneficial drug for the patient (Tandon *et al.*, 2010: 6).

According to the WHO model formulary (2008: 455), the recommended antipsychotics are chlorpromazine or haloperidol for the relief of psychotic symptoms. Risperidone is also considered as an essential drug in the treatment of schizophrenia in South Africa (Maartens *et al.*, 2015: 15.14). These antipsychotics may be continuously administered as maintenance therapy at the same effective dosage. Dosage

reduction must be avoided as the risk of relapse is exacerbated (Swingler, 2013: 154). The SASOP treatment guidelines consider clozapine as the core antipsychotic for schizophrenia. However, due to its severe adverse effects it is considered as the third-line treatment monotherapy and indicated for treatment-resistant schizophrenia (Swingler, 2013: 154; Mauri *et al*., 2018: 3).

The treatment algorithm adapted from the Maudsley Prescribing Guidelines for Psychiatry during maintenance treatment for fully adherent patients is depicted in figure 2–7 (adapted from Taylor *et al.*, 2018: 41):

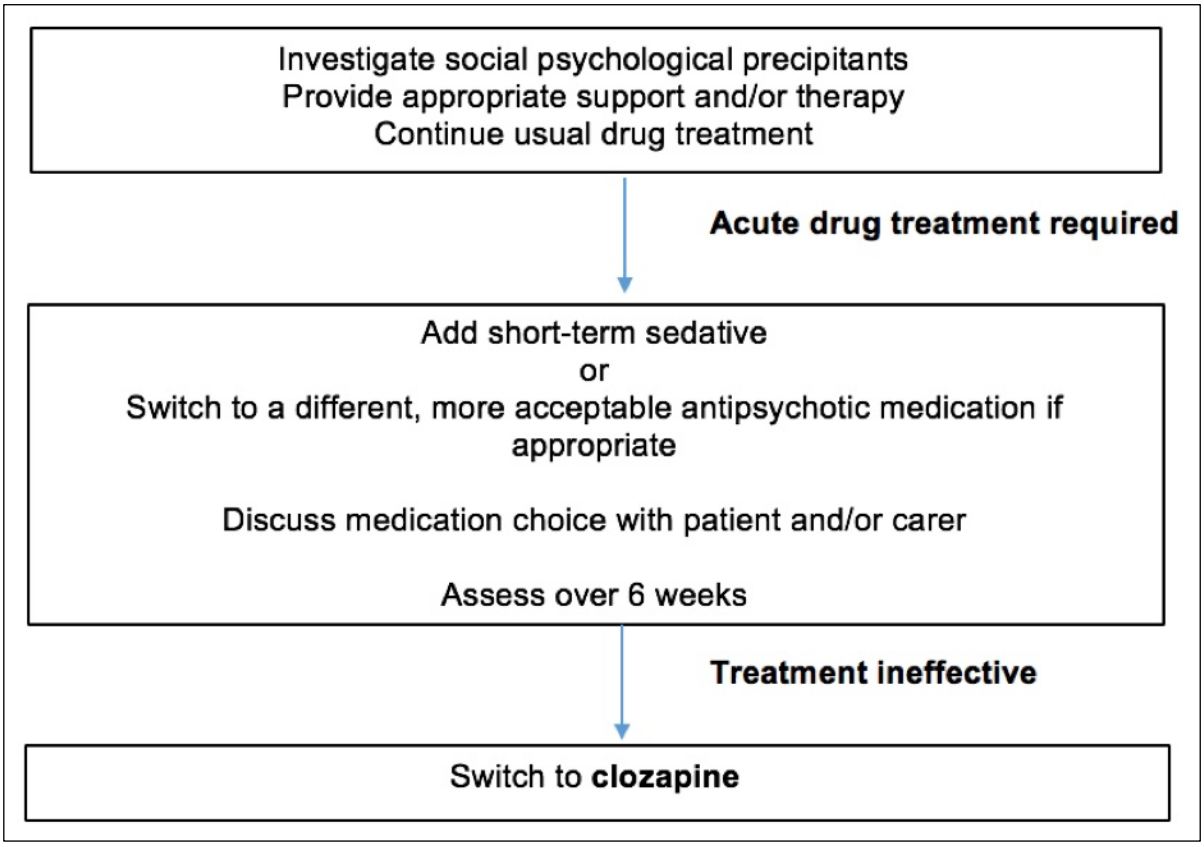

Figure 2–8. Treatment algorithm for maintenance treatment for fully adherent patients (Taylor *et al.*, 2018: 41).

A different algorithm is followed when the patient was previously non-adherent to treatment plans. Figure 2–8 illustrates a treatment algorithm, adapted from the Maudsley Prescribing Guidelines for Psychiatry, which considers different treatment options according to the reason for non-adherence (adapted from Taylor *et al.*, 2018: 42):

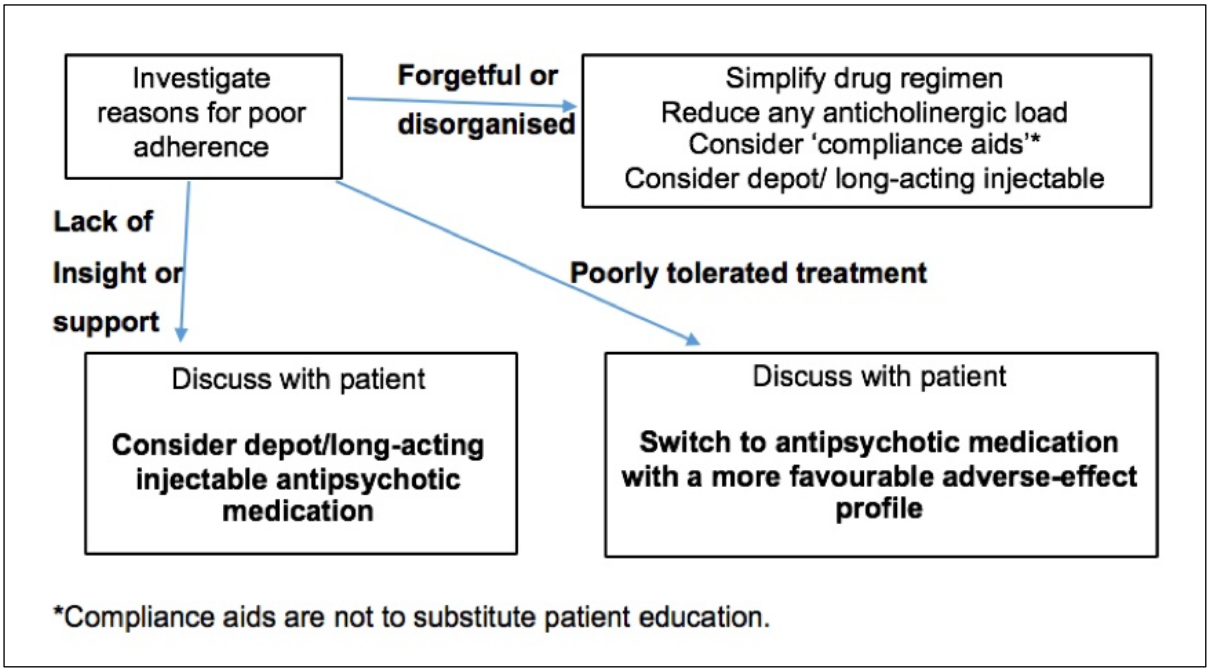

Figure 2–9. Treatment algorithm for the non-adherent patients.

Adjunctive therapy using psychotherapeutic medications such as anticonvulsants, antidepressants, benzodiazepines and lithium is often useful in the pharmacotherapy of schizophrenia (Tandon *et al.*, 2010: 7). Augmentation therapy is useful for the relief of symptoms. An example of this are antidepressants which are effective in the treatment of negative symptoms, such as affective flattening, alogia and avolition (Taylor *et al.*, 2018: 159).

2.3.5.3 Non-pharmacological treatment

Psychosocial interventions are advantageous in promoting the treatment of psychosis and rehabilitation to achieve holistic health (Frangou & Byrne, 2002: 523). Psychosocial interventions include cognitive behavioural therapy (CBT), psycho-education and supportive psychotherapy for the patient alongside the family, as recommended in the SASOP treatment guidelines (Swingler, 2013: 154).

Psycho-education includes the provision of information about the disorder and its treatment to aid in the prevention of relapse. It is recommended by the American Psychiatric Association (APA) and the German Society for Psychiatry, Psychotherapy and Neurology (DGPPN) under the standard treatment guidelines for acute and post-acute phases of schizophrenia (Bäuml *et al.*, 2006: S1). A precise definition of psycho-education is as follows (Bäuml *et al.*, 2006: S3): "*The term psychoeducation comprises*

systemic, didactic-psychotherapeutic interventions, which are adequate for informing patients and their relatives about the illness and its treatment, facilitating both an understanding and personally responsible handling of the illness and supporting those afflicted in coping with the disorder… Within the framework of psychotherapy, psychoeducation refers to the components of treatment where active communication of information, exchange of information among those afflicted, and treatment of general aspects of the illness are prominent."

Cognitive behavioural therapy is useful in the relief of persistent positive symptoms (hallucinations and delusions), however, it does not benefit the relief of negative and chronic symptoms, or the prevention of relapse (Tandon *et al.*, 2010: 7; Hofmann *et al.*, 2012: 11). Additional goals of CBT include improvement of functioning and remission of the disorder (Hofmann *et al.*, 2012: 2). Social functioning is assisted by cognitive remediation as it reintroduces basic social skills (Frangou & Byrne, 2002: 523). Although the permanency of the effects of cognitive remediation are uncertain, studies have found that it is most useful when there are adjunctive psychiatric rehabilitation programs (Tandon *et al.*, 2010: 8).

The SASOP treatment guidelines consider electro-convulsive therapy (ECT) as a last resort treatment in uncomplicated schizophrenia. Electro-convulsive therapy has a beneficial role in early acute treatment, when excessive psychomotor agitation, catatonia, pregnancy, or when the patient's life is at risk (Emsley & Seedat, 2013: 155).

2.4 Clozapine

2.4.1 Background and history of clozapine

The discovery of clozapine was influenced largely by the discovery of chlorpromazine as an antipsychotic agent largely used to treat symptoms of schizophrenia. In 1959, the compound clozapine was identified amongst other compounds in synthesised tricyclic antidepressants which had some neuroleptic properties (Crilly, 2007: 40). The pharmacological profile of clozapine differed from the typical neuroleptics which all convey extrapyramidal side effects. However, clozapine did not cause catalepsy, parkinsonism, dystonia, or tardive dyskinesia and it did not increase prolactin levels (Alvir*, et al.,* 1993: 162). The stereochemistry of clozapine suggests that it would have

antidepressant properties, however it has proven to have antipsychotic properties suited to treat schizophrenia (Hippius, 1989:S3; Crilly, 2007: 41).

The notion amongst pharmacologists in the early 1960s was that the presence of extrapyramidal symptoms directly correlated with the efficacy of an antipsychotic drug. Consequently, clozapine was not marketed as a new therapeutic drug for schizophrenia (Hippius, 1989: S4). The end of the decade was marked by an increased number of clinical trials throughout Europe led by Stille and Hippius, administering clozapine to nearly 2200 patients. Although the results showed positive therapeutic outcomes, they were not convincing enough to influence the conception previously believed by pharmacologists (Crilly, 2007: 42).

Clozapine was marketed under the European trade name Leponex® in Finland in 1975. Within the first five months of exposure to the market the first case of agranulocytosis was reported, and a month later the drug was taken off the market due to an increase in cases of agranulocytosis. An estimated one to two percent of treated patients suffered from this severe adverse reaction (Chapelle *et al*., 1977: 183; Alvir *et al*., 1993: 162). Of the sixteen patients who developed agranulocytosis, eight resulted in fatalities (Crilly, 2007: 43). The frequency of this occurrence in Finland was twenty-one times higher than in any other country which had also marketed clozapine, leading to the indepth analysis of agranulocytosis induced by clozapine (Anderman & Griffith, 1977: 201). It is recorded that in 1974 clozapine was avaliable in South Africa (Hemphill *et al.*, 1975: 2121). Between 1972 and the 31st August 1976, South Africa reported only one case of agranulocytosis and no fatalities. This compared differently with Finland which displayed a higher calculated frequency of patients reporting agranulocytosis (Anderman & Griffith, 1977: 200).

The United States Food and Drug Administration (US FDA) ceased the manufacturing of clozapine by pharmaceutical company Sandoz in 1976 due to the toxic effects experienced in Finland (Crilly, 2007: 46). Other countries continued to market clozapine whilst consistently monitoring the effects of the drug on the blood profile (Hippius, 1989: S4).

A pioneering double-blind study of clozapine and chlorpromazine was undertaken in 1988. A double-blinded study is a scientific research method whereby both the

investigator of the study and the participant are unaware of the treatment the participant is receiving, this results in unbiased and objective outcomes (Stolerman, 2010: 418). This study proved the superiority of clozapine in comparison with chlorpromazine regarding its efficacy in treating schizophrenic patients resistant to maximum dosages of haloperidol (Barnes & Talmud, 2007: 245). In October 1989, the FDA approved the clinical use of clozapine and by February 1990 it was reintroduced into the United States market (Shen, 1999: 409). Many other atypical antipsychotics were developed after clozapine, however, none have matched the efficacy of clozapine (Khokhar *et al.*, 2018: 139).

2.4.2 Pharmacological properties

Clozapine is employed for the treatment of treatment-resistant schizophrenia and schizoaffective disorder (Aitchison *et al.*, 2000: 353). It is an atypical antipsychotic and falls into the dibenzodiazepine chemical class (Mauri *et al.*, 2007: 362). The chemical structure of clozapine is shown in figure 2–9 (adapted from Jafari *et al.*, 2012: 374):

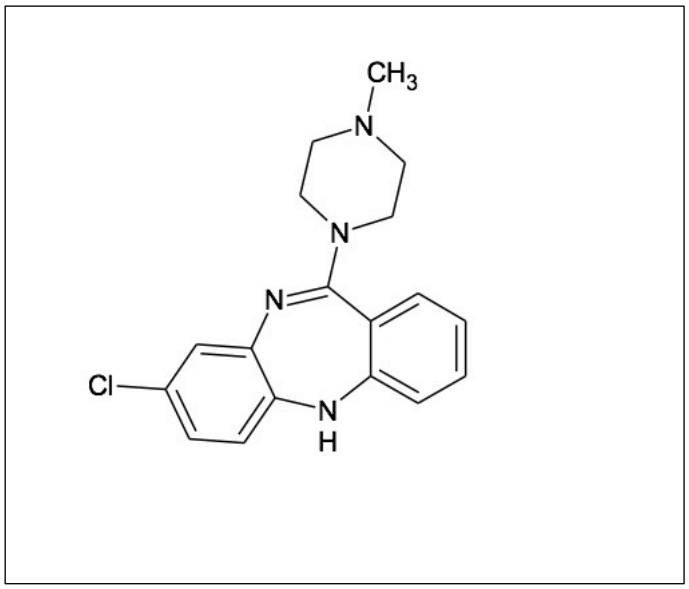

Figure 2–10. Chemical structure of clozapine.

The chemical structural of clozapine has been suggested to contribute to the receptor-binding affinities for histamine H_1 or serotonin $5HT_{2C}$ receptors. The structure activity relationship of clozapine may indicate to the occurrences of some of its adverse effects. It is postulated that affinity for the histamine H_1 receptors plays a role in the

weight gain adverse effect that is prominent in patients using clozapine (Jafari *et al.*, 2012: 380). Conversely, the tetracyclic structure of clozapine is hypothesized to decrease the risk of extrapyramidal side effects (EPSE) and tardive dyskinesia.

2.4.2.1 Pharmacodynamics

2.4.2.1.1 Mechanism of action

The dopamine signalling pathway is considered the principal common target for all antipsychotic drugs. Of the five subtypes of dopamine receptors (D_1, D_2, D_3, D_4, and D_5), only the D_2 dopamine receptor is blocked by antipsychotic drugs relative to their clinical antipsychotic potencies. The clinical efficacy of antipsychotics is associated with a blockade of 60-80% of D_2 receptors in the brain (Mauri *et al.*, 2014: 1164). Atypical antipsychotics are related to their pharmacodynamic qualities and can be classed according to their affinity for certain pharmacological receptors as shown in table 2–7 (adapted from Horacek *et al.*, 2006: 391):

Table 2–7. Classification of pharmacological receptors targeted by atypical antipsychotics.

Classification
D_2/D_3 dopamine receptor antagonist
Partial dopamine D_2 receptor agonist
Serotonin-dopamine receptor antagonists (SDA)
Multi-acting receptor-targeted antipsychotics (MARTA)

Clozapine is classified as a multi-acting receptor-targeted antipsychotic (MARTA), similar to olanzapine and quetiapine. The MARTA drugs have an affinity for multiple receptors, including serotonin (subtypes 5-HT_{2A}, 5-HT_{1A}, 5-HT_{2C}), dopamine D_2, cholinergic, histaminergic H_1, muscarinic M_1 and α_1 adrenoceptors (Horacek *et al.*, 2006:391). Clozapine has shown superior antagonistic activity on cortical and limbic dopamine D_4 than D_2 receptors (Mauri *et al.*, 2007: 362). Comparatively, typical antipsychotics exhibit high striatal dopamine receptor binding (Khokhar *et al.*, 2018: 140). The occupancy of clozapine at the dopamine D_2 receptors is between 38 - 63% at normal doses. This is below the threshold for inducing EPSE (Jafari, Fernandez-Enright & Huang, 2012: 376). An estimated 96% of serotonin 5-HT_{2A} receptors are occupied by clozapine in an average clinical dosage of between 300-600 milligrams

per day (mg/day). Comparatively, risperidone occupies ~100% of these receptors at an average dosage of 6 milligrams per day (Seeman, 2014: 26).

The clinical and adverse effects of antipsychotics are conditional on the combination of receptors occupancy. The occupancy theory is based on the link between the action of a drug to the proportion of receptors occupied by the drug at equilibrium (Christopoulos & El-Fakahany, 1999: 735). The dopamine pathway is considered to be the major target for all antipsychotics; this is proven by the fact that all antipsychotics have a significant affinity for D_2 receptors (Mauri *et al.*, 2014: 1164). The most valuable clinical effects of clozapine (and other antipsychotics such as risperidone) are likely due to the selective antagonistic effects on mesolimbic and mesocortical dopaminergic neurons (Ayano, 2016: 2).

2.4.2.1.2 Neuroendocrine effects

Hyperprolactinaemia is a common adverse effect of most atypical antipsychotics (Turrone *et al.*, 2002: 133). Typical antipsychotics block non-selective dopamine D_2 receptors, and atypical antipsychotics have a high affinity for serotonin $5HT_2$/dopamine D_2 receptors. The inhibition of dopamine D_2 receptors in the tuberoinfundibular system of the hypothalamus, which is the prolactin secretion regulation system, results in elevated prolactin levels (Bargiota *et al*., 2013: 2). The use of clozapine may produce temporary prolactin elevation within the first few hours after administration, and occasionally periodic elevations could occur during long-term therapy. In comparison to chlorpromazine, prolactin levels are not significantly elevated by clozapine (Jann *et al.*, 1993). Risperidone is similar to clozapine in that slight prolactin elevation in long term patients may be dose-related (Turrone *et al.*, 2002: 134).

2.4.2.2 Pharmacokinetics

Clozapine is formulated in an oral dosage form (tablet) (Snyman & Webb, 2015:53a). The recommended dosage may differ in individual patients. It ranges from ~150 mg/day to 1000 mg/day (Thorn *et al.*, 2018: 1), however the SAMF states the maximum dose of 900 mg/day (Rossiter, 2016: 481). Clozapine may also be used in paediatric patients (patients below the age of 18 years, diagnosed with childhood-onset schizophrenia), however, dose-dependent adverse effects and leukopenia are a frequent occurrence due to the age-related pharmacokinetic differences *(Frazier et*

al., 1994: 658, 2003: 87). This indication is an off-label use of the drug (Rossiter, 2016: 481).

2.4.2.3 Absorption

Most antipsychotics are understood to be lipophilic and they can therefore freely cross lipoidal membranes (Javaid, 1994: 286). Clozapine is absorbed well in the gastrointestinal tract, however, its bioavailability is limited to approximately 50% as a consequence of first-pass metabolism in the liver (Sweetman, 2018). Generally, antipsychotics are susceptible to significant pre-systemic elimination (Javaid, 1994: 286). The time taken for clozapine to reach peak plasma concentrations (T_{max}) after oral administration in patients with schizophrenia ranges between 1.1 to 3.6 hours (Jann *et al.*, 1993: 161). There has been no evidence to prove that food affects the absorption of clozapine when it is orally administered (Mauri *et al.*, 2007: 363, Sweetman, 2018). Clozapine plasma levels are mostly lower in males, smokers, and younger patients (Taylor *et al.*, 2018).

2.4.2.4 Distribution

Antipsychotic drugs have a high affinity to bind to plasma proteins (75-99%) (Javaid, 1994: 286). Clozapine is 95% bound to plasma proteins, and it predominantly binds to α1-glycoprotein (Mauri *et al.*, 2018: 3). The volume of distribution of clozapine ranges between 1.6 and 7.3 L/kg (Jann *et al.*, 1993: 161; Kennedy *et al.*, 2013: 1023).

2.4.2.5 Metabolism

Clozapine is susceptible to hepatic enzymatic metabolism (Snyman & Webb, 2015: 53a). There are several routes of metabolism that it follows, including N-demethylation, hydroxylation, and N-oxidation. The main enzyme mediating its metabolism, situated exclusively in the liver, is cytochrome P450 isoenzyme CYP1A2 (Meyer, 2001: 569; Sweetman, 2018). Two principle metabolites are formed via the hepatic microsomal system, namely desmethylclozapine and clozapine N-oxide (Jann *et al.*, 1993: 161; Frazier *et al.*, 2003: 87). The formation of clozapine-N-oxide is largely facilitated by CYP3A4 (Eiermann *et al.*, 1997: 443). Other metabolites are present in the urine of patients, however, the clinical significance of this remains a factor to be investigated. N-desmethylclozapine is considered the active metabolite

which employs its effects on the multitude of receptors, whereas clozapine-N-oxide is deliberated to be inactive and may be metabolised back to clozapine (Thorn *et al.*, 2018: 1).

Some compounds are capable of inducing or inhibiting CYP1A2 activity, resulting in decreased or increased serum clozapine concentrations respectively. Nicotine and proton pump inhibitors, such as omeprazole, are considered inducers of CYP1A2. Conversely, selective serotonin reuptake inhibitors, such as fluvoxamine, and quinolone antibiotics, such as ciprofloxacin, are CYP1A2 inhibitors (Meyer, 2001: 569). Two other minor metabolic pathways that are also followed by clozapine are CYP2C19 and CYP2D6 (Kennedy *et al.*, 2013: 1023).

2.4.2.6 Elimination

Interindividual studies have shown the range of the half-life of clozapine to be from 9 to 17 hours (Mauri *et al.*, 2007b: 363). Meanwhile, steady-state plasma concentration is achieved after 7 to 10 days of dosing (Mauri *et al.*, 2018: 4). The average elimination half-life at steady-state is 12 hours (Snyman & Webb, 2015: 53a).

Metabolites and trace amounts of unchanged drug are excreted mainly in the urine and also in the faeces. Isoenzyme CYP1A2 is hypothesised to be a major determinant (about 61%) of clozapine clearance (Aitchison *et al.*, 2000: 356). A short-term study by Mauri *et al*. found that plasma clearance was between 9 and 53 litres per hour (Mauri *et al.*, 2007b: 363; Kennedy *et al.*, 2013: 1023).

2.4.3 Indications

Clozapine is primarily indicated for treatment-resistant schizophrenia, in cases where patients have not responded to at least two different antipsychotic drugs (excluding clozapine) (Taylor *et al.*, 2009: 22; Taylor *et al.*, 2018). At least one of the antipsychotic drugs should be a non-clozapine second-generation antipsychotic (SGA) (National Institute for Health and Care Excellence, 2015: 24). The SASOP treatment guidelines recommended the initiation of clozapine after the failure of two antipsychotic drugs (one of which is a non-clozapine SGA) for at least 4-6 weeks (Swingler, 2013: 154). It is also indicated for recurrent suicidal behaviour in patients with psychotic disorders (schizophrenia and schizoaffective disorder) as well as drug-induced psychosis during

the course of Parkinson's disease (Rossiter, 2016: 481). Clozapine is also the drug of choice for treatment-resistant bipolar disorder and violent aggressive patients with psychosis as well as other brain disorders not responsive to other treatments (Ayano, 2016: 3).

Less commonly, clozapine is also useful in conditions where the patient is sensitive to the adverse effects of neuroleptic drugs. Dementia with Lewy bodies is a condition that utilises clozapine in this scenario (Emsley *et al.*, 2013: 142). Clozapine may also be useful in dementia for treatment-resistant psychoses and disruptive vocalisers (Emsley *et al.*, 2013: 149).

In the maintenance pharmacotherapy for bipolar disorder, clozapine is indicated as an option for third line adjunctive therapy, however, there is no evidence of clozapine being as effective as monotherapy for the treatment of acute bipolar type 2 depression (Malhi *et al.*, 2009: 37).

2.4.4 Dosing

The recommended initial dose of clozapine is as low as 12.5 to 25 mg/day and titrated upwards gradually. Titration of doses can reach a maximum of 500 mg/day within the first two weeks of treatment, and an overall maximum of 900 mg/day at maintenance therapeutic doses (Novartis Pharmaceuticals Corporation, 2014: 29).

The following dosing guideline is adapted from the NHS Southern Health Clozapine Guidelines (2018: 39). Table 2–8 depicts the recommended dosing regimen for outpatients between the ages of 18 to 60 years old who are on clozapine treatment (adapted from Southern Health NHS Foundation Trust, 2018: 39):

Table 2–8. Clozapine dosing guidelines for outpatients between the ages of 18 to 60 years.

Day	Clozapine dosage in the morning (mg)	Clozapine dosage in the evening (mg)	Total daily dose (mg)
1	6.25	6.25	12.5
2	6.25	6.25	12.5
3	6.25	6.25	12.5
4	6.25	12.5	18.75
5	12.5	12.5	25
6	12.5	12.5	25
7	12.5	12.5	25
8	12.5	25	37.5
9	12.5	25	37.5
10	25	25	50
11	25	37.5	62.5
12	25	37.5	62.5
13	25	37.5	62.5
14	25	37.5	62.5
15	37.5	37.5	75
16	37.5	37.5	75
17	37.5	50	87.5
18	37.5	50	87.5
19	50	50	100
20	50	50	100
21	50	50	100
22	50	75	125
23	50	75	125
24	75	75	150
25	75	75	150
26	75	100	175
27	75	100	175
28	75	100	175

The average dose for clozapine treatment is 250-450 mg daily for effective treatment. At doses greater than 600 mg/day, the frequency of seizure occurrence is significantly increased (Semple & Smyth, 2013: 212).

In some cases clozapine may be discontinued, for example in cases of severe adverse reactions (neutropenia) and in cases of non-compliance (Shaker & Jones, 2018: 7). A study by Davis *et al.* (2014: 32,37) showed that discontinuation of clozapine treatment was most likely to occur in over 50% of all patients between 3 and 6 months after initiation. The dosages must be gradually tapered down for a duration of 1 to 2 weeks until treatment is terminated (HLS Therapeutics, 2015: 8).

In instances when clozapine dosages have not been taken for 48 or more hours, it is required that clozapine re-titration is performed from the minimum dose of 12.5 mg per day (Southern Health NHS Foundation Trust, 2018: 10). When clozapine is withdraw abruptly, drug plasma levels decrease at a high rate which results in less tolerability of adverse effects (Southern Health NHS Foundation Trust, 2018: 10). The onset of some adverse effects of clozapine, such as hypotension, tachycardia, seizures and sedation, are dependent on the speed of the upward dosage titration. The slower or gradual upward dosage titration of clozapine is preferable to minimize these adverse effects from occurring (Citrome *et al.*, 2016: 164–175). Some of these adverse effects, such as seizures, are very serious and potentially life-threatening (Citrome *et al.*, 2016: 164).

A clozapine rechallenge is typically viable in patients who do not experience life-threatening adverse effects, although it is has become a common practice (Ittasakul *et al.*, 2016: ON1). Manu *et al*. (2018: e219) concluded that patients who returned to baseline after experiencing neutropenia and neuroleptic malignant syndrome were considerable for rechallenge, however, those who experienced agranulocytosis and myocarditis were not. When rechallenge is as a consequence of previously experienced non-clozapine-induced neutropenia, the concomitant use of lithium with clozapine may increase the chances of a successful outcome from 40% to approximately 95%. However, this same strategy does not have a positive effect for rechallenge in cases of previous clozapine-induced neutropenia (Howes, 2018). Clozapine rechallenge must only be considered when it is certain that the benefit

outweighs the risk, therefore it is still possible to re-expose patients who have previously experienced neutropenia or leukopoenia as clozapine adverse effects.

2.4.5 Monitoring

Prior to the commencement of clozapine treatment, several baseline observations are recommended to assess the patient for eligibility for clozapine treatment. These baseline tests are listed below (Government of Western Australia Department of Health, 2015:4; Kim, 2018: 119):

- Complete blood count (CBC), including an absolute neutrophil count (ANC).
- Weight.
- Height.
- Body mass index (BMI).
- Waist circumference.
- Blood pressure (BP).
- Pulse.
- Respiratory rate (RR).
- Fasting blood sugar (or HbA1c).
- Fasting lipid profile.
- Physical examination.
- Vital signs.
- Electrocardiogram (ECG).
- Liver function tests (LFTs).
- Prolactin.
- Pregnancy test in women of child bearing age.

After commencement of clozapine treatment, haematological monitoring is vital. The primary intention of monitoring the use of clozapine is mainly to decrease the rate of mortality due to agranulocytosis (Kar *et al.*, 2016: 325). A differential count of white blood cells is required for the initial 18 weeks of treatment with clozapine. During this period, the risk of experiencing agranulocytosis as an adverse effect is at its highest (Latif *et al.*, 2011: 27). Following the first 18 weeks, haematological monitoring continues every 2 weeks for up to one year (19-52 weeks), and then follow-up monthly

monitoring is recommended for the duration of the treatment (Nielsen *et al.*, 2016: 153).

The SASOP treatment guideline, which were formulated to suit the South African context, recommends slightly altered WBC monitoring intervals (Emsley & Seedat, 2013: 10). These guidelines do not require the fortnightly intervals for the WBC count after the first 18 weeks of clozapine therapy. Instead, they advise that the WBC count should be done at weekly intervals for the first 18 weeks of therapy, and monthly thereafter for the duration of the clozapine therapy (Swingler, 2013: 154). The SAMF also recommends this dosing schedule in the resource limited environments (Rossiter, 2016: 481).

The baseline white blood cell (WBC) count monitoring patterns differ in patients diagnosed with benign ethnic neutropenia (BEN) due to their lower levels of neutrophils. This condition is most prevalent in individuals of African descent (approximately 25-50%) (Clozapine REMS Program, 2015: 4–6). A summary of the haematological monitoring patterns recommended by the Clozapine Risk Evaluation and Mitigation Strategy (REMS) program is shown in table 2–9 (adapted from Clozapine REMS Program, 2015: 6):

Table 2–9. Recommended white blood cell count monitoring schedule.

Baseline WBC count	Treatment recommendation	WBC Monitoring
General population **WBC ≥ 1500 cells/µL**	Initiate treatment If treatment interrupted:	Weekly from initiation to six months Every 2 weeks from 6
BEN Population **WBC ≥ 1500 cells/µL** **Obtain at least two baseline WBC counts before initiating treatment**	< 30 days, continue monitoring as before ≥ 30 days, monitor as if new patient Discontinuation for reasons other than neutropenia	months to 12 months Monthly after 12 months

The abrupt or unplanned discontinuation of clozapine causes for alterations in the haematological monitoring schedule to be adapted. When the clozapine dosage is not administered for more than 48 hours, upward re-titration of clozapine from a dosage of 12.5 mg per day is recommended (Southern Health NHS Foundation Trust, 2018: 10). Alterations to the WBC count monitoring schedule are shown in table 2–10 (adapted from Southern Health NHS Foundation Trust, 2018: 10):

Table 2–10. WBC count monitoring schedule for patients on following a discontinuation of therapy.

Monitoring frequency	OFF clozapine for less than 48 hours	OFF more 48 hours but less than 7 days	OFF for 7 days or more
Weekly	No change to blood monitoring frequency. Continue as normal	No change to monitoring. Re-titration dosage as per initial titration	Restart the 18 weeks of weekly monitoring. Re-titration dosage as for initial titration

Table 2–11 applies to patients who are on fortnightly and 4 weekly monitoring schedules when the discontinuation of therapy occurs (adapted from Southern Health NHS Foundation Trust, 2018: 10):

Table 2–11. White blood cell count monitoring for patients who are on fortnightly and 4 weekly monitoring schedules when the discontinuation of therapy occurs.

Monitoring frequency	OFF clozapine less than 48 hours	OFF more than 48 hours but less than 4 whole days	OFF for 4 days or more but less than 28 whole days	Off for more than 28 days
Fortnightly and 4 weekly	No change to blood monitoring frequency. Continue as normal	No change to monitoring. Re-titrate dosage as per initial titration	TREATMENT BREAK Weekly for 6 weeks and the back to previous monitoring frequency. Re-titrate dosage	Restart the 18 weeks of weekly monitoring. Re-titrate dosage as for initial titration

Metabolic syndrome is a common adverse effect in patients on clozapine treatment (Faasen *et al.*, 2014: 54). Monitoring tests that assess metabolic changes (recommended by the American Diabetes Association and American Psychiatric Association) from baseline and throughout the duration of clozapine treatment are portrayed in table 2–12 according to the recommended intervals (adapted from Hertzman & Adler, 2010: 350):

Table 2–12. Recommended intervals of patient monitoring tests required for the duration of clozapine treatment.

	Baseline	4 weeks	8 weeks	12 weeks	Every 3 months	Annually	Every 5 years
Medical history	X						
Weight (BMI)	X	X	X	X	X	X	
Waist circumference	X						
Blood pressure	X			X		X	
Fasting glucose	X			X		X	
Fasting lipogram	X			X			X

2.4.6 Contraindications

Clozapine treatment is contraindicated and should be avoided when any of the following conditions have been experienced by the patient (Dunk *et al.*, 2006: 255; Turner *et al*., 2010: 461):

- Drug-induced agranulocytosis.
- Bone marrow disorders.
- Severe hepatic impairment.
- Severe renal disease.
- Severe cardiac disease.
- Toxic or alcohol psychoses.
- Uncontrolled epilepsy.
- Paralytic ileus.

2.4.7 Cautions in specific populations

Caution needs to be exercised in specific population groups with regards to clozapine administration. The SAMF (Rossiter, 2016: 481) listed the following groups as those that require caution:

- Prostatic enlargement
- Closed angle glaucoma
- Patients with a history of seizures

Clozapine use in elderly patients, and in patients with renal or hepatic impairment may require dose reductions (Rossiter, 2016: 481). The burden of severe adverse effects, such as agranulocytosis, is approximately five to ten times higher in the elderly (Kim, 2018: 117). In the case of renal impairment, literature recommends that dose adjustment is not required in mild to moderate cases, but preferably in severe cases to allow for effective therapy (Ward *et al.*, 2016: 61).

The safe use of clozapine in paediatric patients has not been founded, therefore they are also classified as a vulnerable population (HLS Therapeutics, 2015: 8.4). Despite the lack of approval in this specific population group, clozapine has proven to be more effective than other antipsychotics, such as olanzapine, in childhood-onset schizophrenia (COS) (Kim, 2018: 116).

2.4.8 Pregnancy and lactation

Both typical and atypical antipsychotics have adverse outcomes when used in a pregnant women, however, some studies have opposed this view and concluded that schizophrenia itself is the cause of some birth complications (Robinson, 2012: v381). Clozapine is categorised in the risk factor B for pregnancy. Risk factor B is the category whereby animal studies may have shown adverse effects with the drug, however none have been replicated in controlled studies in pregnant women. The implication of this is that the drug must only be used during pregnancy if the benefit outweighs the risk (The Pharmaceutical Society of South Africa, 2010: 461). Maternal and foetal factors also contribute to the possibility of adverse outcomes of antipsychotic medications. The partial placental passage of clozapine during childbirth delivery is suggested in some studies, whilst other studies confirm the full

accumulation of clozapine in the foetal serum (Imaz *et al.*, 2018: 7). The exposure of clozapine to neonates in the last trimester of pregnancy increases the risk of the occurrence of extrapyramidal and/or withdrawal symptoms after delivery (HLS Therapeutics, 2015: 8.1).

A breastfeeding infant is at risk of experiencing the adverse effects of the antipsychotic medication taken by the nursing woman (Robinson, 2012: e385). The risk remains low, as less than 5% of the maternal dosage of an atypical antipsychotic is found in breast milk. Compared to other atypical antipsychotic drugs, clozapine has the higher milk to plasma ratio. Clozapine has been associated with causing sedative effects, decreased sucking reflex, restlessness and irritability, seizures and cardiovascular instability in the nursing infant (Malone *et al.*, 2004: 41). It is recommended that breastfeeding be avoided during clozapine use by a nursing mother (Rossiter, 2008: 485; The Pharmaceutical Society of South Africa, 2010: 461).

2.4.9 Clozapine augmentation

Lally *et al.* (2016: 2) defined augmentation as the coadministration of diverse classes of medications or other antipsychotic medications to enhance the effectiveness of clozapine. An effective outcome of clozapine monotherapy in treatment-resistant schizophrenia is only evident in 30-50% of patients (Lierberman & Murray, 2012: 149). Clozapine augmentation with another psychotropic drug does not guarantee a more favourable result, and many interpatient variables play a role in the overall outcome of a treatment plan. The literature is inconsistent with regards to the successes of augmentation strategies, therefore clozapine augmentation is a subjective approach (Souza *et al.*, 2010: 154).

Some adjunctive medications have proven to improve the treatment of psychotic symptoms. Augmentation with aripiprazole, amisulpride, memantine or sulpiride improves the alleviation of positive and negative symptoms in patients who are partially or non-respondent to clozapine treatment (Kudva & Gupta, 2016: 12). The duration of the adjunct treatment may correlate with a successful outcome for the patient. Taylor & Smith (2009: 420) discussed the minimal effect that augmentation therapy had within 6 to 16 weeks, however, studies showed the benefits of those that extended longer than 10 weeks.

Common augmentative strategies include the addition of a mood stabiliser, antidepressants, conventional and atypical antipsychotics, cognitive behavioural therapy, and less commonly, electroconvulsive therapy and transcranial magnetic stimulation (Siskind *et al.*, 2018: 752).

Table 2–13 shows the commonly used medications to augment clozapine therapy, according to their classes (adapted from Feszczur, 2004: 2; Kudva & Gupta, 2016: 7; Siskind *et al.*, 2018: 13):

Table 2–13. Commonly used medications to augment clozapine treatment.

Antipsychotics	Antidepressants	Mood Stabilisers	Glutamergic Agents
Risperidone	Fluoxetine	Lamotrigine	Memantine
Olanzapine	Citalopram	(Sodium) Valproate	
Amisulpride	Fluvoxamine	Carbamazepine	
Sulpiride	Sertraline	Lithium	
Quetiapine	Amitriptyline	Topiramate	
Aripiprazole	Mirtazapine	Gabapentin	
Chlorpromazine			
Haloperidol			
Fluphenazine			
Pimozide			

2.4.10 Adverse effects

2.4.10.1 Overview

Clozapine is the most successful pharmacotherapy for schizophrenia in comparison to other antipsychotic drugs. It is notably better at treating symptoms than first-generation and some second-generation antipsychotics (Farooq *et al.*, 2018: 1). However, due to its severe and possibly life-threatening adverse effects, clozapine is reserved for treatment-resistant schizophrenia (Menkes *et al.*, 2017: 134). An estimated 17% of patients who use clozapine end up withdrawing from their treatment due to the adverse effects experienced (Newman & Newman, 2016a: 40).

Table 2–14 summarises the adverse effects caused by clozapine, their prevalence and onset after treatment (adapted from Citrome *et al.*, 2016: 164–165):

Table 2–14. Summary of the adverse effects of clozapine.

	Adverse event	Estimated prevalence (%)	Usual period of onset after treatment	Dose related? (Y/N)	Often/usually Transient? (Y/N)
Serious adverse events/Black box warning	Agranulocytosis	1.3	First 6 weeks to 6 months	N	N
	Myocarditis/ cardiomyopathy	0.02-1.0	Mainly first month	N	N
	Orthostatic hypotension	9	First weeks, and lasting 4-6 weeks	Y*	Y
	Seizures	1.3-1.8	Nonspecific, but risk is increased with rapid upward dose titration	Y	N
Less severe adverse events	Fever	≤55	First 2 weeks	-	Y
	Sinus tachycardia	25	First 2 weeks	Y	Y
	Neuroleptic malignant syndrome	Rare/unknown	First 2 to 4 weeks	N	N
	Weight gain and metabolic syndrome	60-75 gain weight 54-62 develop metabolic syndrome	First 6 to 12 months	Y+	N
	Constipation	30	First 1 to 2 years	-	N
	Sedation	44	First 6 weeks	Y	Y
	Hypersalivation	30-80	First 2 weeks	Y	Y
	Night-time enuresis	21	First 2 weeks	Y	Y

Adverse event	Estimated prevalence (%)	Usual period of onset after treatment	Dose related ? (Y/N)	Often/usually Transient? (Y/N)
*Related to dose titration ⁺Evidence is ambiguous				

The severity of the adverse effects caused by clozapine use differ. A comparative summary of the severity of the adverse effects of clozapine are found in table 2–15 (adapted from Iqbal *et al.*, 2003: 35; Muench & Hamer, 2010: 619; Taylor *et al.*, 2018: 39):

Table 2–15. Summary of the severity of the adverse effects of clozapine.

Adverse effect	Severity
Sedation	High
Weight gain	High
Anticholinergic	High
Hypotension	High
Haematological	Moderate
Type 2 diabetes mellitus	Moderate
Seizures	Moderate
Sexual dysfunction	Low
Neuroleptic malignant syndrome	Low
Akathisia	Very low
Parkinsonism/extrapyramidal effects	Very low
Prolactin elevation	Very low
QTc prolongation	Very low/none
Increased liver enzymes	Very low/none

2.4.10.2 Agranulocytosis and haematological events

In comparison to the other atypical antipsychotics, clozapine poses the greatest risk of instigating a haematological event (Brown *et al.*, 1999: 212). The first cases of agranulocytosis were recorded in 1975 when 8 patients in Finland died due to this dire adverse event (Newman & Newman, 2016b: 44). Studies on this adverse event has been undertaken for up to 40 years to date (Chapelle *et al.*, 1977: 183). Agranulocytosis occurs in approximately 1% of all patients on clozapine treatment

(Rettenbacher *et al.*, 2010: 41; De Berardis *et al.*, 2012: 55). As a result, the Clozapine Risk Evaluation and Mitigation Strategy (REMS) was formulated in the United States to provide a registry whereby all clozapine patients will be recorded with the aim to monitor their blood cell counts according to an algorithm during therapy *(*Citrome *et al.*, 2016: 164).

Life-threatening agranulocytosis or severe neutropenia occurs when the absolute neutrophil count (ANC) is below 500 cells/μL. It is likely to occur in the first 8 weeks in more than 84% of patients, and diminishes significantly after 6 months (Haddad & Sharma, 2007: 927; Newman & Newman, 2016a: 41). The risk of agranulocytosis and neutropenia remains typically for the first 18 months of treatment (Velayudhan & Kakkan, 2014: 425). The occurrence of neutropenia (ANC value between 1 500 and 500 cells/μL) is suggestive of emergent agranulocytosis. An estimated 2-3% of patients who take clozapine will suffer from acute neutropenia *(*Esposito *et al.*, 2005: 759). Toxicity mainly affects the myeloid (neutrophil) precursor cells (Dunk *et al.*, 2006: 259).

There is a lack of literature regarding the prevalence of this adverse effect in South Africa and the African context. An extensive study by Munro *et al.* demonstrates the possible baseline haematological differences in various ethnic groups. Caucasians were 2.4 times less likely to develop agranulocytosis compared to Asians. Meanwhile, the risk of acquiring neutropenia was 77% higher in the African-Caribbean, Oriental/Mixed-race and Asian groups compared to Caucasians (Munro *et al.*, 1999: 578). The risk of the occurrence of agranulocytosis also rises with older age and in the female population (Muench & Hamer, 2010: 620).

Agranulocytosis is often asymptomatic, or it may present as a range of symptoms including fever, headache, sore throat, stomatitis, diarrhoea, myalgia, arthralgia and urinary frequency (Haddad & Sharma, 2007: 927). It is hypothesised that these symptoms occur as a result of either the direct cytotoxic effects of clozapine or N-desmethylclozapine which is not detoxified or excreted by a vulnerable patient and reaches toxic levels in the body as a result. Alternatively, an immune mechanism that destroys select white blood cell precursors may be the causative factor, or a combination of all these hypotheses (Pisciotta *et al.*, 1992: 41; Esposito *et al.*, 2005: 762).

Due to the toxic effects of agranulocytosis, the U.S. Food and Drug Administration (FDA) requires the monitoring of all patients who are on clozapine. Their guidelines state that clozapine therapy should be terminated if the white blood cell count drops below 3 000 cells/μL (Muench & Hamer, 2010: 620). The decision to stop the use of clozapine is often controversial as it remains the last resort for patients with treatment-resistant schizophrenia and may be the only effective therapy for other complex symptomatologies which are not responsive to conventional therapies (Esposito *et al.*, 2005: 762).

Other haematological events that are likely to occur with the administration of clozapine include eosinophilia, anaemia, lymphopenia, leucocytosis and thrombocytopenia. These events are all commonly asymptomatic. Eosinophilia usually occurs in females, between 3 and 5 weeks after initiating clozapine treatment, and is self-limiting (Mendelowitz *et al.*, 1995: 417; Rajagopal, 2005: 545).

Clozapine is discontinued when a haematological event occurs, such as when the leucocyte count drops below 3000 cells/μL or the absolute neutrophil count recorded is below 1500 cells/μL (Rossiter, 2016: 481). A rechallenge is often done to prevent the chances of a schizophrenia relapse, considering that the benefits outweigh the risks with the most caution being taken in the initial 10 weeks following rechallenge (Dunk *et al.*, 2006: 261). Rechallenge has proven to be more favourable in cases of neutropenia, however, the opposite is evident in cases of agranulocytosis where a secondary event of blood dyscrasias occurred (Prokopez *et al.*, 2016: 380).

2.4.10.3 Central nervous system effects

2.4.10.3.1 Seizures

All antipsychotics can increase the risk of seizures by less than 2%, and caution must be especially taken in patients who have a history of seizures, head trauma and other organic brain disorders such as Alzheimer's disease (Young *et al.*, 1998: 383; Brown *et al.*, 1999: 211; Haddad & Sharma, 2007: 928).

Seizures most commonly occur in patients using first-generation antipsychotics, but less commonly with the other atypical antipsychotics at therapeutic doses (Muench & Hamer, 2010: 621). The overall incidence of clozapine-induced seizures are

dependent on the duration of clozapine treatment, as summarised in table 2–16 (adapted from Citrome *et al.*, 2016: 172):

Table 2–16. Incidence of clozapine-induced seizures according to the duration of treatment.

Duration of treatment	Incidence (%)
6 months	1 – 2
1 year	3 – 5
3.8 years	10

Clozapine-induced seizures are postulated to be dependent on the dose. Higher doses predispose the patient to potentially experience seizures (Rossiter, 2016: 481). The correlation of risk of seizures with increased dose, based off the results of an extensive study and the results are shown in table 2–17 (adapted from Citrome *et al.*, 2016: 172):

Table 2–17. The risk of seizures depending on the dosage of clozapine.

Clozapine dosage	Seizure risk (%)
<300 mg/day	1
300-600 mg/day	2.7
>600 mg/day	4.4

On the contrary, more recent studies do not confirm the statistical significance of the correlation between the occurrence of clozapine-induced seizures and higher doses. This may be owing to the difficulty in predicting the plasma levels from the dose alone, many other factors contribute to the occurrence of seizures (Varma *et al.*, 2011: 61). Another suggestion by researchers is the induction of seizures due to a sudden increase in titration (Ayaydın *et al.*, 2018: 2).

A variety of seizures may occur, but most common are the generalised tonic-clonic seizures. Myoclonic jerks and atonic seizures are reported in approximately 25% of the patients who experience clozapine-induced seizures, both types serving as potential precursors to tonic-clonic seizures. Partial seizures may also be induced. Valproic acid and lamotrigine are the first-line drugs used as anticonvulsant therapy in

schizophrenia patients experiencing seizures due to their broad spectrum capabilities (Wong & Delva, 2007: 461).

2.4.10.3.2 Sedation and drowsiness

Sedation is a dose related adverse event which is common amongst most antipsychotic drugs (Muench & Hamer, 2010: 618). This adverse effect is the most frequently reported in patients using clozapine in comparison to the other atypical antipsychotics, occurring in approximately 44% of all patients (Iqbal *et al.*, 2003: 38; Citrome *et al.*, 2016: 175). As a result, dose limitations may be needed, and patients may become poorly compliant to clozapine therapy (Haddad & Sharma, 2007: 928). Tolerability improves within 4 to 6 weeks after initiation of clozapine treatment (Young *et al.*, 1998: 383).

To prevent potentiating sedative effects, the concomitant use of other sedative drugs should be avoided, the dose of clozapine should be reduced, the drug administered at night, and/or a slower upward titration to the required dose should be done (Citrome *et al.*, 2016: 175).

2.4.10.3.3 Delirium

The anticholinergic qualities of clozapine predispose patients to experience delirium or confusion in the most vulnerable patients. These vulnerable groups include the elderly, people with organic cognitive deficits and those currently receiving other anticholinergic or central nervous system depressant drugs. A dose reduction or a decreased rate of titration is advised in cases of clozapine-induced delirium. Physostigmine is intravenously administered to temporarily overturn the effects of the delirium (Young *et al.*, 1998: 383; Iqbal *et al.*, 2003: 38).

2.4.10.4 Metabolic effects

2.4.10.4.1 Weight gain

Weight gain is a common antihistaminic adverse effect associated with atypical antipsychotics, especially with olanzapine and clozapine (Citrome *et al.*, 2016:174). An average weight increase of greater than 7% is noted with all atypical antipsychotics, which is generally considered a high risk event (Haddad & Sharma, 2007: 921). The

effects of weight gain are more detrimental to patients presenting with a higher body mass index (BMI) at baseline, as well as males and the elderly (Henderson *et al.*, 2005:1116). A minor study reported the average weight increase, after 10 weeks of treatment with clozapine, was 4.45 kg. Clozapine showed the greatest average weight increase when compared with olanzapine, thioridazine, sertindole, risperidone and haloperidol (Jafari *et al.*, 2012: 377).

2.4.10.4.2 Other metabolic effects

Metabolic syndrome is a group of conditions including obesity, increased blood pressure, and the dysregulation of glucose and lipid metabolism (Tirupati & Chua, 2007: 470). Clozapine can therefore predispose vulnerable patients to hypertension, new-onset diabetes mellitus and dyslipidaemia, which are all inter-related risk factors for cardiovascular disease (CVD) (Henderson *et al.*, 2005: 1119). In South Africa, a study has shown that black females are more susceptible to metabolic syndrome and obesity compared to black males (Saloojee *et al.*, 2017: 1).

Clozapine and olanzapine are the two most likely second-generation antipsychotic drugs to predispose a patient to diabetes mellitus. Drug-induced insulin resistance may arise as a result of weight gain, a change in the distribution of body fat or a direct effect on insulin-sensitive target tissues. Similarly, clozapine and olanzapine are also responsible for the greatest increases in total cholesterol, LDL cholesterol and triglycerides, as well as decreased HDL cholesterol (American Diabetes Association *et al.*, 2004: 598).

2.4.10.5 Cardiovascular effects

2.4.10.5.1 Myocarditis and cardiomyopathy

Cardiovascular disease remains one of the major causes of death in psychiatric patients. Cardiovascular deaths in schizophrenia surpasses those in the general population (Mackin, 2008: 10; Maaroganye *et al.*, 2013). The effect of having all factors of metabolic syndrome increases the probability of the occurrence of cardiac disease by almost 12-fold compared to those without metabolic syndrome (Henderson *et al.*, 2005: 1117).

Fatal myocarditis and cardiomyopathy has been associated with clozapine usage, commonly occurring early after the initiation of treatment (Rossiter, 2008: 485). According to the prescribing information for Clozaril®, myocarditis will typically present within the first 2 months of initiating clozapine, and similarly cardiomyopathy may present after 8 weeks of treatment (Novartis Pharmaceuticals Corporation, 2014). Cases and deaths arising from clozapine-induced myocarditis and cardiomyopathy have also been reported (Girardin & Sztajzel, 2007: 93). The immediate discontinuation of clozapine is required in the cases of both these conditions (Citrome *et al.*, 2016: 171).

2.4.10.5.2 QT-prolongation

Clozapine is categorised as an antipsychotic drug that causes dose-related QT-prolongation. The QT varies inversely with heart rate, and measurements are corrected for this. The corrected QT interval (QT_C) is defined as the measured QT interval adjusted to a heart rate of 60 beats/min. The normal upper limit for QT_C is 0.44 seconds in males, and 0.46 seconds in females (Sidebotham, 2007: 126). A prolonged QT interval typically signifies a delayed ventricular repolarization (prolonged QT segment) in the patient (Sidebotham, 2007: 126). The risk of drug-induced QT-prolongation is largely related to the dose of the drug and its plasma concentration (Drug and Therapeutics Bulletin, 2016: 2; Rossiter, 2016: 472). QT prolongation is a serious adverse event which can lead to cardiac arrhythmias such as Torsades de pointes (TdP) and ventricular arrhythmias (Mackin, 2008: 5). Clozapine discontinuation without a rechallenge is the recommended outcome in the case of QT_c-prolongation (Citrome *et al.*, 2016: 167).

2.4.10.5.3 Tachycardia

Tachycardia is most prominent during the initiation phase of clozapine treatment, and the long-term use of clozapine commonly causes a sustained tachycardia (Ronaldson, 2017: 782). Sinus tachycardia, defined as a mean increase of 10 to 15 beats/min and illustrated as 100 to 200 beats/min, is induced by clozapine in 1 out of 2 patients. It is asymptomatic and self-limiting, subsiding 4 to 6 weeks after initiation of clozapine treatment. Although the event is seemingly innocuous, it could be an indicator of

myocarditis, cardiomyopathy and neuroleptic malignant syndrome (Citrome *et al.*, 2016: 173).

2.4.10.5.4 Orthostatic hypotension

Orthostatic hypotension is defined as the decrease in systolic blood pressure of ≥20 mm Hg, or a decrease of systolic pressure to < 90 mm Hg during upright posture (Mackin, 2008: 4). Orthostatic hypotension is likely to occur at the initiation stages of clozapine treatment. It is frequent amongst most patients using antipsychotic drugs, occurring in up to 75% of patients. Clozapine is one of four antipsychotics that is associated with postural hypotension. The underlying mechanism of this occurrence is the antagonistic properties of clozapine on cholinergic and α_1-adrenergic receptors (Mackin, 2008: 4; Rossiter, 2016: 481). This adverse effect may be symptomatic or asymptomatic and it is most common in the elderly patients. Caution must be exercised in patients concomitantly using drugs with anticholinergic properties and those that also cause orthostatic hypotension (Marano *et al.*, 2011: 247; Ronaldson, 2017: 783).

2.4.10.6 Constipation

Constipation is the most common gastrointestinal adverse effect that occurs with clozapine usage. Approximately 14 to 30% of patients will experience this adverse effect, with some reports recording an incidence of up to 60% (Safferman *et al.*, 1991: 253; Sagy *et al.*, 2014: 315). Clozapine is the most likely second-generation antipsychotic to produce constipation. In most cases it is chronic and leads to complications such intestinal obstruction which in turn may have fatal consequences in 12 to 22% of patients (Haddad & Sharma, 2007: 926; Rossiter, 2016: 481). Some studies have estimated that clozapine-induced constipation fatalities are three times more prominent than its most feared adverse effect of agranulocytosis (Citrome *et al.*, 2016: 175). The anticholinergic properties of clozapine are associated with the occurrence constipation. Delayed stomach emptying, abdominal pain and bloating, gastrocolic reflux and duodenal contractions are caused by clozapine (De Hert *et al.*, 2011: 42; Sagy *et al.*, 2014: 315).

2.4.10.7 Fever

During the initiation phases of clozapine treatment, 5% of patients are likely to experience a benign fever which is self-limiting and lasting only a few days. This typically occurs within 3 weeks and it has been shown that the greatest chance of occurrence is on the 10th day of initiation (Safferman *et al.*, 1991: 254; Young *et al.*, 1998: 386). Other studies report that fever generally occurs in 0.5 to 55% of all patients on clozapine treatment, where their body temperature rises to 38-39 °C (Citrome *et al.*, 2016: 173). Fever may also be a symptom of another adverse effect caused by clozapine, such as myocarditis or cardiomyopathy, blood dyscrasias and neuroleptic malignant syndrome (Haddad & Sharma, 2007: 926).

2.4.10.8 Nocturnal enuresis, urinary incontinence and retention

Compared to the other atypical antipsychotics (such as risperidone, olanzapine and quetiapine), clozapine produces the higher ratio of patients who experience nocturnal enuresis. This adverse effect remains lesser known with a wide range of incidence amongst patients, from less than 1% to up to 42% in various studies (Harrison-Woolrych *et al.*, 2011: 140; Barnes *et al.*, 2012: 7).

The mechanism by which nocturnal enuresis occurs remains ambiguous and possibly multifactorial. It is hypothesised that the anticholinergic properties of antipsychotic drugs may inhibit detrusor contraction, resulting in urinary retention and overflow incontinence. There is also a decrease of the bladder tone due to anti-adrenergic activities. Another hypothesis is that the sedative effects of clozapine inhibits the patient's ability to wake up during sleep to empty the bladder. A minor case study also postulated that clozapine-induced diabetes mellitus results in polyuria, and that generalised epilepsy may present as enuresis (Kho & Nielsen, 2001: 233; Harrison-Woolrych *et al.*, 2011: 144; Barnes *et al.*, 2012: 8).

2.4.10.9 Hypersalivation

Hypersalivation (sialorrhoea) is the second most common adverse effect of clozapine, occurring in 30 to 80% of patients shortly after the initiation of treatment (Sockalingam *et al.*, 2007: 378; Sagy *et al.*, 2014: 314). The pathophysiology remains unclear and complex. It is proposed that the agonistic effects clozapine has on M_4 muscarinic

receptors and its antagonistic effects on α_2-adrenergic receptors increase salivation (Davydov & Botts, 2000: 662; Sockalingam *et al.*, 2007: 378). The symptomatic effects of hypersalivation are most prominent during sleep compared to the daytime (Safferman *et al.*, 1991: 252). Tolerance is unlikely to develop, however, there are various pharmacological and non-pharmacological management options available for the patient (Sagy *et al.*, 2014:314).

2.4.10.10 Neuroleptic malignant syndrome

Although neuroleptic malignant syndrome (NMS) is a rare occurrence with clozapine use, it has potentially fatal consequences. It typically occurs within the first 14 days after initiation of treatment, and it occurs more commonly in men than in women (Iqbal *et al.*, 2003: 38). Symptoms include tachycardia, hyperthermia, mental state changes, diaphoresis, muscle rigidity, hypertension and hypotension (Brown *et al.*, 1999: 211; Citrome *et al.*, 2016: 173). Due to the dire consequences of experiencing NMS, clozapine treatment is immediately discontinued (Iqbal *et al.*, 2003: 39).

2.4.10.11 Extrapyramidal effects

Extrapyramidal symptoms (EPS), also commonly referred to as extrapyramidal side effects, are a major adverse effect of antipsychotic drugs. Extrapyramidal symptoms include pseudo-parkinsonism, dystonia, akathisia and tardive dyskinesia; all of which have a lower incidence with clozapine treatment (Muench & Hamer, 2010: 619; Citrome *et al.*, 2016: 164).

A common misconception about antipsychotic drugs is that they all produce EPS. This claim may have been due to the fact that the first-generation antipsychotics almost always produced EPS (Tarsy *et al.*, 2002: 24). Clozapine proved to be the first second-generation antipsychotic that has a low incidence of causing EPS (Divac *et al.*, 2014: 2). This is further demonstrated by a meta-analysis of 30 trials of clozapine comprising of 2530 patients with a psychotic condition. The analysis showed that clozapine causes less EPS compared to conventional antipsychotics (Wahlbeck *et al.*, 1999: 996). The development of second-generation antipsychotics was motivated by the lesser chance of clozapine causing EPS (Rummel-Kluge *et al.*, 2012: 167).

2.4.10.12 Management of adverse effects

Depicted in table 2–18 are the interventions for the management of the common adverse effects of clozapine (Iqbal *et al.*, 2003: 38; Semple & Smyth, 2013: 215; Winckel & Siskind, 2017: 232; Kim, 2018: 120):

Table 2–18. Interventions for the management of the common adverse effects of clozapine.

Adverse effect	Pharmacological intervention	Non-pharmacological intervention
Agranulocytosis/neutropenia	Stop clozapine	Admit outpatient to hospital
Myocarditis	Stop clozapine	Admit outpatient to hospital
Seizures	Withhold clozapine for 24 hours Recommence at a lower dose, half the previous dose is advised Consider prophylactic valproate, lamotrigine, or gabapentin at a high dose (>500mg/day)	
Delirium	Reduce clozapine dose or decrease the rate of titration	
Sedation	Decrease total clozapine dose Slow down rate of titration Increase doses at night	Review other sedative drugs
Weight gain	Consider metformin controlled-released (1000 mg daily)	Nutrition intervention and exercise-based counselling Lifestyle modifications

Adverse effect	Pharmacological intervention	Non-pharmacological intervention
Hypertension	Slow down the rate or halt any dose increase Addition of an antihypertensive drug (such as atenolol).	Monitoring
Nausea	Consider an anti-emetic, however avoid metoclopramide and prochlorperazine in patients with a history of EPS	
Constipation	Stool softeners, osmotic laxatives or enemas may be considered	Encourage high fibre diet Sufficient fluid intake Encourage exercise
Hypotension	Reduce the dose or slow down the rate of titration In severe cases, consider fludrocortisones	Exercise caution when standing up quickly Increase fluid and salt intake
Fever	Paracetamol	Check full blood count (FBC) Check sources of infection Rule out myocarditis and NMS
Nocturnal enuresis	Alter dose scheduling of clozapine Consider desmopressin nasal spray (at night) in severe cases Anticholinergic drugs may also be considered	Avoid fluid intake, especially coffee, in the evening

Adverse effect	Pharmacological intervention	Non-pharmacological intervention
Hypersalivation	Consider hyoscine hydrobromide (up to 300 mg three times a day) Also consider amisulpride (100-400 mg/day), amitriptyline, modafinil	Chewing gum to increase swallowing Use a towel over pillow at night
Tachycardia	Persistent cases can be treated with atenolol, metoprolol and ivabradine	Monitor for signs and symptoms of myocarditis
QT prolongation	Consider clozapine dose reductions, especially in cases of polypharmacy	

2.4.11 Drug interactions

2.4.11.1 Introduction

Polypharmacy is a common practice in psychotherapeutics, occurring in approximately 1 out of 4 of outpatients, and up to 50% of inpatients depending on the patient population and their circumstances (Stahl, 1999: 426; Fleischhacker & Uchida, 2014: 1084). Augmentative treatment with other antipsychotics and other drugs is generally inevitable in most schizophrenia cases, either to treat psychosis, co-morbid disease states or to manage adverse effects. Drug interactions may be present during therapy as a result of polypharmacy. These interactions are categorised as either pharmaceutic, pharmacodynamic or pharmacokinetic interactions (Edge *et al*., 1997: 5). Pharmaceutical interactions occur prior to drug administration by the patient. This type of interaction generally signifies incompatibilities in intravenously infused drugs. Pharmacodynamic interactions occurs when one drug alters the sensitivity or responsiveness of tissues to another drug by duplicating the agonist or antagonist effect. This may occur at the identical pharmacological receptor sites or by other diverse mechanisms on identical or related organs. Pharmacokinetic interactions occur when a drug alters the absorption, distribution, protein binding, metabolism or

excretion of another drug, which may result in diminished therapeutic effects (Becker, 2011: 32; Tamminga, 2018).

2.4.11.2 Antidiabetics

The following information was obtained from Karalliedde *et al*. (2010: 256); Turner *et al.* (2010: 460) and Rossiter (2016: 484):

Effect: Clozapine may cause decreased glucose tolerance and a loss of control of blood sugar levels.

Postulated mechanism: Clozapine can cause resistance to the action of insulin.

Severity: Important interaction.

Precautions: Patients on treatment for diabetes mellitus alongside chronic clozapine treatment must be monitored. Weight gain and metabolic syndrome are common occurrences in patients on clozapine treatment.

2.4.11.3 Antihypertensives

The following information was obtained from Karalliedde *et al.* (2010: 257) and Turner *et al.* (2010: 460):

Effect: Generally, antipsychotics increase the hypotensive effect of antihypertensive drugs. In the case of beta blockers, concomitant clozapine administration causes dizziness, sedation, significant hypotension, syncope and potentially fatal respiratory depression.

Postulated mechanism: A dose-related decreased blood pressure is an adverse effect which commonly occurs with antipsychotic drugs. Clozapine has an additive pharmacodynamic effect with enalapril, alpha-adrenergic antagonists and calcium channel blockers. Although the clinical significance is ambiguous, clozapine may block the activity of clonidine, causing a decreased hypotensive effect of the drug.

Precautions: During the initiation stages of clozapine treatment, the blood pressure must be carefully and regularly monitored and any hypotensive symptoms noted.

2.4.11.4 Antineoplastics

The following information was obtained from Karalliedde *et al.* (2010: 254); Turner *et al.* (2010: 460) and Sankaranarayanan *et al.* (2013: 421):

Effect: Agranulocytosis occurs when antineoplastic drugs, such as procarbazine, are used concomitantly with clozapine. Some immunomodulating drugs have specific interactions with clozapine, such as imatinib which causes clozapine plasma levels to rise to potentially toxic levels.

Postulated mechanism: There is an increased risk of bone marrow toxicity with cytotoxic drugs as they have an additive effect on bone marrow suppression caused by clozapine. Imatinib also has an inhibitory action on the CYP2D6-mediated metabolic pathway of clozapine and other selected antipsychotics.

Precautions: Antineoplastic drugs should not be used concomitantly with clozapine as the management is seemingly complex. Assessment of any symptoms of toxicity of clozapine must be analysed with imatinib administration.

2.4.11.5 Benzodiazepines

The following information was obtained from Karalliedde *et al.* (2010: 259) and Rossiter (2016: 485):

Effect: An increased risk of sedation occurs with all antipsychotics, specifically with clozapine.

Postulated mechanism: Benzodiazepines typically have drowsiness and sedative adverse effects and the use of another sedative-hypnotic is not advised.

Precautions: In the case of the emergency administration of benzodiazepines, caution should be exercised.

2.4.11.6 Antibiotics

The following information was obtained from Karalliedde *et al.* (2010: 253) and Turner *et al.* (2010: 460):

Effect: Specific antibiotics have different effects on clozapine. Rifampicin decreases the levels of clozapine, whereas ciprofloxacin and erythromycin have an opposing effect whereby they increase clozapine levels with the risk of toxicity. Chloramphenicol increases the risk of bone marrow toxicity.

Postulated mechanism: Rifampicin increases the metabolism of clozapine. Ciprofloxacin and erythromycin inhibit the enzymes that metabolise clozapine leading to decreased clearance of clozapine. Chloramphenicol has an additive effect to clozapine-induced agranulocytosis.

Precautions: In the cases of possible drug toxicity, any early symptoms must be analysed, and a decreased dose of clozapine administered. The contrary applies when the antibiotic causes decreased levels of clozapine.

2.4.11.7 Long-acting antipsychotics

The following information was obtained from Turner *et al*. (2010: 460); Rossiter (2016: 476) and Souaiby *et al.* (2017: 91):

Effect: The incidence of prolonged bone marrow toxicity is apparent with clozapine and depot antipsychotics co-administration.

Postulated mechanism: Long-acting antipsychotic drugs have an additive effect on clozapine with regards to the incidence of agranulocytosis.

Precautions: Although a small study by Souaiby *et al.* (2017: 91) showed no induced agranulocytosis in patients using a combination of clozapine and a long-acting injectable antipsychotic drug, literature advises against the combination.

2.4.11.8 Haloperidol

Effect: Patients are likely to be predisposed to neutropenia when using haloperidol and clozapine simultaneously (Turner *et al.*, 2010: 458).

Minimal information was found concerning the interaction of haloperidol with clozapine. The likelihood of worsened adverse effects, such as drowsiness and seizures, is likely with coadministration of these drugs (Prescribers' Digital Reference, 2019).

2.4.11.9 Selective serotonin reuptake inhibitors

The following information was obtained from Karalliedde *et al.* (2010: 255); Turner *et al.* (2010: 470) and HLS Therapeutics (2015: 7.1):

Effect: The plasma clozapine concentration levels are increased when selective serotonin reuptake inhibitors (SSRIs), such as fluvoxamine and paroxetine, are administered concomitantly with clozapine.

Mechanism: SSRIs inhibit the enzyme CYP2D6 and the CYP1A2-mediated metabolism of several antipsychotic drugs, including clozapine.

Precautions: Any increased adverse effects are a warning of this interaction. The antipsychotic dose may need to be reduced in response to this interaction.

2.4.11.10 Risperidone

The following information was obtained from Tyson *et al. (1995: 1401); Kontaxakis et al.* (2002: 408); Turner *et al.* (2010: 462) and Singh *et al.* (2015: 59):

Effect: Neutropenia is likely to occur with the simultaneous administration of clozapine. Increased clozapine plasma levels have been noted with the concomitant use of risperidone. This could potentiate adverse effects such as seizures.

Mechanism: The postulated mechanism is the pharmacokinetic interaction of competitive cytochrome P450 2D6 enzyme metabolism.

Precautions: Transient light-headedness may be an adverse effect of the addition of risperidone. A case study on an adult male with first-episode schizophrenia noted the development of a mild form of NMS upon the addition of clozapine to his risperidone treatment. Although it is a rare occurrence, the continuous assessment for neurotoxic syndromes was suggested from the study for the duration treatment when there is the concomitant use of clozapine with risperidone. The initiation of risperidone augmentation should be done so cautiously, and clozapine plasma levels should be carefully monitored.

2.4.11.11 Antiepileptics

The following information was obtained from Pharmaplan (2002) and Karalliedde *et al.* (2010: 257):

Effect: The efficacy of antiepileptic drugs is decreased by clozapine.

Postulated mechanism: Clozapine can lower the seizure threshold in epileptic patients.

Precautions: Epileptic patients need to be carefully monitored as the frequency of seizures may increase. An increase in the dose of antiepileptic drugs may be required.

2.4.11.11.1 Carbamazepine

The following information was obtained from (Karalliedde *et al.* (2010: 257) and Novartis Pharmaceuticals Corporation (2014: 7.1):

Effect: Clozapine levels are reduced when co-administered with carbamazepine. In turn, clozapine may also have an effect on carbamazepine plasma levels as they may increase to toxic levels.

Postulated mechanism: Carbamazepine is a strong CYP3A4 inducer, therefore the metabolism of clozapine using this pathway is induced resulting in a decreased plasma concentration of the drug.

Precautions: The dose of clozapine should be monitored and increased if the current dose seems to be ineffective.

2.4.11.11.2 Valproic acid/sodium valproate

The following information was obtained from Turner *et al.* (2010: 462):

Effect: The levels of clozapine are reduced.

Postulated mechanism: Clozapine metabolism is induced by valproic acid.

2.4.11.12 Lithium

The following information was obtained from (Blake *et al.* (1992: 298); Pharmaplan (2002); Bender *et al.* (2004: 62); Whiskey & Taylor (2007: 30); Karalliedde *et al.* (2010: 255):

Effect: The risk of extrapyramidal adverse effects and neurotoxicity are increased with the use of lithium. The development of neuroleptic malignant syndrome is also enhanced when lithium is used with clozapine.

Postulated mechanism: The mechanism by which these effects occur is ambiguous. Blake *et al.* (1992: 298) suggested that the serotonergic interaction of both drugs produce this effect. It has also been hypothesised that lithium can increase granulocyte production, and it may also enhance cortisol secretion which results in increased white blood cell counts.

Precautions: Exact clinical guidelines must be followed when clozapine and lithium are used concurrently. The use of other serotonergic drugs must be avoided so as to lessen the chances of adverse effects. Careful monitoring for the prominence of any symptoms during this therapy is important.

2.4.11.13 Smoking

The following information was obtained from Meyer (2001: 573), Meyer (2007: 8); and Kennedy *et al.* (2013: 1042):

Effect: The plasma concentration of clozapine is significantly reduced in patients who smoke.

Postulated mechanism: Cigarette smoke contains polycyclic aromatic hydrocarbons that primarily induce CYP1A1, CYP1A2 AND CYP2E1 enzymes.

Precautions: Plasma levels of clozapine may rise exponentially upon smoking cessation for chronic smokers in the initial 2 weeks. There is a need to carefully monitor the plasma concentration of clozapine and adjust the dose where necessary.

2.4.11.14 Caffeine

The following information was obtained from Hagg *et al.* (2000: 59); Kennedy *et al.* (2013: 1043):

Effect: A case report claims that caffeine significantly increases the plasma concentration of clozapine.

Postulated mechanism: It is hypothesised that caffeine inhibits the CYP1A2 enzyme, therefore inhibiting the clearance of clozapine. However, a direct correlation has not been established.

Precautions: The plasma concentration of clozapine should be carefully monitored to avoid the accumulation of the drug to toxic levels.

2.4.11.15 Alcohol

The following information was obtained from (Karalliedde *et al.* (2010: 252) and Kennedy *et al.* (2013: 1025):

Effect: Excessive sedation is likely to occur when alcohol is used alongside clozapine.

Postulated mechanism: Alcohol is a central nervous system depressant. The sedative effects of clozapine are intensified by the sedative effects of alcohol.

Precautions: The concomitant use of alcohol must be discouraged in patients on clozapine treatment.

2.4.11.16 Oral contraceptives

The following information was obtained from (Seeman & Ross (2011: 264); Bookholt & Bogers (2014: 389); and Cadeddu *et al.* (2015: 2):

Effect: Plasma concentration levels of clozapine are increased with the use of oral contraceptives (OCs).

Postulated mechanism: The oestrogen component of OCs is suggested to inhibit the enzymes CYP1A2, CYP2C19 and CYP3A4. Progesterone, also a component of some

OCs, is a more potent inhibitor of the CYP3A4 enzyme. The clearance of clozapine is reduced when these metabolic pathways are inhibited.

Precautions: Careful monitoring for possible clozapine toxicity is necessary. The substitution of OCs to another form of contraceptive, such as the intrauterine device (IUD), should be considered.

2.5 Drug utilisation review

2.5.1 Introduction

This section will explain the concept of a drug utilisation review (DUR) that was employed as part of the methodology for this study.

2.5.2 Definition

The WHO has defined the term DUR as "a system of ongoing, systematic, criteria-based evaluation of drug use that will help ensure that medicines are used appropriately (at the individual patient level)" (World Health Organization, 2003b: 85). An alternative WHO definiton defines the term as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting, medical, social and economic consequences" (World Health Organization, 2003b: 8). The objective of a DUR is to achieve the most successful therapeutic decisions, resulting in optimal patient outcomes by analysis of patient history and their prescribed drug as well as to ensure the rational use of medicines and their affordability (World Health Organization, 2003a: 9; Navarro, 2009: 216). It bridges the recommended therapeutic practices obtained from clinical trials (for example: Indications, dosage, drug interactions, contraindications) with the actual clinical practice employed by healthcare professionals (World Health Organization, 2003b: 85).

The term DUR may be used interchangeably with drug use evaluation (DUE) and medication utilisation evaluations (MUE). The evaluation includes a detailed examination of the patient's information and prescription prior to, during and after the dispensing process (Navarro, 2009: 216). However, a MUE is distinguishable from a DUR as it focuses on medicine-associated problems to improve the use of medicines (American Society of Health-System Pharmacists, 1996: 175).

Pharmacoepidemiology studies offer a similar definition to that of a DUR. The major distinction between a DUR and pharmacoepidemiology studies is the main focus of the study. Drug utilisation reviews focus on quality and quantity of medicine use in different settings and the reason for the observed patterns, whereby pharmacoepidemiology uses large databases to assess the quantitative risks and benefits of the drug and treatment (Wettermark *et al.*, 2016: 7).

2.5.3 Types of drug utilisation reviews

Drug utilisation studies may be focused on different aspects of the drug-use chain:

- Systems and structures of drug use.
- Processes of drug use.
- Outcomes of drug use.

In addition, these studies focus on the processes and outcomes of drug use, specifically outlining drug use at the individual patient level, adverse reactions, rational drug use and patient compliance, amongst other factors (World Health Organization, 2003a: 17).

Depending on the design of the study, DURs can be categorised into three different sections as stated below:

- Cross-sectional studies.
- Longitudinal studies.
- Continuous longitudinal studies.

The current study adopted the cross-sectional study design which is also characterised as an observational and descriptive study. It focused on raw patient data often in the form of a survey (Setia, 2016:261; Levin, 2006:24). This study design allows for the comparison of data from diverse population groups either over one point of time or during a short period of time (World Health Organisation, 2003a: 17; Levin, 2006: 24).

There are three classifications for DURs which depend on the timing of data collection as listed below:

- Prospective.
- Concurrent.
- Retrospective.

Prospective studies focus on data collected at the initiation of the drug therapy, prior to the drug being dispensed to the patient. Concurrent studies focus on ongoing data collection throughout the dispensing process and treatment of the patient (Academy of Managed Care Pharmacy, 2009: 1). Retrospective studies focus on the evaluation of drug therapy after the patient has received their medication. This allows for the assessment of prescribing practices and analysis of trends followed by healthcare professionals (Truter, 2008: 95). This research project constituted of a retrospective study as analyses of data in patient files were undertaken.

2.5.4 Stages of drug utilisation reviews

The stages of a DUR are divided into four phases as illustrated in figure 2–10 (adapted from Ashok & Subramanian, 2017: 158; Priya *et al.*, 2018: 2663):

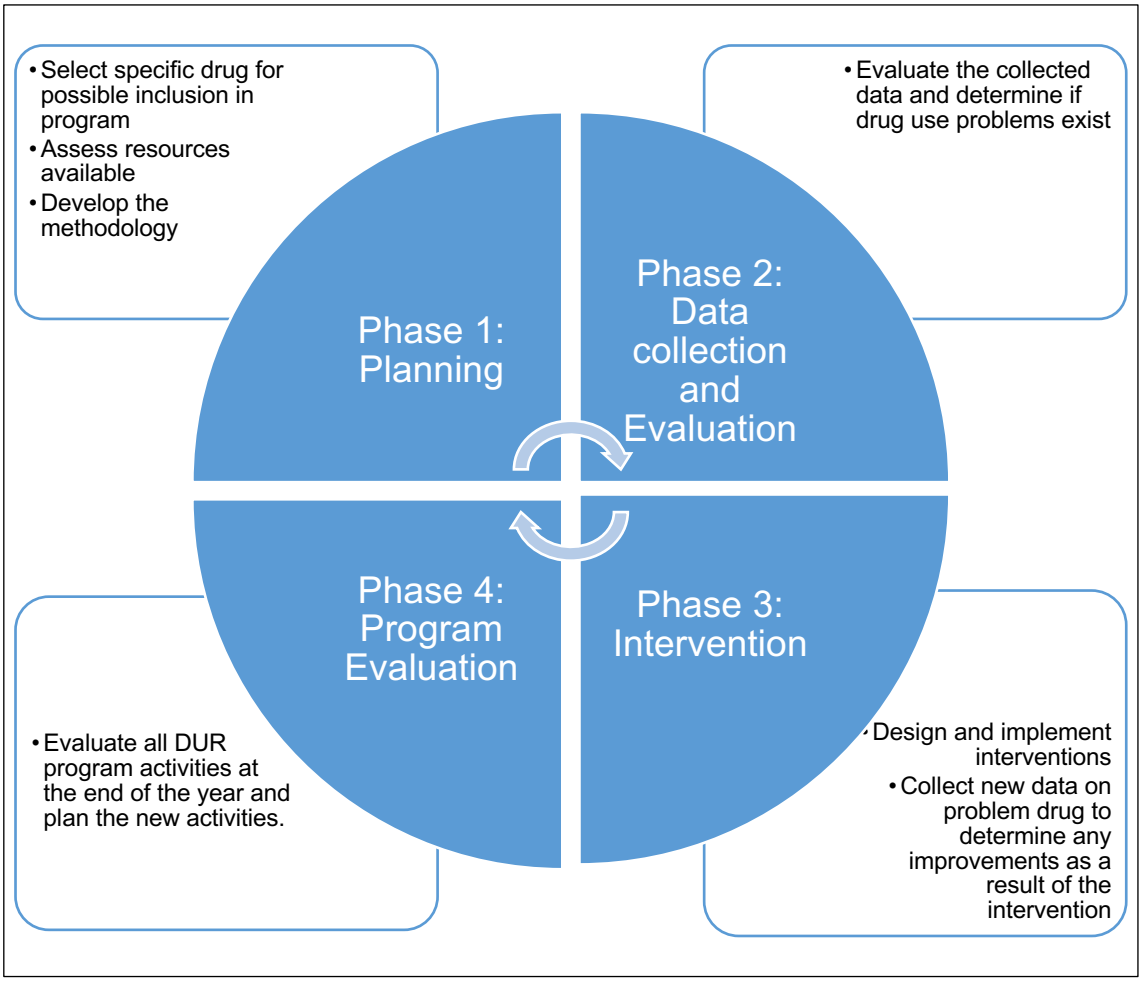

Figure 2–11. Stages of a drug utilisation.

2.5.5 Types of drug use and drug prescribing information

Drug use information is an important source of information in research. The types of information that can be evaluated in a DUR are as follows (World Health Organization, 2003a: 13; Shalini *et al.*, 2010: 805):

- *Drug based information*. This includes detailed information explaining indications, dosages and dosage regimens.
- *Problem or encounter-based information*. The reason for the problem and its management.
- *Patient information*. This includes the patient's demographics, including age, gender, ethnicity, co-morbidities, knowledge, beliefs and perceptions.
- *Prescriber information*. The prescribing patterns considering the demographic information of the patient.

Drug use, including drug prescribing patterns, are also analysed in DURs and they are presented in table 2–19 (adapted from Shalini *et al.*, 2010: 804; Sharma, 2018: 453):

Table 2–19. Topics of analyses for drug utilisation reviews and their descriptions.

Topic of analyses	Description
Pattern of use	Extent and profiles of drug use and trends in use and cost over time
Quality of use	Audited comparison of national treatment guidelines or local formularies and actual drug use
Indices of quality of drug use	Drug choice, drug cost, drug dosage, understanding of drug interactions and adverse drug reactions, and analysis of patient's perception of cost and benefit of their treatment
Determination of use	Patient, prescriber and drug characteristics
Outcomes of use	Health outcomes and economic consequences
Efficiency of drug use	Rational allocation of healthcare budgets
Rational use of drugs in populations	The prescription of a well-documented drug at optimal dosage, accurate information at an affordable price

2.5.6 Published literature on drug utilisation reviews of clozapine

The prescribing and monitoring patterns of clozapine in Christchurch, New Zealand, were investigated by McKean *et al.* (2008: 263). This retrospective study on 353 patients focused on identifying the pattern of clozapine usage by analysing the daily dosage and indication. It also monitored the drug concentration. The average daily dosage differed amongst the genders. The mean dosage of clozapine in male patients was 348 mg, and the mean dosage in female patients was lower at 278 mg. The mean daily dosage of clozapine was also noted to be much lower in patients over the age of

65 years. A significant finding was the age-related decline in the rate of clearance in female participants which could be further investigated for correlations between age, gender and clozapine clearance. This research paper also recommended that the less common indications of clozapine be formally licensed in Christchurch. These indications include the treatment of psychosis in dementia and Parkinson's disease as well as drug-induced psychosis in Parkinson's disease (McKean *et al.*, 2008: 266).

The use of antipsychotics in a psychiatric hospital in the Eastern Cape Province, South Africa, was investigated by Eloff *et al.* (2017: 5) The research entailed a retrospective chart review on 169 inpatient files for a period of 8 weeks. Although the sample size was small, the research provided insight on the frequency of drugs switched from conventional to atypical antipsychotics in resource-limited areas in South Africa. 9% of the patients were switched from a conventional antipsychotic to clozapine. Clozapine has proven to be more superior in efficacy than conventional antipsychotics, unlike other second-generation antipsychotics (Eloff *et al.*, 2017: 5).

The patterns of clozapine and other antipsychotics were analysed in patients diagnosed with treatment resistant schizophrenia in São Paulo, Brazil. Silveira *et al.* (2015: 166) conducted a cross-sectional study consisting of 103 participants, of which only 21.4% of the patients were on clozapine treatment. Of the 15 psychiatrists in the study setting, 60% of them prescribed clozapine for at least one patient. This study also analysed the barriers faced by prescribers when prescribing clozapine. The most common barrier was the patient's low adherence to blood counts for haematological monitoring. The recommended prescribing guidelines were not strictly adhered to by the psychiatrists in the study, suggesting that this may be a common occurrence in other parts of the world (Silveira *et al.*, 2015: 166).

A retrospective DUR on clozapine usage in the Nelson Mandela Metropole, South Africa, was piloted by Moolman during the period of 1 December 2010 and 29 February 2012. The study focused on the prescribing and monitoring patterns of clozapine in 65 patients. The National Institute for Health and Clinical Excellence guideline were used as a standard to assess the level of compliance regarding the prescribing and monitoring of clozapine in this region. Moolman (2013: 258–261) concluded that the majority of the monitoring patterns were not compliant with the guidelines and recommended that prescribers should be educated to ensure the rational use of

clozapine. It was suggested that the results may be reflective of the current prescribing and monitoring practices prevalent in South Africa (Moolman, 2013: 258–261).

2.6 Chapter 2 summary

This chapter explored the literature on psychiatric disorders, focusing on schizophrenia and schizoaffective disorders. The pharmacological properties of clozapine were reviewed, focusing on its adverse effects, drug interactions, dosing patterns and monitoring. An overview of DURs was given and literature pertaining to DURs conducted specifically on clozapine explained. The following chapter will discuss the research methodology employed in this study.

CHAPTER 3.
RESEARCH METHODOLOGY

3.1 Introduction

This chapter describes the research methods utilised to conduct this drug utilisation review (DUR). In addition, statistical terminologies and ethical considerations are discussed in detail. A brief overview of the aim and objectives of the research are given.

3.2 Aim and research objectives of the empirical study

3.2.1 General Aim

The aim of the study was to investigate the prescribing and monitoring patterns of clozapine to outpatients at Fort England Hospital in Grahamstown (Cacadu District Municipality, Makana Local Municipality, Eastern Cape Province, South Africa).

3.2.2 Specific research objectives of the empirical study

The specific research objectives included the following:

- To determine the prescribing patterns of clozapine (dosages and treatment period) and compliance with the recommended treatment guidelines (the pharmacoepidemiology component of this study).
- To identify medication problems (interactions and adverse effects) associated with the use of clozapine (the pharmacovigilance component of this study).

3.3 Study design

A DUR of the observational, descriptive, cross-sectional and retrospective type was conducted. Secondary data sources were utilised, i.e. existing patient clinical files were surveyed to collect the retrospective data. The research instrument implemented was a data collection tool (structured data collection form). The collected data was collated in an electronic spreadsheet for analysis.

A descriptive study design can be used to recognise current problems, justify current practice, make judgements or determine what other individuals in similar situations are doing, or to develop theories (Burns & Grove, 2011: 256). Therefore, a descriptive study can describe certain variables, such as medication prescribing and monitoring patterns, as well as therapeutic drug levels for example.

Cross-sectional research can be exploratory, descriptive or explanatory. However, a descriptive design is the most reliable (Neuman, 2014: 44). A cross-sectional study examines the data at one point in time and can be used to observe correlations between variables in the data set (Mann, 2003: 56).

In a retrospective study, data of interest that has already been documented will be used (Lyman Ott & Longnecker, 2010: 20).

3.4 Study setting

The research was conducted at Fort England Hospital in Grahamstown. Fort England Hospital was established in 1875 as the first dedicated mental health hospital in South Africa. It is a 313-bed tertiary specialist psychiatric hospital with multidisciplinary healthcare teams that cares for both in- and outpatients.

Fort England Hospital also supplies specialised medicines to four other general hospitals in the Eastern Cape region (listed in table 3–1), to which some patients were down-referred:

Table 3–1. List of hospitals to which patients in the study sample at Fort England Hospital were down-referred to

List of general hospitals situated in the Eastern Cape to which patients in the study sample at Fort England Hospital were down-referred to
1. Fort Beaufort Provincial Hospital 2. Victoria Hospital (Alice) 3. Nompumelelo Hospital (Peddie) 4. Adelaide Hospital (Bedford)

3.5 Target and study population

The target population were outpatients (> 18 years) who met the set inclusion criteria and who were on treatment with clozapine for the study period 1 January 2017-31 December 2017. A total number of 57 patients were identified and included in this study.

Patients of all race groups and both genders were included. The basis of the patient's diagnosis was not an exclusion criterion. Patients who were discontinued on clozapine therapy during the study period were still included in the study. Due to the relatively small sample size, non-random sampling was employed and this allowed for all the outpatients on clozapine to be included in the study.

3.6 Data source

The data source was the patient files of all outpatients on clozapine treatment during the study period.

3.7 Research instrument

The research instrument was a data collection tool. The patient file is a rich source of data, however, it is imperative that it should be checked for accuracy, completeness and consistency. Therefore, a precise data collection tool that correlates with the reliability of the data in patient files was developed to document the data.

3.7.1 Data collection tool

The data collection tool consisted of a structured data collection form. The purpose of the data collection form was to record demographical and clinical information from the patient file.

3.7.1.1 Testing the data collection tool

Five patient files were randomly selected from the outpatient files at Fort England Hospital that met the inclusion criteria. These patient files were surveyed to record the data on the initial data collection form (ANNEXURE A). Upon testing, the necessary changes were made on the data collection form to create a more accurate final data collection form that contains only the most relevant study variables (ANNEXURE B).

3.7.1.2 Structure of the data collection tool

The criteria used to investigate the prescribing patterns of clozapine, the compliance with the recommended treatment guidelines and the identification of medication problems are discussed below.

3.7.1.3 Study variables

The subjective data on the data collection form encompasses patient demographical information, such as social and family history, hospital and surgical histories. The objective data encompasses the medication to assess the prescribing patterns as well as the monitoring of the patients according to specific guidelines. The information recorded may be useful to identify, resolve and prevent potential and actual drug-related problems as well as shortcomings in patient monitoring. This may contribute to quality care that psychiatric patients receive.

The study variables and measurements are summarised in table 3–2:

Table 3–2. Patient data that comprise the study variables and measurements

Variables	Measurements
Age	Past/chronic medical conditions
Gender	Allergies
Race	Medical alerts
Tobacco use	Co-morbid disease states
Substance use	Diagnosis
Alcohol use	Clozapine dosages
Occupation	Current and past medication
Marital status	Drug interactions
Pregnancy status	Adverse reactions
Breast feeding	Monitoring
Hospital and surgical history	
Family history	

3.7.1.4 Demographics

3.7.1.4.1 Patient identification number

No patient identifiable information was captured, therefore an exclusive number was assigned to each patient file and documented on the respective data collection form. Each patient file was allocated a number between 1 and 57.

3.7.1.4.2 Date of birth and age

The age of the patient was obtained from their patient file. In most cases the patient file only recorded the date of birth of the patient. The age of the patient during this study period was then calculated using the date of birth and classified for the purposes of this study as shown in table 3–3 (Knox College Library, 2018):

Table 3–3. Classification of various age groups

Age in years	Classification
13 – 17	Adolescence
> 18	Adulthood
18 – 29	Young adulthood
30 – 39	Thirties
40 – 64	Middle age
> 65	Aged/Elderly
> 85	Very old

Castberg *et al.* (2017: 1) suggests that age has an impact on the serum concentration of second-generation antipsychotic drugs, including clozapine. The elderly is more inclined to have an innately reduced hepatic metabolic function, resulting in lower hepatic clearance of drugs, as well as lower liver volume and decreased hepatic blood flow. Higher dosage-adjustments and consistent therapeutic drug monitoring are necessary in the elderly (Castberg *et al.*, 2017: 6). Other studies, however, do not confirm the significance of age affecting the plasma concentration of clozapine (Ismail *et al.*, 2012: 57).

3.7.1.4.3 Gender

The gender of each patient was obtained from their patient file. Gender was classified as either male or female and recorded as shown in table 3–4:

Table 3–4. Classification of the genders analysed

Gender	
1	Male
2	Female

A study has shown that males are more likely to develop schizophrenia (Messias *et al.*, 2007: 323). A study by McGrath and Susser (2009: S7) portrays that the incidence ratio of males to females diagnosed with schizophrenia is 1.4 to 1 respectively (McGrath & Susser, 2009: S7). A former study portrayed the cumulative lifetime risk of schizophrenia for males and females to be identical (Rössler *et al.*, 2005: 405).

Gender plays a role in the plasma concentration of clozapine, with females displaying significantly higher concentrations than males (Tang *et al.*, 2007: 49). Clozapine is metabolised primarily by two enzymes in the liver, namely CYP2D6 and CYP1A2 (Eiermann *et al.*, 1997: 439). Therefore, clozapine metabolism is proven to be strongly dependent on the activity of CYP1A2 (Frazier *et al.*, 2003: 91). It is hypothesised that females have decreased CYP1A2 enzyme activity, therefore resulting in a higher clozapine concentration (Ismail *et al.*, 2012: 58).

3.7.1.4.4 Race

The patient file was the source of the race for each patient. This information was recorded onto the data collection form in the specific category as shown in table 3–5:

Table 3–5. Classification of the races in the study population

Race	
1	Caucasian
2	African
3	Asian
4	Coloured
5	Other

Ethnicity and race have an effect on the adverse effects profile of clozapine. Krakowski *et al.* (2009: 101) stated the importance of genetic polymorphisms and the differences of distribution of the 5-HT_{2C} and 5-HTTLPR receptor allele according to ethnicity and race. These alleles present certain adverse effects due to clozapine. Weight gain and aggression were the most prevalent adverse reactions in patients of African-American descent (Krakowski *et al.*, 2009: 101).

3.7.1.5 Social history

3.7.1.5.1 Tobacco use

The patient file included social history which stated the smoking status of the patient. This history was recorded onto the data collection form using the key shown in table 3–6:

Table 3–6. History of tobacco use

Tobacco use	
1	Yes
2	No
3	Other information

The hepatic metabolism of clozapine by the enzyme CYP1A2 is induced by the polycyclic aromatic hydrocarbons found in tobacco smoke (Gee *et al.*, 2017: 79). The enzyme CYP1A2 is a major enzyme catalysing the metabolism of clozapine (Eiermann *et al.*, 1997: 439). When CYP1A2 is induced, the rate of metabolism of clozapine is increased. This results in decreased plasma concentrations of clozapine, effectively decreasing the efficacy of the drug (Gee *et al.*, 2017: 79).

3.7.1.5.2 Alcohol use

The concomitant use of alcohol while on clozapine therapy is not recommended (Rossiter, 2016: 481). Information regarding the patient's alcohol use (as categorised in table 3–7) was recorded from the patient file onto the data collection form:

Table 3–7. History of alcohol use

Alcohol use	
1	Yes
2	No
3	Other information

Sedation is an adverse effect of clozapine. This adverse effect is exacerbated by the concomitant use of alcohol and can increase central nervous system depression, leading to potentially dire consequences for the patient such as respiratory depression and death (Taylor *et al.*, 2009: 486).

3.7.1.5.3 Substance abuse

The use of any substances was recorded on the data collection form as stated in the patient files, using the key shown in table 3–8:

Table 3–8. History of substance abuse

Substance abuse	
0	None
1	Cannabis (dagga)
2	Methaqualone
3	Methamphetamine
4	Glue

The co-morbid use of substances is common in patients diagnosed with schizophrenia. This may cause relapse, hospitalisation, violence, decreased functioning, homelessness and infections such as HIV (Drake *et al.*, 2000: 441).

3.7.1.5.4 Suicide risk

The risk of suicide in the study population (as categorised in table 3–9) was analysed in each patient file and recorded:

Table 3–9. History of suicide attempts

Suicide risk	
1	Yes
2	No
3	No information

This was investigated because approximately 90% of people who commit suicide suffered from a psychiatric disorder at their time of death, highlighting the burden of mental illnesses (Jacob & Coetzee, 2018: 177).

3.7.1.5.5 Occupation

Table 3–10 depicts the different categories explored with regards to each patient's occupation status during the study period:

Table 3–10. Current occupational status

Occupation	
1	Employed
2	Unemployed
3	Retired
4	Student
5	Disability grant
6	No information

The effects of clozapine treatment were also present in a patient's lifestyle, including their employability, job tenancy and work productivity (Percudani *et al.,* 2004: 708).

Lindström assessed the capability of a patient to hold employment 2 years after the initiation of clozapine treatment. Of the 62 patients in the study sample, 39% were employment as full-time or part-time employees, whilst the remaining 61% were unemployed (Lindström, 1988: 526). A similar study explored the employability outcomes of 122 patients with chronic treatment resistant schizophrenia treated with clozapine. Of the 74 patients assessed in the study, 40% of them were full-time or half-time employees after receiving clozapine for at least 2 years (Percudani *et al.*, 2004: 709).

3.7.1.5.6 Marital status

Information regarding the marital status of each patient was extracted from the patient file and recorded according to the categories shown in table 3–11:

Table 3–11. Current marital status

Marital status	
1	Single
2	Married
3	Divorced or separated
4	No information

Clozapine treatment has a social and emotional impact on not only the patient, but also on family members (Kotcher & Smith, 1993: 745). The outcome of the treatment

is also dependent on the family's outlook, as conflict concerning the treatment can further exacerbate underlying tensions within the family system or marriage covenants (Kotcher & Smith, 1993: 745). Norman *et al.* (2000: 305) explored the well-being and quality of life of schizophrenic patients. The results portrayed that married individuals had a higher quality of life according to the Quality of Life scale, compared to divorced/separated or single individuals.

3.7.1.5.7 Pregnancy status

The pregnancy status (listed in table 3–12) at the time of the study period was assessed and recorded for all the female patients in the study sample:

Table 3–12. Current pregnancy status

Pregnancy status	
1	Yes
2	No

Clozapine is categorised as a category B drug, unlike most of the other atypical antipsychotics which fall under category C (Gentile, 2004: 1266). The SAMF has defined these categories, according to the FDA-assigned pregnancy categories, as follows (Rossiter, 2016: 6):

Category B: Animal studies have revealed no evidence of harm to the foetus; however there was no adequate and well-controlled studies in pregnant women to demonstrate to a risk to a foetus.

Category C: Animal studies have shown as adverse effect and there are no adequate and well-controlled studies in pregnant women.

Definitive evidence for increased risk of teratogenesis has not been determined for atypical antipsychotics (Robinson, 2012: e383).

3.7.1.5.8 Breastfeeding

The breastfeeding status (listed in table 3–13) at the time of the study period was assessed and recorded for all the female patients in the study sample:

Table 3–13. Current breastfeeding status

Breastfeeding status	
1	Yes
2	No

Clozapine is found in relatively high concentrations in breast milk, therefore resulting in the presentation of adverse effects by the drug in the neonate (Gentile, 2004: 1268). Some of these adverse effects include sedation, restlessness, seizures, cardiovascular instability and agranulocytosis (Gentile, 2004: 1268; Iqbal *et al.*, 2005: 41).

3.7.1.6 Medical history

3.7.1.6.1 Allergies

Any history of drug allergies was determined in the patient files and documented using the key shown in table 3–14:

Table 3–14. Known allergy information

Allergies	
1	Yes
2	No
3	No information

The occurrence and evidence of drug allergies of antipsychotic drugs are not well known (Nurenberg and Schleifer, 2009: 491).

3.7.1.6.2 Porphyria

Any evidence of porphyria (options listed in table 3–15) in the patient files was recorded:

Table 3–15. A diagnosis of porphyria

Porphyria	
1	Yes
2	No

3	No information

Porphyria shares common symptoms with psychiatric disorders, such as schizophrenia, therefore it may be disguised as psychosis (Burgoyne *et al.*, 1995: 121). Holroyd and Seward (1993: 324) explored the effect of antipsychotic drugs on a case study presenting with acute intermittent porphyria. Clozapine was amongst the antipsychotics that did not exacerbate porphyria (Holroyd and Seward, 1999: 324).

3.7.1.6.3 Past or chronic medical conditions

The contents of the patient file were examined for any past or chronic medical conditions and recorded.

3.7.1.6.3.1 Co-morbid disease states

At least one co-morbid disease state is present in approximately 50% of all patients diagnosed with schizophrenia. These diseases states could either be psychiatric conditions or another medical condition. Common co-morbid diseases states include (Green *et al.*, 2003: 130):

- Depressive disorders.
- Obsessive compulsive disorders.
- Substance use disorders.
- Sexually transmitted diseases (such as HIV and hepatitis).
- Obesity.
- Hyperlipidaemia.
- Hypertension.
- Diabetes mellitus type II.

3.7.1.6.3.2 Hospital and surgical history

Any hospital or surgical history noted in the patient file was recorded according to table 3–16:

Table 3–16. History or hospital admissions or surgical procedures

Hospital and/or surgical history	
1	Yes

2	No

Any details of this history were also summarised onto the data collection form. The value of attaining this information was to assess the safety of clozapine use in the patient. The FDA noted the occurrence of seizures for patients using clozapine who had a previous history or seizures or other predisposing factors (Novartis Pharmaceuticals Corporation, 2004: 15).

The number of hospital admissions were categorised as listed in table 3–17:

Table 3–17. Number of hospital admissions

Hospital admissions	
1	< 10
2	> 10
3	Undefined

3.7.1.6.4 Family history

Information regarding the family history (as listed in table 3–18) was documented on the data collection form. Unfortunately, in the majority of the patient files no information was found.

Table 3–18. Family history of any psychotic disorders

Family history	
1	Yes
2	No
3	No information

Family history is important in understanding the aetiology of schizophrenia in some patient cases, as there is evidence that the condition could possibly be hereditary. This information would be valuable in predicting the early onset of the condition (Nuhu *et al.*, 2016: 284). The support of family during the treatment period has also proven to be valuable for a successful therapeutic outcome in patients with schizophrenia (Dickson *et al.*, 1995: 627). A study by Raguraman *et al.* (2005: 104) showed that significant improvement in clozapine therapy was witnessed in patients who had the support of their family. Another study conveyed similar results of the benefits of

clozapine therapy in a member of the family. 90% of the families identified noticed an improvement in the quality of life, a higher level of functioning and decreased hospital admissions in family member on clozapine therapy (Stebbin & How, 1995: 17). The NICE guidelines include family intervention as part of the psychological therapies for treating psychosis and schizophrenia. This intervention would improve the coping mechanisms of the patients and decrease the rate of relapse of patients taking clozapine (National Institute for Health and Care Excellence, 2015: 21).

3.7.1.6.5 Medical alerts

The MedicAlert® Foundation of Southern Africa provides patients with a 'medical alert' bracelet that summaries their essential and emergency medical information. This information includes allergies, hidden medical conditions (such as epilepsy), a type of implant and blood group (Medic Alert Foundation of Southern Africa, 2019). Medical alerts are especially important in a state of medical emergency, or when patients are incapable of communicating their ailments. The medical alert assists health care professionals understand the patient history and make the best therapeutic decisions for the patient. It was assessed whether medical alerts such as epilepsy and diabetes were recorded in the patient files. There was minimal to no information in the majority of the patient files concerning this category. The outcomes were noted as shown in table3 3–19:

Table 3–19. Known medical alerts

Medical alerts	
1	Yes
2	No
3	No information

3.7.1.6.6 Diagnosis

The most current diagnosis of the patient (options listed in table 3–20) was assessed in the patient file, and this was recorded:

Table 3–20. Current diagnosis

Diagnosis	
1	Schizophrenia
2	Schizoaffective disorder
3	Bipolar disorder with psychotic features
4	Other condition

Clozapine may be prescribed to treat the symptoms of schizophrenia and other psychotic disorders (Si *et al.*, 2012: 101). It is the most effective antipsychotic to treat the symptoms of treatment-resistant schizophrenia (Alessi-Severini *et al.*, 2013: 1).

Schizophrenia can further be classified into sub-types (listed in table 3–21) according to the presentation of symptoms:

Table 3–21. Classification of the sub-types of schizophrenia

Schizophrenia sub-types	
1	Paranoid-type
2	Disorganised-type
3	Catatonic
4	Treatment-resistant
5	Undefined

3.7.1.6.7 Initial episode

The initial psychotic episode of the patient was obtained from the patient file and documented. Schizophrenia is often difficult to diagnose due to the subtle or unrecognisable nature of the symptoms at onset of the condition. Symptoms such as neurotic features, antisocial behaviour, and substance abuse can often mask the underlying condition (Frangou & Byrne, 2002: 523). The most prominent features that often unmask the condition are auditory and visual hallucinations, delusions, unusual or aggressive behaviour and a blunted affect (Khamker, 2015: 30).

Symptoms are presented in three ways, either as positive, negative or cognitive symptoms. These were categorised as shown in tables 3–22 to 3–24:

Table 3–22. Categories of the positive symptoms of schizophrenia

Positive symptoms	
0	None recorded
1	Hallucinations
2	Delusions
3	Thought disorders
4	Movement disorder
5	Other

Table 3–23. Categories of the negative symptoms of schizophrenia.

Negative symptoms	
0	None recorded
1	Blunted affect
2	Avolition
4	Reduced speech
5	Other

Table 3–24. Categories of the cognitive symptoms of schizophrenia.

Cognitive symptoms	
0	None recorded
1	Poor executive functioning
2	Poor attention
3	Poor working memory
4	Other

3.7.1.7 Clozapine usage

The history of the patient regarding clozapine treatment was explored by assessing whether clozapine therapy was discontinued prior to the study period and recorded according to the possibilities listed in table 3–25:

Table 3–25. History of the prior use of clozapine

Has the patient taken clozapine before?	
1	Yes
2	No
3	No information

The factors influencing the prior discontinuation of clozapine were also explored. Poor adherence is one of the major factors why patients may default on their treatment and as a result relapse.

3.7.1.8 Current and past medication

Information regarding each patient's medication history was documented as shown in table 3–26:

Table 3–26. Past and current information of the drugs used

Information obtained from current and past medication
Drug name
Dosage route
Dosage
Interval
Date started
Date stopped
Reason for commencement or discontinuation

Understanding the past medication history, and its evolution to the current medication of the patient is a vital stage in health care research. This information is especially valuable in epidemiological studies (Gearing *et al.*, 2006: 131). This allows for a full clinical picture to be depicted for each patient.

3.7.1.8.1 Reasons for discontinuation of a medication

The reasons for the commencement or discontinuation of medication was obtained from the patient file and recorded using the key shown in table 3–27:

Table 3–27. Reasons for the commencement or discontinuation of any antipsychotic therapy

Reason(s) for commencement or discontinuation	
1	Successful therapy
2	Failed therapy
3	Adverse effects
4	Allergy
5	Formulary change
6	Non-adherence
7	Safety
8	Change in diagnosis
9	No information

3.7.1.8.2 Other antipsychotics

A history of the previous antipsychotics, if any, that were prescribed before clozapine treatment commenced were documented as shown in table 3–28:

Table 3–28. History of the use of other antipsychotics prior to clozapine use

Were any other antipsychotics used before clozapine?	
1	Yes
2	No
3	No information

Clozapine is the third line treatment for schizophrenia. Prior to the prescription of clozapine for schizophrenia treatment, the patient should have been initiated on at least two other antipsychotics which did not result in successful therapy (Maartens *et al.*, 2015: 15.15).

3.7.1.9 Drug interactions

After analysis of the current medication for each patient file, any possible drug-drug interaction, particularly those with clozapine, were noted and recorded following the key provided in table 3–29:

Table 3–29. Possible drug interactions identified

Possible drug interactions identified	
1	Yes
2	No

Clozapine typically interacts with other drugs that have a similar pharmacological profile or those that can cause similar adverse effects, resulting in the exacerbation of that effect (Edge *et al.*, 1997: 16).

3.7.1.10 Adverse effects

Adverse effects are common with clozapine therapy. The patient files were assessed for any information reported (possibilities listed in table 3–30) pertaining to adverse effects experienced by the patient.

Table 3–30. Information on reported adverse effects

Reported adverse effects	
1	Yes
2	No
3	No information

The most common adverse effects were recorded by Taylor *et al.* (2009: 62) as indicated in table 3–31:

Table 3–31. Categories of adverse reactions experienced.

Which adverse reactions were experienced?	
1	Agranulocytosis
2	Hypersalivation
3	Constipation
4	Weight gain
5	Hypertension
6	Nausea
7	Fever
8	Seizures
9	Hypotension

10	Tachycardia
11	Other

The neurological functions of each patient were also explored and were categorised into:

- Changes in mood
- Psychomotor skills
- Extrapyramidal symptoms

This information was related to the current medication to assess if any adverse effects were treated (shown in table 3–32).

Table 3–32. Management of adverse effects

Is the reported adverse effect being treated?	
1	Yes
2	No
3	None to treat

Interventions were required for adverse effects as some of them could have dire consequences and are potentially life-threatening (Taylor *et al.*, 2018: 62).

3.7.1.11 Monitoring

3.7.1.11.1 Haematological monitoring

Agranulocytosis can be a dire consequence of clozapine treatment which can be life-threatening (Taylor *et al.*, 2009: 66). Haematological monitoring is therefore a recommendation in all patients on clozapine treatment. According to the clozapine REMS strategy, a baseline absolute neutrophil count (ANC) result should be at least 1500 cells/μL prior to initiation of clozapine in the general patient and 1000 cells/μL for patients with documented Benign Ethnic Neutropenia (Clozapine Risk and Mitigation Strategy, 2015: 2). Absolute neutrophil count monitoring must be continued throughout the clozapine treatment (Clozapine Risk and Mitigation Strategy, 2015: 2).

The following parameters were obtained in each patient file and documented using the key shown in table 3–33:

- Full blood count.
- White cell count.
- Absolute neutrophil count.
- Absolute monocyte count.
- Absolute lymphocyte count.
- Absolute eosinophil count.
- Absolute basophil count.

Table 3–33. Haematological monitoring assessment

Was haematological monitoring done?	
1	Yes
2	No
3	No information

3.7.1.11.2 Metabolic monitoring

Patients on clozapine therapy are often susceptible to acquiring other conditions such as hyperglycaemia or diabetes mellitus, cholesterol dyslipidaemia, low-density lipoprotein dyslipidaemia, triglyceride dyslipidaemia, overweight or obesity, and hypertension (Maaroganye *et al.*, 2013: 415). These conditions may occur as a consequence of the metabolic adverse effects clozapine presents (Clozapine Risk and Mitigation Strategy, 2015: 1).

The following parameters were obtained from the patient files and recorded (as shown in tables 3–34 and 3–35):

- Weight
- Height
- Body mass index (BMI)
- Fasting blood glucose
- Fasting lipogram:
  - Total cholesterol
  - Triglycerides
  - Low-density lipoprotein (LDL)

- High-density lipoprotein (HDL)

- Pulse
- Blood pressure

Table 3–34 Metabolic monitoring assessment

Was metabolic monitoring done?	
1	Yes
2	No
3	None information

Table 3–35. Fasting lipogram assessment

Was fasting lipogram done?	
1	Yes
2	No
3	None information

3.7.1.12 Clozapine titration chart

3.7.1.12.1 Titration from the initial dosage

Any information that was available in the patient file regarding the titration of clozapine upon initiation was recorded as shown in table 3–36:

Table 3–36. Clozapine initial titration assessment

Was titration performed from the initial dosage?	
1	Yes
2	No
3	No information

3.7.1.12.2 Initial dosage supplied on day 1 of administration

Clozapine should be initiated on a starting dosage of 12.5 mg once or twice daily (Clozapine Risk and Mitigation Strategy, 2015: 1). The initial dosage of clozapine was recorded as shown in table 3–37:

Table 3–37. Clozapine dosage upon initiation

Initial dosage supplied on day 1 of administration	
1	12.5 mg
2	25 mg
3	37.5 mg
4	Other

3.7.1.12.3 Dosage supplied on day 2 of administration

The initial dosage of clozapine should be titrated gradually over several days to reduce the occurrence of adverse effects (Citrome & Volavka, 2002: 283). The dosage supplied on the second day of the titration were documented as shown in table 3–38:

Table 3–38. Clozapine dosage on day 2 after initiation.

Dosage supplied on day 2 of administration	
1	25 mg
2	50 mg
3	75 mg
4	Other

3.7.1.12.4 Dosage increment during the titration period

The South African Medicines Formulary recommends that clozapine is titrated in increments of 25-50 mg until therapeutic range is achieved in 2-3 weeks (Rossiter, 2016: 481). The prescription charts in the patient files were analysed for the incremental increases in clozapine dosage upon initiation and recorded according to the categories shown in table 3–39:

Table 3–39. Assessment of the incremental dosages during the titration period.

Dosage increment during the titration period	
1	< 50 mg/day
2	= 50 mg/day
3	> 50 mg/day

3.7.1.12.5 Maintenance and maximum dosages

The recommended target dosage for clozapine is 300-450 mg daily (Citrome & Volavka, 2002: 283). Clozapine induces more dosage-related adverse effects such as seizures should the dosage exceed 450 mg daily. The highest tolerable dosage is 900 mg daily (Emsley & Seedat, 2013: 154). The maintenance and maximum dosages for each patient was also recorded.

3.7.2 Validity and reliability

Validity and reliability are concerned with how specific measurements or indicators for the current study were developed since it may influence the conclusion based on the results (Neuman, 2014: 212).

The validity of the data collection tool is a measure of its accuracy to collect the data. In this study, only content and face validity were applied. In face validity, the data collection tool was evaluated to determine whether it was measuring what it was supposed to be measuring (Sim & Wright, 2000: 123, 125). Content validity was used to determine how well the data collection tool represented all the components of the variables to be measured and to ensure that it met the study objectives (Kimberlin & Winterstein, 2008: 2279).

Reliability is used to determine to what level the instrument can be dependent on to provide consistent results if the study will be repeated (Kimberlin & Winterstein, 2008: 2277). Reliability of the data was ensured as only the researcher used the data collection tool to minimise possible mistakes.

Reliability can be achieved without validity, however validity cannot be achieved without reliability. As a result, the degree of validity for a set of measurements is limited by the degree of reliability (De Muth, 2006: 46).

The data collection form was printed in hard copies that were easy to collect and capture afterwards on an electronic spreadsheet.

3.8 Implementation plan

3.8.1 Data collection process

3.8.1.1 Dates and places

Data collection and capturing took place over a period of 3 months on a daily basis after the necessary approval were granted. Data collection utilising the patient files happened on the study site (Fort England Hospital pharmacy) during office hours on Wednesdays and Fridays, or as per prior arrangement with the pharmacy manager.

3.8.1.2 Roles and responsibilities of the researcher

The roles and responsibilities of the researcher is outlined as follows:

- Only the researcher was involved in collecting and capturing the data to avoid any possible errors that may occur if more people were involved, thus ensuring reliability.
- The researcher assigned a unique identification number to each filled data collection form to avoid potential duplication of information.
- The researcher thoroughly checked the collected data for accurateness and completeness before returning the patient files to the filing cabinets in the pharmacy.

3.8.1.3 Data collection methods

The researcher acquired a register consisting of all the outpatients at Fort England Hospital between the study period of 1 January 2017-31 December 2017. Each patient who was currently on clozapine treatment was identified on the register and a list was compiled which formed the study sample.

A patient file for each identified patient was obtained from the pharmacy patient filing cabinet. Each patient file was assigned a unique identification number on the respective data collection form. Each patient file was analysed by the researcher and the necessary information was extracted and documented on the data collection form.

3.8.2 Data coding

This method was employed to capture the information documented on the data collection form onto an electronic spreadsheet. Data coding is a crucial step as it provides a channel whereby the researcher can convey and translate the data to promote the theory. It consists of several steps such as subdividing the data and allocating categories so as to organise it for data analysis (Basit, 2003: 152).

An example of how the data coding was used is shown in table 3–40:

Table 3–40. History of tobacco use

Tobacco use	Yes	No	Other information

The above data was coded as follows before being captured on the spreadsheet using the key shown in table 3–41:

Table 3–41. An illustration of the data codes for tobacco use

Data code	**Tobacco use**
1	Yes
2	No
3	Other information

3.8.3 Data capturing

After coding the data, it was captured onto an electronic spreadsheet using Microsoft Office Excel® 2018.

In the Excel spreadsheet, a fixed column with the unique patient identification number was captured. This number correlated with the unique identification number assigned to each patient file. All the information from a specific patient file was captured in the row that corresponded with its unique identification number.

The columns in the Excel spreadsheet represented each of the variables investigated in the empirical study.

3.9 Data analysis

The collected data was arranged, analysed, summarised and presented (graphs and tables). Statistical analysis was done using the computer software Statistical Analysis System® (SAS Institute Inc.).

Statistical significance was considered with a two-sided probability of $p < 0.05$. The practical significance of differences was explained when results were statistically significant.

Variables were analysed using descriptive statistics. These include frequencies (n), percentages (%), means, medians and standard deviations.

Comparisons were made using inferential statistics and specifically the chi-square test.

3.9.1 Descriptive statistics

Descriptive statistics describe the collected or observed data. Mathematical techniques that organise, summarise, categorise and present the collected data are characterised as descriptive statistics (De Muth, 2006: 1).

3.9.1.1 Variables

De Muth (2006: 4) defines a variable as any attribute, characteristic or measurable property that can vary from one observation to another. Statistical variables can be categorised as discrete or continuous (Mendenhall, *et al*., 2008: 8).

3.9.1.1.1 Discrete

Variables are discrete if the possible values that it can attain are distinguishable from each other (Mendenhall, *et al*., 2008: 10). For example, the gender of a patient can be categorised as “0” for male and “1” for female. There are no values in-between. Therefore, these variables are also referred to as qualitative, categorical or nominal (De Muth, 2006: 5).

3.9.1.1.2 Continuous

In contrast to discrete values, the different possible values of continuous variables are indistinguishable (Mendenhall, *et al*., 2008: 10). For example, the body weights of patients are measured and there can be additional values in-between two possible values.

3.9.1.1.3 Frequency

Frequency (f) is defined as the number of times that a specific value is obtained for a specific variable in the study population (Argyrous, 2011: 79). For example, substance abuse can be categorised as discrete data in terms of alcohol, tobacco and drug abuse and the number of occurrences expressed as relative percentage frequencies. In cases of data on an ordinal scale, cumulative frequencies are useful to answer questions such as (Frankfort-Nachimias & Leon-Guerrero, 2008: 43):

- How many observations are smaller than or equal to a given value?
- What percentage of observations falls between two given values?

3.9.1.1.4 Mode

The category of variable that has the highest number of occurrences is defined as the mode and it can be easily deduced from a data spread diagram, frequency table, bar diagram and circle diagram (Rosner, 2011: 11).

3.9.1.1.5 Median

The median ($\tilde{x}$, if x is the variable) for discrete data is a number in the middle of observations arranged in ascending order. It divides the observations into two equal sides, one side to the left and one side to the right of the median. For an uneven number of observations (n) the median is the middle value and can be calculated as $\frac{n+1}{2}$, whilst for an even number there are two middle values calculated from $\frac{n}{2}$ and $\frac{n}{2}+1$ and the median is taken as the value in-between (Rosner, 2011: 9). A relative accumulative frequency polygon can also be constructed, and the median determined from $\frac{n}{2}$ irrespective if the observations are even or uneven in number (Das, 2009: 141).

3.9.1.1.6 Arithmetic mean (average)

The average ($\bar{x}$, if x is the variable) is one of the best-known and popular statistics and is calculated by the sum of all the observations in the data set, divided by the total number of measurements. The data set needs to be in the form of an interval- or ratio scale. The average is calculated with the following equation (Rosner, 2011: 8):

$$\bar{x} = \frac{1}{n} \times \sum_{i=1}^{n} x_i$$

Where: x = variable and n = the total number of observations.

3.9.1.1.7 Standard deviation

The standard deviation (SD) is the measure of the spread of the data that is most commonly used. It attempts to give the average distance of the observations from their arithmetic mean and is calculated with the following equation (Rosner, 2011: 17):

$$SD = \sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{n-1}}$$

Where: x = variable, n = the total number of observations, and $\bar{x}$ = arithmetic mean.

3.9.1.2 Inferential Statistics

Inferential statistics infer or make predictions about a population based on a sample from the given population (De Muth, 2006:1). This definition is summarised by Asadoorian & Kantarelis (2005: 2) as shown in figure 3–1:

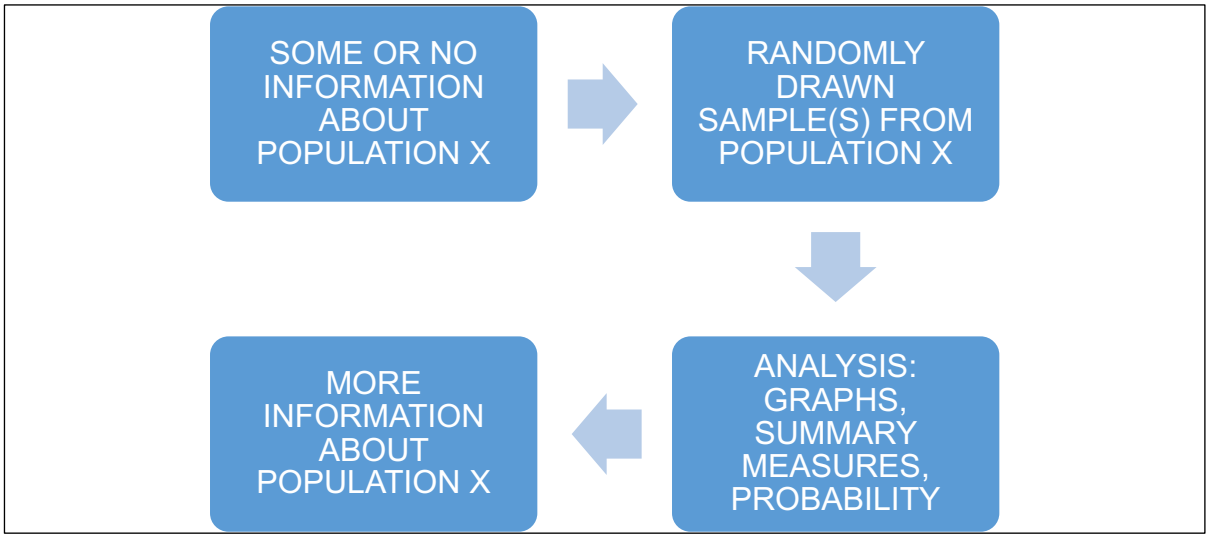

Figure 3–1. A summary of inferential statistics.

3.9.1.2.1 Chi-square test

The chi-square test (χ^2) determines whether there is an association between proportions of two or more categorical variables (Neuman, 2014: 424). The chi-square test can be used to analyse the difference between expected and observed distributions. The null hypothesis (H_0) states that there is no significant difference between these two distributions. The alternative hypothesis (H_1) states that there is a significant difference between the expected and observed data (Weaver *et al.*, 2017: 35). The larger the differences, the more likely the hypothesis is incorrect (Mendenhall *et al.*, 2012: 576). The following equation is the test statistic for the chi-square test (Mendenhall *et al.*, 2012: 576):

$$\chi^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

Where: O = observed value and E = expected value.

If the hypothesised expected cell counts are correct, the ($O_i - E_i$) are small and χ^2 is close to zero.

3.9.1.2.2 *P*-value

When the *p*-value is associated with the chi-squared test, it is indicating the probability that the differences between the expected and observed frequencies could be the result of a sampling error (Randolph & Myers, 2013). The larger the chi-square score,

the smaller the probability for the null hypothesis to be true. When the probability (*p*-value) is equal to or smaller than 0.05, the null hypothesis is rejected. This would conclude that the relationship between the observed and expected variables is statistically significant (Vaughan, 2001: 81).

In this study where the chi-square test returned a $p < 0.05$ (statistical significance), the Cramér's V value was calculated to determine the relative strength of the relationship between the 2 parameters compared.

3.9.1.2.3 Cramér's V

The phi coefficient and Cramér's V correct for sample size and measure the degree of association between two variables that are analysed by the chi-squared test. The phi coefficient is a useful statistic for large sample sizes where statistical significance is easily achievable. However, the Cramér's V is used for data in tables that are larger than 2 x 2 (Osborn, 2006: 260). The formula for Cramér's V is shown below (Warner, 2013: 334):

$$V = \sqrt{\frac{\chi^2}{n \times m}}$$

Where:

V = Cramér's V
n = The total number of cases
m = The minimum of (number of rows – 1),(number of columns-1)

The Cramér's V is useful in interpreting the relative strength of the association between two variables. Cramér's V value can range from 0 (no association) to 1 (perfect association) (Crewson, 2016). An interpretation of its strength of association is summarised in table 3–42 (adapted from Parker & Rea, 2005: 255):

Table 3–42. A description of the relative strength for the Cramér's V value

Cramér's V value	Relative strength
0.8 – 1.00	Very strong association
0.60 – 0.79	Strong association
0.40 – 0.59	Relatively strong association
0.20 – 0.39	Moderate association
0.10 – 0.19	Weak association
0.00 – 0.09	Negligible association

3.10 Ethical considerations

The research project made use of clinical data obtained retrospectively from patient files. There was no interaction with patients and the project was unobtrusive and non-invasive in nature. No patient identifiable information was recorded. The researcher conducted the study in an ethically sound manner during all phases of the study. This includes the conceptualisation, research and development phase, through the implementation and data collection phase.

3.10.1 Permission

Approval from the following institutions were obtained prior to the commencement of the study:

- Rhodes University Faculty of Pharmacy Higher Degrees Committee (ANNEXURE C).
- Rhodes University Faculty of Pharmacy Research Ethics Committee (PHARM-2018-04; ANNEXURE D).
- Fort England Hospital Research Committee (PHARM-2018-04; ANNEXURE E).
- Eastern Cape Department of Health Research Committee (EC_201808_009; ANNEXURE F).

Informed consent from patients was not necessary as the study used retrospective data from patient files.

3.10.2 Data management and storage

Data privacy and confidentiality were maintained at all times. Captured and processed data were stored on password-protected computers in locked offices, protected further by a firewall and the latest antivirus software.

3.10.2.1 During data collection

No patient file left the pharmacy and study site. The collected data from the patient files was only accessed and processed by the researcher and supervisors. Hard copies of the data collection forms as well as the electronic spreadsheet were kept safe during the study period with the researcher.

3.10.2.2 After study completion

All data was stored in a secure cabinet by the supervisor and it was only used for research purposes and not distributed to any other parties.

3.11 Limitations of the research method

Patient information in the files was often incomplete. This depended on the clinical documentation completed by the healthcare practitioners, or when the patient was referred from other healthcare facilities to Fort England Hospital for treatment. The data concerning the initiation of clozapine treatment was limited due to the information being available in the inpatient files, but not in the outpatient files. Some patients defaulted on their treatment and did not return to the hospital for follow-up visits or to collect their medication, which affected the completeness of the data.

3.12 Chapter 3 summary

This chapter provided an in-depth explanation of the methodology employed to conduct the DUR and to analyse the data. The ethical considerations were also explained. The following chapter will explore the results and discussion thereof.

CHAPTER 4. RESULTS AND DISCUSSION

4.1 Introduction

The results of the empirical study obtained with the data collection tool will be analysed, presented and discussed in this chapter.

The figures displayed in as percentages are rounded off to two decimal places.

4.2 Data collection tool

The data collection tool was used to gather the necessary data from the 57 patients that constituted the study sample. The results below were analysed to assess the prescribing and monitoring patterns of clozapine at Fort England Hospital in Grahamstown, Eastern Cape Province, South Africa.

4.2.1 Patient demographics

The demographical information of the patients in the study sample are analysed below.

4.2.1.1 Age

Table 4–1 depicts the age distribution of the study sample. The ages were categorised into age groups for ease of interpretation of the data.

Table 4–1. Age distribution of the study sample (n=57)

Age categories	n	Percentage (%)
> 18 and ≤ 29 years	10	17.54
≥ 30 and ≤ 38 years	17	29.82
≥ 39 and ≤ 47 years	16	28.07
≥ 48 and ≤ 56 years	11	19.30
≥ 57 and ≤ 65 years	3	5.26
> 65 years	0	0
Total	**57**	**100**

Most of the patients in the study sample were between the ages of 30 and 38 years old (n=17; 29.82%). The mean age of the patients in the sample was 39.79 ± 10.27 years. The youngest patient was 21 years and the oldest patient was 65 years old.

The literature has not been consistent with the effect of age on clozapine pharmacokinetics. There is evidence that the clozapine plasma concentration increases with increasing age (Ismail *et al.*, 2012: 57). The metabolism and excretion of an elderly patient (over the age of 65 years) is slower than that of a younger patient. This is due to the decreased efficacy of hepatic function, as well as a loss of nephrons resulting in decreased renal function (Martin, 2012: 142). Clinical trials are rarely conducted in elderly patients, which makes it more difficult to prescribe clozapine. Castberg *et al.* (2017: 9) suggested that elderly patients should only receive half the dose that is usually administered to the younger patients. The results show that this study sample did not include any patients over the age of 65 years. As a result the prescribing patterns of the patients did not have to be analysed for dosage alterations due to increasing age.

4.2.1.2 Gender

Figure 4–1 below is a representation of the gender distribution of the study sample.

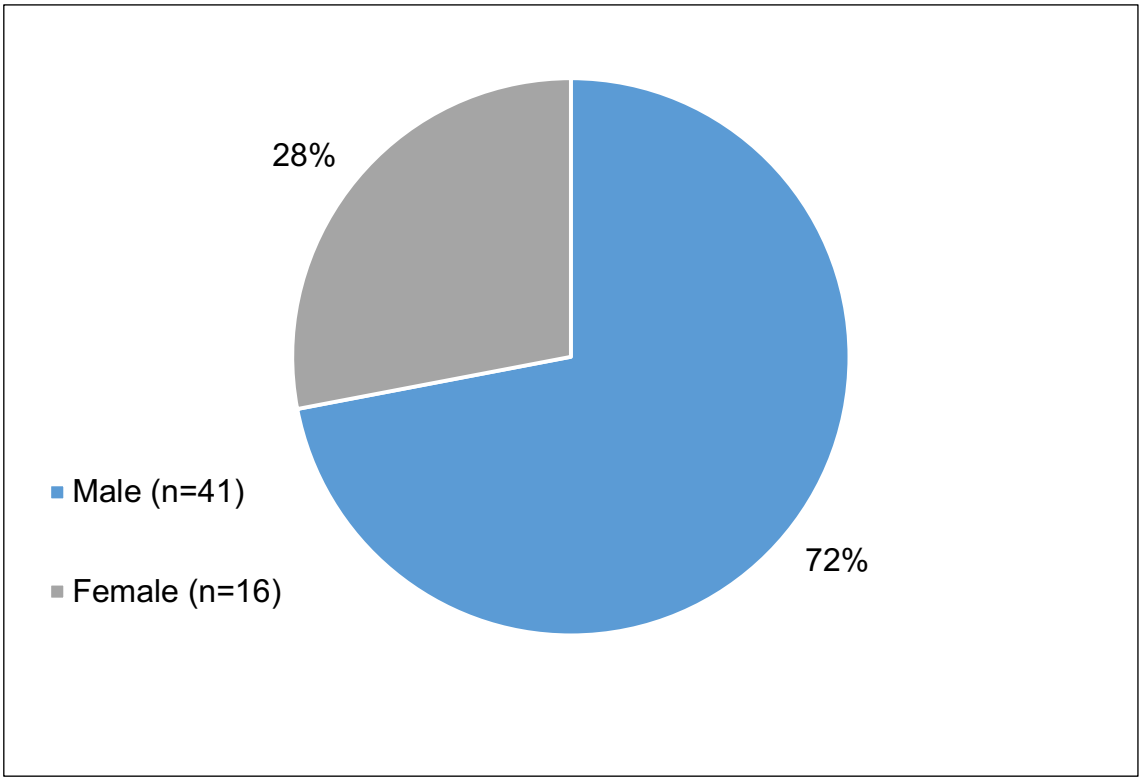

Figure 4–1. Gender distribution of the study sample (n=57)

Gender can affect the plasma concentration levels of clozapine. The literature has been consistent in stating that males are likely to have increased clozapine clearance,

and as a result have lower clozapine plasma concentration compared to females (Ismail *et al.*, 2012: 58). It has also been postulated that females have decreased CYP1A2 enzyme activity compared to males. This enzyme is a major enzyme in the metabolic pathway of clozapine (Frazier *et al*., 2003: 91). Most of the patients in the study sample were male (n=41; 72%). The average dosage of clozapine may have slightly higher average as a result of the larger male population.

In a study by Manteuffel *et al.* (2014: 112) the influence of gender on drug use was explored. The results of this study claimed that women were less likely to receive the recommended treatment stipulated in the national and professional clinical guidelines (Manteuffel *et al.*, 2014: 117). The treatment guidelines in this study were extensively explored to ensure that no gender biases played a role in the prescribing and monitoring patterns of the patients.

4.2.1.3 Age by gender

Table 4–2 below depicts the age by gender distribution for this study sample.

Table 4–2. Age by gender distribution of the study sample (n=57)

Age categories	Gender		Total
	Male n (%)	Female n (%)	n (%)
> 18 and ≤ 29 years	10 (100.00%)	0 (0.00%)	10 (100.00%)
≥ 30 and ≤ 38 years	14 (82.35%)	3 (17.65%)	17 (100.00%)
≥ 39 and ≤ 47 years	10 (62.50%)	6 (37.50%)	16 (100.00%)
≥ 48 and ≤ 56 years	6 (54.55%)	5 (45.45%)	11 (100.00%)
≥ 57 and ≤ 65 years	1 (33.33%)	2 (66.67%)	3 (100.00%)
> 65 years	0 (0.00%)	0 (0.00%)	0 (100.00%)
Total	**41 (100.00%)**	**16 (100.00%)**	**57 (100.00%)**

The onset of schizophrenia occurs at approximately 24.3 years of age in males and at approximately 27.5 years of age in females (Haffner *et al.*, 1994: 30). Females are late in the development of schizophrenia compared to males. A small study (n=45) in South Africa identified that the mean age of onset in patients diagnosed with schizoaffective disorder was 25 years (Singh & Subramaney, 2016: 3). The results obtained from the study show that the majority of the patients were males in the age group 30 to 38 years (n=14; 82.35%) and most of the females were in the age group 39 to 47 years (n=6; 37.50%). At this point in the development of schizophrenia, both genders would have likely experienced the first-episode and will be on maintenance doses of clozapine.

There were no elderly patients (>65 years of age) in the study sample. The elderly is more inclined to have an innately reduced hepatic metabolic function, resulting in lower hepatic clearance of drugs, as well as lower liver volume and decreased hepatic blood flow. Higher dosage-adjustments and consistent therapeutic drug monitoring are

necessary in the elderly (Castberg *et al.*, 2017: 6). Such dose-adjustments did not need to be explored in the empirical study.

Results from the chi-square test did not show statistical significance between age and gender (p=0.05).

4.2.1.4 Race distribution

The race distribution results obtained in the study sample is displayed in the graph in figure 4–2.

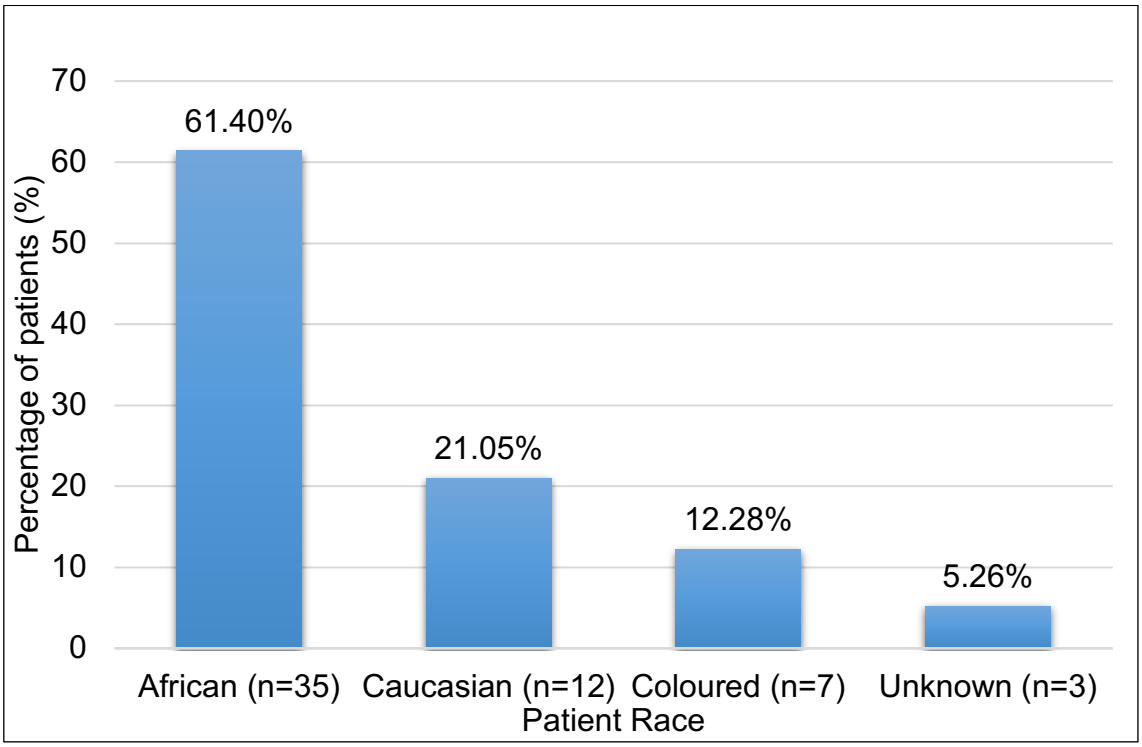

Figure 4–2. Race distribution of the study sample (n=57)

Results show that most of the patients were African (n=35; 61.4%). Ethnicity and race have an effect on the adverse effects profile of clozapine. Krakowski *et al.* (2009: 101) stated the importance of genetic polymorphisms and the differences of distribution of the 5-HT_{2C} and 5-HTTLPR receptor allele according to ethnicity and race. These alleles present certain adverse effects due to clozapine. Weight gain and aggression were the most prevalent adverse reactions in patients of African-American descent (Krakowski *et al.*, 2009: 101). A study concerning the "undiagnosed metabolic syndrome and other adverse effects among clozapine users of Xhosa descent" reveals that 44.8% of the population under study suffered from a metabolic adverse effect due

to clozapine administration (Faasen *et al.*, 2014: 56). Very minimal literature for African patients and the effect of their ethnicity on clozapine treatment is available. This is an area that needs vast research.

In the study sample, 3 patients did not have any data present to determine their race category, and therefore their race was categorised as Unknown.

4.2.1.5 Age by race

Table 4–3 depicts the age by race distribution of the study sample.

Table 4–3. Age by race distribution of the study sample (n=57)

Age categories	Race				Total n (%)
	African n (%)	Caucasian n (%)	Coloured n (%)	Unknown n (%)	
> 18 and ≤ 29 years	9 (90.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)	10 (100.00%)
≥ 30 and ≤ 38 years	10 (58.82%)	4 (23.53%)	2 (11.76%)	1 (5.88%)	17 (100.00%)
≥ 39 and ≤ 47 years	11 (68.75%)	3 (18.75%)	1 (6.25%)	1 (6.25%)	16 (100.00%)
≥ 48 and ≤ 56 years	5 (45.45%)	3 27.27%)	2 (18.18%)	1 (9.09%)	11 (100.00%)
≥ 57 and ≤ 65 years	0 (0.00%)	2 (66.67%)	1 (33.33%)	0 (0.00%)	3 (100.00%)
> 65 years	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (100.00%)
Total	**35 (100.00%)**	**12 (100.00%)**	**7 (100.00%)**	**3 (100.00%)**	**57 (100.00%)**

The results obtained from the relationship between age and race show that the majority of the African patients were in the age group 39 to 47 years (n=11; 68.75%). Amongst the Caucasian patients, the majority of them were in the age range of 30 to 38 years (n=4; 23.53%). In both of these races, the majority of the patients were at

their prime employable and reproductive ages. The effects of clozapine on these factors were considered in sub-sections 4.2.2.5 and 4.2.3.4.

Results of the chi-square test show that a comparison of age and race was not statistically significant (p=0.53).

4.2.2 Social History

4.2.2.1 Smoking status

Table 4–4 depicts the results of the smoking status of the sample population.

Table 4–4. Smoking status of the study sample (n=57)

Smoking status	n	Percentage (%)
Smoker	5	8.77
Non-smoker	2	3.51
No information	50	87.72
Total	**57**	**100**

The literature states how tobacco smoke contains polycyclic hydrocarbons which induce the enzyme CYP1A2 (Gee *et al*., 2017: 79). This enzyme is also responsible for the hepatic metabolism of clozapine. Smoking tobacco results in decreased plasma concentrations of clozapine which in turn decreases the efficacy of the drug therapy (Gee *et al*., 2017: 79). Unfortunately, there was no information on the smoking status for the majority of the patients in the study sample (n=50; 87.72%). This is a cause for concern for the accurate prescribing and monitoring practices for clozapine therapy. Smokers may need to be prescribed higher dosages of clozapine to ensure therapeutic efficacy. Monitoring the plasma levels of clozapine in smokers is necessary in order to adjust the dosage to meet the therapeutic requirements. Careful monitoring of clozapine plasma concentration upon smoking cessation is essential particularly within the first 14 days, as an exponential increase in plasma concentration levels may occur (Meyer, 2001: 572, Meyer 2007: 8). Without any information on tobacco use, these practices will not be employed. The NICE guidelines include smoking cessation as one of the necessary interventions during schizophrenia treatment (National Institute for Health and Care Excellence, 2015: 35).

4.2.2.2 Alcohol use

Figure 4–3 summarises the results of the patients in the study sample who used alcohol.

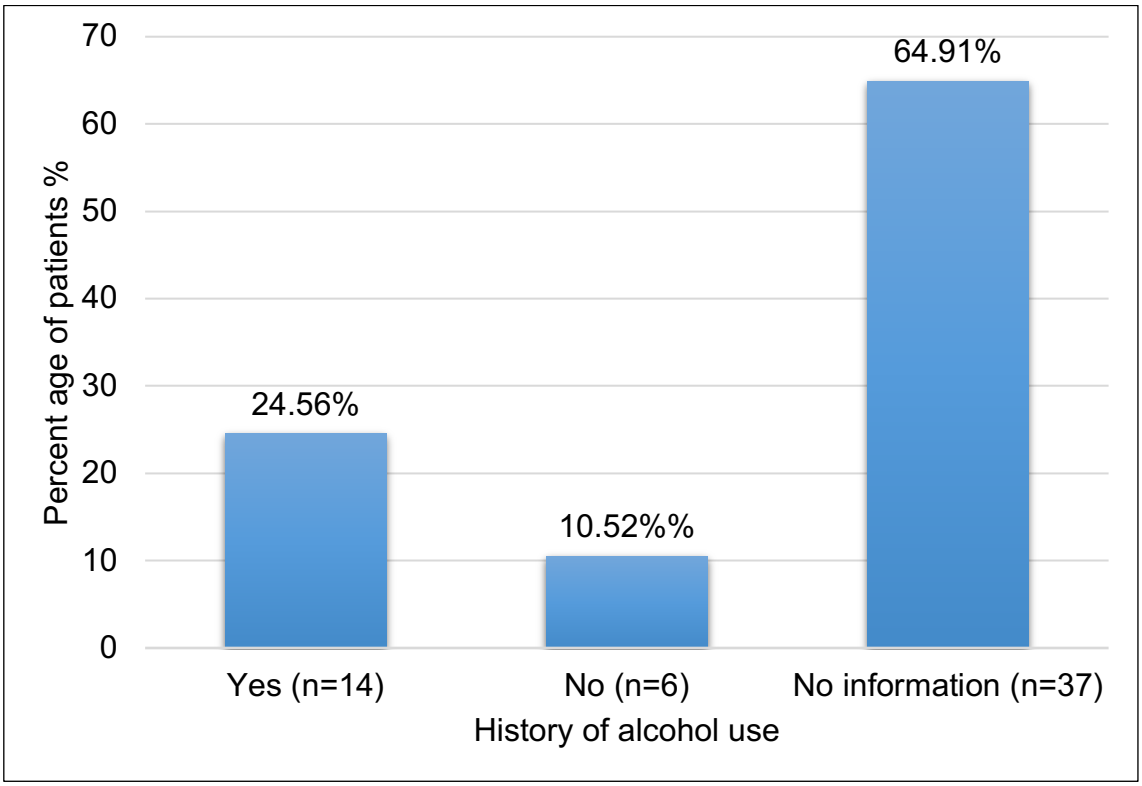

Figure 4–3. History of alcohol use (n=57)

The concomitant use of alcohol whilst on clozapine treatment is not recommended. Alcohol and SGAs, including clozapine, are CNS depressants (Karalliedde *et al.*, 2010: 252). Therefore the additive effects of alcohol on the sedative effects of clozapine cause excessive sedation in the patient (Karalliedde *et al.*, 2010: 252; Kennedy *et al.*, 2013: 1025). There was insufficient information for the majority of the patients in the study sample to determine their alcohol habits (n=37; 64.91%). The lack of information is a cause for concern as patients may be prescribed clozapine without the knowledge of the effects of alcohol on clozapine treatment.

4.2.2.3 Substance abuse

Table 4–5 depicts the results of the substance abuse amongst the study sample.

Table 4–5. History of substance abuse in the study sample (n=57)

Substance	n	Percentage (%)
None	37	64.91
Cannabis	12	21.05
Cannabis and methamphetamine	3	5.26
Methaqualone	1	1.75
Cannabis, methaqualone and methamphetamine	1	1.75
Cannabis, methaqualone and glue	1	1.75
Methaqualone and methamphetamine	1	1.75
Cannabis and methaqualone	1	1.75
Total	**57**	**100**

Psychiatric symptoms of schizophrenia, particularly the positive symptoms, are often aggravated by substance abuse (Margolese *et al*., 2004: 158). It is evident that the majority of the patients in the study sample had no history of substance abuse (n=37; 64.91%). Patient history is important in understanding the aetiology of the condition and the most beneficial treatment plan to prescribe. Clozapine has been found to be beneficial in treating schizophrenic patients with comorbid substance abuse, and patients with a history of substance abuse. These patients are responsive to clozapine treatment (Kelly *et al.*, 2003: 111).

The most common substance abused amongst the remaining patients in the study sample was cannabis (dagga) (n=12, 21.05%). It has been postulated that the use of dagga in the adolescent phase may predispose the person to developing early-onset schizophrenia. With regard to antipsychotic therapy, cannabis may also limit the effectiveness of the antipsychotic drug (Tandon *et al.*, 2009: 11). Information regarding substance abuse is a vital aspect to be considered for accurate prescribing on clozapine.

4.2.2.4 Suicide risk

Table 4–6 shows the number of patients who were at risk of suicide in the study sample.

Table 4–6. History of suicide risk in the study sample (n=57)

Suicide risk	n	Percentage (%)
Yes	12	21.05
No	1	1.75
No information	44	77.19
Total	**57**	**100**

The majority of the patients in the study sample had no information regarding any risk of suicide. Suicide risk is a factor that needs to be explored in the patient history. The incidence of attempted suicide has been reported to occur at least twenty times more frequently in patients suffering from schizophrenia, and it is estimated to be completed in 10% of all sufferers (Siris, 2001: 127). Clozapine has demonstrated its usefulness in preventing suicide attempts in patients with schizophrenia and schizoaffective disorder. As a result of clozapine treatment, there is reduced suicidal behaviour prevalent in these populations (Meltzer *et al.*, 2003: 82).

4.2.2.5 Occupation

Figure 4–4 shown depicts the occupational status of the patients in this study sample.

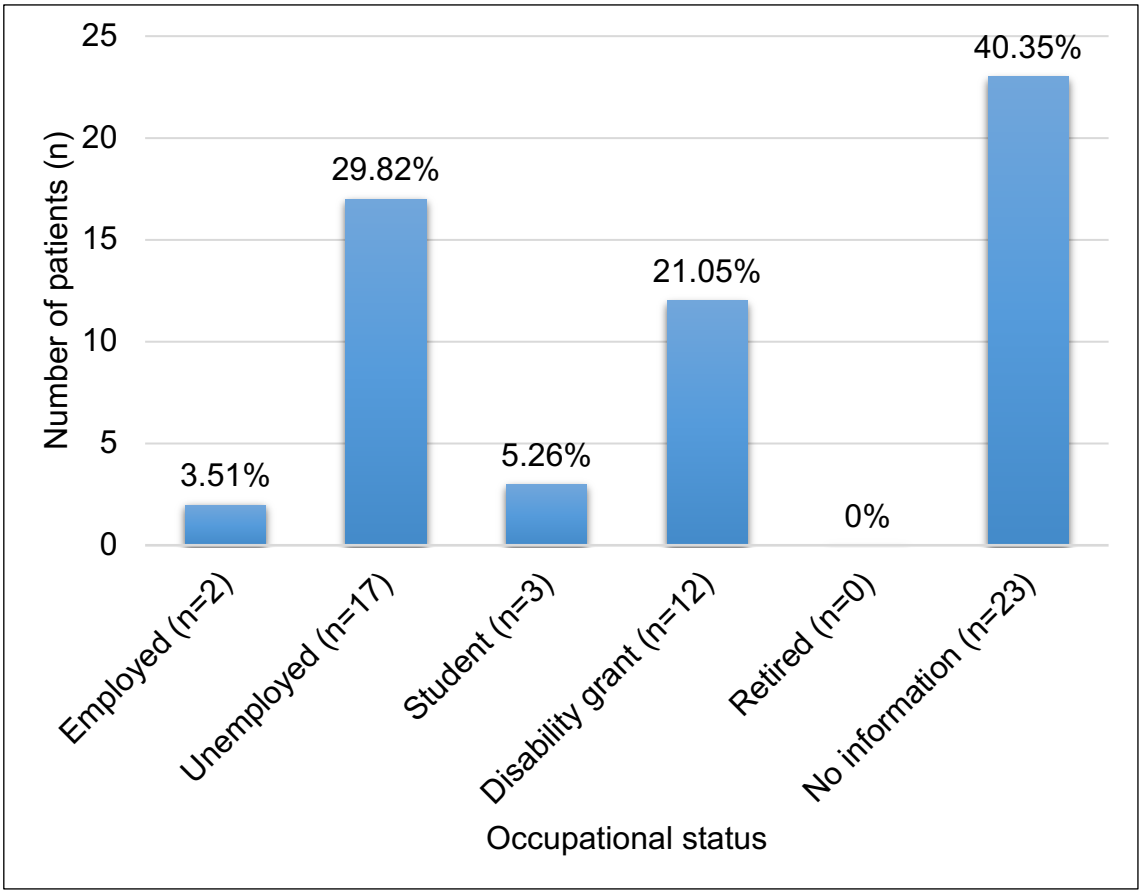

Figure 4–4 Occupational status of patients in the study sample (n=57)

There was no information regarding the occupational status for 40.35% (n=23) of the patients. The majority of the remaining patients were unemployed (n=17; 29.82%). The active employment age group within the South African population is between 15 and 64 years (Statistics South Africa, 2013). The results obtained from the relationship between age and race show that the majority of the African patients were in the age group 39 to 47 years (n=11; 68.75%). Nationwide, African males constitute for 42.7% of the economically active population (EAP). Specifically in the Eastern Cape, 42.3% of African males make up the EAP (Department of Labour, 2018: 13–14). The results of the occupation status of the participants were not expected. However the literature does state that clozapine treatment can affect patient's lifestyle, including their employability, job tenancy and work productivity (Percudani *et al.,* 2004: 708). It is a common phenomenon for patients on clozapine to be marginalised in the employment sector due to their diagnosis or therapy. The WHO Mental Health Action Plan 2013-2020 advocates for the inclusion of mental health patients within development and

poverty-reduction strategies, such as education and employment (World Health Organization, 2013: 13).

4.2.2.6 Marital status

Table 4–7 shows the marital status of the study sample.

Table 4–7. Marital status of patients in the study sample (n=57)

Marital status	n	Percentage (%)
Single	24	42.11
Married	2	3.51
Divorced or separated	4	7.02
No information	27	47.37
Total	**57**	**100**

Clozapine treatment has a social and emotional impact on not only the patient, but also their family members. The success of the outcome of the patient's treatment is also dependent on the family's outlook. Any conflict concerning the treatment can further exacerbate underlying tensions within the family system or marriage covenants (Kotcher & Smith, 1993: 745). Unfortunately, there was no information regarding the marital status for approximately half of the patients in the study sample (n=27; 47.37%). The majority of the remaining patients were single (n=24; 42.11%). The marital statuses of patients can be explored in further studies which have more data, to gain understanding of the effects of relationships on clozapine therapy.

4.2.3 Medical history

4.2.3.1 Hospital admissions

The number of hospital admissions were categorised into two as shown in table 4–8.

Table 4–8. Number of previous hospital admissions (n=57)

Number of hospital admissions	n	Percentage (%)
≤ 10	17	29.82
> 10	18	31.58
Undefined	22	38.60
Total	**57**	**100**

It was not clear for the majority of patients in the study sample how many previous hospital admissions they had (n=22; 38.60%). A study by Kirwan *et al.* (2017: 3) concluded that there is a statistically significant association between initiation of clozapine and a reduction in the number of both hospital admissions and days spent in hospital, as compared to other antipsychotic therapies. A limitation to the study was the relatively small sample size (n=62). However, future extensive studies using data, such as that obtained in this current study, could be done to assess the effects of clozapine on the frequency of hospital admissions. None of the patients in this study were admitted into hospital during the study period.

4.2.3.2 Hospital or surgical history

All the patients were assessed for any previous hospital or surgical history, including minor procedures independent of any mental illness. Figure 4–5 summarises the results.

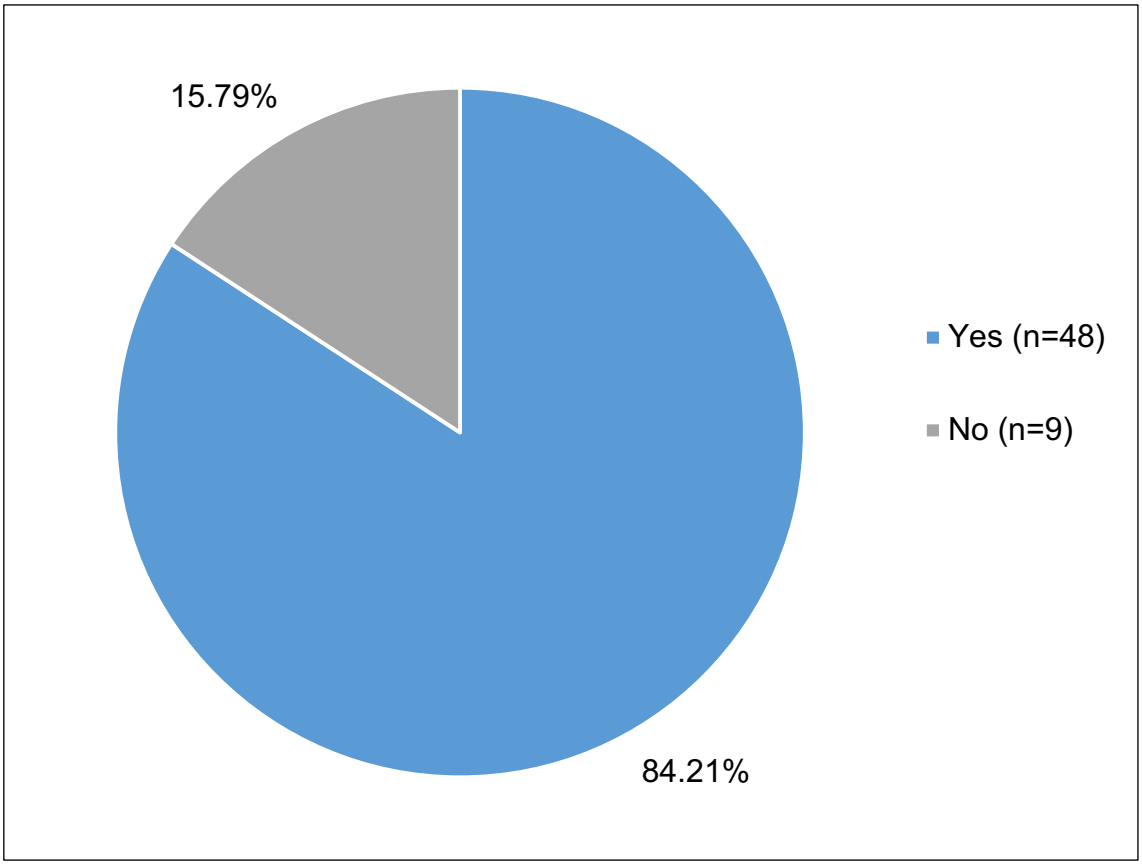

Figure 4–5. Hospital or surgical history (n=57)

The majority of patients in the study sample had a hospital/surgical history (n=48; 84.21%). Some of these procedures included a bladder suspension operation, an above knee amputation and a hysterectomy. Hospital and surgical history is useful in understanding the factors that may culminate to affect prescribing or monitoring of clozapine.

4.2.3.3 Family history of mental illness

Table 4–9 depicts the results concerning the information of the family history of the participants.

Table 4–9. Family history of mental illnesses (n=57)

Family History	n	Percentage (%)
Yes	5	8.77
No	0	0.00
No information	52	91.23
Total	**57**	**100**

Minimal information on the family history of the participants was found, with the majority of the patient files missing this information (n=52; 91.23%). This not a suitable outcome as research has shown that family history is important in understanding the aetiology of schizophrenia in some patient cases. There is evidence that the condition could possibly be hereditary. This information would be valuable in predicting the early onset of the condition (Nuhu *et al.*, 2016: 284). Family history also allows for greater family support as they are more likely to be understanding of the diagnosis and its therapy. The NICE guidelines include family intervention as part of the psychological therapies for treating psychosis and schizophrenia. This intervention would improve the coping mechanisms of the patients and decrease the rate of relapse of patients taking clozapine (National Institute for Health and Care Excellence, 2015: 21).

4.2.3.4 Pregnancy status

Clozapine is categorised as a category B drug, which does not confirm any evidence of harm to the foetus. None of the patients in the study sample were pregnant, therefore no monitoring patterns are assessed.

4.2.3.5 Breastfeeding status

There were no patients breastfeeding in the study sample. This variable was explored because clozapine is found in relatively high concentrations in breast milk. As a result the presentation of adverse effects of clozapine by the drug may be visible in the neonate (Gentile, 2004: 1268).

4.2.3.6 Allergies

The following pie chart (illustrated in figure 4–6) depicts the proportion of patients who had allergies in the study sample.

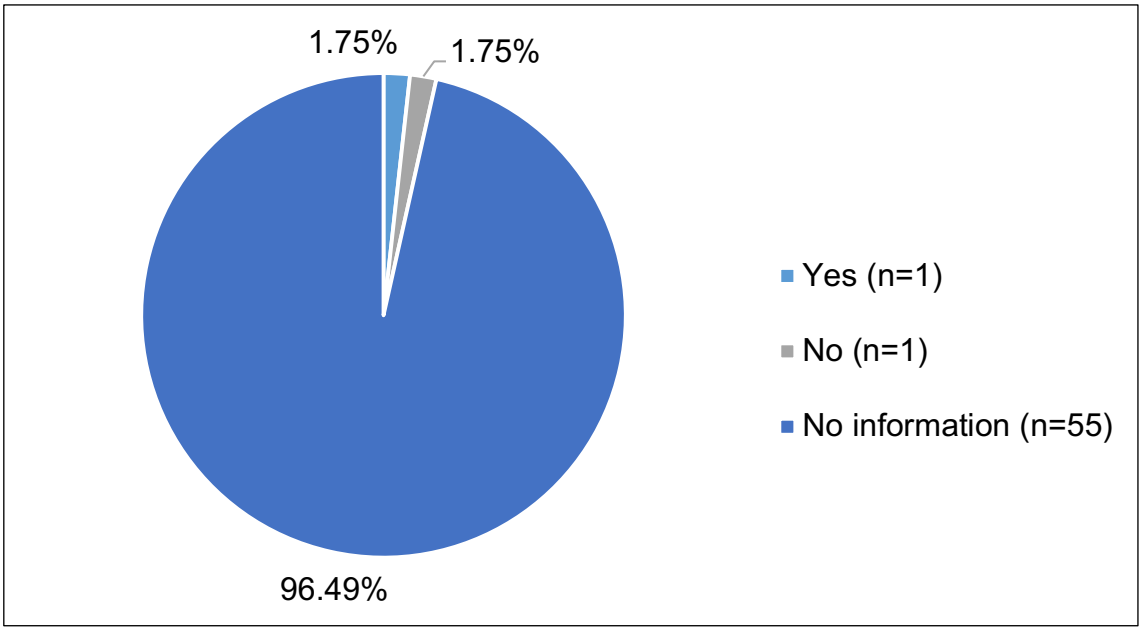

Figure 4–6. Patients who had any medication allergies (n=57)

One patient had a drug allergy confirmed, which was for penicillin. The remaining patients (n=55; 96.49%) did not have any information regarding allergies. The occurrence and evidence of drug allergies of antipsychotic drugs are not well known (Nurenberg and Schleifer, 2009: 491). Future studies on the allergies of clozapine and other antipsychotic drugs may be explored to ensure the safe use and monitoring of clozapine therapy.

4.2.3.7 Porphyria

Table 4–10 below analyse the amount of people experiencing porphyria in the study sample.

Table 4–10. Porphyria occurrence in the study sample (n=57)

Porphyria	n	Percentage (%)
Yes	0	0.00
No	1	1.75
No information	56	98.25
Total	**57**	**100**

There was no information regarding porphyria for the majority of patients (n=56; 98.25%). Porphyria shares common symptoms with psychiatric disorders, such as

schizophrenia, therefore it may be disguised as psychosis (Burgoyne *et al.*, 1995: 121). The lack of information regarding any history or diagnosis of porphyria is a cause of concern.

4.2.3.8 Past medical conditions

The most common past medical conditions experienced in the study sample are shown in table 4–11.

Table 4–11. Past medical conditions (n=57)

Past medical conditions	n	Percentage (%)
None	33	57.89
Polysubstance abuse disorder	1	1.75
Major depressive disorder/depressive episode	3	5.26
Alcohol abuse disorder	1	1.75
Psychosis/psychotic disorder	3	5.26
Movement disorder	1	1.75
Bipolar mood disorder	1	1.75
Major depressive disorder/depressive episode and personality disorder	1	1.75
Mood disorder	1	1.75
Major depressive disorder/depressive episode, metabolic disorder and other disorders	1	1.75
Bipolar mood disorder and psychosis/psychotic disorder	1	1.75
Bipolar mood disorder and other disorder	1	1.75
Polysubstance abuse disorder and psychosis/psychotic disorder	1	1.75
Polysubstance abuse disorder and cannabis-induced psychosis	1	1.75
Polysubstance abuse disorder and metabolic disorder	1	1.75
Personality disorder and movement disorder	1	1.75
Other disorders	5	8.77
Total	**57**	**100**

There were no reports on the past medical conditions for the majority of the patients (n=33; 57.89%). Schizophrenia and affective disorders such as schizoaffective disorders, psychotic depression, bipolar illness and atypical psychosis are all distinct diagnostic entities (Somnath *et al.*, 2002: 243). However, there is a significant overlapping of underlying clinical syndromes when these functional psychoses are considered (Marneros & Akiskal, 2006: 55). This may account for the previous diagnoses of mood and affective disorders seen in this study sample. A study based in KwaZulu-Natal, South Africa, exploring substance abuse amongst adults with a severe mental illness portrayed that the majority of the patients in the study sample were diagnosed with schizophrenia (Davis *et al.*, 2016: 3). The study also suggested that some illicit drugs can induce psychosis in individuals who were not previously diagnosed with a mental illness (Davis *et al.*, 2016: 5). This was discussed briefly in sub-section 2.3.3.2.3. Poly-substance abuse disorder and cannabis-induced psychosis was evident in the past medical histories' of some patients in the study sample.

4.2.3.9 Co-morbid diseases

Some patients had the following co-morbid diseases during the study period (illustrated in table 4–12).

Table 4–12. Co-morbid diseases in the study sample (n=57)

Co-morbid diseases	n	Percentage (%)
None	20	35.09
Personality disorder	1	1.75
Hypertension	1	1.75
Metabolic or endocrine disorders	5	8.77
Depressive disorder or depressive episode	3	5.26
Movement disorders	3	5.26
Alcohol abuse disorder	1	1.75
Polysubstance abuse disorder	2	3.51
Mood disorder	1	1.75
Bipolar mood disorder	1	1.75
Personality and Retroviral disease (RVD)	1	1.75

Co-morbid diseases	n	Percentage (%)
Hypertension and RVD	1	1.75
Hypertension and Diabetes Mellitus	1	1.75
Hypertension, metabolic or endocrine disorders and gastro-intestinal disorder	1	1.75
Cannabis use disorder and hypertension	1	1.75
Cannabis use disorder and polysubstance abuse disorder	1	1.75
Cannabis use disorder and metabolic or endocrine disorder	1	1.75
Cannabis use disorder and movement disorders	1	1.75
Polysubstance abuse disorder and metabolic or endocrine disorders	1	1.75
Metabolic or endocrine disorders and Diabetes Mellitus II	3	5.26
Metabolic or endocrine disorders and movement disorders	1	1.75
Metabolic or endocrine disorders and nephrological or urological disorders	1	1.75
Metabolic or endocrine disorders and behavioural disorders	1	1.75
Hypertension, metabolic or endocrine disorders, movement disorders and RVD	1	1.75
Nephrological or urological disorders and gastro-intestinal disorders	1	1.75
Alcohol abuse disorder, metabolic or endocrine disorders, CVS disorders and movement disorders	1	1.75
Hypertension, Diabetes Mellitus II, CVS disorders, movement disorders and nephrological and urological disorders	1	1.75
Total	**57**	**100**

The results indicate that most patients had no reported co-morbid disease states alongside their primary diagnosis (n=20; 35.09%). This was followed by metabolic or

endocrine disorders (n=17; 29.82%). One of the most common adverse effects of clozapine is metabolic syndrome and weight gain. Hypersalivation is also highly likely to be prevalent as an adverse effect of clozapine therapy (Citrome & Volavka, 2002: 164–165). Therefore, the most prevalent co-morbid diseases states of the participants in the study could be as a result of clozapine adverse effects.

4.2.4 Diagnosis

4.2.4.1 Differential diagnosis

The primary diagnosis of the patients in the study sample is summarised in table 4–13.

Table 4–13. Primary diagnosis of participants in the study sample (n=57)

Diagnosis	n	Percentage (%)
Schizophrenia	52	91.23
Schizoaffective disorder	1	1.75
Bipolar disorder with psychotic features	1	1.75
Schizophrenia and schizoaffective disorder	1	1.75
Schizophrenia and bipolar disorder with psychotic features	1	1.75
Schizoaffective disorder and bipolar disorder with psychotic features	1	1.75
Total	**57**	**100**

Clozapine is indicated for the treatment of treatment-resistant schizophrenia (Rossiter, 2016: 481). The most common diagnosis amongst the patients in the study sample was schizophrenia (n=54; 94.74%). These findings from the empirical study are expected.

The NICE guidelines stipulate that schizoaffective disorder adopts the same treatment guidelines for that of schizophrenia (National Institute for Health and Care Excellence, 2015: 6). Therefore, in some cases of schizoaffective disorder, clozapine is the recommended therapeutic drug choice. Clozapine is also the drug of choice for treatment-resistant bipolar disorder and violent aggressive patients with psychosis as well as other brain disorders not responsive to other treatments (Ayano, 2016: 3).

4.2.4.2 Diagnosis by race

The diagnosis by race distribution was analysed for the study sample (illustrated in table 4–14).

Table 4–14. Diagnosis by race distribution for the study sample (n=57)

Diagnosis	Race				Total
	African n (%)	Caucasian n (%)	Coloured n (%)	Unknown n (%)	n (%)
Schizophrenia	33 (61.11%)	12 (22.22%)	6 (11.11%)	3 (5.56%)	54 (100.00%)
Schizoaffective disorder	2 (66.67%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	3 (100.00%)
Bipolar with psychotic features	2 (66.67%)	1 (33.33%)	0 (0.00%	0 (0.00%)	3 (100.00%)
Total	**35 (100.00%)**	**12 (100.00%)**	**7 (100.00%)**	**3 (100%)**	**57 (100.00%)**

Treatment-resistant schizophrenia is the main indication for the use of clozapine (Remington *et al*., 2017: 610). The majority of the patients in the study sample was diagnosed with schizophrenia (n=54; 94.74%). The findings of the relationship between diagnosis and race distribution were expected as schizophrenia was the most prevalent diagnosis across all the races in the study sample. The majority of the patients in the study sample (61.40%) were of African descent, therefore it was also expected that Africans would represent the highest prevalence of schizophrenia in study.

Results of the chi-square test show that a comparison between diagnosis and race was not statistically significant (p=0.42).

4.2.4.3 Subtypes of schizophrenia

Table 4–15 depicts the different subtypes of schizophrenia that the patients were diagnosed with.

Table 4–15. Subtypes of schizophrenia in the study sample (n=57)

Type of schizophrenia	n	Percentage (%)
Paranoid	14	24.56
Disorganised	6	10.53
Treatment-resistant	11	19.30
Paranoid and treatment-resistant	3	5.26
Paranoid and disorganised	1	1.75
Paranoid and catatonic	1	1.75
Disorganised and treatment-resistant	1	1.75
Disorganised and catatonic	1	1.75
Undefined	19	33.33
Total	**57**	**100**

The most common subtype of schizophrenia amongst the patients in the study sample was the paranoid type (n=14; 24.56%). Treatment-resistant schizophrenia was prevalent in 26.32% of the study sample (n=15). The DSM-5® has eliminated the schizophrenia subtypes as they do not give an accurate description of the heterogeneity of schizophrenia (Tandon *et al.*, 2013: 5). Despite of this, the subtypes were still explored in this study to ascertain the number of patients who were diagnosed with treatment-resistant schizophrenia as well as to explore the diverse subtypes that are treated by clozapine.

4.2.4.4 Positive, negative and cognitive symptoms

Tables 4–16 to 4–18 outlines the distribution of the positive, negative and cognitive symptoms experienced by the patients in the study sample.

Table 4–16. Positive symptoms experienced (n=57)

Positive symptoms	n	Percentage (%)
None	24	42.11
Hallucinations	4	7.02
Delusions	4	7.02
Thought disorders	4	7.02
Movement disorders	1	1.75
Hallucinations and delusions	3	5.26
Hallucinations, delusions and thought disorders	3	5.26
Hallucinations, delusions and other symptoms	4	7.02
Hallucinations, thought disorders and other symptoms	1	1.75
Hallucinations and other symptoms	1	1.75
Delusions and thought disorders	1	1.75
Delusions and other symptoms	1	1.75
Thought disorders, movement disorders and other symptoms	1	1.75
Other symptoms	5	8.77
Total	**57**	**100**

Results show that hallucinations, delusions and thought disorders or combinations thereof were the most frequently experienced. This outcome was expected, as clozapine is superior in alleviating positive symptoms of schizophrenia (Remington *et al*., 2017: 610).

Table 4–17. Negative symptoms experienced (n=57)

Negative symptoms	n	Percentage (%)
None	37	64.91
Blunted affect	2	3.51
Avolition	3	5.26
Blunted affect and reduced speech	3	5.26
Blunted affect and avolition	1	1.75
Blunted affect, avolition and other symptoms	2	3.51
Avolition and reduced speech	1	1.75
Avolition and other symptoms	5	8.77
Blunted affect and other symptoms	1	1.75
Other symptoms	2	3.51
Total	**57**	**100**

It is evident that the most common negative symptom experienced in the study sample was avolition (n=12; 21.05%). Clozapine is more beneficial than conventional antipsychotics in the treatment of negative symptoms of TRS (Khan & Zaidi, 2017: 1).

Table 4–18. Cognitive symptoms experienced (n=57)

Cognitive symptoms	n	Percentage (%)
None	42	73.68
Poor executive functioning	2	3.51
Poor executive functioning and other symptoms	2	3.51
Poor working memory and symptoms	1	1.75
Poor attention and poor working memory	2	3.51
Poor attention and other symptoms	1	1.75
Other symptoms	7	12.28
Total	**57**	**100**

Poor executive functioning was the most common cognitive symptom experienced in the study sample (n=4; 7.02%). Improvement of cognitive functioning has been conveyed after 6 weeks of clozapine therapy in patients diagnosed with TRS (Hagger *et al.*, 1993: 707).

4.2.5 Clozapine usage

4.2.5.1 Previous clozapine usage

The patient files were analysed for any information on the prior use and termination of clozapine treatment before the study period (illustrated in table 4–19).

Table 4–19. Previous clozapine treatment (n=57)

Previous clozapine treatment	n	Percentage (%)
Yes	6	10.53
No	45	78.95
No information	6	10.53
Total	**57**	**100**

A total of 6 patients (10.53%) were on previous clozapine treatment that was terminated. The circumstances of the previous cease of clozapine therapy were not investigated in this study. Future studies can explore the reasons for a clozapine rechallenge. An estimated 17% of patients who use clozapine end up withdrawing from their treatment due to the adverse effects experienced (Newman & Newman, 2016a: 40). Adverse effects could have been a contributing factor to the withdrawal of patients from clozapine. A clozapine rechallenge is typically viable in patients who do not experience life-threatening adverse effects (Ittasakul *et al.*, 2016: ON1). A study by Davis *et al.* (2014: 32,37) showed that discontinuation of clozapine treatment was most likely to occur in over 50% of all patients between 3 and 6 months after initiation. The results portrayed a much smaller proportion as opposed to the literature.

4.2.5.2 Current clozapine treatment

Titration upon initiation of clozapine treatment was analysed in the study sample and the results are depicted in figure 4–7.

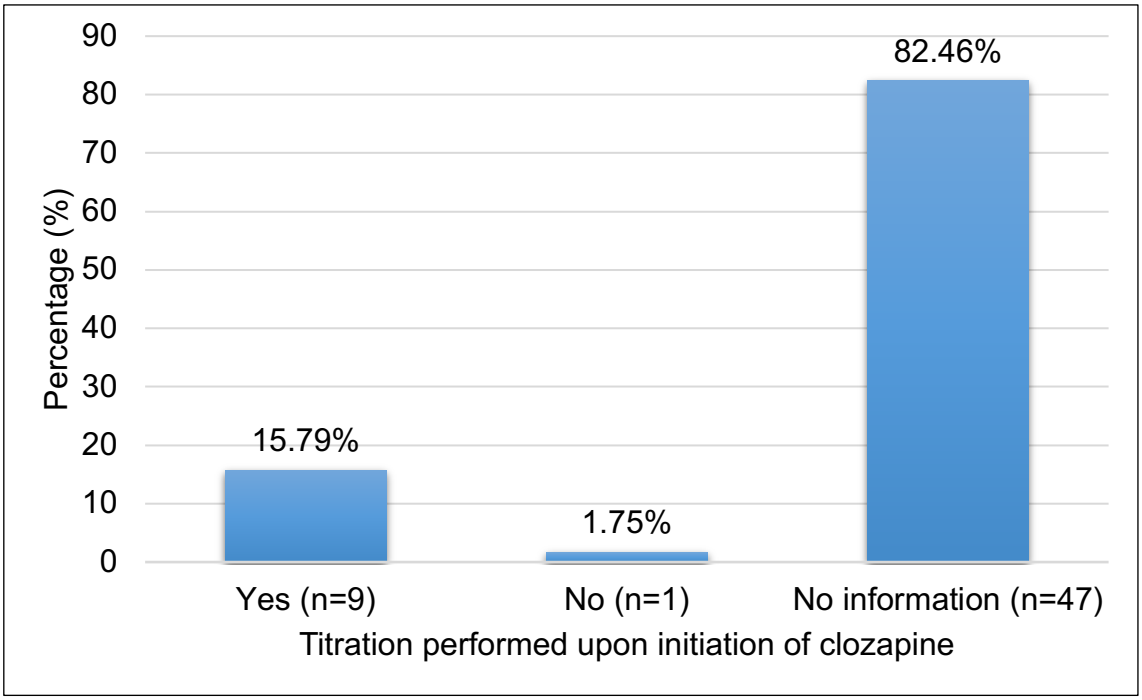

Figure 4–7. Titration performed upon initiation (n=57)

The results show that 82.46% (n=47) of the patients had no information concerning titration of clozapine upon initiation of the treatment. It was assumed that a substantial amount of data concerning the initiation of clozapine by titration was in the inpatient file in some cases. Titration of doses can reach a maximum of 500 mg/day within the first two weeks of treatment, and an overall maximum of 900 mg/day at maintenance therapeutic doses (Novartis Pharmaceuticals Corporation, 2014: 29).

Titration was performed upon initiation of clozapine treatment in 15.79% (n=9) of the study sample. Although titration data was found for a small proportion of the study sample, the dosing intervals were not adhered to as recommended in the Southern Health Clozapine Guidelines titration chart (Southern Health NHS Foundation Trust, 2018: 39). The prescribing patterns of the initiation of clozapine were no explored extensively in this study as a result of limited data.

4.2.5.2.1 Duration of clozapine treatment

The information on the average duration of clozapine treatment was only available in 52 patient files. The average time that a patient was on clozapine treatment since their initiation was 6.69 ± 5.43 years. The median was found to be 6.00 years. The

minimum and maximum number of years that a patient were on clozapine treatment was 0.20 and 22.00 years respectively.

4.2.5.2.2 Clozapine dosage

The dosages of each patient in the study sample were analysed and a summary of the findings are depicted in table 4–20.

Table 4–20. Clozapine dosage summary (n=57)

	Maximum dosage	Maintenance dosage
n	57	57
Mean (mg)	352	295
Standard deviation (mg)	134.50	116.20
Median (mg)	350	300
Minimum (mg)	100	100
Maximum (mg)	600	600

Titration of doses can reach a maximum of 500 mg/day within the first two weeks of treatment, and an overall maximum of 900 mg/day at maintenance therapeutic doses (Novartis Pharmaceuticals Corporation, 2014: 29). The average dose for clozapine treatment is 250-450 mg daily for effective treatment (Semple & Smyth, 2013: 212). The results obtained in the study concerning the average maximum and maintenance dosages were within the ranges recommended in the literature. This indicates that the patients were well controlled on dosages that ensure the safe use of the drug. The frequency of seizure occurrence is significantly increased at doses greater than 600 mg/day, (Semple & Smyth, 2013: 212). None of the patients in the study sample had doses that exceeded 600 mg/day, therefore no patients were predisposed to experiencing seizures.

4.2.6 Adverse effects

4.2.6.1 Reported adverse effects

Reports on any adverse effect caused by clozapine treatment was analysed in the study sample as illustrated in figure 4–8.

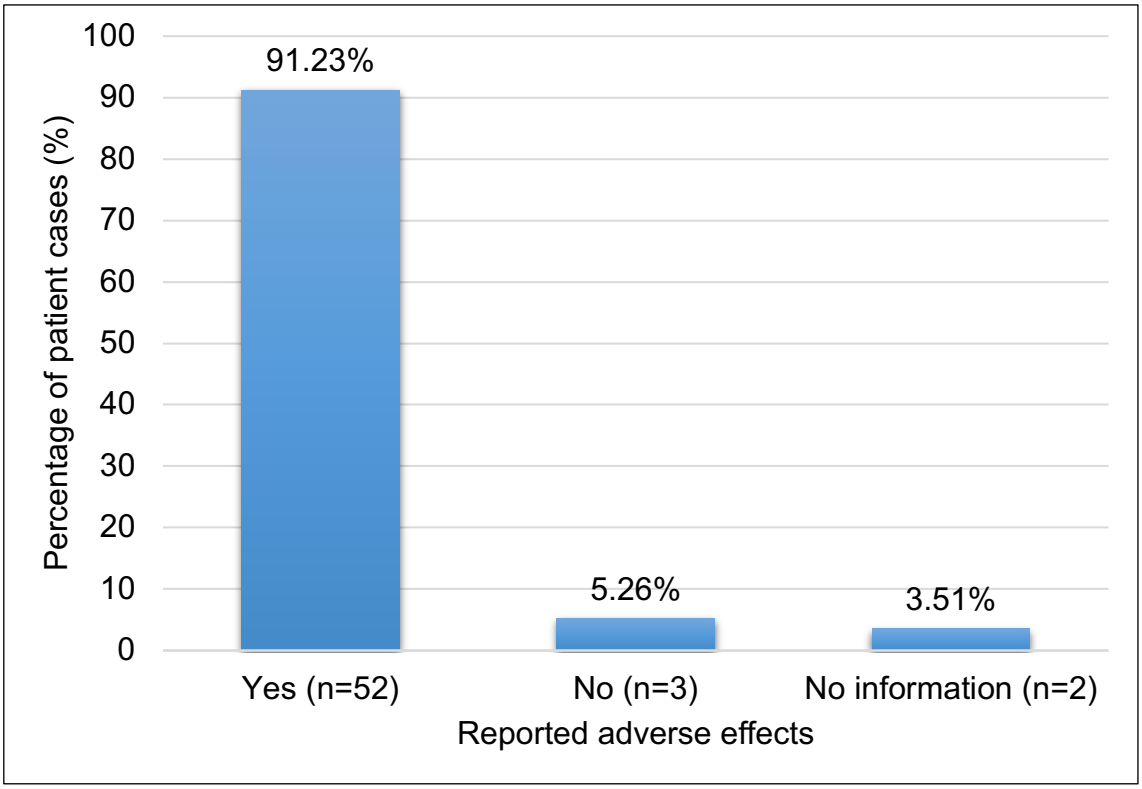

Figure 4–8. Reported adverse effects (n=57)

A total of 52 patients (91.23%) had an adverse effect of clozapine treatment noted in their patient file.

4.2.6.2 Common adverse effects

The most commonly occurring adverse effects experienced as a result of clozapine treatment are shown in the table 4–21. Clozapine causes a vast array of adverse effects, most commonly weight gain and metabolic syndrome, hypersalivation, fever and sedation.

Table 4–21. Common adverse effects (n=52)

Adverse effects	n	Percentage (%)
Hypersalivation	1	1.92
Weight gain	2	3.85
Hypertension	1	1.92
Constipation, weight gain, hypertension and other	1	1.92
Constipation, weight gain, tachycardia and other	1	1.92
Constipation, weight gain, seizures, tachycardia and other	1	1.92
Constipation, weight gain and other	1	1.92
Hypersalivation, constipation, weight gain and other	1	1.92
Hypersalivation, constipation, tachycardia and other	2	3.85
Hypersalivation, constipation and other	1	1.92
Constipation and tachycardia and weight gain	1	1.92
Constipation, tachycardia and other	1	1.92
Hypersalivation, weight gain and tachycardia	1	1.92
Hypersalivation, weight gain and other	1	1.92
Hypersalivation, weight gain, tachycardia and other	1	1.92
Weight gain and other	5	9.62
Hypersalivation and hypertension	1	1.92
Hypersalivation and other	3	5.77
Weight gain, tachycardia and other	1	1.92
Tachycardia and other	4	7.69
Hypotension and other	1	1.92
Constipation and other	1	1.92
Other	19	33.54
Total	**52**	**100**

The most common adverse effect that was evident amongst the participants was weight gain (n=16; 30.77%). This correlates with findings in the literature which portray weight gain and metabolic syndrome as the most prevalent adverse effect that occurs with clozapine therapy. The rate of prevalence of this adverse effect is 60-75% (Citrome & Volavka, 2002: 164–165).

Tachycardia was the second most prominent adverse effect recorded amongst the participants in the study (n=13; 25%). Tachycardia typically occurs within the first two weeks upon initiation of clozapine, and it was prevalent in approximately 25% of all patients who use clozapine (Citrome & Volavka, 2002: 164–165). The rate of prevalence of this adverse effect in the study population is an expected outcome.

An estimated 30-80% prevalence rate of the occurrence of hypersalivation with the use of clozapine is stated in the literature (Citrome & Volavka, 2002: 164–165). Hypersalivation was recorded as an adverse effect of clozapine in in 23.08% (n=12) of the patients in the study sample. The results from the study sample portray a slightly lower prevalence rate. This is a positive outcome, as less patients are experiencing this adverse effect. The management options of the adverse effects experienced by the participants were also explored in sub-section 4.2.6.4.

4.2.6.3 Less common adverse effects

The less common adverse effects of clozapine in this study sample were summarised in table 4–22.

Table 4–22. Less common adverse effects (n=52)

Less common adverse effects	n	Percentage (%)
None	14	29.92
Extrapyramidal side effects (EPSE)	5	9.62
Heartburn	1	1.92
Sleepiness/drowsiness	3	5.77
Dyslipidaemia	2	3.85
Hyperglycaemia	3	5.77
Metabolic changes	1	1.75
Central nervous system (CNS) effects	5	9.62
EPSE and CNS effects	5	9.62
EPSE and heartburn	1	1.92
EPSE and dyslipidaemia	1	1.92
EPSE, endocrine/urological conditions and dyslipidaemia	1	1.92
EPSE, sleepiness/drowsiness and CNS effects	1	1.92
Sleepiness/drowsiness, endocrine/urological conditions and metabolic changes	1	1.92
Heartburn, gastro-intestinal conditions and behavioural changes	1	1.92
Heartburn and CNS effects	1	1.92
Dyslipidaemia, Hyperglycaemia and CNS effects	1	1.92
CNS effects and behavioural changes	1	1.92
Metabolic changes and CNS effects	1	1.92
Endocrine/urological conditions and CNS effects	1	1.92
Gastro-intestinal conditions, sleepiness/drowsiness, metabolic changes and CNS effects	1	1.92
Gastro-intestinal conditions and metabolic changes	1	1.92
Total	**52**	**100**

Central nervous system (CNS) adverse effects were the most commonly experienced in the study sample (n=17; 32.69%). The CNS adverse effects of clozapine includes seizures, sedation and drowsiness and delirium (Citrome *et al.*, 2016: 175). The

prevalence rates of the aforementioned CNS effects differ. Sedation is the most prevalent of these effects (44%), unlike seizures which present in a small proportion of patients who use clozapine (1.3-1.8%). The prevalence of the CNS effects experienced by the participants in this study is accurate with the literature (Citrome & Volavka, 2002: 164–165). Further investigations can be made into each specific CNS effect experienced by the participants.

Clozapine has proved to be the first second-generation antipsychotic that has a low incidence of causing EPS (Divac *et al.*, 2014: 2). The results of the study shows that EPSE were experienced by 14 patients (26.92%). This is a small proportion of the overall study population, therefore the result is expected.

4.2.6.4 Management of adverse effects

The pharmacological management of adverse effects were analysed in the study sample. The results are presented in figure 4–9.

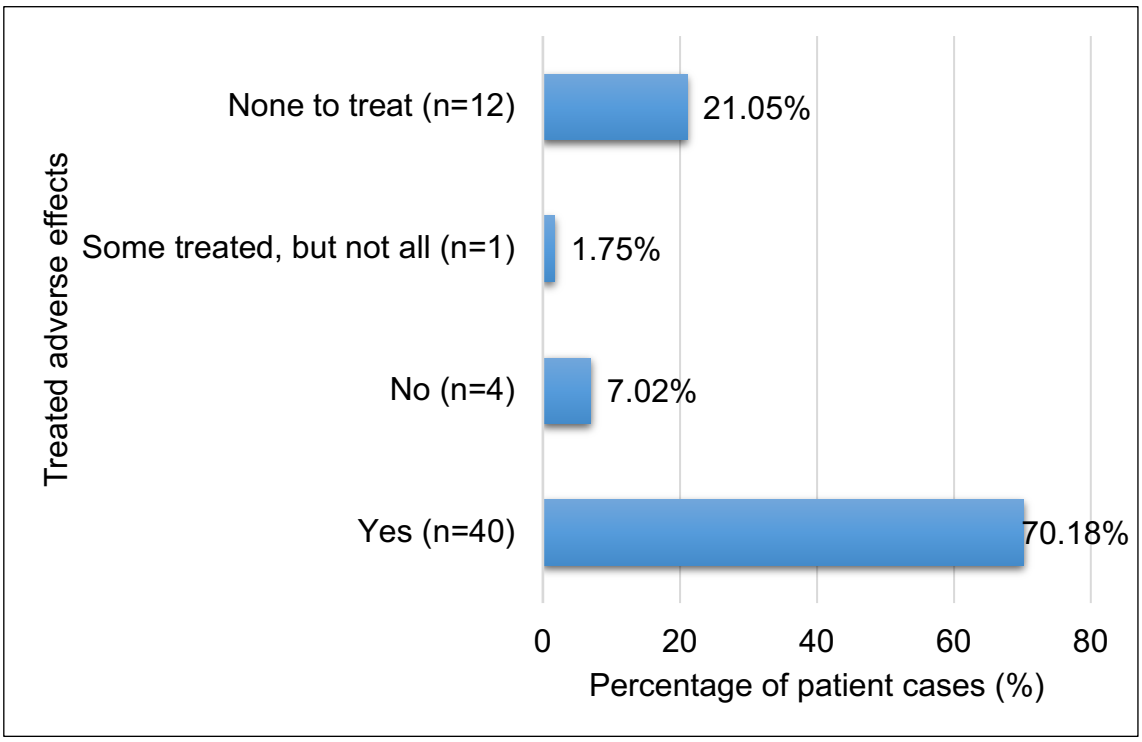

Figure 4–9. Pharmacological management of adverse effect (n=57)

The majority of patients who experienced adverse effects were treated for them (n=40; 70.18%). There are several recommended pharmacological and non-pharmacological interventions to manage the adverse effects of clozapine. These interventions include

ceasing clozapine treatment in cases of life-threatening consequences, the addition of a drug to manage psychotic and other symptoms, consistent monitoring patterns and lifestyle changes that should be adopted by the patient (Iqbal *et al.*, 2003: 38; Semple & Smyth, 2013: 215; Winckel & Siskind, 2017: 232; Kim, 2018: 120). The results obtained indicate that prescribers chose suitable therapies in each patient case to alleviate or manage their adverse effects. 7.02% (n=4) of the patients did not receive any pharmacological treatment to manage their adverse effects. Non-pharmacological and other alternative therapies can be further explored in another study to gain more insight on the management of adverse effects in this study population.

4.2.7 Other drugs

4.2.7.1 Previous antipsychotics administered prior to clozapine

Information regarding the antipsychotics administered prior to clozapine was analysed. The results are shown in figure 4–10.

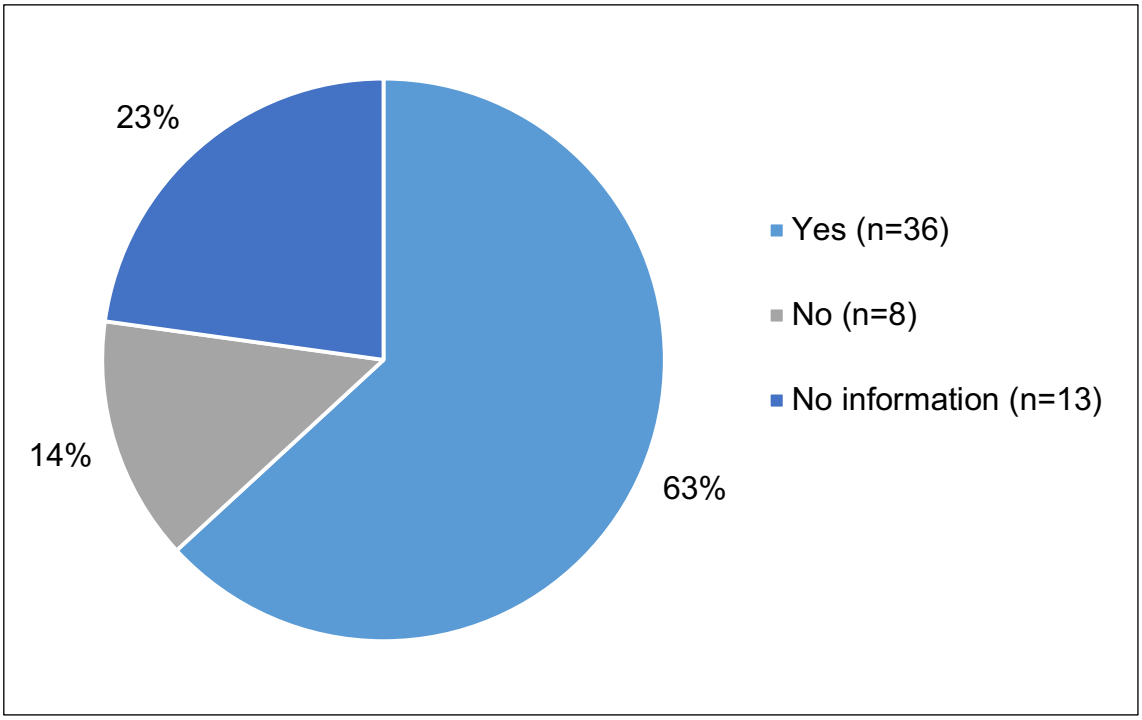

Figure 4–10. Previous antipsychotics administered prior to clozapine (n=57)

Other antipsychotic drugs were used prior to the initiation of clozapine treatment in 63.16% (n=36) of the patients in the study sample. This was investigated to assess the compliance of clozapine prescribing. The NICE guidelines states that at least two antipsychotic drugs are offered to patients before clozapine is prescribed in patients diagnosed with schizophrenia (National Institute for Health and Care Excellence, 2015: 24).

4.2.7.2 Names of previous antipsychotics used

The names of the previous antipsychotic drugs were noted and analysed in table 4–23.

Table 4–23. Names of the previous antipsychotics used (n=36)

Names of previous antipsychotics used	n	Percentage (%)
Haloperidol	1	2.78
Amisulpride	2	5.56
Sulpiride	1	2.78
Risperidone	3	8.33
Zuclopenthixol	1	2.78
Zuclopenthixol and Risperidone	2	5.56
Zuclopenthixol and Amisulpride	1	2.78
Zuclopenthixol and Fluphenazine	1	2.78
Zuclopenthixol, Fluphenazine and Chlorpromazine	1	2.78
Ziprasidone and Risperidone	1	2.78
Olanzapine and Risperidone	1	2.78
Fluphenazine and Chlorpromazine	1	2.78
Fluphenazine, Chlorpromazine and Risperidone	1	2.78
Fluphenazine, Risperidone, Quetiapine and Aripiprazole	1	2.78
Zuclopenthixol, Fluphenazine, Chlorpromazine, Olanzapine, Risperidone and Amisulpride	1	2.78
Haloperidol and Risperidone	4	11.11
Haloperidol and Chlorpromazine	2	5.56
Haloperidol and Fluphenazine	1	2.78
Haloperidol and Zuclopenthixol	1	2.78

Names of previous antipsychotics used	n	Percentage (%)
Haloperidol, Zuclopenthixol, Olanzapine and Risperidone	1	2.78
Haloperidol, Zuclopenthixol, Flupenthixol, Chlorpromazine and Risperidone	1	2.78
Haloperidol, Prochlorperazine and Risperidone	1	2.78
Haloperidol, Thioridazine[1], Zuclopenthixol, Sulpiride, Fluphenazine and Chlorpromazine	1	2.78
Haloperidol, Thioridazine, Zuclopenthixol, Sulpiride, Flupenthixol, Fluphenazine and Chlorpromazine	1	2.78
Haloperidol, Zuclopenthixol, Sulpiride, Risperidone and Amisulpride	1	2.78
Chlorpromazine and Risperidone	1	2.78
Chlorpromazine, Risperidone and Amisulpride	1	2.78
Olanzapine, Risperidone, Amisulpride and Aripiprazole	1	2.78
Total	**36**	**100**

The most common antipsychotic used prior to clozapine was risperidone (n=21; 58.33%). Risperidone is a widely used antipsychotic drug in the treatment of schizophrenia. It has be shown to be slightly less efficacious than olanzapine and clozapine, but slightly more efficacious than quetiapine and ziprasidone. Compared to other SGAs, risperidone is known to produce more EPSE, more prolactin increase and immediate weight gain. The efficacy of risperidone is almost parallel to that of clozapine, however clozapine remains superior in managing the positive symptoms of schizophrenia (Komossa *et al.*, 2011: 28–29). Considering the comparable efficacy of clozapine and risperidone, it is surprising that its therapy was discontinued in so many patient therapies.

The second most commonly used antipsychotic used prior to clozapine the conventional antipsychotic, haloperidol. It was used by 41.67% (n=15) of patients in the study sample. Clozapine has also proven to be more efficacious than haloperidol in the treatment of TRS. Haloperidol also presents with more EPSE, and longer hospital durations than clozapine (Rosenheck *et al.*, 1997: 813). The discontinuation

[1] Thioridazine has since then been withdrawn and is no longer available on the South African market.

of haloperidol treatment is not as surprising as a result. Other studies have shown the vast discontinuation rates of haloperidol due to adverse effects (Lally & MacCabe, 2015: 171).

Haloperidol and risperidone are the first line treatment in South Africa for the acute management of schizophrenia, particularly first-episode psychosis (Maartens *et al.*, 2015: 15.14). Therefore, it is expected they would be the most common antipsychotics used prior to clozapine treatment.

4.2.7.3 Trials of previous antipsychotics prior to clozapine use

Table 4–24 summarises the results obtained from the trials of previous antipsychotics prior to the initiation of clozapine therapy.

Table 4–24. Trials of previous antipsychotics (n=57)

Trials of previous antipsychotics	Frequency (n)
At least two previous antipsychotics of which one was a typical antipsychotic	10
At least two previous antipsychotics of which one was a second-generation antipsychotic (SGA)	15
At least two previous antipsychotics of which both were a typical antipsychotic	15
At least two previous antipsychotics of which both were an SGA	9
One previous antipsychotic which was a typical antipsychotic	2
One previous antipsychotic which was an SGA	4

The NICE guidelines have stipulated how at least two antipsychotic drugs should be used before the initiation of clozapine monotherapy. At least one of these antipsychotic drugs must be an SGA, excluding clozapine (National Institute for Health and Care Excellence, 2015: 24). Similarly, the SASOP treatment guidelines (Swingler, 2013: 155) suggest monotherapy use of an SGA or FGA initially. The addition of a second antipsychotic drug is suggested as the second line treatment (excluding clozapine). Only upon a failed therapeutic response is clozapine advised as the third line treatment (Swingler, 2013: 155). The results from the empirical study show that

in 15 cases this criteria was met (26.3%). This is a seemingly a poor outcome when it comes to compliance to these prescribing guidelines. However, other clinical guidelines only state that the trial of two previous antipsychotics, excluding clozapine, are sufficient before clozapine monotherapy is initiated. These guidelines do not specify the need for one of the antipsychotic drugs to be an SGA (Dold & Leucht, 2014: 36; Remington *et al.*, 2017: 610). With this criteria, 73.1% (n=49) of the patients were prescribing according to these guidelines. This is a better outcome, however there is still a proportion of cases that are non-adherent to the prescribing guidelines of clozapine.

4.2.7.4 Reasons for stopping previous antipsychotic

The reasons for stopping the previous antipsychotics were analysed and summarised in figure 4–11.

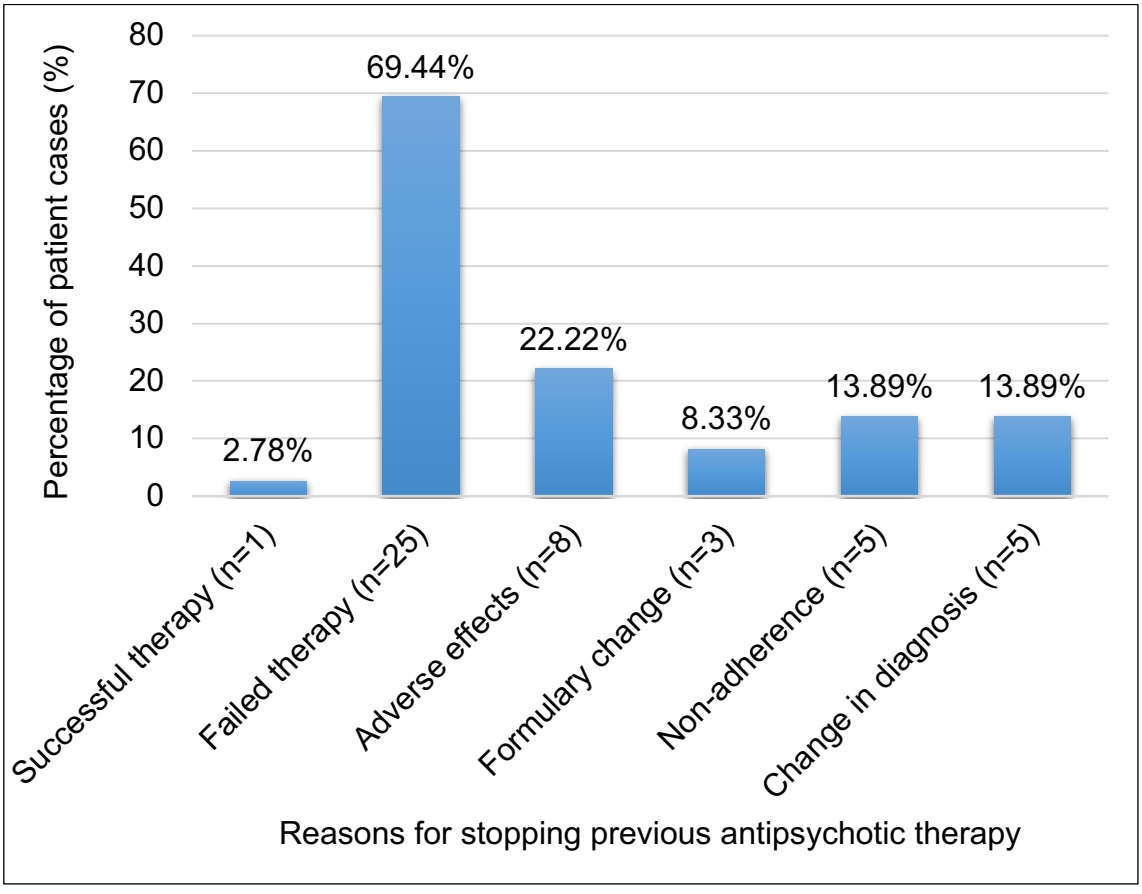

Figure 4–11. Reasons for stopping previous antipsychotic (n=57)

Several factors could result in the stopping of treatment with a specific antipsychotic. These factors could include re-evaluation of the diagnosis, non-compliance of the

patient regarding drug intake, incorrect dosages leading to failed therapy, or severe adverse effects (Dold & Leucht, 2014: 33–34). The resolution of symptoms resulting in successful therapy is also another factor that is considered. The results indicate that the most common reason for stopping any previous antipsychotic was due to failed therapeutic outcome of the drug (n=25; 69.44%). This is a likely outcome as cases of treatment-resistant are unresponsive to other antipsychotic drugs, except for clozapine (Dold & Leucht, 2014: 36). The second most common reason was due to adverse effects experienced (n=8; 22.22%). This is an expected outcome due to the adverse effect profiles of both conventional antipsychotics and SGAs. Conventional antipsychotics are more likely to cause EPSE and hyperprolactinemia, whilst SGAs are likely to cause metabolic effects such as weight gain and dyslipidaemia (Muench & Hamer, 2010: 619).

4.2.8 Augmentation treatment

The number of drugs that were used as augmentation treatment were assessed and are displayed in figure 4–12.

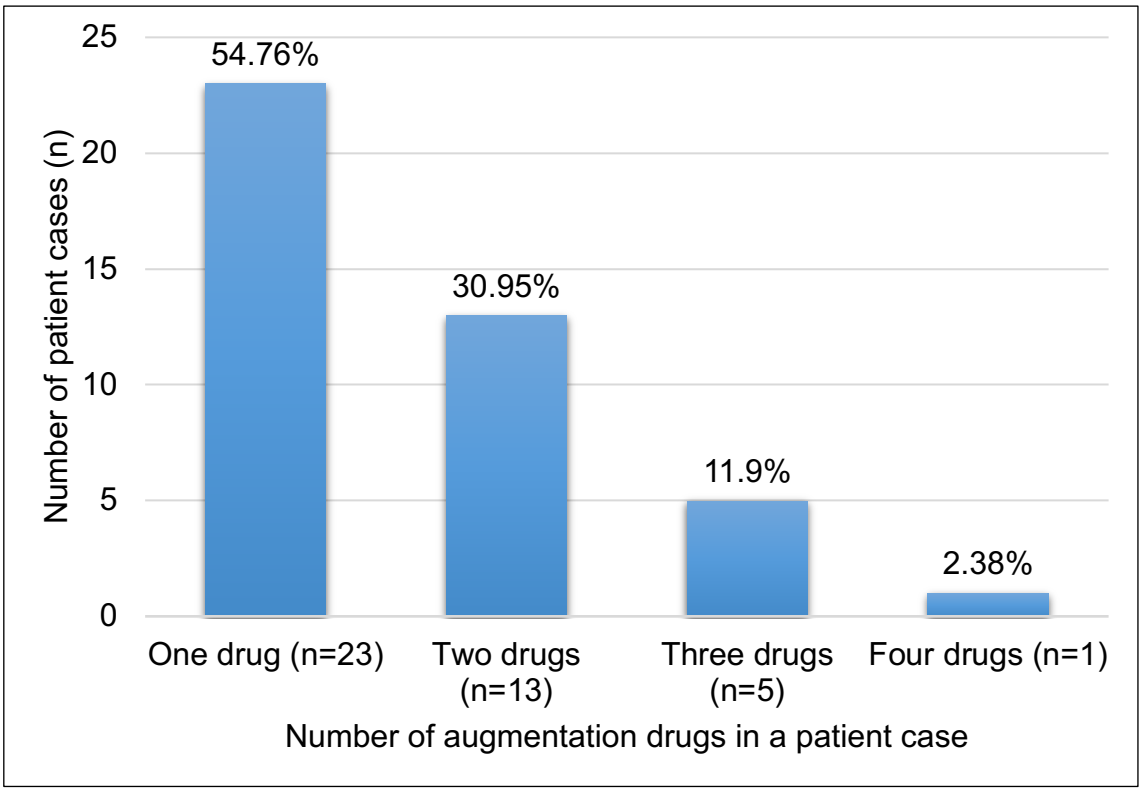

Figure 4–12. Number of augmentation drugs used (n=42)

According to the results amongst the 42 patients (73.68%) in the study sample who were identified with augmentation treatment, 23 patients (54.76%) were on one additional drug alongside clozapine. Polypharmacy is a frequent occurrence in the treatment of schizophrenia, in some cases it is justified but not so in others (Stahl, 1999: 426). Some studies have advocated against the practice of polypharmacy with antipsychotic drugs. However, polypharmacy remains common in many clinical settings, with a widely variable prevalence rate (4-70%) (Fleischhacker & Uchida, 2014: 1084). Therefore the results obtained are expected as an overall 73.68% (n=42) of the patients were prescribed additional drugs to augment their clozapine treatment. Clozapine polypharmacy is the most common of the antipsychotic drugs to be frequently coadministered with other drugs. In some studies clozapine polypharmacy has proven to be more superior than clozapine monotherapy (Fleischhacker & Uchida, 2014: 1085). The names of the drugs used for clozapine augmentation are depicted in table 4–25.

Table 4–25. Names of drugs used for clozapine augmentation (n=42)

Names of drug augmenting clozapine	Frequency (n)
Sodium Valproate	12
Sulpiride	5
Amisulpride	5
Flupenthixol	1
Citalopram	7
Topiramate	2
Zuclopenthixol	9
Aripiprazole	3
Amitriptyline	7
Imipramine	2
Venlafaxine	2
Methylphenidate	1
Clomipramine	1
Risperidone	1
Fluphenazine	1
Fluoxetine	7
Diazepam	1
Carbamazepine	1

Augmentation therapy is useful to improve the limited response rate of clozapine. In the cases of TRS, mood stabilisers, benzodiazepines, beta-blockers and antidepressants are very useful augmentation drugs. Sodium Valproate was the most widely used drug for augmenting clozapine treatment (n=12; 28.57%). This result is consistent with the literature which confirms the importance of the role that valproate plays in enhancing the effects of antipsychotics. Significantly better therapeutic outcomes were achieved in schizophrenia and schizoaffective cases, due to the addition of valproate to the clozapine therapy (Tseng *et al.*, 2016: 7).

Zuclopenthixol was used in the treatment plans of 9 patients (21.43%). Zuclopenthixol is a long-acting injectable (LAI) antipsychotic, which is commonly used to manage nonadherent patients (Haddad *et al.*, 2014: 55). However, the concomitant use of LAIs and clozapine is not recommended as this can cause neutropenia (Turner *et al.*,

2010: 462). Prescribers are required to assess the pharmacodynamic profiles of the drugs they wish to combined with clozapine, preferably choosing a drug with a different receptor-binding profile (Lally *et al.*, 2016: 174).

4.2.9 Drug interactions

4.2.9.1 Possible drug interactions

The various drugs that were used by each patient were analysed and a summary of the possible drug interactions that may occur with clozapine are shown in table 4–26.

Table 4–26. Possible drug interactions with clozapine (n=57)

Possible drug interactions with clozapine	n	Percentage (%)
Yes	32	56.14
No	25	43.86
Total	**57**	**100**

Due to the augmentation of clozapine therapy with other drugs and the treatment of co-morbid disease states, it is possible that patients will administer a drug that will interact with clozapine. The most current prescription was assessed for any possible drug interaction with clozapine. A total of 56.14% (n=32) of the patients in study sample could have possibly experienced some drug interactions with clozapine. This result is expected, as there were 42 patients (73.68%) who were on augmentation therapy with other drugs.

4.2.9.2 Number of drug interactions with clozapine

The number drug interactions in the study sample were analysed and the results in illustrated figure 4–13.

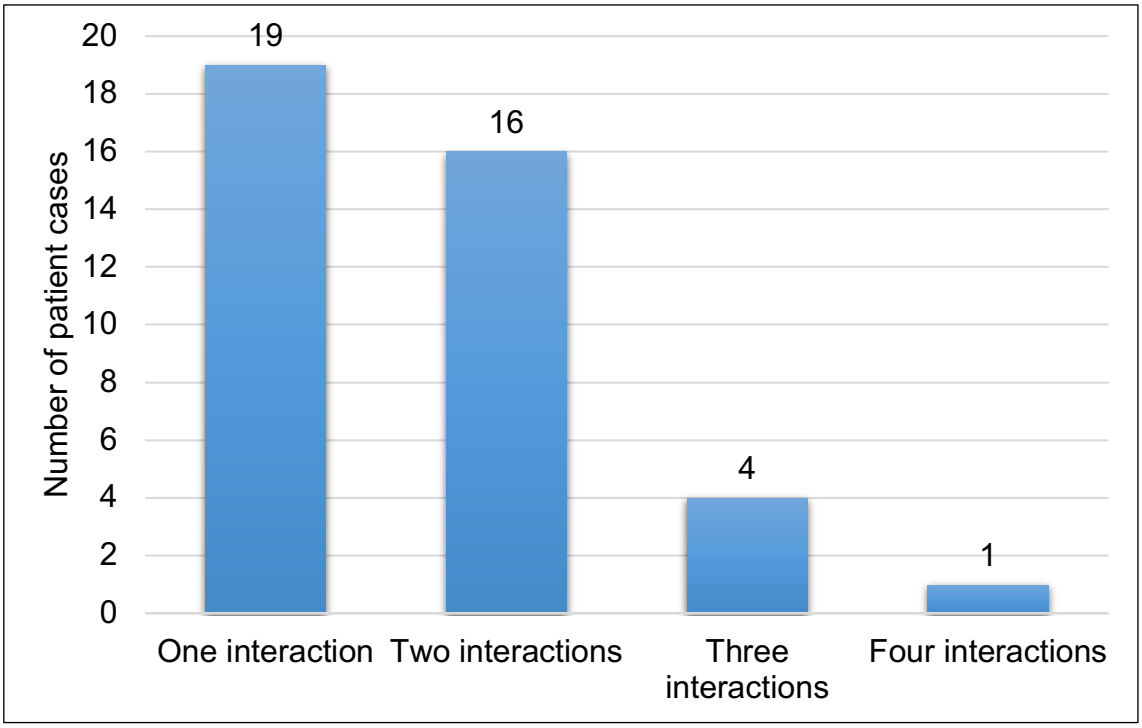

Figure 4–13. The number of drug interactions (n=40)

Patient files were assessed for any information on drug interactions. The results show that 19 patients (47.50%) had one drug interaction with clozapine, followed by 16 patients (40.00%) with two drug interactions.

4.2.9.3 Names of drug-drug interactions with clozapine

The names of the drugs that were prescribed to the study sample that were interacting with clozapine are noted in table 4–27.

Table 4–27. Names of drugs interacting with clozapine

Names of drug interacting with clozapine	Frequency (n)
Sodium Valproate	12
Atenolol	11
Metformin	12
Citalopram	6
Propranolol	6
Zuclopenthixol	9
Ritonavir	1
Fluoxetine	7
Fluphenazine	1
Carbamazepine	1
Risperidone	1

The most common drugs that were prescribed to this study sample and interacted with clozapine are sodium valproate and metformin (Turner *et al.*, 2010: 460). Independently of each other, these interactions occurred in 12 patients (21.05%) in each case. Sodium valproate is used as a prophylaxis for seizures that may occur as an adverse reaction of clozapine. It is postulated that sodium valproate induces clozapine metabolism, and this results in reduced clozapine plasma concentration (Turner *et al.*, 2010: 462). Metformin is often prescribed for the management of the adverse effect weight gain. Clozapine is amongst one of the SGAs that has a high chances of inducing weight gain and metabolic syndrome (Chiu *et al.*, 2016: 2). The high frequency of metformin administration alongside clozapine therapy is therefore expected. Clozapine has an important interaction with antidiabetics because it impairs glucose tolerance and increase blood glucose levels. The careful monitoring of diabetic patients is recommended (Karalliedde *et al.*, 2010: 256; Turner *et al.*, 2010: 460).

4.2.10 Monitoring

4.2.10.1 Haematological monitoring

Haematological monitoring was assessed in the study sample and the results are depicted in table 4–28.

Table 4–28. Haematological monitoring (n=57)

Haematological monitoring	n	Percentage (%)
Yes	42	73.68
No	14	24.56
No information	1	1.75
Total	**57**	**100**

Agranulocytosis is a serious adverse effect of clozapine. According to the Maudsley prescribing guidelines, haematological monitoring is a recommendation in all patients on clozapine treatment to manage the risk of agranulocytosis (Taylor *et al.*, 2009: 66). The results show that in most cases (n=42; 73.68%) haematological monitoring was done in the study sample. Although haematological monitoring was done in most cases, there is still a large proportion of patients who were not monitored. This raises concern over the compliance with the recommended guidelines, both nationally and internationally, that emphasise the mandatory nature of haematological monitoring. The Maudsley prescribing guidelines, the Clozapine REMS, the SAMF and the South African STGs stipulate the same haematological monitoring patterns. These monitoring patterns state that pre-treatment baseline blood tests (WBC total and differential counts) are required. Upon clozapine initiation, the WBC counts are monitored weekly for the first 18 weeks, and then fortnightly for the remainder of the year. Thereafter, monthly WBC counts are recommended for the duration of the treatment (Taylor *et al.*, 2009: 75; Clozapine Risk and Mitigation Strategy, 2015: 6; Maartens *et al.*, 2015: 15.15; Rossiter, 2016: 481). In resource limited areas, the SAMF has stipulated that during the maintenance period of therapy, WBC counts may be done monthly following the initial 18 weeks of therapy (Rossiter, 2016: 481). Similarly, the SASOP treatment guidelines also stipulate that monthly monitoring is commenced after the initial 18 weeks of weekly monitoring (Swingler, 2013: 154).

4.2.10.1.1 Monitoring interval

The interval of the haematological monitoring was reviewed in the patient files and the results displayed in figure 4–14.

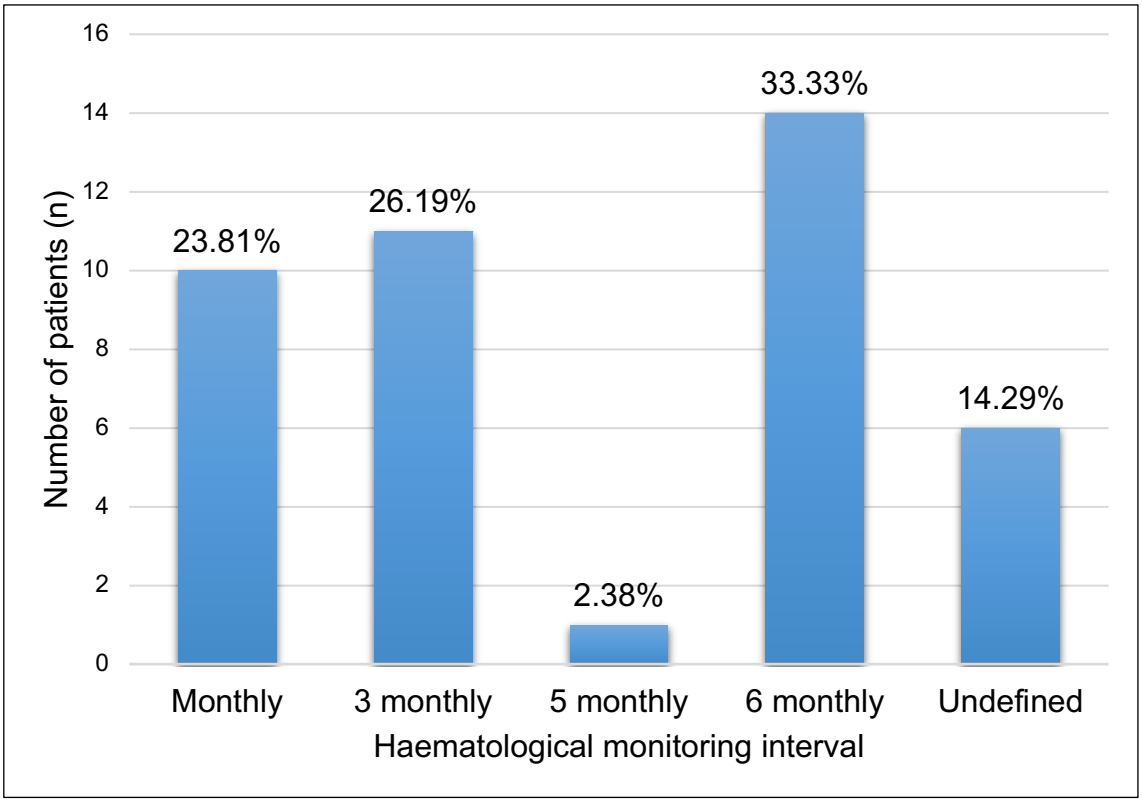

Figure 4–14. Haematological monitoring intervals of patients in the study sample (n=42)

The majority of the patients had their haematological monitoring done in 6 month intervals (n=14; 33.33%). Of the patients who had data for the intervals of monitoring, 26.19% (n=11) were monitored every 3 months for haematological effects of clozapine. According to the SAMF, the South African STGs and Maudsley prescribing guidelines, and the Clozapine REMS, the WBC counts during the maintenance period (after 12 months) of clozapine treatment must be done at monthly intervals (Taylor *et al.*, 2009: 75; Clozapine Risk and Mitigation Strategy, 2015: 6; Maartens *et al.*, 2015: 15.15; Rossiter, 2016: 481). The SASOP treatment guidelines recommend monthly haematological monitoring after the first 18 weeks following initiation of clozapine therapy (Swingler, 2013: 154). However, the results from this study show the lack of compliance to these guidelines. This as a result may predispose the patient to agranulocytosis. Adherence to these guidelines during monitoring practices must be emphasised to health care professionals, to ensure the safe use of clozapine in the patients.

4.2.10.1.2 Metabolic monitoring

Metabolic monitoring is also a mandatory practice for patients using clozapine. The results in the case study are illustrated in figure 4–15.

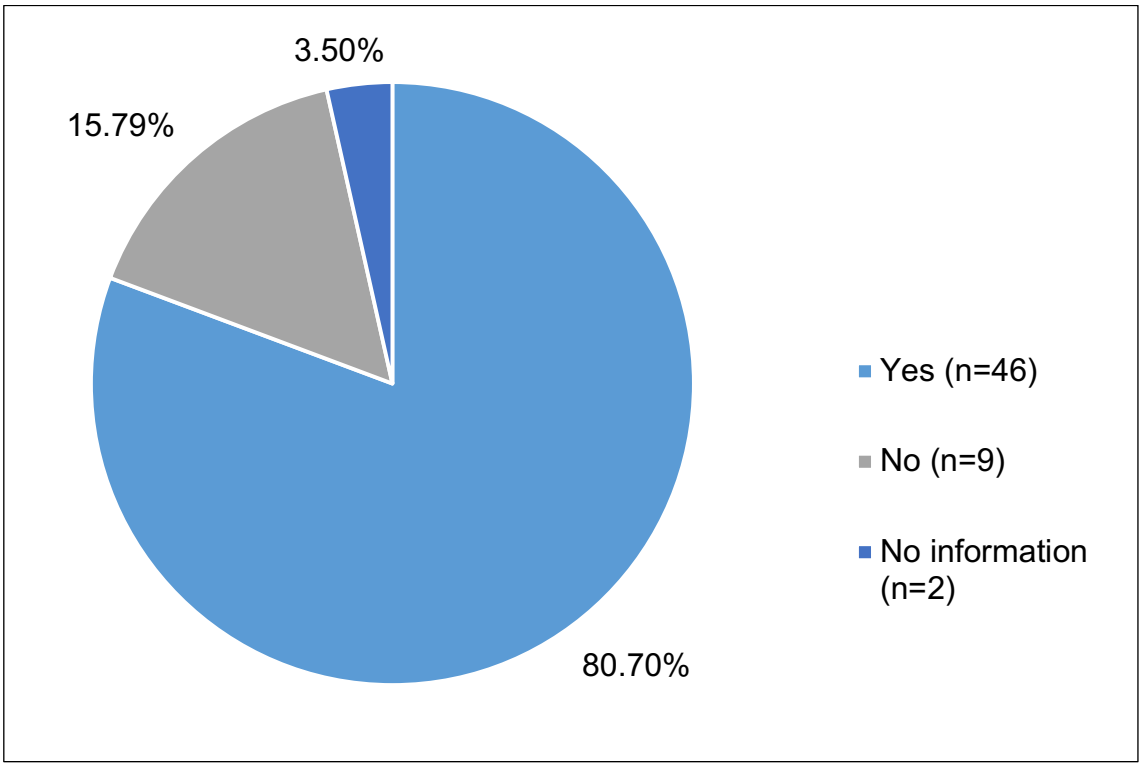

Figure 4–15. Metabolic monitoring of patients in the study sample (n=57)

Metabolic syndrome is a common adverse effect in patients on clozapine treatment (Faasen *et al.*, 2014: 54). Monitoring tests that assess metabolic changes are recommended by the American Diabetes Association and American Psychiatric Association. These tests include weight or BMI, waist circumference, blood pressure, fasting glucose and fasting lipogram tests. Each parameter is assessed at a prescribed interval for the duration of clozapine treatment (Hertzman & Adler, 2010: 350). Similarly, the South African STGs recommend the regular monitoring of metabolic adverse effects during clozapine treatment. The parameters to be monitored include weight, BMI, waist circumference and serum glucose and lipids (Maartens *et al.*, 2015: 15.14). The results show that the majority of the patients (n=46; 80.70%) had metabolic monitoring done during the study period.

Part of the metabolic monitoring entails evaluating the weight, height and body mass index of the patients. The results illustrated in table 4–29 were obtained in the patient files.

Table 4–29. A summary of the metabolic parameters

	n	Mean	SD	Median	Min	Max
Weight (kg)	39	84.11	20.66	78.00	47.40	132.60
Height (m)	16	1.69	0.07	1.68	1.56	1.83
BMI (kg/m^2)	15	27.82	7.03	25.82	19.30	44.28

The weight of 39 patients were obtained during the study period. It was found that the average weight was 84.11 ± 20.66 kg. The minimum and maximum weights recorded in this study sample were 47.40 kg and 132.60 kg respectively. Weight monitoring is recommended at monthly intervals for the duration of clozapine treatment (Hertzman & Adler, 2010: 350). The results portray that weight monitoring data for only 39 patients (68.42%) was available. This indicates the possible lack of compliance to the weight monitoring guidelines during clozapine treatment. Weight gain is a common adverse effect of clozapine, and it can also be a complicating one too as it can predispose the patient to other conditions such as hypertension and type II diabetes (Puoane *et al.*, 2002: 1038; Rossiter, 2016: 481). An average weight increase of greater than 7% is noted with all atypical antipsychotics (Haddad & Sharma, 2007: 921). The effects of weight gain are more detrimental to patients presenting with a higher BMI at baseline, as well as in males and the elderly (Henderson *et al.*, 2005:1116).

The height of 16 patients were gathered. The average height in the study sample was 1.69 ± 0.07 metres. Height is a necessary parameter for the calculation of the body mass index (BMI) (Franco *et al.*, 2016: 25). The BMI of 15 patients was calculated using the weights and heights in the study sample. The average BMI was 27.82 ± 7.03 kg/m^2. The minimum and maximum BMIs calculated were 19.30 kg/m^2 and 44.28 kg/m^2 respectively. The average BMI in this study sample falls between the range of 25 kg/m^2 and 29.9 kg/m^2, this indicates that the average patient was overweight (National Health Insurance, 2019). According to the WHO, there is an increased risk of co-morbidities for patients who are within this BMI range (World Health

Organization, 2019b). Due to these risks, BMI should be calculated for every patient using clozapine.

4.2.10.1.3 Fasting blood glucose

The fasting blood glucose was analysed in the study sample and summarised in table 4–30.

Table 4–30. Normal fasting blood glucose monitoring (n=35)

Normal Fasting glucose (mmol/L)	n	Percentage (%)
3.9 – 5.5	18	51.43
≥ 5.5	17	48.57
Total	**35**	**100**

The fasting glucose tests are necessary as clozapine may cause drug-insulin resistance as an adverse effect. As a result this can predispose patients to new-onset diabetes mellitus (Henderson *et al.*, 2005: 1119). The majority of the patients (n=18; 51.43%) presented with fasting glucose levels that were within the normal range for fasting blood glucose levels. The remaining patients (n=17; 48.57%) had results that indicated impaired fasting glucose metabolism. These results emphasise the importance of monitoring blood glucose levels for the management of adverse effects. Fasting blood glucose monitoring is recommended as a baseline test, at 12 weeks, and annually in well controlled patients for the duration of the clozapine treatment (Hertzman & Adler, 2010: 350).

4.2.10.1.4 Fasting lipogram

The fasting lipogram tests were analysed and results of this analysis are shown in table 4–31.

Table 4–31. Fasting lipogram monitoring (n=57)

Fasting lipogram monitoring	n	Percentage (%)
Yes	38	66.67
No	18	31.58
No information	1	1.75
Total	**57**	**100**

The majority of the patients in study sample had their fasting lipograms performed during the study period (n=38; 66.67%). Fasting lipogram tests are required to be done at baseline, followed by at 12 weeks after initiation, and every 5 years for patients who have well controlled lipid levels (Hertzman & Adler, 2010: 350). These tests are important because clozapine can predispose patients to obesity, dyslipidaemia and increase the risk developing CVD (Henderson *et al.*, 2005: 1119). Although the majority of the patients had their fasting lipogram monitoring adhered to, investigations must still be done for the non-compliance of the remaining 31.58% of patients.

4.3 Chapter 4 summary

The results of the study obtained with the data collection tool were presented and discussed. The following chapter will discuss the conclusions drawn from the results. The recommendations of the study as well as limitations will also be discussed.

CHAPTER 5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Introduction

This chapter will discuss the conclusions of this study, the limitations and recommendations.

5.2 Conclusions

Conclusions will be based on the primary aim and specific objectives that were set out in Chapter 1. The research questions will be answered in this chapter.

A drug utilisation review focusing on the prescribing and monitoring patterns of clozapine use at a public sector psychiatric hospital was conducted. The study assessed the prescribing and monitoring patterns at the hospital and compared it with the current international and national monitoring guidelines.

5.2.1 Literature Review

Below are the conclusions that were obtained in the literature review. Each objective will be stated and conclusions from the literature will be discussed.

The first research objective was to describe psychiatric disorders in general and their prevalence in South Africa:

- Neuropsychiatric conditions account for 13% of the total disability-adjusted life years (DALYs) lost due to diseases and injuries in the world and are increasingly on the rise (World Health Organization, 2004: 13).
- Schizophrenia is responsible for 2.8% out of the overall 31.7% of the years of life disabled (YLD) for the neuropsychiatric disorders in the global context (Prince *et al.*, 2007: 859–860).
- It is estimated that the lifetime prevalence of schizophrenia is 0.3-0.7% (American Psychiatric Association, 2013b: 102).
- Treatment-resistant schizophrenia is prevalent in 30% of patients diagnosed with schizophrenia (Swingler, 2013: 154).
- Schizoaffective disorder was estimated to have a lifetime prevalence slightly lower than schizophrenia (American Psychiatric Association, 2013b: 107).
- The lifetime prevalence of mental disorders in South Africa was found to be 30.3% (Herman *et al.*, 2009: 3).

- A lack of research exploring the prevalence of psychiatric disorders in adolescents and younger children in South Africa was apparent (Mayosi *et al.*, 2009: 937).

The second research objective was to discuss the pathophysiology (hypotheses) of schizoaffective disorders and schizophrenia:

- Psychotic disorders are categorised, depending on their diagnosis, into either secondary or primary psychoses (Freundenreich, 2016: 24).
- Four main conditions cause secondary psychosis, namely delirium, dementia, medical and neurological diseases as well as substance-induced psychosis (Freundenreich, 2016: 25).
- Primary psychosis is not dependant on a prior disorder (Johnson *et al*, 2009: 80), schizophrenia and schizoaffective disorder fall in this category (American Psychiatric Association, 2013b: xv).
- The aetiology of schizophrenia has been established to be multifactorial (Tandon *et al*, 2008: 12). The onset of the condition is a useful factor that can be used to understand the possible causes of the development of schizophrenia (DeLisi, 1992: 209).
- A complex set of clinical symptoms can occur with schizophrenia, and there is wide interpatient variability (Khamker, 2015: 30).
- The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5®) and the International Statistical Classification of Disease and Related Health Problems 11th Revision (ICD-11) are the recognisable and current international diagnostic criteria, and they have been previously harmonised to improve the diagnostic accuracy of schizophrenia (Kupfer *et al.*, 2008: 4; Bhati, 2013: 3).
- Schizoaffective disorder is recognised as a separate illness from schizophrenia, although literature debates which category of illnesses it falls under (Cheniaux *et al.*, 2008: 214; Leposavić *et al.*, 2015: 395).
- The exact aetiology of schizoaffective disorder has not been conclusive (Cardno & Owen, 2014: 510), similarly the age of onset has not been predicted (Cheniaux *et al.*, 2008: 214).
- The DSM-5® differentiates the criteria for schizoaffective disorder and schizophrenia more distinctly (American Psychiatric Association, 2013b: 106).

The third research objective was to determine the medicine treatment guidelines of schizoaffective disorders and schizophrenia:

- The recommended treatment for an acute psychotic episode is haloperidol, or alternatively a second-generation antipsychotic (SGA) such as chlorpromazine or risperidone (Maartens *et al.*, 2015: 15.14).
- In the case of multi-episode or a relapse, a more effective drug has to be chosen compared to the prior one used for the acute episode (Emsley *et al.*, 2013: 154).
- SGAs are more preferable due to the lack of extrapyramidal adverse effects (Emsley *et al.*, 2013: 154).
- Long-term antipsychotic therapy is individualised, with the common therapeutic outcome being the rapid remission of the acute psychotic episode (Tandon *et al.*, 2010: 6).
- The lowest possible dosage of the preferred antipsychotic is prescribed for maintenance therapy (World Health Organization, 2008: 455).
- Patients with a history of relapse or non-compliance are usually prescribed a depot antipsychotic medication (Taylor *et al.*, 2018: 42).
- Clozapine is only prescribed in cases of treatment-resistant schizophrenia due to its severe adverse effect profile.
- Clozapine is the third-line monotherapy treatment in cases of treatment-resistant schizophrenia (TRS), it may also be indicated for other forms of psychoses (Emsley *et al.*, 2013: 154; Mauri *et al.*, 2018: 3).
- Adjunctive therapy is recommended to assist in the relief of symptoms (Kudva & Gupta, 2016: 12).
- A variety of non-pharmacological interventions are useful alongside pharmacological treatment to provide a holistic therapeutic outcome for the patient (Iqbal *et al.*, 2003: 38; Semple & Smyth, 2013: 215; Winckel & Siskind, 2017: 232; Kim, 2018: 120).

The fourth research objective was to describe the history of the development of clozapine:

- Clozapine was identified amongst tricyclic antidepressants (Crilly, 2007: 40).

- Clozapine has a distinct adverse effect profile which differed from the known neuroleptics, no extrapyramidal effects were evident (Alvir*, et al.,* 1993: 162).
- Due to the lack of extrapyramidal effects, the efficacy of clozapine was initially questioned amongst researchers in the 1960s (Hippius, 1989: S4).
- The first cases of agranulocytosis induced by clozapine were recorded in Finland, 50% of which resulted in fatalities (Chapelle *et al*., 1977: 183; Alvir *et al*., 1993: 162).
- Clozapine was made available in South Africa in 1974. Cases of agranulocytosis without fatalities had been recorded (Anderman & Griffith, 1977: 200).
- The FDA ceased the manufacturing of clozapine in 1976 (Crilly, 2007: 46).
- The efficacy of clozapine was later proved in 1988 and the FDA reapproved the clinical use of clozapine (Stolerman, 2010: 418).
- Clozapine still presents with the most effective therapeutic outcomes in comparison with other antipsychotics (Barnes & Talmud, 2007: 245).

The fifth research objective was to discuss the pharmacological properties of clozapine and compare it to other psycholeptics:

- Clozapine is a dibenzodiazepine (Mauri *et al*., 2007: 362).
- Clozapine is classified as a multi-acting receptor-targeted antipsychotic (MARTA), similar to olanzapine and quetiapine (Horacek *et al*., 2006: 391).
- Superior affinity is shown at specific dopamine receptors (Mauri *et al*., 2007: 362).
- Clozapine shows activity at the cortical and limbic dopamine receptors, while other SGAs show more activity at striatal dopamine receptors (Khokhar *et al*., 2018: 140).
- Clozapine does not significantly raise prolactin levels in comparison with chlorpromazine (Jann *et al*., 1993).
- Clozapine is administered in tablet form with dosages ranging from 150 mg/day to 900 mg/day (Rossiter, 2016: 481).
- Other medications may interfere with the pharmacokinetic properties of clozapine as the induction or inhibition of important enzymes that metabolise clozapine may be affected (Mauri *et al*., 2014: 1164).

- The indication of clozapine is primarily for TRS, as well as recurrent suicidal behaviour in patients with psychotic disorders, drug-induced psychosis, treatment-resistant bipolar disorder and other conditions (Rossiter, 2016: 481; Ayano, 2016: 3).
- A dosage titration from the initiation of clozapine therapy is recommended until the optimal dosage is reached (Novartis Pharmaceuticals Corporation, 2014: 29).
- Several baseline tests must be adhered to before the initiation of clozapine, and some tests must be continued throughout the duration of clozapine therapy (Hertzman & Adler, 2010: 350).
- Haematological monitoring must be adhered to especially to ensure that agranulocytosis is detected early (Kar *et al*., 2016: 325).
- Patients must be assessed for any contraindications before treatment with clozapine is initiated (Dunk *et al.*, 2006: 255; Turner *et al.*, 2010: 461).
- The benefits of clozapine augmentation with other medications is still subjective and varies in different patients (Souza *et al.*, 2010: 154).

The sixth research objective was to discuss the toxicological properties of clozapine and compare it to other antipsychotics:

- In comparison to olanzapine, clozapine has superior efficacy in cases of childhood-onset schizophrenia (Kim, 2018: 116).
- Clozapine has a significantly high milk to plasma ratio compared to other antipsychotics, and breastfeeding is not recommended in nursing mothers (Turner *et al.*, 2010: 461; Rossiter, 2016: 485).
- The most prevalent adverse effects of clozapine are weight gain and metabolic syndrome (60-75%) as well as hypersalivation (30-80%) (Citrome & Volavka, 2002: 164–165).
- Clozapine poses the greatest risk of causing agranulocytosis compared to other SGAs (Brown *et al.*, 1999: 212).
- The clozapine Risk Evaluation and Mitigation Strategy (REMS) is a system used in the United States to monitor white blood cell counts for patients on clozapine (Citrome *et al.*, 2016: 164).
- Pharmacological and non-pharmacological interventions are useful to manage the adverse effects (Iqbal *et al.*, 2003; Semple & Smyth, 2013: 215).

- Co-morbidities, drug augmentation and adverse effect management are common reasons for polypharmacy in patients suffering from a psychotic disorder.
- Numerous drug interactions may occur with clozapine and other medications (Edge *et al*., 1997: 5).

The seventh research objective was to determine what constitutes a drug utilisation review and discuss the components thereof:

- Drug utilisation reviews (DURs) are complex, systematic processes.
- The terms drug use evaluation and medication utilisation evaluation (MUE) are used interchangeably with DUR.
- The objective of a DUR is to ensure the rational use of medications (World Health Organization, 2003a: 9; Navarro, 2009: 216).
- DURs assess the drug-use chain, including the processes and outcomes of drug use (World Health Organization, 2003a: 17).
- Three designs are used to describe the type of DUR being performed, namely cross-sectional, longitudinal and continuous (Setia, 2016: 261; Levin, 2006: 24).
- The timing at which the DUR is performed also classifies it as either a prospective, concurrent or a retrospective study (Academy of Managed Care Pharmacy, 2009: 1).
- DUR are performed in four phases (Ashok & Subramanian, 2017: 158; Priya *et al.*, 2018: 2663).
- Different aspects of drug use information can be analysed in DUR studies (World Health Organization, 2003a: 13; Shalini *et al.*, 2010: 805).

The eight research objective was to discuss drug utilisation reviews on psycholeptics in general and specifically on clozapine in the public and private sectors, locally and internationally:

- DUR studies on clozapine in South Africa and Africa are minimal.
- International DUR studies on clozapine are apparent and may be applicable in South Africa (McKean *et al.*, 2008: 266). However, many environmental and patient factors vary in different settings. As a result of this, international study outcomes may not always to suited in the South African context (Emsley & Seedat, 2013: 134).

- A recent DUR study on clozapine in South Africa concluded that compliance with the guidelines for monitoring and prescribing was poor (Moolman, 2013: 258–261).
- Similarly, a study in Brazil also concluded that prescribing guidelines were not being adhered to by psychiatrists, nor was haematological monitoring (Silveira *et al.*, 2015: 166).

The ninth research objective was to conceptualise the most appropriate parameters to conduct a drug utilisation review on clozapine by investigating patient files:

- Different types of drug use information can be evaluated in a DUR (World Health Organization, 2003a: 13; Shalini *et al.*, 2010: 805).
- Topics of analyses for DURs were identified. These include the pattern of use, quality of use and the indices of quality of drug use (Shalini *et al.*, 2010: 804; Sharma, 2018: 453).
- A structured data collection tool to investigate the prescribing patterns of clozapine, the compliance with the recommended treatment guidelines and the identification of medicine problems was developed (ANNEXURE B).
- Study variable and measurement were identified in the patient files (Table 3–2).

The tenth research objective was to explain statistical terminologies that will be used to analyse the data obtained from the empirical study:

- Statistical analysis was done using the computer software Statistical Analysis System® (SAS Institute Inc.).
- Variables were analysed using descriptive statistics, including frequencies (n), percentages (%), means, medians and standard deviations.
- Descriptive statistics are mathematical techniques to organise, summarise, categorise and present the collected data (De Muth, 2006: 1).
- Comparisons were made using inferential statistics and specifically the chi-square test.

- Inferential statistics infer or make predictions about a population based on a sample from the given population (De Muth, 2006:1).
- The chi-square test (χ^2) determines whether there is an association between proportions of two or more categorical variables (Neuman, 2014: 424).
- When the *p*-value is associated with the chi-squared test, it is indicating the probability that the differences between the expected and observed frequencies could be the result of a sampling error (Randolph & Myers, 2013).
- The Cramér's V is useful in interpreting the relative strength of the association between two variables. Cramér's V value can range from 0 (no association) to 1 (perfect association) (Crewson, 2016).

5.2.2 Empirical Study

Conclusions were drawn from the investigation done during the empirical study. The results obtained from this study will address the objectives that were set out in Chapter 1.

The first research objective was to determine the prescribing patterns of clozapine and compliance with the recommended treatment guidelines:

- The demographical profile of the patients on clozapine was investigated to understand the prescribing patterns.
- A total of 57 patients on clozapine therapy were identified as the sample population who met the inclusion criteria.
- Of the 57 patients, 72.00% were male (n=41) and 28.00% were female (n=16).
- 29.82% (n=17) of the patients in the sample were between the age of 30 and 38 years, and 28.07% (n=16) of the patients were between the age of 39 and 47 years.
- Most males were between the ages of 30 and 38 (n=14; 82.35%), while most females were between the age of 39 and 47 years (n=6; 37.50%). This correlated with the studies done by Haffner *et al.* (1994: 30) depicted in the literature review. The literature described the earlier development of male psychosis compared to female psychosis.

- Patients of African descent made up the majority of the sample population (n=35; 61.40%), followed by patients of Caucasian descent who made up 21.05% (n=12) of the patients.
- Literature has indicated that genetic polymorphisms differ in different ethnicities and races and this affects the prevalence of certain adverse effects according to ethnicity. Patients of African-American descent portray more prevalent cases of weight gain and aggressive behaviour as an adverse effect of clozapine.
- The age range of the majority of the patients of African descent was between 30 and 47 years.
- The social histories of the patients in the study sample were obtained. There was a lack of information regarding the smoking status of most patients in the sample. This result does not allow for the dosages of clozapine to be accurately assessed for correctness.
- Only 20 (30.09%) of the patients had accessible information of any history on alcohol use. The majority of this percentage had a history of alcohol use (n=14; 24.56%). Alcohol causes CNS effects which have an additive sedative effect in patients on treatment with clozapine.
- More than half of the patients in the study sample had no history of substance use. Amongst the other patients, cannabis (dagga) was the most widely used substance (n=12; 21.05%). Substance-induced psychosis has the potential to develop into schizophrenia in vulnerable patients, cannabis provides the strongest association (Alderson *et al*., 2017: 2548).
- A significant proportion of the study sample had no information in their patient files concerning their history of suicide risk. Psychiatric conditions are a notable factor in many suicide cases. There were 12 patients (21.05%) in the study sample that previously had a suicidal encounter.
- Although the age distribution suggests that the majority of the patients in the study sample are in their prime employable years, only 2 patients were recorded to be employed (3.51%). This result may be accounted for by the missing information regarding the occupation of 40.35% (n=23) of the patients. It was still noted that 29.82% were confirmed to be unemployed (n=17). Literature has confirmed the capabilities of patients on clozapine to be fully employed after initiation of the drug.

- Research has stated that the quality of life and overall wellbeing of a married person is higher than a divorcee or a single person. It is suggested that married people are more prone to remission. The results obtained portrayed that 42.11% (n=24) of the study sample were single, and only 2 of the patients (3.51%) were married. The majority of the patients did not have any information expressing their current marital status (n=27; 47.37%).
- The number of previous hospital admissions were investigated in an attempt to understand if patients on clozapine treatment were initiated as outpatients or inpatients. Inpatient information was kept in separate files that were not accessible, therefore initial data on dosage titration was scarce or inconsistent. As a result, no evident correlation of previous hospital admission and adherence to clozapine prescribing guidelines were identified.
- The genetic risk of acquiring schizophrenia has been established in the literature, with the highest risk occurring in monozygotic twins and where both parents were diagnosed with schizophrenia. The family history of the patients in the study sample was investigated and the overwhelming majority did not have any information of their family history present (n=52; 91.23%). Only 8.77% of the patients were confirmed to have a history of schizophrenia occurring in a family member (n=5).
- There were no pregnant or breast-feeding female patients in the study sample. Clozapine is a Risk B medication in pregnant patients, the use of the drug is not recommended unless the benefit outweighs the risk. Lactating mothers are not advised to take clozapine whilst breast-feeding.
- No cases of porphyria were reported in the study sample. Porphyria has similar symptoms compared to psychotic disorders.
- Many patients present with co-morbid disease states, some of which could be pre-existing conditions or as a result of the adverse effects of clozapine. Metabolic or endocrine disorders were the most prevalent, occurring in 29.82% of patients in the study sample (n=17). This also highlights the importance of metabolic monitoring during clozapine treatment.
- Psychiatrists diagnosed the patients at the study site as recommended in the South African STGs. Schizophrenia was the most common primary diagnosis.

- The majority of the patients diagnosed with schizophrenia were of African descent (n=33; 61.11%).
- Male patients made up 72.22% of the patients diagnosed with schizophrenia in the study population (n=39). This correlates with the literature which indicated that males are more likely to develop schizophrenia, although the lifetime risk of both genders is equal.
- The different types of schizophrenia were explored, with the majority of the patients diagnosed with paranoid-type schizophrenia (n=14; 24.56%), followed by treatment-resistant schizophrenia (n=11; 19.30%).
- Positive symptoms occurred more frequently than negative or cognitive symptoms. Of the positive symptoms, hallucinations and delusions were the most frequently, occurring in 29.82% of the patients (n=17). As the literature stated, these symptoms are amongst those that allow for the most accurate diagnosis of schizophrenia.
- Most of the patients in this study sample were on their first trial of clozapine (n=45; 78.95%). There were 6 patients (10.53%) who had previously been on a trial of clozapine; this could indicate to a number of factors that could be further investigated such as including previously failed therapy, remission and non-adherence.
- Clozapine is offered in cases of schizophrenia that has not been responsive to at least two antipsychotic drugs, one of which is a non-clozapine SGA (National Institute for Health and Care Excellence, 2015: 24). Previous trials of other antipsychotic medications were investigated and 63.16% (n=36) of the patients were on treatment with other antipsychotics before being initiated on clozapine.
- Risperidone, which is an SGA, was the most commonly used antipsychotic drug prior to clozapine initiation (n=21; 58.33%). Haloperidol which is an FGA was the second most common antipsychotic used (n=15; 41.67%).
- The compliance to the guidelines regarding previous antipsychotic drug trials were assessed in the empirical study. Of the 36 patient files that had available data, 61.11% (n=22) complied with the recommended guidelines. The most common trials included at least two previous antipsychotics of which one was an SGA (n=15), and at least two previous antipsychotics of which both were an FGA (n=15).

- The most common reason for stopping the previous trials of antipsychotics was due to failed therapy (n=25; 69.44%). Adverse effects were also prevalent in 22.22% of the patients (n=8).
- The historical and current clozapine treatment was analysed. The dosages and intervals for the initial titration of clozapine in most outpatient files was not available. It was assumed that many initiation dosage titrations are found in the inpatient files that were not available in this study. Most data alluded to the fact that patients were initiated on a maintenance dosage of clozapine without titration, which does not imply compliance with the guidelines.
- Only 15.79% (n=9) of the patients were confirmed to have clozapine titration performed upon initiation. The Maudsley prescribing guidelines suggest that a cross-tapering method be applied when patients are switching from a previous antipsychotic to clozapine (Taylor *et al.*, 2009: 76).
- The average duration of current clozapine treatment was 6.69 years ± 5.43 years (n=52). The standard deviation signifies the interpatient variability of this result. The minimum duration of years for a patient on clozapine in this study sample was 2.4 months, while the maximum duration for another patient in this study was 22.00 years.
- The maximum and maintenance dosages of the current clozapine treatment for each patient was analysed and assessed for compliance with the guidelines (n=57).
- The mean maximum dosage was 352 mg ± 134.50 mg. This was well below the stipulated maximum dosage for patients on clozapine which should not exceed 900 mg (Rossiter, 2016: 481). The patients with the highest dosages of clozapine did not exceed 600 mg per day, including divided dosages. The highest maximum dosage recorded was 600 mg, whilst the lowest recorded was 100 mg.
- The mean maintenance dosage was 295 mg ± 116.20 mg. This was within the range of the recommended 200-450 mg/day stated in the South African Medicines Formulary (SAMF) (Rossiter, 2016: 481). The highest maintenance dosage recorded was 600 mg, whilst the lowest dosage recorded was 100 mg.
- Baseline haematological and metabolic monitoring was not evident in the majority of the outpatient files assessed.

- Haematological monitoring was done in 42 patients (73.68%). Of these patients, the monitoring intervals were found to be varied and inconsistent in many cases. The guidelines express how the interval of monitoring is dependent on the duration of clozapine treatment. A monthly WBC count is required for the duration of the treatment after the initial year (Swingler, 2013: 154). A cause of concern is evident as only 23.81% (n=10) of the patients were fully compliant with the recommended guidelines.
- Metabolic monitoring was done in 80.70% of the patients in the study sample (n=46). Compliance with the guidelines were analysed.
- Of the 46 patients, monthly checks were recorded for weight in 39 patients (84.78%), and the height was recorded in 16 patients (34.78%). It is concluded that weight monitoring is not fully compliant with the guidelines in at least 31.58% of the study sample.
- The fasting lipogram monitoring should be assessed at 12 weeks and every 5 years. This monitoring was done at least once in 66.67% of the patients (n=38). However, the recommended intervals varied and were not strictly adhered to.
- Fasting blood glucose tests were recorded in 61.40% (n=35) of the patients. The intervals of testing varied in patients and were not in compliance with the guideline.
- Haematological and metabolic monitoring were not fully compliant with the guidelines regarding consistent monitoring patterns and correct monitoring intervals.

The second research objective was to identify medication problems associated with the use of clozapine:

- Augmentation treatment was identified in 73.68% (n=42) of patients in the study sample. One drug was used to augment clozapine treatment in 54.76% of these patients (n=23).
- Sodium valproate was the most frequently prescribed drug used in augmentation treatment (n=12).
- A pharmacotherapeutic assessment using the literature concluded that 32 patients (56.14%) could have possibly encountered drug interactions with clozapine.

- Drug interactions with clozapine were evident in 40 patients (56.14%).
- In 19 patients (47.50%), one drug interaction with clozapine was recorded.
- In 16 patients (40.00%) two drug interactions with clozapine were recorded.
- In 4 patients (10.00%) three drug interactions with clozapine were recorded.
- Only 1 patient (2.50%) had four drug interactions with clozapine recorded.
- In 12 cases, sodium valproate interacted with clozapine (30.00%). In 12 cases metformin interacted with clozapine (30.00%). In 11 cases atenolol interacted with clozapine (27.50%).
- One case of an interaction of carbamazepine with clozapine was recorded. The result of this could be the occurrence of neuroleptic malignant syndrome, or pancytopenia which is potentially life-threatening. Six cases of propranolol interacting with clozapine was recorded. Beta blockers used concomitantly with clozapine could result in respiratory depression which is potentially fatal.
- Most depot formulations are not advised to be used concomitantly with clozapine as they are prone to induce neutropenia. There were 9 cases of zuclopenthixol and 1 case of fluphenazine recorded on the current prescription of patients in the study sample.
- Caution needs to be exercised when additional drugs are prescribed concomitantly with clozapine. Careful patient assessments are required to ensure drug interactions are noticeable at an early stage and the necessary treatment is initiated.
- Any adverse reactions caused by clozapine treatment was analysed in the patient files.
- Adverse reactions were recorded in 91.23% (n=52) of the patients in the study sample. This is a significant proportion of the study population.
- Weight gain was the most frequently reported adverse effect amongst the patients (n=16; 30.77%). This was followed by the occurrence of tachycardia reported in 25.00% of the patients (n=13). Hypersalivation was also very common in 23.08% of the patients (n=12).
- The less common adverse effects were also investigated. Adverse effects that primarily affect the CNS were experienced in 32.69% of the patients (n=17), followed by EPSE that occured in 14 patients (26.92%).

- Any management of the reported adverse effects were analysed on the most current prescriptions in the outpatient files. Pharmacological management of adverse reactions caused by clozapine was noted in 70.18% (n=40) of the patients. These medications were suited to each patient individually, they included antidiabetics, antihypertensives and anticholinergics among others.

5.3 Recommendations

The drug utilisation review yielded valuable results and conclusions that allows for the following recommendations to be made:

- A multi-disciplinary team of healthcare professionals play a valuable role in attaining information that will result in better therapeutic outcomes for the patients. The acquiring of demographical information allow for all factors to be assessed for the most suitable therapeutic decisions to be made at the patient level. The primary investigator noted the lack of consistent demographical information in the outpatient files. Social histories must be attained prior to clozapine treatment consistently by healthcare professionals in the patient file, and follow-ups on the current social factors of the patient must be made and recorded. Healthcare professionals should keep promoting healthy lifestyle practices to the patients on clozapine treatment.
- The lack of inpatient information in patients who have any history of hospital admissions was also evident. This made analysis of patient history more difficult for professionals who have never encountered the patient previously. It is recommended that copies of these records be included in the outpatient file to allow for the full clinical history of the patient to be easily accessible. Healthcare professionals would then be able to make effective consultations knowing their history and previous interventions. This would allow for more effective prescriptions.
- In some cases there was an overlap of prescribed medicines for co-morbid disease states or adverse reaction management in the psychiatric hospital and the primary health care clinics or private prescriptions. Prescribers and pharmacists of different institutions must liaise with each other about patient prescriptions to ensure that patients are not over-prescribed medications and the safe use of medicines is ensured.

- Information in patient files from other institutions that the patient visits must be acquired by the multidisciplinary health care team to allow for a more accurate outlook of the patients' treatment plans. Clinics that the patient may been down-referred to may continue therapy according to the guidelines and ensure the correct monitoring patterns are ensured.
- Healthcare professionals must continue their professional development regarding to the treatment guidelines of clozapine. **The primary investigator provided a presentation to a multidisciplinary team of healthcare professionals on the use, effects and monitoring of clozapine. The audience of the presentation was the nursing staff, psychiatrists and pharmacists at the hospital.** Presentations such as these allow for healthcare professionals to further understand the treatment of the patients on clozapine, to be aware of the symptoms of any adverse reactions, for suitable interventions to be employed in cases of adverse reactions as well as the following of the recommended monitoring guidelines.
- The severe-adverse effects of clozapine need to be emphasised to patients and healthcare professionals. Recognising the symptoms of agranulocytosis is paramount to ensure that the adverse reaction is managed timeously. All healthcare professionals should emphasise the importance of this to all patients on clozapine treatment. It is a big responsibility for pharmacists to ensure that critical information is given to the patient when they are counselled on their medication.
- Educating not only the patient, but also their family or caregiver on treatment with clozapine is important. The importance of adherence to dosages, reporting of adverse effects and their management must be outlined. Pharmacists are responsible for the counselling. **The primary investigator pioneered these exercises as part of a wellness clinic at the psychiatric hospital for inpatients who were being discharged. This exercise was beneficial to ensure adherence by the patient and for the families to understand the treatment.**

- The use of alcohol, tobacco and substances must be thoroughly investigated during patient counselling. A lack of information on the smoking status of the patients does not allow for the dosages of the patients who smoke to be accurately assessed for correctness. Psychiatrists and other healthcare professionals must be educated on the implications of tobacco use and its effects on clozapine plasma levels to ensure that the patient is prescribed the most accurate dosage for an effective outcome. Patients must be educated on the harmful effects of smoking on their health and its effects on clozapine metabolism.
- Patients should be educated on the harmful effects of substances, such as alcohol and cannabis (dagga). These substances induce psychotic symptoms which are counterproductive in the treatment of psychotic disorders. Some may also effect the metabolism of clozapine and decrease its efficacy.
- **Patient information leaflets were prepared by the primary investigator to assist outpatients with information on clozapine, such as indications, adverse effects and monitoring requirements. The patient information leaflet that was prepared by the researcher and handed out to patients and their family members as well as nursing staff is shown in ANNEXURE G.**
- The metabolic and haematological baseline and maintenance monitoring patterns were not adhered to according to the guidelines. The healthcare team must take responsibility in ensuring that these tests are completed in all patients on clozapine treatment. Referral to the monitoring guidelines, such as the NICE guidelines or the SAMF must be made to ensure the correct procedures are being adhered to.
- A haematological monitoring chart was present in some, but not all outpatient files. The charts were not always fully completed, or adhered to systematically. It is recommended that these monitoring charts are always included in the file in a visible place. A systematic approach to adhering to the monitoring patterns can be formulated amongst the health care team to allow for responsibility in ensuring that the white blood cell (WBC) count are done consistently at the correct intervals.

- Follow-ups on patients who are not adhering to the haematological monitoring patterns should be prioritised and education on the dire consequences of non-adherence should be reiterated to all patients on clozapine treatment.
- A chart for the routine metabolic monitoring in patients on clozapine would be a useful tool as it was evident that the monitoring guidelines were not being adhered to. This tool could be implemented for nursing staff at the psychiatric hospital to be consistent in their efforts to perform the monitoring tests at the correct intervals, and for easier monitoring of the intervals of tests for each specific patient.
- Following knowledge in the literature on the life-threatening adverse effect of agranulocytosis caused by clozapine, interventions to monitor the occurrence of neutropenia should be employed in the national guidelines. These guidelines may be adapted from the clozapine REMS strategy which ensures that prescribers, in this case psychiatrists, and patients who take clozapine are registered to a program that solely ensure the safety of clozapine use in all patients. Such a program in South Africa would ensure national accountability of correct prescribing and early detection of adverse effects of clozapine.
- Nationally, there is no template for the initiation of clozapine. The South African STGs (Maartens *et al.*, 2015: 15.15) do no stipulate a dosage titration pattern and the SAMF gives a very brief outline of a dosage titration of clozapine upon initiation (Rossiter, 2016: 481). The study by Moolman (2013: 266) recommended the adaptation of NICE guidelines in the STGs. This is reiterated in this study as similar results made it evident of the lack of national guidelines.
- The National Health Insurance (NHI) has acknowledged the high burden that mental illness has in South Africa. The government notice stipulated that mental health services of focus include increased prevention, screening, care, treatment and rehabilitation inclusive of community mental health services (Department of Health, 2017: 37). Clozapine prescribing and monitoring strategies would be ideally initiated by the NHI to ensure consistent interventions nationally in public sector hospitals. The strategies employed must take into account the resource-limited areas and present practical outcomes to allow for efficacious and safe use of medicines.

- Investigations may be performed on the reasons for discontinuation and rechallenge of clozapine treatment in patients previously on clozapine treatment.
- Adherence to clozapine treatment may be investigated to understand the extent of efficacy of clozapine treatment.
- The effects of pharmacological and non-pharmacological augmentation interventions of clozapine may also be investigated to understand the benefit of the treatment.
- More drug utilisation reviews on clozapine should be done in South Africa to explore the trend of the prescribing and monitoring patterns. Suitable interventions would be applied nationwide with more extensive studies.
- A clozapine monitoring program should be adapted across all public sector hospitals to allow for consistency in patient care.
- The incidence of metabolic adverse effects with clozapine treatment should be researched more extensively.

5.4 Limitations of the study

The following limitation were found during the study research:

- The data was based in one public hospital in one province in South Africa, therefore the results cannot be generalised to suit the nationwide prescribing and monitoring trends.
- The study setting was a public sector institution, and this did not account for clozapine use in patients in the private sector. Monitoring and prescribing patterns may differ in the private sector.
- Some patient files were not fully comprehensive and lacked data. This did not allow for all factors to be fully explored in depth.
- The prescribing and monitoring guidelines were based on national and international guidelines. However, the national guidelines were not as extensive and many programs for consistent monitoring patterns could be adopted from the international guidelines.
- None of the diagnoses made were according to the latest DSM-5® or the ICD 11.

- The study focused only on outpatients, therefore caution needs to be exercised not to generalise these results to represent inpatient prescribing and monitoring patterns.

5.5 Chapter 5 summary

The objectives of the study were discussed in this chapter according to the outcomes of the literature review and the empirical study. All the objectives were achieved. Recommendations were made according to the conclusions and the limitations of the study were stated.

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ANNEXURE A.
INITIAL DATA COLLECTION TOOL

DATA COLLECTION TOOL

Demographics					
Patient identification					
Date of birth			**Age**		
Gender	Male			Female	
Race	Caucasian	African	Asian	Coloured	Other:
Weight	kg	**Height**	m	**Body Mass Index**	kg/m^2

Social history				
Tobacco use	Y	N	Details:	
Alcohol use	Y	N	Details:	
Substance/Drug use	Y	N	Details:	
Suicide risk	Y	N	Details:	
Occupation/Employment			**Marital status**	
Pregnancy status	Y	N	Details:	Weeks
Breast feeding	Y	N	Details	
Living circumstances				
Daily activities				

Medical history				
Allergies	Y	N	Details:	
Porphyria	Y	N	Details:	
Past/Chronic medical conditions				
Co-morbid diseases states				
Hospital and surgical history	Y	N	Details:	
Family history				
Medical alerts	Y	N	Details	
Chief complaint				
Diagnosis			Date of initial diagnosis:	
Initial episode			Date of initial episode:	
General condition				

Admission History	
Date of admission	
Date of discharge	

Number of previous admissions	1	2	3	Other:

Clozapine usage				
Date of first initiation of clozapine available?	Y	N	Date:	
Has the patient taken clozapine before?	Y	N	Details:	
How long has the patient been on clozapine?	Weeks/months/years			
Date on which clozapine was initiated in hospital				
Duration of hospital stay after clozapine initiation	Weeks/months/years			

Current medication (excluding Clozapine)

Drug	Dosage form	Route	Dosage	Interval	Date started	Date stopped	Reason

Past medication (excluding Clozapine)

Drug	Dosage form	Route	Dosage	Interval	Date started	Date stopped	Reason

Reason for stopping medication codes:
ST = Successful Therapy; FT = Failed Therapy; SE = Side effect; AL = Allergy; FC = Formulary change; NC = Non- adherent; Saf = Safety; DxC = Change in Diagnosis

Other medications			
Is there information of any previous antipsychotics that were used?	Y	N	
If yes, what are the names?			
Were any antipsychotics used before clozapine?	Y	N	

Drug interactions			
Possible interactions identified	Y	N	
If yes, give information on possible interactions			

Adverse reactions				
Reported adverse reactions	Y	N		
If yes, which reactions were experienced?	Agranulocytosis	Hypersalivation	Constipation	Weight gain
	Hypertension	Nausea	Fever	Seizures
	Hypotension	Tachycardia		
	Other:			
Was the adverse reaction treated?	Y	N	Details:	
	Y	N	Details:	
	Y	N	Details:	
	Y	N	Details:	
	Y	N	Details:	
Neurological functions	Changes in symptom complex; mood:			
	Depressed	Euphoric	Anxious	Irritable/hostile
	Sleepy	Energetic	Self-esteem:	
	Psychomotor Skills:			
	Agitation	Retardation	Suicidal	High risk behaviour
	Racing thoughts	Talkative	Reserved	
	Extrapyramidal symptoms:			
	Pseudoparkinsonism		Other:	

Baseline monitoring				
Parameter	**Y**	**N**	**Date**	**Result**
Haematological monitoring				
Full blood count (FBC)				
White blood cell count (WBC)				
Absolute Neutrophil Count (ANC)				
Differential Count (DC)				
Metabolic monitoring				
Weight (kg)				
Height (m)				
Body Mass Index (kg/m^2)				
Waist circumference (cm)				
ECG				
Fasting blood glucose (mmol/l)				
Fasting lipogram:				
Total cholesterol (mmol/l)				
Triglycerides				
LDL (mmol/l)				
Pulse (beats/min)				
Temperature (^{o}C)				
Respiratory rate (breaths/min)				
Blood Pressure (mmHg)				
Physical examination				

Clozapine dosage titration chart					
Was titration performed from the initial dosage?			Y	N	No info
What was the initial dosage supplied upon first administration on day 1 of clozapine use?					
	12.5mg	25mg	37.5mg	Other:	
What was the dosage supplied upon first administration on day 2 of clozapine use?					
	25mg	50mg	75mg	Other:	
Which increment was the dosage increased for the first 2-3 weeks of the titration period?					
Increments < 50 mg/day		Increments = 50 mg/day		Increments > 50 mg/day	
Maintenance dosage:			**Maximum dosage:**		

Recorded titration of clozapine from initiation			
Day of titration period	Date	Dosage	Frequency

Prescriber details				
Who prescribed clozapine?				
Was it in consultation with a psychiatrist?		Y	N	No info

ANNEXURE B.
REVISED DATA COLLECTION TOOL

Demographics					
Patient identification number					
Date of birth			Age		
Gender	Male			Female	
Race	Caucasian	African	Asian	Coloured	Other:
Weight	kg	**Height**	m	**Body Mass Index**	kg/m^2

Social history				
Tobacco use	Y	N	Details:	
Alcohol use	Y	N	Details:	
Substance/Drug use	Y	N	Details:	
Suicide risk	Y	N	Details:	
Occupation/Employment			**Marital status**	
Pregnancy status	Y	N	Details:	Weeks
Breast feeding	Y	N	Details	
Living circumstances				
Daily activities				

Medical history				
Allergies	Y	N	Details:	
Porphyria	Y	N	Details:	
Past/Chronic medical conditions				
Co-morbid diseases states				
Hospital and surgical history	Y	N	Details:	
Family history				
Medical alerts	Y	N	Details	
Chief complaint				
Diagnosis			Date of initial diagnosis:	
Initial episode			Date of initial episode:	

Clozapine usage				
Has the patient taken clozapine before?	Y	N	Details:	
Date of first initiation of clozapine (if available)	Y	N	Date:	
How long has the patient been on clozapine?	Weeks/months/years			
Date on which clozapine was initiated in hospital if available				
Duration of hospital stay after clozapine initiation if applicable	Weeks/months/years			

Current medication (excluding clozapine)							
Drug	**Dosage form**	**Route**	**Dosage**	**Interval**	**Date started**	**Date stopped**	**Reason**

Past medication (excluding clozapine)							
Drug	**Dosage form**	**Route**	**Dosage**	**Interval**	**Date started**	**Date stopped**	**Reason**

Reason for stopping medication codes:

ST = Successful Therapy; FT = Failed Therapy; AE = Adverse effect; AL = Allergy; FC = Formulary change; NC = Non- adherent; Saf = Safety; DxC = Change in Diagnosis

Other medication			
Were any antipsychotics used before clozapine?	Y	N	
If yes, what are the names?			
Is there information of any previous antipsychotics that were used?	Y	N	

Drug interactions			
Possible interactions identified	Y	N	
If yes, give information on possible interactions			

Adverse reactions				
Reported adverse reactions	Y	N		
If yes, which reactions were experienced?	Agranulocytosis	Hypersalivation	Constipation	Weight gain
	Hypertension	Nausea	Fever	Seizures
	Hypotension	Tachycardia		
	Other:			
Was the adverse reaction treated?	Y	N	Details:	
	Y	N	Details:	
	Y	N	Details:	
	Y	N	Details:	
	Y	N	Details:	
Neurological functions	Changes in symptom complex; mood:			
	Depressed	Euphoric	Anxious	Irritable/hostile
	Sleepy	Energetic	Self-esteem:	
	Psychomotor Skills:			
	Agitation	Retardation	Suicidal	High risk behaviour
	Racing thoughts	Talkative	Reserved	
	Extrapyramidal symptoms:			
	Pseudoparkinsonism		Other:	

Baseline monitoring				
Parameter	Y	N	Frequency	Result
Haematological monitoring				
Full blood count (FBC)				
White blood cell count (WBC)				
Absolute Neutrophil Count (ANC)				
Differential Count (DC)				
Metabolic monitoring				
Weight (kg)				
Height (m)				
Body Mass Index (kg/m^2)				
Waist circumference (cm)				
ECG				
Fasting blood glucose (mmol/l)				
Fasting lipogram:				
Total cholesterol (mmol/l)				
Triglycerides				
LDL (mmol/l)				
Pulse (beats/min)				
Temperature (^oC)				
Respiratory rate (breaths/min)				

Blood Pressure (mmHg)				

Clozapine dosage titration chart					
Was titration performed from the initial dosage?			Y	N	No info
What was the initial dosage supplied upon first administration on day 1 of clozapine use?					
	12.5mg	25mg	37.5mg	Other:	
What was the dosage supplied upon administration on day 2 of clozapine use?					
	25mg	50mg	75mg	Other:	
With which increment was the dosage increased for the first 2-3 weeks of the titration period?					
Increments < 50 mg/day		Increments = 50 mg/day		Increments > 50 mg/day	
Maintenance dosage:			**Maximum dosage:**		
Recorded titration of clozapine from initiation					
Day of titration period	**Date**	**Dosage**		**Frequency**	

ANNEXURE C.
LETTER OF APPROVAL FOR STUDY FROM RHODES UNIVERSITY FACULTY OF PHARMACY HIGHER DEGREES COMMITTEE

RHODES UNIVERSITY
Where leaders learn

Faculty of Pharmacy
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19 July 2018

Professor J. Bodenstein
Faculty of Pharmacy
Pharmacology Division
Rhodes University
Grahamstown
6139

Dear Professor Bodenstein

HDC APPROVAL: MS VIMBISAI MUKOKO (STUDENT NUMBER 613M3002)

The Faculty of Pharmacy Higher Degrees Committee has approved the project proposal of Ms Vimbisai Mukoko, entitled "An evaluation of the prescribing and monitoring of Clozapine at a public sector Psychiatric Hospital".

Thank you.

Yours sincerely

PROFESSOR S. DAYA
HEAD AND DEAN: FACULTY OF PHARMACY

FACULTY OF PHARMACY
RHODES UNIVERSITY
GRAHAMSTOWN 6139
SOUTH AFRICA

ANNEXURE D.
LETTER OF ETHICAL APPROVAL FOR STUDY FROM RHODES UNIVERSITY FACULTY OF PHARMACY RESEARCH ETHICS COMMITTEE

RHODES UNIVERSITY
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Faculty of Pharmacy
Artillery Road, Grahamstown, 6139, South Africa
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Grahamstown 19th August 2018

From:
Associate Professor Roman Tandlich, PhD
Chairperson of the Faculty of Pharmacy Ethics Committee
Faculty of Pharmacy
Rhodes University
P.O. Box 94
Grahamstown 6140
South Africa
e-mail: r.tandlich@ru.ac.za

To:
Professor Johannes Bodenstein, PhD and collaborators

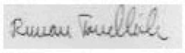
Re: Feedback Letter on Ethics Committee Application PHARM-2018-04.

Dear Professor Johannes Bodenstein, Mrs. Mari-san Bodenstein, Professor Martie S. Lubbe and Ms. Vimbisai M. Mukoko,

Thank for your application for ethical approval entitled: "An evaluating of the prescribing and monitoring of clopazine at a public sector psychiatric hospital". This application was considered by the Faculty of Pharmacy Ethics Committee under the tracking number: PHARM-2018-04. After reviewing the application and after the receipt of the necessary gatekeeper approvals, you have submitted to the Faculty of Pharmacy Ethics Committee I am happy to inform you the Faculty of Pharmacy Ethics Committee grants final approval for your study.

You can proceed with making any necessary arrangements for your project. Please ensure that the Faculty of Pharmacy Ethics Committee is notified should any substantive changes(s) be made, for whatever reason, during the research process.

Yours sincerely,



Roman Tandlich, PhD

CHAIRPERSON: FACULTY OF PHARMACY ETHICS COMMITTEE

ANNEXURE E.
APPROVAL LETTER FOR STUDY FROM FORT ENGLAND HOSPITAL RESEARCH COMMITTEE

FORT ENGLAND HOSPITAL

Private Bag X1002, Grahamstown, 6140. Tel: +27 (0)46 622 7003. Fax: +27 (0)46 622 7630. clinicalsecfeh@gmail.com

RESEARCH PROPOSAL APPROVAL

Date: 02-August-2018

Dear Ms. V.M. Mukoko

Thank you for your application to conduct research at Fort England Hospital. We are pleased to inform you that your research proposal has been approved by the Academic and Research Committee of Fort England Hospital (as indicated below). A copy of our Research Policy is included herewith, for your information. Please do not hesitate to contact us should you require any further information or assistance.

Yours sincerely,

Mo Nagdee
Chair: Academic and Research Committee

Primary Investigator	Name	Ms. V.M. Mukoko		
	Position	M. Pharm. (Pharmacology Student)		
	Student or staff number	G13M3002		
	Address	Artillery Road, Grahamstown, 6139		
	Telephone	046-603 8381		
	Email	Johannes.Bodenstein@ru.ac.za		
Research project	Title	An evaluation of the prescribing and monitoring of Clozapine at a Public Sector Psychiatric Hospital		
	Supervising University / Institution	Rhodes University		
	Supervisor	Prof. J. Bodenstein		
	Ethics Approval from Supervising University / Institution	~~**No**~~	**Yes** (insert ethics clearance reference no.) PHARM-2018-04	
Fort England Hospital Approval	Academic and Research Committee Chair / Clinical Head (M. Nagdee)	~~**No**~~	**Yes** (insert date) 02-August-2018	**Signature**
	Head: Psychology (I. Reid)	~~**No**~~	**Yes** (insert date) 02-August-2018	**Signature**
	Acting CEO (Mr. M. Dyalvane)	~~**No**~~	**Yes** (insert date) 02-August-2018	**Signature** Dyalvane
	Co-Opt Member Head: Pharmacy (S. Willows)	~~**No**~~	**Yes** (insert date) 02-August-2018	**Signature**
Additional comments				

ANNEXURE F.
APPROVAL LETTER FOR STUDY FROM EASTERN CAPE DEPARTMENT OF HEALTH RESEARCH COMMITTEE

Province of the
EASTERN CAPE
HEALTH

Enquiries: Zonwabele Merile
Email: zonwabele.merile@echealth.gov.za
Date: 20 August 2018

Tel no: 083 378 1202
Fax no: 043 642 1409

RE: AN EVALUATION OF THE PRESCRIBING AND MONITORING OF CLOPAZINE AT A PUBLIC SECTOR PSYCHIATRIC HOSPITAL. (EC_201808_009).

Dear Prof J. Bodenstein

The department would like to inform you that your application for the abovementioned research topic has been approved based on the following conditions:

1. During your study, you will follow the submitted amended protocol with ethical approval and can only deviate from it after having a written approval from the Department of Health in writing.

2. You are advised to ensure, observe and respect the rights and culture of your research participants and maintain confidentiality of their identities and shall remove or not collect any information which can be used to link the participants.

3. The Department of Health expects you to provide a progress update on your study every 3 months (from date you received this letter) in writing.

4. At the end of your study, you will be expected to send a full written report with your findings and implementable recommendations to the Eastern Cape Health Research Committee secretariat. You may also be invited to the department to come and present your research findings with your implementable recommendations.

5. Your results on the Eastern Cape will not be presented anywhere unless you have shared them with the Department of Health as indicated above.

Your compliance in this regard will be highly appreciated.

SECRETARIAT: EASTERN CAPE HEALTH RESEARCH COMMITTEE

ANNEXURE G.
PATIENT INFORMATION LEAFLET ON CLOZAPINE

What does clozapine treat?

Clozapine is especially prescribed to patients who have **treatment-resistant schizophrenia**. This means other antipsychotics have failed to show any clinical improvement in the patient.

Other conditions that are indicated for clozapine us:

- Recurring suicidal behaviour in persons with psychotic disorders
- Drug – induced psychosis during the course of Parkinson's disease

References

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RHODES UNIVERSITY
Where leaders learn

Compiled by Vimbisai Mukoko (BPharm). A Rhodes University final-year MPharm (pharmacology) student in collaboration with Pharmaceutical Services at Fort England Hospital

Clozapine

What is clozapine?

Clozapine is an antipsychotic drug which means that it is used to treat psychosis.

How does clozapine work?

A chemical in our brains called dopamine is responsible for regulating our mood and behaviour. Schizophrenia and other psychosis associated conditions occur when there is overactivity of dopamine in our brain.

Clozapine reduces the effect of clozapine in our brain therefore relieving the psychotic symptoms. This helps the patient live a better lifestyle.

The effects of clozapine may not be noticeable immediately. It may take several weeks.

How do you take it?

Clozapine is in the form of tablets that are taken orally with water.

Therapy must be followed as the doctor prescribed and as the pharmacist explained. The first dose given is of low strength and it is increased slowly as prescribed until the required strength is achieved.

⚠ ***Important to note:*** *The dosage plan should be followed accurately for effective therapy to be achieved.*

What are the common side effects?

The highest risk of taking clozapine is developing **agranulocytosis** (lowered white blood cell count) and **neutropenia** (lowered neutrophils – a type of white blood cell).

- Drowsiness
- Sedation
- Fatigue
- Dizziness
- Headaches

- Weight gain
- Constipation
- Excessive saliva
- Dry mouth
- Nausea
- Vomiting

- Loss of bladder control
- Difficulty urinating

What you need to know before and during clozapine therapy:

Due to the risk of developing agranulocytosis and neutropenia, health care professionals will assess your white blood cell count **before** starting clozapine therapy. They must be within the normal range for clozapine to be initiated.

During clozapine therapy white blood cell counts will be assessed weekly for the first 18 weeks after initiation of clozapine. Then every 2 weeks for another year, and then monthly for the remainder of the therapy.

⚠ ***Important to note:*** *sore throat, fever or flu-like symptoms must be reported to the doctor immediately while on clozapine therapy.*

What precautions should I take if I am on clozapine?

Pregnancy: Avoid. Consult your doctor before you plan to get pregnant or if you are already pregnant

Breastfeeding: Avoid. Clozapine is passed into the breast milk of mothers on clozapine

Infants/children: Should not be taken by children under the age of 16

Elderly: Lower doses are prescribed

Hepatic or renal impairment: Lower doses are prescribed

Alcohol and use of substances: Highly discouraged. Avoid