Factors associated with prescribing and dispensing of schizophrenia treatment in the private health sector of South Africa

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PREFACE

This study was conducted in article format, where the results of the empirical objectives stated in the study were presented in Chapter 3 in the form of two manuscripts. The two manuscripts were submitted for publishing in the following journals:

- South African Medical Journal
- Health SA Gesondheid

Use of references in the manuscripts was presented in the style according to the author guidelines for each journal. However, the complete reference list of the dissertation is presented in the reference style of the North-West University.

This dissertation is divided in different chapters. Chapter 1 provides a brief overview of the problem stated for the dissertation, the research aims and objectives as well as the research method followed to conduct the study. Chapter 2 answers and discusses the literature objectives stated in this study, whereas Chapter 3 answers and discusses the empirical objectives. Chapter 4 provides the conclusions made in this study and also provides the strengths, limitations and recommendations that were drawn from the study. References and annexures are provided at the end of the dissertation.

Co-authors named in the manuscripts were also the supervisor and co-supervisors in this study. They gave permission to use the manuscripts as part of the dissertation.

Contributions of each author to the respective manuscripts are provided on the following page.

AUTHOR CONTRIBUTIONS

Contributions of each author involved in the writing of the manuscripts are discussed in the table below:

Manuscript	Author and co-author contributions
Manuscript 3.1 Prescribing and dispensing factors concerning schizophrenia treatment in the South African private health sector during the period 2008-2013	D Husselmann was involved in the following: • Planning and design of the study. • Implementation and data interpretation. • Writing of the manuscript. R Joubert was involved in the following: • Supervision of conception of the study. • Study design. • Implementation and drafting of the study. • Guidance in the interpretation of the results. • Final approval of the version to be published. JR Burger was involved in the following: • Co-supervision of conception of the study. • Study design. • Implementation and drafting of the study. • Data interpretation. • Final approval of the version to be published. MS Lubbe was involved in the following: • Co-supervision of conception of the study. • Acquisition of data. • Performed the statistical analyses. • The study design. • Implementation and drafting of the study. • Data interpretation. M Cockeran was involved in the following: • Responsible for the data analyses. • Content review of the manuscript. All authors read and approved the final manuscript.

Manuscript	Author and co-author contributions
Manuscript 3.2 Maximum potential cost-savings attributable to generic substitution of antipsychotics 2008-2013	D Husselmann was involved in the following: • Planning and design of the study. • Implementation and data interpretation. • Writing of the manuscript. R Joubert was involved in the following: • Supervision of conception of the study. • Study design. • Implementation and drafting of the study. • Guidance in the interpretation of the results. • Final approval of the version to be published. JR Burger was involved in the following: • Co-supervision of conception of the study. • Study design. • Implementation and drafting of the study. • Data interpretation. • Final approval of the version to be published. MS Lubbe was involved in the following: • Co-supervision of conception of the study. • Acquisition of data. • Performed the statistical analyses. • The study design. • Implementation and drafting of the study. • Data interpretation. M Cockeran was involved in the following: • Responsible for the data analyses. • Content review of the manuscript. All authors read and approved the final manuscript.

Authors' declaration of their contribution to the study:

I declare that the above-mentioned contributions to the study are correct. I hereby provide consent that it may be published as part of the MPharm dissertation of D Husselmann.

_____	_____
R Joubert	JR Burger
_____	_____
MS Lubbe	M Cockeran

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ABSTRACT

The aim of this study was to determine the prevalence, medicine prescribing patterns and maximum potential savings through generic substitution in direct treatment costs associated with schizophrenia in the private health sector of South Africa. A literature review and an empirical investigation were employed to achieve the objectives stated in the study.

A retrospective drug utilisation study was conducted in order to analyse antipsychotic medicine prescribing patterns during the period 1 January 2008 to December 31, 2013. Data were obtained from a Pharmaceutical Benefit Management Company while active ingredients used for this study were identified using the MIMS classification system. Results from the study were presented in the form of two manuscripts. Manuscript one employed two study populations. The study population used to determine prescribing patterns consisted of all patients with an ICD-10 code (F20-F20.9) with paid medicine claims from their prescribed minimum benefits (N = 4 410). The population employed to determine dispensing patterns (manuscript one) included all patients with more than two claims reimbursed from their prescribed minimum benefits for antipsychotics in conjunction with ICD-10 codes F20 to F20.9 on claims (N = 1 780). The study population used to determine prescribing patterns (N = 4 410) was also used for manuscript two, for the calculation of potential cost-savings due to generic substitution.

Prescribing patterns were observed by comparing the actual prescribed daily doses (PDDs) with the maximum recommended daily doses (MRDDs) allowed as well as through evaluating the prescribing volume of antipsychotics by prescriber speciality. The medicine possession ratio (MPR) calculation was used as proxy to determine patient compliance related to the antipsychotics prescribed. The maximum potential direct cost-savings were determined by generically substituting all originator and more expensive generic drugs with the least expensive generic item that was available on the dataset during the study period.

In this study, female patients showed a higher prevalence of schizophrenia than males overall; however, patients presented with a higher prevalence between the ages 18 to 35 years, whereas women had a higher prevalence above the age of 35 years. The majority of prescriptions were prescribed by psychiatrists (60.88%). Several antipsychotics were prescribed above the maximum recommended doses.

Factors that played a significant role in compliance were the type of active ingredient ($p < 0.0001$; Cramer's $V = 0.1287$) and length of treatment period ($p < 0.0001$; Cramer's $V = 0.2477$). Clozapine (59.61%) and haloperidol (56.95%) had the highest compliance status

categorised in the compliance group. Compliance increased for patients on antipsychotic treatment for longer than four months (54.76%).

The total cost of antipsychotic treatment amounted to R 52 647 520.38 during the study period. If generic substitution was fully applied R 4 642 685.45 (39.21%) could have been saved. As the availability of generic items on the South African market increased, the number of generic items claimed also increased (60.31%) during the study period; however, psychiatrists still favoured prescribing of non-generic items (40.63%) during 2013. This may also be one of the factors that caused the large increase in patient contribution (726.94%) during the study period.

In conclusion, this study emphasised possible factors that impact on patient compliance towards antipsychotic treatment and the economic strain schizophrenia medicine treatment places on patients and healthcare systems. Factors influencing a prescriber's choice of drug, including factors influencing a patient's compliance and the potential economic impact of schizophrenia were highlighted.

KEYWORDS: schizophrenia, antipsychotics, active ingredients, antipsychotic treatment, therapeutic algorithm, prescribed minimum benefits, ICD-10 codes, prescribing patterns, dispensing patterns, compliance, symptoms, generic items, originator items, generic substitution, costs, potential cost-savings

OPSOMMING

Die doel van hierdie studie was om die voorkomssyfer, medisynevoorskryfpatrone, en maksimum potensiële besparings deur die gebruik van generiese substitusie in direkte behandelingskostes verbonde aan skisofrenie in die private gesondheidsektor van Suid-Afrika te bepaal. 'n Literatuuroorsig en empiriese ondersoek is ingespan om die gestelde doelwitte te bereik.

'n Retrospektiewe medisyneverbruikstudie is uitgevoer om sodoende die antipsigotiese medisynevoorskryfpatrone vanaf 1 Januarie 2008 tot 31 Desember 2013 te analiseer. Data is bekom vanaf 'n farmaseutiese voordeelbestuursmaatskappy, terwyl aktiewe bestanddele gebruik in hierdie studie geïdentifiseer is deur gebruik te maak van die MIMS-klassifikasiestelsel. Resultate van die studie is voorgelê in twee manuskripte. Manuskrip een het van twee studiepopulasies gebruik gemaak. Die studiepopulasie gebruik om die voorskryfpatrone te bepaal het bestaan uit alle pasiënte met 'n ICD-10-kode (F20-F20.9) met betaalde mediese eise vir hul voorgeskrewe minimum voordele (N = 4 410). Die populasie gebruik om reseptuurpatrone te bepaal (manuskrip 33n) het alle pasiënte ingesluit met meer as twee eise terugbetaal vanuit hul minimum voordele vir antipsigotiese middels tesame met ICD-kodes F20 tot F20.9 op eise (N = 1 780). Die studiepopulasie gebruik om voorskryfpatrone (N = 4 410) te bepaal is ook gebruik in manuskrip twee vir die berekening van potensiële kostebesparings weens generiese substitusie.

Voorskryfpatrone is waargeneem deur die vergelyking van die werklike voorgeskrewe daaglikse doserings met die maksimum aanbevole daaglikse doserings toegelaat sowel as deur die evaluering van die voorskrifvolume van antipsigotiese middels deur voorskrywerspesialiteit. Die veranderde-medisyne besit verhouding berekening is gebruik as prokurasie om pasiëntvoldoening verwant aan die antipsigotiese middels wat voorgeskryf is, te bepaal. Die maksimum potensiële direkte kostebesparing is bepaal deur die generiese substitusie van alle oorspronklike en duurder generiese medisyne met die goedkoopste generiese item wat op die datastel beskikbaar was gedurende die studietydperk.

In hierdie studie het vroulike pasiënte 'n hoër voorkoms van skisofrenie getoon as mans oor die algemeen; pasiënte het egter hoër voorkoms getoon tussen die ouderdomme 18 en 35 jaar, terwyl vroue 'n hoër voorkoms gehad het bo die ouderdom van 35. Die meerderheid van voorskrifte is voorgeskryf deur psigiaters (60.88%). Verskeie antipsigotiese middels is bo die maksimum aanbevole dosis voorgeskryf.

Faktore wat 'n beduidende rol gespeel het in voldoening was die tipe aktiewe bestanddeel ($p < 0.0001$; Cramer se $V = 0.1287$) en duurte van behandelingstydperk ($p < 0.0001$; Cramer se $V = 0.2477$). Clozapine (59.61%) en haloperidol (56.95%) het die hoogste voldoeningstatus in die voldoeningsgroep gehad. Voldoening het toegeneem vir pasiënte op antipsigotiese behandeling vir langer as vier maande (54.76%).

Die totale koste van antipsigotiese behandeling het R52 647 520.38 gedurende die studietydperk beloop. Indien generiese substitusie ten volle toegepas is, kon R4 642 685.45 (39.21%) gespaar gewees het. Soos wat die beskikbaarheid van generiese items in die Suid-Afrikaanse mark toegeneem het, het die aantal generiese items geëis ook, gedurende die studie, toegeneem (60.31%); psigiaters verkies egter steeds om nie-generiese items gedurende 2013 voor te skryf (40.63%). Dit mag ook een van die faktore wees wat die groot toename in pasiëntebydraes (726.94%) gedurende die studietydperk veroorsaak het.

Hierdie studie beklemtoon gevolglik moontlike faktore wat 'n impak het op pasiënte se voldoening aan antipsigotiese behandeling en die ekonomiese spanning wat mediese behandeling vir skisofrenie op pasiënte en gesondheidsorgstelsels plaas. Faktore wat 'n voorskrywer se keuse van middel beïnvloed, insluitend faktore wat pasiënte se meewerkendheid beïnvloed asook die potensiële ekonomiese impak van skisofrenie is beklemtoon.

SLEUTELWOORDE: skisofrenie, antipsigotiese middels, aktiewe bestanddele, antipsigotiese behandeling, terapeutiese algoritme, voorgeskewe minimum voordele, ICD-10-kodes, voorskryfpatrone, resepteringspatrone, meewerkendheid, simptome, generiese items, oorspronklike items, generiese substitusie, kostes, potensiële kostebesparings

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LIST OF ABBREVIATIONS

AMCP	Academy of Managed Care Pharmacy
ANOVA	Analysis of variance
APA	American Psychological Association
APA	American Psychiatric Association
CDL	Chronic disease list
DA	Dopamine
DALY	Disability adjusted life years
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth edition
DUR	Drug utilisation review
EE	Expressed emotion
FGA	First generation antipsychotic
GDP	Gross domestic product
ICD-10	International Classification of Diseases, 10th revision of the World Health Organization
MIMS	Monthly Index of Medical Speciality
MRC	Medical Research Council
MPR	Medicine Possession Ratio
MRDD	Maximum recommended daily dose
NAMI	National Alliance on Mental Illness

NDP	National Drug Policy
NICE	National Institute for Health and Care Excellence
NRF	National Research Foundation
PBM	Pharmaceutical Benefit Management Company
PDD	Prescribed daily dose
PMB	Prescribed Minimum Benefit
SAMF	South African Medicines Formulary
SD	Standard deviation
SEP	Single exit price
SGA	Second generation antipsychotic
WHO	World Health Organization
WMA	World Medical Association

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CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

In this chapter, the background, problem statement, research questions, aims and objectives, research method followed as well as the ethical considerations were included.

1.2 BACKGROUND

Schizophrenia can be classified as a major mental disorder that causes an increase in morbidity and mortality of an individual, leading to poor quality of life (Swingler, 2013:153). It is a serious long-term medical illness that influences human nature into thinking unclearly, suppressing the ability of managing emotions, making decisions, or the inability of relating to others. This illness leads to changes in brain chemistry and structure (Machado-Alba & Morales-Plaza, 2013:418) and is triggered through a complex, heterogeneous and multifactorial fashion by risk factors such as genetic, epigenetic, environmental and developmental complicities (Millan *et al*., 2014:645).

Medical diagnoses of psychosis are difficult to make (Freudenreich, 2012:2). Medical toxic psychosis can be the cause of a variety of treatments; this being the case, a medical check-up is needed after every new-onset psychosis in order to exclude any possible treatment initiated psychosis, thereby resulting in schizophrenia being a diagnosed exclusion. Although schizophrenia has such a big differential diagnosis, it can be narrowed by looking at the epidemiological and clinical situation in order to measure the degree of urgency (Freudenreich, 2012:2). According to Swingler (2013:153), diagnosis can be made in terms of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) when a patient is experiencing two or more of the following active phase symptoms for at least one month (referred to as criterion A), which include clinical characteristics such as positive symptoms (hallucinations), negative symptoms (blunting of affect), mood and cognitive impairment and abnormal behaviour and speech.

Patients diagnosed with schizophrenia are usually between the ages of 12 and 40 years old (Duckworth, 2013:1). Common mistakes when a diagnosis of primary or secondary psychosis is made, include attributing casualty to incidental findings, excluding medical toxic psychosis, when family or medical history is not obtained, a premature diagnostic closure and when an initial diagnostic impression of a primary psychotic disorder is not re-evaluated (Freudenreich,

2012:2). Schizophrenic patients may furthermore struggle with a number of co-morbidities, including higher rates of hypothyroidism, type 2 diabetes, obesity, eczema, dermatitis, viral hepatitis, epilepsy, hypertension, fluid disorders and chronic obstructive pulmonary disease (Mitchell *et al*., 2012:435). In addition, these patients are also more likely to smoke and drink alcohol excessively and have a very poor appetite (Emsley & Booysen, 2004:65).

Drug therapy can improve the manifestations linked to schizophrenia (Duckworth, 2013:1). According to Swingler (2013:154), the treatment of schizophrenia consists of either an acute pharmacological treatment or long-term maintenance. Acute treatment should be considered when a first episode of psychosis is suspected, giving either a first generation (typical) antipsychotic such as haloperidol and chlorpromazine or second generation (atypical) antipsychotic such as risperidone and olanzapine as monotherapy. It can be treated as multi-episode or relapse, where second generation antipsychotics are preferred. Acute treatment can also involve second-line treatment, where another antipsychotic should be given after four to six weeks if there is no response to treatment. It could also involve a third-line treatment where clozapine is given orally (Swingler, 2013:154). Clozapine has no effect on managing negative symptoms, neurocognitive function or impaired social cognition (Millan *et al*., 2014:645). Long-term maintenance is advised, because intermittent or targeted dosing may lead to risk of relapse (Millan *et al*., 2014:645).

According to Covell *et al*. (2002:17), an evidence-based medication algorithm will help to reduce racial as well as ethnic disproportions in prescribing patterns. Covell *et al*. (2002:18) describe seven barriers to the adoptions of these existing algorithms by physicians: 1) unawareness, 2) unfamiliarity, 3) non-agreement with the algorithm, 4) lack of outcome expectancy, 5) lack of self-efficacy, 6) external barriers, and 7) disinterest of previous practice. Although these algorithms exist, there are still prescribing patterns with polypharmacy (more than one antipsychotic). This leads to drug interaction, medication errors, adverse effects, non-compliance and an increase in mortality (Covell *et al*., 2002:17). When treatment is prescribed according to the therapeutic algorithm with the requirement that patients take their medication as prescribed, the following goals can be achieved: abuse such as smoking and substance abuse can be managed, harm to self and others can be suppressed, symptom alleviation and treatment adherence can be achieved and maintained, treatment side-effects can be minimised and physical health and drug adverse effects can be monitored (Swingler, 2013:153). According to the American Psychological Association Dictionary (APA), prescribing through a medical practitioner can be described as “the advice and authorize of the use of medicine or treatment

for someone, especially in writing". Dispensing can be defined, according to the APA, as "the make-up and give out of (medicine) according to a doctor's prescription".

Although schizophrenia is a low prevalence disorder, cost of treatment is excessively high (Phanthunane *et al*., 2012:29). It has been shown that schizophrenic patients often cannot cover the medicine costs with additional costs of follow-up consultations as well as the usual psychotherapy sessions (Bettinger *et al*., 2007:201). In South Africa, a therapeutic algorithm was developed for the treatment of schizophrenia in the private health sector to expand access for patients with minimum health benefits and treatment (Council for Medical Schemes, 2009) and also to make it more cost-effective.

Schizophrenia, according to the Medical Schemes Act (131 of 1998), is one of the 27 Chronic Disease List (CDL) conditions of which the Council for Medical Schemes is obliged to cover diagnosis, treatment and the cost of care. However, medical aid schemes will only provide full cover of diagnosis, treatment and cost of care if the algorithms that are published in the Government Gazette are followed (Department of Health, 2003). To qualify as a CDL condition, the disease should be life-threatening, and using medication will improve the quality of life of this member. Clinicians do not always follow the algorithm when prescribing antipsychotics (Sweileh *et al*., 2013:1). According to Loga and Loga-Zec (2010:343), the new development of psycho-pharmacotherapy puts seasoned psychiatrists in a difficult situation. New guidelines and algorithms force psychiatrists to reconsider their previous experiences (sometimes effective experiences) in order to follow that which is expected from them from practice. Not following this algorithm may imply that patients will be moved from private hospitals or rehabilitation facilities to public healthcare facilities, with subsequent changes in psychiatrists and new medication (Council for Medical Schemes, 2009:37). This may lead to higher medication costs and patient non-adherence.

Non-adherence to medication is a significant problem in schizophrenic patients, ranging from 20-89% with an average rate of 50% (Dolder *et al.,* 2002:159; Haddad *et al*., 2009:20; Higashi *et al*., 2013:200). Covell *et al.* (2002:20) further showed that only 31% (n = 13) of patients who initially received prescriptions with more than one antipsychotic, remained on these prescriptions at the end of a two-year study period. Poor adherence influences the effectiveness of the maintenance of antipsychotic treatment, as a 10-day period of missed medication increases the risk of readmission because of possible relapses (Haddad *et al*., 2009:20). Major reasons cited for non-adherence are insufficient efficacy and intolerable side effects (Higashi *et al*., 2013:200). In addition, patients stop with their treatment because of forgetfulness, lack of

responsibility, when starting to feel better, or when they live in denial of accepting that the condition needs treatment (Loga & Loga-Zec, 2010:343). According to Higashi *et al.* (2013:210), one of the most common factors of patient non-adherence is a lack of illness insight; the patient's obliviousness about his/her disease's symptoms and the dangerous consequences involved.

Non-adherence of patients affects not only themselves, but also the society and healthcare systems (Higashi *et al*., 2013:2010). Consequences may include relapse, rehospitalisation, an increase in clinic and emergency room visits that all contributes to a higher annual cost of schizophrenia (Dolder *et al*., 2002:159). Premature death can also be associated with schizophrenia, mainly because of non-adherence leading to schizophrenic patients committing suicide (Higashi *et al*., 2013:2010).

In addition to not following algorithms, serious concern has been raised about the quality of medical service that patients with severe mental illnesses receive. Evidence has been provided that schizophrenic patients receive suboptimal treatment for established medical conditions (Mitchell *et al*., 2012:435). In this same study, eight out of nine analyses showed that schizophrenic patients had inferior preventive care in several areas, including blood pressure monitoring, cholesterol monitoring, mammography, vaccinations and also osteoporosis (Mitchell *et al*., 2012:435). By reducing non-adherence to antipsychotic medication, the psychiatric morbidity and also the cost of care can be substantially reduced (Higashi *et al*., 2013:212).

1.3 PROBLEM STATEMENT

Schizophrenia places a large economic burden on patients, healthcare systems, families and society (Emsley & Booysen, 2004:58). It is a highly disabling disease and is costly to treat (Chisholm *et al*., 2008:542). Of all psychiatric illnesses, schizophrenia is the most costly illness to treat (Emsley & Booysen, 2004:58). Incorrect prescribing patterns may lead to higher cost in medicine treatment for schizophrenic patients with the outcome that patients' adherence could be less. Identifying the factors associated with prescribing (by prescribers) and dispensing (by providers) of medicine indicated for the treatment of schizophrenia by analysing medicine claims, will generate knowledge that can be used in the decision-making of managed healthcare organisations.

Derived from the foregoing discussion, the following research questions may assist in answering the problem statement:

- How can the condition and treatment of schizophrenia be conceptualised?
- What are the current patterns regarding prescribing and dispensing of treatment associated with schizophrenia in the private South African health sector?
- Which prescribing and dispensing factors can be associated with schizophrenia?

1.4 RESEARCH AIMS AND OBJECTIVES

The aim and objectives that were relevant to the research follow below.

1.4.1 Research aim

This study focused on current prescribing and dispensing patterns of medicine treatment for patients with schizophrenia in the South African private health sector.

1.4.2 Specific research objectives

Specific research objectives for the study were divided into two main sections, namely literature- and empirical objectives.

1.4.2.1 Literature objectives

Literature objectives can be defined as all sources that are significant to the topic of interest of a study (Brink *et al*., 2012:85). The following specific objectives were answered from the literature review:

- Review treatment of schizophrenia.
- Identify factors influencing treatment guidelines with regard to schizophrenia.
- Determine the effect of treatment for schizophrenic patients.
- Determine factors influencing the dispensing of antipsychotic treatment of schizophrenic patients.
- Determine factors influencing schizophrenic patients, for example adherence.
- Determine optimal direct medicine treatment cost (using the single exit price and generic substitution) associated with schizophrenia treatment.

1.4.2.2 Empirical objectives

Empirical objectives tend to describe what the researcher implements during the collection of data for the study (Brink *et al*., 2012:56). Specific objectives addressed from the empirical study were as follows:

- To determine the prevalence of schizophrenic patients on the database during the study period stratified by gender and age.
- To determine the prescribing and dispensing patterns of schizophrenia treatment during the study period.
- Conducting a cost analysis on schizophrenia treatment in order to determine possible cost savings due to generic substitution.
- To establish the factors influencing the direct medicine treatment costs of schizophrenia treatment, using database-related variables (medicine-related factors for example cost per item, single exit price, scheme amount and patient contribution as well as prescriber speciality).

1.5 RESEARCH METHODOLOGY

The research method consisted of a literature review followed by an empirical investigation.

1.5.1 Literature review

Literature objectives of the study were achieved by gaining information from several books, articles, journals and websites. Databases implemented in this study were Scopus, ScienceDirect, EBSCOHost, PubMed, Medline and Google Scholar.

1.5.2 Empirical investigation

A retrospective, quantitative drug utilisation study was performed and discussed in the research design by identifying patients from the period 2008 to 2013 registered on the chronic disease list for schizophrenia by analysing their medicine usage data in order to detect their first day of treatment.

The results from the empirical investigation are presented in the form of two manuscripts (refer to Chapter 3). Table 1.1 shows which empirical investigation objectives are addressed in each respective manuscript.

Table 1.1: Specific empirical research objectives met according to their corresponding manuscripts

Specific research objectives from the empirical investigation	Manuscripts (Chapter 3)
To determine the prevalence of schizophrenic patients on the database during the study period stratified by gender and age. To determine the prescribing and dispensing patterns of schizophrenia treatment during the study period.	Manuscript 1 Prescribing and dispensing factors concerning schizophrenia treatment in the South African private health sector during the period 2008-2013 Authors: Husselmann, D., Joubert, R., Burger, J.R., Lubbe, M.S. & Cockeran, M. This manuscript is submitted for peer review and possible publishing to the *South African Medical journal*.
Conducting a cost analysis on schizophrenia treatment in order to determine possible cost savings due to generic substitution. To establish the factors influencing the direct medicine treatment costs of schizophrenia treatment, using database-related variables (medicine-related factors and prescriber speciality.	Manuscript 2 Maximum potential cost-savings attributable to generic substitution of antipsychotics 2008 to 2013 Authors: Husselmann, D., Joubert, R., Burger, J.R., Lubbe, M.S. & Cockeran, M. This manuscript is submitted for peer review and possible publishing to the *Health SA Gesondheid journal.*

1.5.3 Research design

This empirical investigation followed a quantitative, descriptive, observational, longitudinal design.

When using a descriptive design, variables are described in order to answer the research questions (Brink *et al*., 2012:112). Data used for the study were already gathered from a representative sample of the population and were used to address problems with current practice or to justify current practice. It is also used to make judgements or to determine what other professionals are doing in the same situations (Brink *et al*., 2012:112). Maree and Pieterson (2013a:145) define quantitative research as a method that uses numerical data in a systematic and objective manner to study a selected subgroup of a subject and then generalise the findings of that subject that is being studied. Longitudinal studies can be used for descriptive, exploratory as well as explanatory purposes (Neuman, 2014:44). These studies follow the same participants over time with an emphasis on patients' development and how they age (Briggs *et al*., 2012:284). According to Bryman (2012:63), an advantage of longitudinal studies is that it decreases the uncertainty about the direction of causal influence. For this

research project, a panel study, which is a powerful type of longitudinal research, was used. This type of study is done by observing or gathering data on exactly the same patients across different time points (Neuman, 2014:45). When a study is observational, descriptive data on behaviour, events and situations are collected. For an observational study to be considered scientific, careful record-keeping in a systematic and objective order should be conducted. Observational studies involve time sampling, which refers to observations being made during certain specific times (Brink *et al*., 2012:150).

1.5.4 Data source and data fields

Data were obtained from a pharmaceutical benefit management company by identifying patients from the period 2008 to 2013 registered on the chronic disease list for schizophrenia by analysing their medicine usage data retrospectively in order to detect their first day of treatment.

This company is responsible for the management of more than 1.5 million members, including all South African pharmacies and generally all dispensing doctors. With a track record of more than 20 years offering services to more than 20 medical schemes registered in South Africa, it can be assumed that the database used is trustworthy.

According to Hall *et al*. (2011:3), a checklist was developed to assist investigators using an observational study in pharmacoepidemiology in order to ensure the validity of a database. This ensures the protection of privacy because it ensures that researchers work within local and regional policy and legislations. This checklist covers six sections: 1) selection of a database; 2) use of multiple data resources; 3) extraction and analyses of the study population; 4) privacy and security; 5) quality and validation procedures; and 6) documentation.

- **The selection of a database:** In terms of size, a suitable population is selected for this study and includes approximately 4 410 patients. The outcomes and variables were identified as far as possible (refer to data analyses).
- **Extraction and analysis of the study population:** The study population was listed by paid claimed prescriptions for schizophrenia treatment according to ICD-10 codes and data analyses are also discussed in section 1.6.
- **Privacy and security:** Data were secured safely and information was restricted to prevent any means of tracing identifiers (patients). The researcher first gained access to data after permission was given by the Pharmaceutical Benefit Management Company.

- **Quality and validation procedures:** Certain processes are followed by the PBM to ensure quality and validity of the data, namely i) data integrity validation and eligibility management, ii) medicine utilisation management, iii) clinical management, iv) pricing management and v) formulary management (refer to Annexure B).
- **Documentation:** Guidelines for good pharmacoepidemiology practices should be followed. In this study, information from the database complied with the privacy policy. The handling and protection of data, including transfer of data and the usage of information on computer systems were discussed and implemented by the researcher.

The following fields available on the database were obtained for the study: 1) Patient's date of birth; 2) Treatment date; 3) NAPPI code[1] and NAPPI code extension; 4) The description of the medicine (active ingredient); 5) Gender of the patient; 6) Direct medicine cost associated with each transaction (single exit price, patient's contribution and medical scheme's contribution; 7) The prescriber and provider's speciality, and 8) ICD-10 codes.

Also included in the database was the Monthly Index of Medical Specialities (MIMS) classification for antipsychotic drugs, divided into oral and injection form of treatment, using trade names for the injection treatment.

1.5.5 Target population

According to Neuman (2014:252), a target population can be defined as the concrete specified large group of elements from which the researcher draws a sample. Generalisations are made from the sample results. This study's target population involved all patients diagnosed with schizophrenia in the private health sector of South Africa, with similar medical scheme profiles as those contracted by the pharmaceutical benefit management company.

All the prescriptions on the database from 1 January 2008 to 31 December 2013 were screened for the following active ingredients as specified in the MIMS (Snyman, 2012:29) classification system (See Table 1.3).

[1] NAPPI codes are defined by the MIMS (2012:6a) as a nine-digit product code that is unique and can be used to check product name, pack size, strength etc.

1.5.6 Study population

In Table 1.2, the study population is described as used in each manuscript for the study.

Table 1.2: Study population according to manuscripts

Study population	Manuscript
Results from the study were presented in two manuscripts, each employing a different study population. Manuscript one employed two study populations and were as follows: • The study population used to determine prescribing patterns consisted of 4 410 patients that had a paid prescription from a patient's prescribed minimum benefit during the period 1 January 2008 to 31 December 2013 in conjunction with any one or more of the following ICD-10 codes: F20.0-F20.9, identified by applying three diagnostic codes to each patient. 1) ICD-10 MPA code (this is the detailed ICD-10 code based on the pre-authorisation by the PBM or the medical aid scheme; 2) ICD-10 claim code (this is the ICD-10 code as indicated by the prescriber or the provider), and 3) diagnosed code (this is the overall diagnostic code based on the pre-authorisation by the PBM or the medical scheme). • The study population used to determine dispensing patterns consisted of 1 780 patients. Only patients with valid ICD-10 codes associated with schizophrenia with more than two paid claims for a prescription for schizophrenia treatment claimed from the patient's prescribed minimum benefits as a chronic disease were used during the period 1 January 2008 to 31 December 2013. Inclusion criteria: • All patients with valid ICD-10 codes (F20.0-F20.9) associated with a paid claim for one or more of the active substances summarised in Table 1.3. Exclusion criteria: • Patients with incomplete data profiles on the database (for example unidentified gender, age, etc.).	Manuscript 1 Prescribing and dispensing factors concerning schizophrenia treatment in the South African private health sector during the period 2008-2013 Husselmann, D., Joubert, R., Burger, J.R., Lubbe, M.S. & Cockeran, M.

Study population	Manuscript
Manuscript two employed the same study population as manuscript one and consisted of a population of 4 410 patients that had prescriptions paid from a patient's prescribed minimum benefit during the period 1 January 2008 to 31 December 2013 in conjunction with any one or more of the following ICD-10 codes: F20.0-F20.9, identified by applying three diagnostic codes to each patient. 1) ICD-10 MPA code (this is the detailed ICD-10 code based on the pre-authorisation by the PBM or the medical aid scheme); 2) ICD-10 claim code (this is the ICD-10 code as indicated by the prescriber or the provider); and 3) diagnosed code (this is the overall diagnostic code based on the pre-authorisation by the PBM or the medical scheme). Inclusion criteria: • All patients with valid ICD-10 codes (F20.0-F20.9) associated with a paid claim for one or more of the active substances summarised in Table 1.3. Exclusion criteria: • Patients with incomplete data profiles on the database (for example unidentified gender, age, etc.).	Manuscript 2 Husselmann, D., Joubert, R., Burger, J.R., Lubbe, M.S. & Cockeran, M. Maximum potential cost-savings attributable to generic substitution of antipsychotics 2008 to 2013

In Table 1.3, all the active ingredients available for the treatment of schizophrenia according to the MIMS classification system (Snyman, 2012:29) are listed.

Table 1.3: Antipsychotic treatment for schizophrenia

Pharmacological class	Active ingredient	Oral	Injection
Phenothiazine (injections are classified according to trade names)	Chlopromazine	Yes	No
	Fluphenazine	No	Yes (Modecate®)
	Pimozide	Yes	No
	Prochlorperazine	Yes	No
	Trifluoperazine	Yes	No
Butyrophenones (injections are classified according to trade names)	Haloperidol	Yes	Yes (Serenace®)
Atypical antipsychotics	Aripiprazole	Yes	No
	Risperidone	Yes	No
	Clozapine	Yes	No
	Quetiapine	Yes	No
	Ziprasidone	Yes	Yes (Geodon®)
	Paliperidone	Yes	No
	Olanzapine	Yes	Yes (Zyprexa®)

Pharmacological class	Active ingredient	Oral	Injection
	Amisulpiride	Yes	No
Others	Sulpiride	Yes	No
	Zuclopenthixol	Yes	Yes (Clopixol®)
	Clothiapine	Yes	Yes (Etomine®)
	Flupenthixol	Yes	Yes (Fluanxol®) (Fluanxol depot®)

1.5.7 Sampling size and sampling technique

Sampling is done in order to make it possible for the researcher to study a subgroup of a population while being able to make generalisations about the population from the group obtained (Joubert & Katzenellenbogen, 2014:104). According to Maree and Pieterson (2013b:179), larger sample sizes are better in terms of three factors, namely representativeness, statistical analysis and accuracy. For this research project, patients from the period 2008 to 2013 registered on the chronic disease list for schizophrenia were used, in order to obtain a large enough sample size. No sampling techniques were used to recruit subjects as an existing available database was employed for the study. Furthermore, no budget in terms of money and time available had to be considered and therefore sampling was unnecessary.

1.6 DATA ANALYSES

This section describes the techniques and statistical analysis used to conduct the data analysis for this study. A validation process was developed by the PBM to ensure that the data employed are valid and reliable (refer to Annexure B).

1.6.1 Description of research techniques

In this section, the techniques that were followed to complete this research study are described.

1.6.1.1 Drug utilisation review

According to the Academy of Managed Care Pharmacy (AMCP), drug utilisation review (DUR) can be classified as prospective, concurrent or retrospective (AMCP, 2009). DUR studies focus on the patterns of drug use to identify areas of inappropriate drug use without initiating efforts in correcting these errors (Truter, 2008:92). Drug utilisation is defined by the WHO (World Health Organization) as “the marketing, distribution, prescription, and use of drugs in a society, with

special emphasis on the resulting medical, social and economic consequences" (WHO, 2003:8). It is a valid technique that uses audits to compare actual use to national prescription guidelines or local drug formularies (WHO, 2003:9). DUR can be defined as the evaluation of drug use patterns to predetermined criteria in order to enhance prescribing patterns in a corrective way (Hennessey *et al*., 2003:1494). DUR studies can be followed to improve quality of care, to determine the cost of medical care and to identify and control fraud and abuse (Truter, 2008:94). Retrospective DUR can be defined, according to the AMCP, as a review of drug therapy after medication is given to a patient (AMCP, 2009). A retrospective DUR study was performed to identify where prescribing and patient drug dispensing were less than optimum and to evaluate the high costs of treatment by calculating single exit price values.

According to AMCP (2009), three steps were performed during this DUR study:

(1) **Identify or determine optimal use:** It is essential to create the criteria to which optimal use can be compared to actual use (AMCP, 2009). Criteria are the standards against which a judgment, evaluation or comparison can be made (APA Dictionary of Psychology, 2007:243). For this study, the optimal prescribing of drugs was determined by using the Monthly Index of Medicine Specialities (MIMS) classification method (Snyman, 2014), South African Medicines Formulary (SAMF) (Rossiter, 2014) and the Martindale (2015). The maximum recommended daily dose was derived from empirical studies obtained from human clinical trials that are above the dose where a drug's efficacy is agreed on and where the beneficial effects are outweighed by the side effects (Contrera *et al*., 2004:186). This plays a critical role in the safe use of pharmaceuticals through the labelling of drugs (Contrera *et al*., 2004:186).

According to Hess *et al.* (2006:1280) poor adherence can lead to false negative results reducing the statistical power of detecting differences between treatments affecting the validity of clinical research. Medicine adherence, as determined by the medicine possession ratio calculation (MPR), is a reflection of the number of days a patient use the correct dose of a drug in relation to the number of days the drug is prescribed (Hess *et al*., 2006:1281). The MPR requires at least two fill dates of the patient in order to calculate the ratio (Peterson *et al*., 2007:3). The MPR can be calculated using the following formula:

$$\text{MPR} = \frac{Total\ Rx\ days\ of\ supply - last\ Rx\ days\ of\ supply}{Last\ Rx\ date - first\ Rx\ date} \times 100$$

(2) **Measure actual use:** For this study, a database was used from a pharmaceutical benefit management company and actual use of medication was measured using DUR measures such as the medicine possession ratio calculation and prescribed daily dose (PDD) methodology.

Medication compliance was determined by the modified medicine possession ratio (MPR) calculation. By using this method, the number of doses dispensed in relation to the dispensing period were determined (Cramer *et al.,* 2008:46). An MPR < 80% represented a presence of refill gaps and indicated an undersupply as the possession ratio is too low. An MPR > 110% represented an oversupply and indicated that the possession ratio is too high. Therefore, an MPR ≥ 80% but ≤ 110% was taken as acceptable.

Prescribed daily doses are the average daily dose of a drug prescribed according to a representative sample of prescriptions (WHO, 2003:39). This method is used to overcome limitations of the DDD and reflects drug exposure more accurately than the DDD does. It can be calculated by the following formula (WHO, 2003:39):

$$\text{PDD} = \frac{Quantity\ of\ drug\ dispensed \times Strength\ of\ the\ drug}{Days\ supply}$$

(3) **Evaluate**: This step involves identifying members who meet the criteria and by making comparisons between optimal/appropriate use to actual use of medicine using the determined criteria (AMCP, 2009).

1.6.1.2 Description of data analyses plan

According to Denscombe (2010:241), a descriptive analysis will be conducted in order to: organise the data, summarise the findings and make it possible to display the evidence, describe how the data are distributed and to explore connections between parts of the data. Descriptive statistics used during the analysis are described in the following section.

1.6.1.2.1 Independent variables

- **Prescriber speciality**

Prescriber speciality refers to the degree of medical education that the prescriber holds who is responsible for prescribing the medicine in this research study. The following prescribers were investigated; general practitioners, psychiatrists, neurologists, endocrinologists and others (including, *inter alia*, nurse prescribers, specialists and community practitioners).

- **Age groups**

The age of patients was divided into six groups, i.e.:

- Group 1 = 0 < age ≤ 5 years
- Group 2 = 5 < age ≤ 12 years
- Group 3 = 12 < age ≤ 18 years
- Group 4 = 18 < age ≤ 35 years
- Group 5 = 35 < age ≤ 65 years
- Group 6 = 65 years > age

Because of the lack of data on weight, children were excluded from the analyses of the PDD. For the analyses of the PDD, the age of patients was divided into two age groups, i.e.:

- Group 1 = 18 > age ≤ 65 years
- Group 2 = 65 years > age

- **Gender**

Gender was included in the study, distinguishing between male and female patients based on prevalence of age.

- **Co-morbidities**

Patients with schizophrenia have high rates of developing physical comorbidities (Lambert *et al*., 2003:67). According to Carney *et al*. (2006:1133), it is mandatory to determine which chronic medical conditions are associated with schizophrenia patients in order to be ensured of the best preventive and primary care for this condition. Fifty per cent of all schizophrenic patients have comorbid depression, 29% have posttraumatic stress disorder, 23% have obsessive compulsive disorder and 15% have panic disorder (Buckley *et al*., 2009:383). According to Carney *et al*. (2006:1134), when schizophrenic patients (subjects) are compared to non-schizophrenic patients (controls), it is estimated that the subjects have increased odds of developing the following conditions:

- hepatitis (7.54%)
- fluid/electrolyte disorders (4.21%)
- hypothyroidism (2.62%)
- diabetes (2.11%)

Co-morbidities were identified by paid claims from schizophrenic patients for medicine with ICD-10 codes associated with the prescribed minimum benefit CDL conditions. The CDL codes are as follows: Addison's disease (ICD-10 code E27.1), asthma (J45, J45.8), bronchiectasis (J47, Q33.4), cardiac failure (I50, I50.0, I50.1), cardiomyopathy (I42, I42.0, I25.5), chronic obstructive pulmonary disease (J43, J44), chronic renal disease (N03, N11, N18), coronary artery disease (I20, I20.0, I25), Crohn's disease (K50, K50.8), diabetes insipidus (E23.2), diabetes mellitus (E11.0- E11.9), dysrhythmias (I47, I47.2, I48), epilepsy (G40, G40.8), glaucoma (H40, Q15.0), haemophilia (D66, D67), hyperlipidaemia (E78.0-E78.5), hypertension (I10.0, I11.0, I12.0, I13.0, I15.0), hypothyroidism (E02, E03, E03.8), multiple sclerosis (G35), Parkinson's disease (G20, G21), rheumatoid arthritis (M05, M06, M08.0), schizophrenia (F20), systemic lupus erythematosus (M32, L93, L93.2) and ulcerative colitis (K51, K51.9) (Department of Health, 2003).

- **Treatment period**

The treatment period was categorised into three groups, i.e.:

- Period 1: 0 ≤ 30 days
- Period 2: > 30 ≤ 120 days
- Period 3: > 120 days

- **Costs of treatment**

For this study, the researcher focused on the total direct cost per item, scheme- and the patient's contribution as well as the single exit price (SEP) paid for each active ingredient while looking at the generic versus the original drug prices. This was used to determine potential cost-savings. The SEP can be defined as the price set by the manufacturer and/or importer for medicines or scheduled substances in terms of regulations, combined with both logistic fee and VAT (Department of Health, 2004:3). According to the medicines and Related Substances Act (101 of 1965), the SEP is the lowest price of medicines and scheduled substances of a unit within a pack, multiplied by the number of units in the pack.

- **Generic indicator**

Active ingredients used for this study were identified by using the MIMS classification system. When costs were determined, the active ingredient was divided into three groups; originator items, generic items and non-generic items. Non-generic drugs are drugs that have no generic versions available. Generic drugs can be referred to as drugs of the same formula (the same quantity and type of active ingredient administrated with the same route) and offer the same

therapeutic effectiveness as the original (brand name) drug (Borgherini, 2003:1578). Generic drugs are less expensive for the reason that the manufacturer does not have to pay for registration studies (Borgherini, 2003:1578). Originator drugs can be referred to as brand name drugs and are more expensive than their generic versions while offering the same therapeutic effect (Fischer & Avorn, 2003:1052).

1.6.1.2.2 Dependent variables

Dependent variables used for the study were described in the drug utilisation process (paragraph 1.6.1.1) and were as follows:

- Medicine possession ratio
- Maximum recommended daily dose
- Prescribed daily dose

1.6.1.2.3 Descriptive statistics

- **Frequency**

In this study, frequency distributions were used in order to determine the numerical counts compared to the type of categories being determined (Pagano & Gauvreau, 2000:12).

- **Mean**

The mean is calculated by summing all the observations in a set of data and then dividing it by the total number of measurements (Pagano & Gauvreau, 2000:39). It is calculated as the arithmetic average of all data values (Maree & Pieterson, 2013:187). It can be used only with interval or ratio-level data. The mean can be calculated using the formula:

$$\frac{1}{n}\sum_{i=1}^{n} X_i$$

Where:
Σ = sum of
n = number of observations or sample size
x_i = the value of each individual item in the list of numbers being averaged
i = any value from 1 to n

- **Standard deviation**

The standard deviation (SD) can be seen as the square root of the variance. The variance is a measure that concentrates on the mean value and indicates how data values are spread around that mean (Maree & Pieterson, 2013:188). The standard deviation can be calculated using the formula:

$$\frac{1}{n-1}\sum_{i=1}^{n}(X_i - \bar{X})^2$$

Where:
Σ = sum of
$\bar{X}$ = mean of the observations
X_i = single measurement
n = number of observations or sample size
$i =$ any value from 1 to n

- **Confidence interval**

A confidence interval (CI) uses an interval to measure the population parameter. When a 95% confidence interval is measured, it can be assumed that there is a 95% confidence that the true value of the population parameter lies within the limits measured (Maree & Pieterson, 2013:201). The 95% CI can be calculated using the formula:

$$\mathbf{95\%}\ \boldsymbol{CI} = \boldsymbol{m}\ \pm (\mathbf{1.96} * \boldsymbol{SE})$$

Where:
SE = standard error
m = mean of the sample population

1.6.1.2.4 Inferential statistics

Testing for statistical significance means that a probability, or odds of finding due to chance, a relationship that is at least as strong as the ones observed in the study's findings, is calculated (Rubin & Babbie, 2014:572). Practical significance can be defined as "*a difference large enough to have an effect in practice"* (Ellis & Steyn, 2003:51).

Inferential statistics is a field of statistics that relies mostly on probability theory, where findings from the sample data are generalised and conclusions are drawn from the population (Miller &

Salkind, 2002:384). The goal of inferential statistics is to reach a conclusion regarding the probability of an outcome accredited to chance rather than to a hypothesised cause (Miller & Salkind, 2002:384)

- **Parametric statistics**
  - *t*-test: The *t*-test is used when the means of two groups are being compared in order to determine whether there is a significant difference between the means or whether it is caused by chance (Brink *et al*., 2013:191). The effect size is then determined by Cohen's *d*-value.
  - ANOVA (analysis of variance): ANOVA uses variances to calculate a value reflecting differences between more than two means and is an extension of the *t*-test (Brink *et al*., 2012:191). If a statistically significant difference is found, Tukey's HSD test can be used to determine which of the means differ significantly. The effect size is then determined by Cohen's *d*-value.

- **Non-parametric statistics**

Chi-square test: Chi-square distribution is a model for the distribution of statistics obtained by sampling from the population (Dowdy *et al*., 2004:95). The effect size is then determined by Cramer's *V*.

- **Effect sizes**
  - Cohen's *d*-value: is used to determine how far the mean from the observation of the study differs from the mean of the null hypothesis. Cohen uses three categories in order to classify an effect size, namely small ($d = 0.2$), medium ($d = 0.5$) and large ($d \geq 0.8$). These categories do not consider other variables such as diversity of the study population or the assessment instrument's accuracy (Sullivan & Feinn, 2012:280).
  - Cramer's *V* is used to calculate correlation in tables when a table consists of more than 2X2 rows and columns. Cramer's $V \geq 0.5$ is taken as practically significant and is regarded as a large effect. Cramer's $V \geq 0.1$ to < 0.3 is a small effect, and Cramer's $V \geq 0.3$ to < 0.5 is regarded as a moderate effect. It is used after the chi-square test has proven significance to determine strengths of association (Liebetrau, 1983:15).

1.7 ETHICAL CONSIDERATIONS

In conducting this study, retrospective data from a South African medicine claims database in the private health sector during the period 1 January 2008 to 31 December 2013 were used. To prevent use of data for purposes other than research, a signed confidentiality agreement with the Board of Directors of the pharmaceutical benefit management company was obtained. Ethical approval from the Faculty of Health Sciences' Research Ethics Committee was obtained (NWU-00179-14-A1). For this study, the benefits outweighed the risks and the study was categorised under a low level of risk.

1.8 CHAPTER SUMMARY

This section briefly discussed the problem stated in the study by providing a summarised background. It was established that schizophrenia is a costly illness to treat and that prescribing patterns can play a role in not only the cost of treatment, but also in a patient's adherence. Empirical and literature objectives were identified and methods were developed in order to determine the objectives stated. The next chapter focuses on the disease as a whole, discussing factors that play a role in patients diagnosed with the disease, for example antipsychotic treatment, adherence, prescribers and costs.

CHAPTER 2: SCHIZOPRHENIA IN A NUTSHELL

2.1 INTRODUCTION

This section provides a background on the etiology of schizophrenia and the global prevalence of the disease, focusing on treatment guidelines nationally and on an international scale. It offers a summary of the treatment used to treat the disease and focuses on factors that influence treatment guidelines as well as the dispensing of the medicine to patients.

Schizophrenia is the most expensive psychiatric illness to treat and it not only places an economic burden on only the patients, but also their families and the society (Emsley & Booysen, 2004:58). Identifying the best possible treatment algorithm and factors that cause non-adherence to treatment guidelines and dispensing may assist in developing a treatment plan that is affordable and ensures optimal adherence from patients.

2.2 DEFINITION AND CLASSIFICATION OF SCHIZOPHRENIA

2.2.1 History of the progress of schizophrenia

Each year, more than 2 000 scientific publications on schizophrenia are published; however, no sufficient progress in finding the cause of the disease has yet been made (Blom, 2004:379). Dr Andrew Pocklington claims that *"development of antipsychotic treatment has not really progressed since findings established in the 1970s, thus a dependable model is needed for schizophrenia, in order to make future directions in developing new medication"* (McIntosch, 2015:1).

There are three important names that need to be mentioned when discussing the development, research and findings in the history of schizophrenia, namely Emil Kraepelin (1856-1926), Eugen Bleuler (1857-1939) and Kurt Schneider (1887-1967) (Blom, 2004:380). Kraepelin was the first scientist to create a broad definition for the disease and coined the condition 'dementia praecox' (Andreasen & Carpenter, 1993:200). Kraepelin described the 'praecox' as a syndrome that has a habit of beginning in an early stage of life. 'Dementia' originated from the cognitive and behavioural function impairment caused by the disease (Andreasen & Carpenter, 1993:201). Bleuler modified the original concept of Kraepelin by suggesting that the term 'dementia praecox' be replaced by the term 'the group of schizophrenias'. He discovered that not all clinical illnesses lead to the terminal state of deterioration as was supposed by Kraepelin to be characteristic of the disease, but were rather caused by a group of diseases (Jablensky,

2010:273). Bleuler believed that 'splitting of associations' was the most significant characteristic of the disease (Andreasen & Carpenter, 1993:201). Kurt Schneider played a fundamental role in defining the characteristics of schizophrenia (Andreasen & Carpenter, 1993:201). Schneider identified nine groups of psychotic manifestations, namely 1) loud and clear thoughts, 2) voices arguing about or discussing the patient, 3) voices making a running commentary about the patient's actions, 4) voices conversing about the patient in the third person, 5) experiences of influences on the body, 6) thought withdrawal and other interference with thought, 7) thought broadcast, 8) delusional perception, and 9) other experiences involving 'made' impulses and feelings experienced that were controlled externally that had a significant weight in the diagnosis of schizophrenia and elected them as 'first-rank symptoms' (Jablensky, 2010:274). The first rank symptoms were incorporated in the Research Diagnostic Criteria, Third Edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-III) and ICD-10 afterwards (Jablensky, 2010:274).

In the 1970s Crow developed the Type I (positive) and Type II (negative) sub-classification system of schizophrenia. After many decades of the 'neo-Kraepelinian revolution' of the 1970s, a turning point in the conceptualisation of schizophrenia aroused through the development of the operational diagnostic criteria that reflected the Kraepelinian categorical nosology and were incorporated in the DSM-III (Jablensky, 2010:277).

2.2.2 Definition and etiology of schizophrenia

Schizophrenia is a major mental disorder that inflicts a poor quality-of-life as well as increases the morbidity and mortality of an individual (Swingler, 2013:153). For schizophrenia, lateral ventricular enlargement in the brain is the most robust structural finding (Chua *et al*., 2003:269). According to Jablensky (2010:271), schizophrenia involves genetic contribution to a large extent affected by environmental factors that interact with genetic exposure. Two systems are linked to the etiology of schizophrenia, the dopamine (DA) system as well as the prefrontal cortex system (Grace, 1991:13). According to Stein and Wise (1971:1032), should a genetically determined enzymatic error occur, it may cause constant forming of endogenous 6-hydroxydopamine that will damage the noradrenergic reward system progressively and will lead to the development of schizophrenia. The hypothesis that schizophrenia may be triggered by an extreme activation of the DA system is supported by amphetamine psychosis- and neuroleptic action studies (Grace, 1991:13).

Figure 2.1 is adapted from Kamajian (Ray, 2015:230) and describes how schizophrenia affects different areas of the brain.

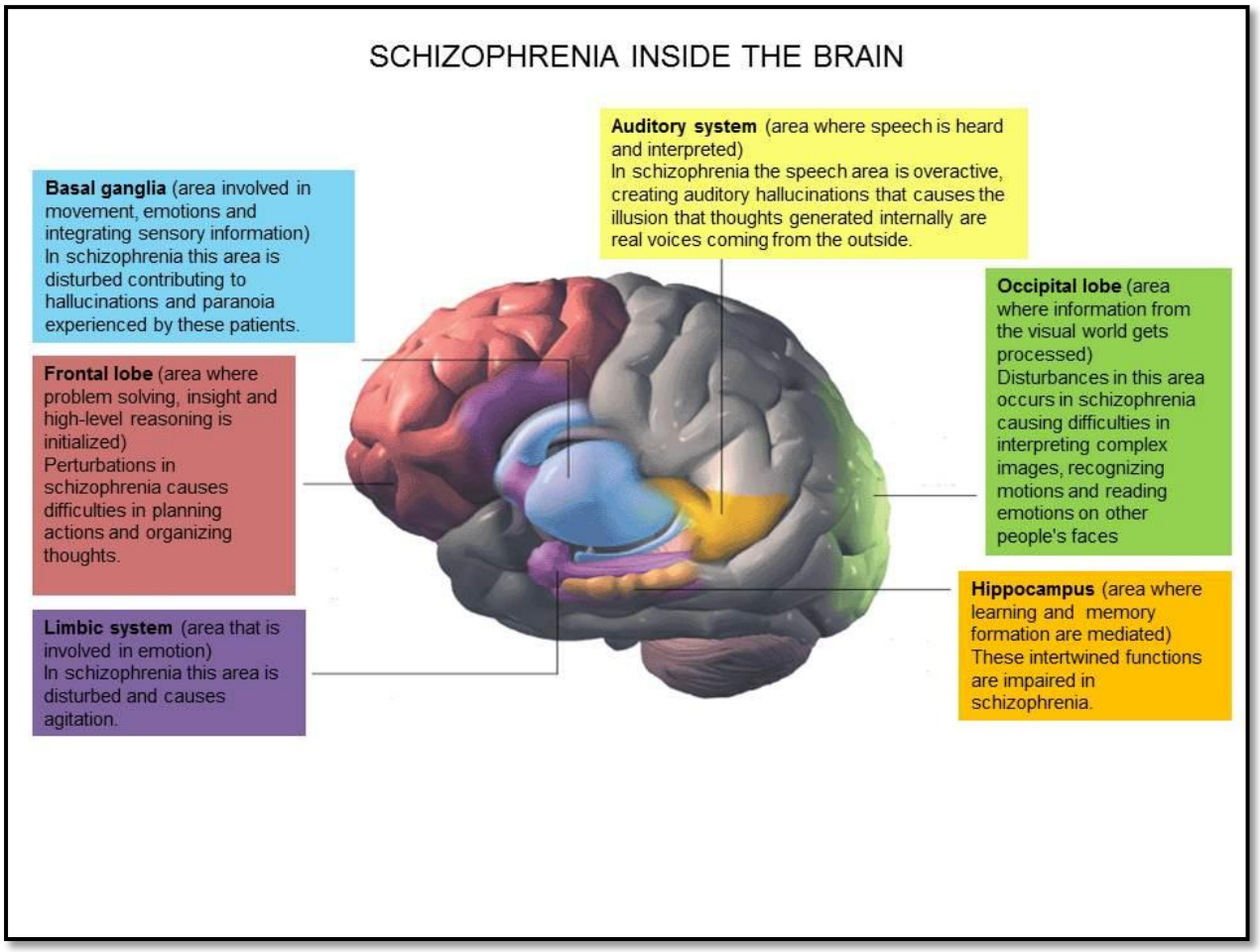

Figure 2.1: Schizophrenia in different parts of the brain (Adapted from Alfred T Kamajian)

2.2.3 Classification of schizophrenia

According to Jablensky (2010:277), there are currently two classification systems providing for schizophrenia; the 10th revision of the World Health Organization's (WHO) International Classification of Diseases (ICD-10) and the 5th edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5). These systems will be described in subsequent paragraphs.

2.2.3.1 WHO classification system

The WHO classifies schizophrenia as a major mental disorder and/or group of disorders that involve a complex set of disturbances influencing a person's way of thinking, affect, his/her perception as well as his/her social behaviour, unfortunately causes of the disease are unknown to a large extent (WHO, 1993:1). Table 2.1 (compiled from WHO, 1993:29) identifies the different types of schizophrenia and stratifies them by their ICD-10 codes.

Table 2.1: ICD-10 classification code of schizophrenia

ICD-10 code	Description
F20.0	Paranoid schizophrenia
F20.1	Hebephrenic schizophrenia
F20.2	Catatonic schizophrenia
F20.3	Undifferentiated schizophrenia
F20.4	Post-schizophrenic depression
F20.5	Residual schizophrenia
F20.6	Simple schizophrenia
F20.8	Other schizophrenia
F20.9	Schizophrenia, unspecified

A fifth character was also developed in order to classify the course of the condition (WHO, 1993:29). These are described in Table 2.2.

Table 2.2: Course of condition classified by a fifth character

Classification	Definition	Description
.x0	Continuous	During the observation period, remission of psychotic symptoms did not occur
.x1	Episodic with progressive deficit	During intervals between psychotic episodes, negative symptoms progressively developed
.x2	Episodic with stable deficit	During intervals between psychotic episodes, negative symptoms were persistent but not progressive
.x3	Episodic remittent	Between the psychotic symptoms, complete or almost complete remissions occurred
.x4	Incomplete remission	
.x5	Complete remission	
.x8	Other	
.x9	Course uncertain	The observation period was too short

A general criterion for F20.0-F20.3 was developed by the World Health Organization in order to diagnose a patient suffering from this disease:

(1) Patient should experience at least one of the following syndromes, symptoms or signs for most of the time in a month's period to be classified as an episode of psychotic illness (WHO, 1993:78):

- Thought echo, thought insertion or withdrawal, or thought broadcasting.
- Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, sensations or delusional perception.
- Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing him/her between themselves, or other types of hallucinatory voices coming from some part of the body.
- Persistent delusions of other kinds that are culturally inappropriate and completely impossible.

(2) Patient should experience at least two of the following syndromes, symptoms or signs for most of the time in a month's period to be classified as an episode of psychotic illness (WHO, 1993:78):

- Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions without clear affective content, or when accompanied by persistent over-valued ideas.
- Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech.
- Catatonic behaviour (for example excitement, posturing or waxy flexibility, negativism, mutism and stupor).
- Negative symptoms such as marked apathy, paucity of speech and blunting or incongruity of emotional responses (it must be clear that these are not due to depression or to neuroleptic medication).

(3) Exclusion criteria: If the patient meets the criteria for manic episode (F30) or depressive episode (F32) as well the syndrome, the symptoms or signs as stated above should have occurred before the mood disorder has developed (WHO, 1993:79).

(4) Organic brain disease, alcohol intoxication, drug-related intoxication, dependence or withdrawal is not ascribed to the disorder.

Table 2.3, (WHO, 1993:78) provides a brief summary of the different existing types of schizophrenia according to their ICD-10 codes.

Table 2.3: Common varieties of schizophrenia categorised by ICD-10 codes

ICD-10 code	Syndromes, symptoms or signs that should be met to qualify for criteria
Paranoid schizophrenia (F20.0)	General criteria for schizophrenia (F20.0-F20.3) have been met. Noticeability of delusions or hallucinations. Flattening or inconsistency of affect, catatonic symptoms, or incongruous speech that does not dominate the clinical picture, but can be slightly present.
Hebephrenic schizophrenia (F20.1)	General criteria for schizophrenia (F20.0-F20.3) have been met. Definite and sustained flattening of shallowness of affect/or definite and sustained incongruity or inappropriateness of affect. Behaviour that is aimless and disjointed rather than goal-directed or definite thought disorder, manifesting as speech that is disjointed, rambling or incoherent. Hallucinations or delusions that do not dominate the clinical picture, but can be slightly present.
Catatonic schizophrenia (F20.2)	General criteria for schizophrenia (F20.0-F20.3) should be met eventually, though there is a slight possibility that this may not be possible primarily due to an uncommunicative patient. At least one of the following catatonic behaviours should be prominent for a minimum period of a week: • Stupor or mutism. • Excitement. • Posturing (inappropriate or bizarre postures). • Negativism. • Rigidity (patient stays rigid even though efforts are made to move). • Waxy flexibility (maintenance of limbs and body in externally imposed positions). • Command automatism (when instructions are given patient follows automatically). Excluding: other possible symptoms of catatonic behaviours, brain diseases or metabolic disturbances.
Undifferentiated schizophrenia (F20.3)	General criteria for schizophrenia (F20.0-F20.3) have been met. Insufficient symptoms meet the criteria of any of the sub-types F20.0, F20.1, F20.4 or F20.5 or there are so many symptoms present that more than one criterion of the subtypes listed are met.

ICD-10 code	Syndromes, symptoms or signs that should be met to qualify for criteria
Post-schizophrenic depression (F20.4)	General criteria for schizophrenia (F20.0-F20.3) have been met in the past 12 months, but are not currently present. One of the following syndromes, symptoms or signs of F20.0 should still be present: • Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions without clear affective content, or when accompanied by persistent over-valued ideas. • Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech. • Catatonic behaviour (for example, excitement, posturing or waxy flexibility, negativism, mutism and stupor). • Negative symptoms such as marked apathy, paucity of speech and blunting or incongruity of emotional responses (it must be clear that these are not due to depression or to neuroleptic medication). • Depressive symptoms should be severe for a long time in order to meet criteria for a mild depressive episode (F32.0).
Residual schizophrenia (F20.5)	General criteria for schizophrenia (F20.0-F20.3) have been met in the past, but are not currently present. At least four of the following symptoms have been present in past 12 months: • Psychomotor slowing or under activity. • Definite blunting of affect. • Passivity and lack of initiative. • Poverty of either the quantity or the content of speech. • Poor non-verbal communication by facial expression, eye contact, voice modulation or posture. • Poor social performance or self-care.
Simple schizophrenia (F20.6)	The following three syndromes should slowly develop progressively over a period of at least a year: • The quality of personal behaviour should show a consistent change in deterioration that leads to idleness, social withdrawal, loss of drive in interests and a self-absorbed attitude. • 'Negative symptoms' are gradually appearing and deepening. • Social, scholastic, or performance at work is significantly decreasing. Absence of any of the symptoms described in the general criterion for F20.0-F20.3 as well as absence of hallucinations or well-formed delusions of any kind. If there is no evidence or the absence of dementia or any other organic mental disorders.
Other schizophrenia (F20.8)	
Schizophrenia, unspecified (F20.9)	

2.2.3.2 DSM-V classification system

The diagnostic criteria were developed to achieve three goals, namely 1) identifying groups of patients whose clinical presentations and prognoses are broadly the same, 2) to ensure early diagnosis and simplify the choice of treatment, and 3) assisting genetic and other aetiological research in defining homogeneous heritable diagnostic criteria (Jablensky, 2010:277). The DSM-V (APA, 2013:99) classifies schizophrenia under the ICD-10 code 'F20.9' only.

Table 2.4 (compiled from Tandon *et al*., 2013:3), provides a brief summary on the criteria used to diagnose schizophrenia using the DSM-V classification system.

Table 2.4: Diagnostic criteria for schizophrenia according to the DSM-V classification system

Criterion A	Characteristic symptoms: Two or more of the following signs, symptoms or syndromes should be present for a substantial amount of time in a month's period or less if sufficiently treated: •Delusions * •Hallucinations * •Disorganised speech * •Grossly disorganised or catatonic behaviour •Negative symptoms * One of these should be present
Criterion B	Social or occupational dysfunction: A noticeable decrease in major areas of the patient's level of functioning that includes work, interpersonal relations and/or self-care for a sufficient period of time, after the onset of the disorder that was achieved before the onset of the condition.
Criterion C	Duration of six months: Signs of the disturbance are significant for at least six months where symptoms of criterion (1) should be present for at least a month, or less if sufficiently treated, which may include periods of prodromal or residual symptoms. In the prodromal and residual periods, signs of the disorder may appear only as negative symptoms or as two or more positive symptoms as described in criterion 1 in a weakened form.
Criterion D	Schizoaffective and mood disorder exclusion: Exclusion criteria: Schizoaffective-, depressive- and bipolar disorder must first be ruled out by either (1) no simultaneous occurrence of major depressive or manic episodes with the active phase symptoms, (2) or if any mood episodes have been present during the occurrence of active phase symptoms, the episodes should have been present for the minority of time during the active and residual periods of the illness.
Criterion E	Substance or general mood condition exclusion: Disorder is not caused by psychological effects due to substance abuse or any other medical conditions.
Criterion F	Relationship to global developmental delay or autism spectrum disorder: Exclusion criteria: If the patient has any history of autism spectrum disorder or any other communication disorder that started during his/her childhood, an additional diagnosis of schizophrenia may only be accepted if delusions or hallucinations are markedly present for at least a period of a month.

2.3 PREVALENCE OF SCHIZOPHRENIA

A number of factors influencing the prevalence of schizophrenia, such as ethnicity, patients' country of origin, gender as well as age will be discussed in subsequent sections. Prevalence can be defined as the proportion of individuals who have a specific disease in a community at a particular point of time, or over a period of time that includes both the group of individuals with the established disease and those who developed the disease over the specific time period (Tandon *et al*., 2008:2).

2.3.1 The prevalence of schizophrenia on a global scale

Schizophrenia has a 1% prevalence worldwide (Millier *et al*., 2014:85). The incidence of schizophrenia, based on the distribution of all rates has an average annual incidence of 15 per 100 000 per population (Saha *et al*., 2008:55; Tandon *et al*., 2008:1), and an average of 0.7% is the risk of developing the disease in a person's lifetime (Tandon *et al*., 2008:1).

In 2011, a study compared the size and burden of mental disorders in the European Union with 2005 data and showed that a prevalence estimate of 0.8% of the country had psychotic disorders in 2005, whilst in 2011, 1.2% of the country suffered from psychotic disorders (Wittchen *et al*., 2011:666). The number of persons affected in 2005 was 18.4 million people, while in 2011, 30.3 million people were affected with psychotic disorders (Wittchen *et al*., 2011:666).

In 2002, a systematic review study was conducted to compare lifetime prevalence rates of schizophrenia in different countries; New Zealand had a lifetime prevalence rate of 0.3 per 100 persons (Goldner *et al*., 2002:838); while Asian countries, which included Hong Kong, Taiwan and Korea had seemingly lower prevalence rates than all the other countries, with Hong Kong a lifetime prevalence rate of 0.12, Taiwan, 0.3 and Korea 0.4 per 100 persons (Goldner *et al*., 2002:838). The highest lifetime prevalence for mental, neurological and substance use disorders according to the WHO World Mental Health Survey is the United States of America (USA) with 47.4% and New Zealand with 39.3%, while the lowest prevalence rates are Nigeria with 12.0% and China with 13.2% (Jack *et al*., 2014:2). In 2010 the estimated resident population for patients between the ages 18 and 65 years who were treated for psychotic illnesses in Australia was 3.1 per 1 000 cases, which results in approximately 43 815 people (Morgan *et al*., 2011:22). According to the WHO (1998:86), the lifetime prevalence of schizophrenia for the USA was 1.5%, 0.6% for Canada and 0.3% for Iceland.

2.3.2 Influence of ethnicity on the prevalence of schizophrenia

It is believed that prevalence may be influenced by ethnicity (Chua *et al*., 2003:269). For example, a study conducted on the mental health data from two national sources of New Zealand showed that for Māori individuals, the prevalence of schizophrenia was 0.97%, but for non-Māori individuals, the prevalence was 0.32% (Kake *et al*., 2008:941).

2.3.3 Influence of age and gender on the prevalence of schizophrenia

The prevalence of schizophrenia is lower in women than in men (APA, 2013:103; Ochoa *et al*., 2012:2; WHO, 1997:77). A study done in Europe showed that the disability adjusted life years lost (DALY) in 2010 for men was 16.4%, while for women only 14.3% (Wittchen *et al*., 2011:669). The age at onset is also later in women than in men. The National Institute of Mental Health states that schizophrenia is scarce in children under the age of 18 years; as one in 100 adults are affected by schizophrenia, but only one in 400 000 children are affected by the disease (Foster, 2015:5). Although the safety and effectiveness of the use of atypical antipsychotic medication in children have not been established, a nationwide study has showed that the number of atypical antipsychotic prescriptions for children has increased five-fold from 1995 to 2002, where more than half of these prescriptions were for off-label uses (Foster, 2015:5).

2.4 TREATMENT FOR SCHIZOPHRENIA

Schizophrenia is treated by antipsychotics that are divided into typical/conventional (first-generation antipsychotics) and atypical (second generation) antipsychotics (Masi *et al*., 2006:849). Although a great variety of antipsychotics exists, each with its own different chemical structures, they all have one main mechanism of action; to block D_2-receptors in the nigrostriatal and mesolimbic brain areas (WHO, 1998:17). What makes the treatment of schizophrenia so challenging, is that dopaminergic transmission needs to be blocked in the limbic pathway, while concurrently being increased in the prefrontal cortex (Schellack & Matlala, 2014:28). However, research has shown that atypical antipsychotic agents have a greater advantage than typical antipsychotic agents by presenting a better tolerance and causing fewer extrapyramidal effects (Cuesta *et al*., 2001:18). The longer a patient with psychosis goes untreated, the lesser the patient's response to the treatment will be (Banerjee, 2012:18).

Table 2.5 compares the South African treatment guidelines for schizophrenia, developed by the Department of Health (2003) with an international guideline, namely the National Institute for Health and Care Excellence (NICE, 2014).

Table 2.5: Difference between South Africa and NICE guidelines for the treatment of schizophrenia

South Africa guidelines	NICE guidelines
Diagnosis: Only the following healthcare professionals may diagnose a patient with schizophrenia: Psychiatrist/ paediatric psychiatrist Provider employed by a state hospital 02200, 056002, 056000, 056003, 056001	Diagnosis: No antipsychotic medication may be taken unless it is done in consultation with a consultant psychiatrist.
Pre-treatment: The following baseline investigations should be carried out before any antipsychotic or drug therapy is initiated: • Body mass index (BMI) • Cardiovascular risk-waist ratio • Metabolic risk – fasting blood glucose and lipogram • Depending on the drug selection – full blood count, liver function tests • An electrocardiogram (ECG) if the product's package insert requires one, or if the patient has a personal history of cardiovascular disease or evidence of cardiovascular disease during the physical examination.	Pre-treatment: Is carried out before initially starting with a new agent of antipsychotic treatment as described below.
First episode psychosis (oral monotherapy): Drug of choice – second-generation antipsychotic (SGA) (other than clozapine) SGAs that can be taken: • Risperidone • Olanzapine • Quetiapine • Aripiprazole • Ziprasidone • Amisulpride Target dosage should start at the lowest point of the therapeutic range (according to the package insert of each agent) and then slowly titrate upwards.	First episode psychosis: Choice of antipsychotic should be made by both the service provider and the healthcare professional. The views of the carer should be taken into account if the service user agrees to this. Offer oral antipsychotic medication Benefits and possible side effects should be discussed to the service user as well as the carer: • Metabolic (weight gain/diabetes) • Extrapyramidal (akathisia/dyskinesia/dystonia • Cardiovascular (prolonging QT interval) • Hormonal (increasing plasma prolactin) • Other (unpleasant subjective experiences)

South Africa guidelines	NICE guidelines
Recommended dosage is preferably in the range of 300-1 000 mg chlorpromazine equivalents. Another agent may only be considered after a 4-6 week trial of an agent.	The following factors should be investigated: • Weight • Waist circumference • Pulse and blood pressure • Assessment of any movement disorders • Assessment of nutritional status, diet and level of physical activity • Fasting blood glucose, glycosylated haemoglobin, blood lipid profile and prolactin levels An electrocardiogram (ECG) should be offered before starting with antipsychotic medication if the patient is experiencing any of the following: • Personal history of cardiovascular disease • Service user is being admitted as an inpatient • Physical examination has identified specific cardiovascular risk • If it is specified in the summary of product characteristics • Offer psychological interventions: • Family intervention • Individual cognitive behavioural therapy (CBT)intervention People who want to use psychological interventions alone should be advised that outcomes are more effective when combined with antipsychotic medication. Psychological interventions alone: • Offer family interventions and CBT. • A time must be agreed on to consider treatment options that will introduce antipsychotic medication therapy. • Symptoms should be monitored regularly including distress, impairment and level of functioning. • Antipsychotic medication treatment should be considered as an individual therapeutic trial for each patient.

South Africa guidelines	NICE guidelines
Recommended dosage is preferably in the range of 300-1 000 mg chlorpromazine equivalents. Another agent may only be considered after a 4-6 week trial of an agent.	The following aspects should be considered for each patient: • Discuss and record the side effects that the patients is most willing to tolerate • Record the indications, expected benefits and risks of oral antipsychotic medication. • Start with a lower dose of the licensed range of the British national formulary or SPC and then titrate upwards slowly according to the licensed range. Do not use a loading dose (rapid neuroleptisation) of antipsychotic medication. • Reasons should be justified and recorded when dosages are outside the range of the BNF or SPC. • Reasons should be recorded when medication is changed, continued or stopped and also the effects for such behaviours should be recorded. • A trial should be carried out at optimum dosage for 4-6 weeks. Depot/long-acting injectable can be offered to patients if: • Patient prefers this type of treatment after an acute episode • Where 'hidden' co-adherence (intentionally/unintentionally) is a clinical priority in the treatment plan and can be avoided.
Multi-episode/relapse (oral monotherapy) SGAs are preferred depending on their availability (Risperidone, Olanzapine, Quetipaine, Aripiprazole, Ziprasidone and Amisulpride). Alternatives are Haloperidol and Chlorpromazine which are first-generation antipsychotics (FGA). Dosages should not exceed 1000mg chlorpromazine equivalents. Another agent may only be considered after a 4 to 6 week trial of an agent. Benzodiazepines (preferably lorazepam) can be used to lighten disruptive behaviour.	Subsequent/recurrence of acute episodes of schizophrenia Oral antipsychotic medication in combination with psychological interventions should be implemented. The same methods should be followed as described in step (1), (2), (3), (4) and (6) referred above in first episode psychosis.
Second-line treatment If response to first-line treatment as referred to above is poor or non-responsive, then the following should be taken into consideration:	Second-line treatment If schizophrenia patient's illness has not responded satisfactorilly to the pharmacological- and psychological treatment, the following should be taken

South Africa guidelines	NICE guidelines
• Is the diagnosis correct? • Were the agent used at the adequate dose as well as duration? • Were adequate psychosocial interventions performed? • Were comorbidities assessed and managed? The following guidelines should be followed if the answer is yes to all of the above statements: • Use another SGA or FGA orally (should be an SGA if there was an unsatisfactory response to an FGA in the first trial). • Other strategies include: cross-titration, overlap-and-taper or an abrupt change. • Oral therapy of the new agent should then be used for doses that do not exceed 1 000mg of chlorpromazine at for a trial of 4-6 weeks before turning to a third-line treatment. • If there was a response after another SGA or FGA was used correctly but the patient was non-adherent then switch over to a depot formulation. If no response, use another depot formulation.	into consideration: • Analyse the diagnosis. • Establish whether the patient has shown adherence to the antipsychotic medication that was given at the adequate dose for the adequate duration. • Establish whether the patient underwent psychological interventions that were performed according to the correct treatment guidelines. • Analyse the possibility of other causes of non-response for example; use of other prescribed medication simultaneously, physical illness, or comorbid substance abuse. • Do not use combination therapy except for short periods, such as changing medication.
Third-line treatment Clozapine oral monotherapy (highest dose 900mg daily) for 6 months. WCC (absolute neutrophil counts specifically) should be monitored beforehand, then weekly for the first 18 weeks and then monthly afterwards. Doses for clozapine should be given above 450mg daily while considering the risk of dose-related seizures.	Third-line treatment Use clozapine only if the patient showed no response to treatment of at least two different agents that were given at the adequate duration and time where a minimum of one of the drugs should have been a non-clozapine second generation antipsychotic. Warn patient of clozapine's potential to cause skin photosensitivity and that sunscreen should be applied.
Fourth-line treatment If there was a partial response, add an augmentation agent: • Mood stabiliser (lamotrigine, valproate, lithium) • ECT • Or combine clozapine with a second-generation antipsychotic • Or review combination therapy of SGAs as well as FGAs.	Fourth-line treatment If no response of the patient's illness was shown to an adequate dose of clozapine, then healthcare professionals should review the steps referred to in the second-line treatment above as well as measure the therapeutic drug levels before augmenting clozapine by adding a second antipsychotic. A sufficient period for such a trial is at least 8-10 weeks. A drug should be chosen that does not cause common side effects when combined with clozapine.

2.5 Antipsychotic medication used for the treatment of schizophrenia

2.5.1 Phenothiazines

Phenothiazines can be associated with antihistaminic, anti-dopaminergic, anticholinergic and adrenolytic activities (Schellack & Matlala, 2014:30).

2.5.1.1 Chlorpromazine

Composition: Chlorpromazine is available in 25 mg, 50 mg and 100 mg tablets (Snyman, 2014:31). It is also available in an injection form in strengths of 25 mg/ml and 50 mg/2ml (Rossiter, 2010:466).

Working mechanism: It acts as a central nervous system depressant, blocking both nicotinic and muscarinic effects of acetylcholine as well as blocking adrenergic alpha-receptor blockers (Intramed, 1987:1).

Contra-indications: It is not indicated for patients suffering from bone-marrow depression, glaucoma, central nervous system depression, who are in a coma, or who have major cardiac disorders (Rossiter, 2014:465).

Dosage: The usual dose for chlorpromazine is 75 mg to 300 mg per day with a maximum dose of 1 000 mg (Department of Health, 2012:15.13; Schellack & Matlala, 2014:30). The initial dose for an adult is 25 mg to 50 mg taken orally three times a day, which may increase gradually as necessary (Snyman, 2014:31). A daily dose of 75 mg may be taken at night (Snyman, 2014:31). Children over the age of five may take one third to a half of the daily dose for adults not exceeding 75 mg of chlorpromazine a day (Snyman, 2014:31). Children between the ages of one and five years may not exceed a dose of 40 mg by per day (Snyman, 2014:31).

Side effects: Chlorpromazine is commonly associated with sedation, weight gain, hyperglycaemia, anticholinergic effects, orthostatic hypotension as well as extrapyramidal symptoms (McKean & Monasterio, 2011:17). It may cause photosensitivity reactions, hypersensitivity reactions regarding obstructive jaundice and has an epileptogenic effect (Taylor *et al*., 2005:15). Elderly patients have an increased risk of developing postural hypotension (Schellack & Matlala, 2014:30).

2.5.1.2 Fluphenazine decanoate

Composition: Fluphenazine decanoate is available as an injection in dosage strength of 25 mg fluphenazine decanoate fluid per ml in sesame oil preserved with 1.5% m/v benzyl alcohol (Snyman, 2014:31).

Working mechanism: It acts as an antipsychotic agent that has an extended action duration period. It works on all the levels of the central nervous system and multiple organ systems (Bristol-Myers Squibb, 2005:2).

Contra-indications: Fluphenazine decanoate is contra-indicated in patients with subcortical brain damage, who suffer from depression or are in a comatose state; it should not be given to patients who use high doses of hypnotics or alcohol and those who have liver damage (Rossiter, 2010:466). Patients who suffer from Parkinsonism, who are pregnant or are breast feeding, or have been exposed to organophosphate insecticides may also not use the medication (Bristol-Myers Squibb, 2005:1).

Dosage: The usual dose per day is 12.5 mg and the maximum dose is 100 mg (Schellack & Matlala, 2014:30). The maintenance dose of fluphenazine decanoate is 12.5 mg to 50 mg injected intramuscularly every four weeks (Department of Health, 2012:15.14).

Side-effects: Fluphenazine decanoate is often associated with blood dyscrasias (Schellack & Matlala, 2014:30). Extrapyramidal side effects are commonly associated with using this antipsychotic and pain may occur at the injection site as well as erythema and swelling (Rossiter, 2010:466).

2.5.1.3 Pimozide

Composition: Pimozide is available in 1 mg and 4 mg tablets (Snyman, 2014:31).

Working mechanism: It acts as a dopamine D_2 receptor blocker, has an opiate receptor antagonism activity and has a low affinity for α-adrenergic receptors (Friedman *et al*., 2011:1289). Pimozide is used in chronic schizophrenic patients as maintenance treatment to those who respond to the anti-delusional and anti-hallucinatory effects of neuroleptics, but are not affected by the hypo-sedative action of these neuroleptics (Schellack & Matlala, 2014:30).

Contra-indications: It is not indicated in concomitant use of drugs that may prolong the QT interval as it can cause cardio-toxicity, ventricular arrhythmias and electrocardiogram abnormalities (Rossiter, 2010:470). Pimozide is also contra-indicated if the person suffers from central nervous system depression, is in a coma, has Parkinson's syndrome or suffers from epilepsy (Snyman, 2014:31). The safety of pimozide during pregnancy, lactation, or children under the age of 12 years has not been determined (Snyman, 2014:31).

Dosage: The usual dose is 2-20 mg per day with a maximum dose of 20 mg daily (Schellack & Matlala, 2014:30). According to Janssen Pharmaceuticals (1999:2) a single dose of pimozide (individually determined for each patient) in the morning is recommended. Combination therapy with pimozide and additional psychotropic medicine is advised for maintenance therapy (Janssen Pharmaceuticals, 1998:2). The initial dose for adults is 2 to 4 mg once daily when used chronically with a weekly increment of 2 to 4 mg until desired therapeutic outcomes is achieved or until adverse effects become unbearable (Snyman, 2014:31). A dosage of 6 mg can be taken as the average maintenance dose with a usual range of 2 to 12 mg per day and a maximum daily dose of 20 mg (Snyman, 2014:31). For elderly patients the maintenance dose is also 6 mg daily but the initial dose is half of the starting dose for adults (Janssen Pharmaceuticals, 1998:2).

Side effects: Pimozide is commonly associated with constipation, dryness of the mouth, visual disturbances and anorexia (Schellack & Matlala, 2014:30). It can also cause akathisia and extrapyramidal side effects (Rabin & Siegel, 2012:272).

2.5.1.4 Prochlorperazine

Composition: Prochlorperazine is available in 5 mg tablets (Snyman, 2013:31).

Working mechanism: It acts as a psychotherapeutic agent working in the subcortical level of the brain in order to suppress the central nervous system (Pharmacare Limited, 2004:1).

Contra-indications: Prochlorperazine is not indicated for patients with phaeochromocytoma, bone marrow suppression, who are in a comatose state or with pre-existing central nervous system depression (Rossiter, 2010:49). According to Pharmacare Limited (2004:2), prochlorperazine should not be given to children weighing less than 10 kg. Safety has not yet been determined with concurrent use during pregnancy or lactation (Pharmacare Limited, 2004:1).

Dosage: It should be administrated in dosage strengths of 15 to 100 mg in divided doses daily for adults (Snyman, 2014:31). Prochlorperazine should be administrated to children calculated in percentage according to the adult dose; 25% for 1 year old, 33% for 3 year old, 50% for 7 year old, 60 % for 10 year old, 75% for 12 year old and 80% for 14 year old (Snyman, 2014:31).

Side effects: Patients may experience the following side effects using prochlorperazine: micturition, constipation, dryness of the mouth, blurred vision and mydriasis (Pharmacare Limited, 2004:2). The patient may also experience hypotension, electrocardiographic changes, tachycardia, neuroleptic malignant syndrome, cholestatic jaundice and leukopenia (Pharmacare Limited, 2004:2).

2.5.1.5 Trifluoperazine

Composition: Trifluoperazine is available in 1 mg and 5 mg tablets (Snyman, 2014:31).

Working mechanism: It acts as a D_2 receptor blocker in the brain (Marques *et al*., 2010:2). When the D_2 receptors are blocked in the mesolimbic and mesocortical pathways in the brain, therapeutic actions of typical antipsychotic medication is activated (Marques *et al*., 2010:2).

Contra-indications: Trifluoperazine may not be used by patients suffering from blood dyscrasias who have liver damage or bone marrow depression and should also not be used in patients who experience central nervous system depression (Snyman, 2014:31).

Dosage: Adults may use 1 to 5 mg twice daily but not exceeding a maximum of 15 to 20 mg per day (Snyman, 2014:31). Children between the ages of six to 12 years may use doses that are calculated by 1 mg/20 kg/day of their body mass (Rossiter, 2010:467).

Side effects: Trifluoperazine is commonly associated with extrapyramidal effects such as akathisia, tardive dyskinesia, pseudo-Parkinsonism and dystonic reactions due to its blockade effect in the striatum of the brain (Marques *et al*., 2010:3). It is also associated with hypotension (Rabin & Siegel, 2012:272). Patients using this medication may also experience drowsiness, dizziness, blurred vision, skin reactions, weakness and amenorrhoea (Snyman, 2014:31).

2.5.2 Butyrophenones

Butyrophenones may be associated with potent neuroleptic activity, but lack in antihistaminic, adrenolytic and anticholinergic activity and do not cause sedative effects during therapy (Schellack & Matlala, 2014:30).

2.5.2.1 Haloperidol

Composition: Haloperidol is available as 1.5 and 5 mg tablets, 0.5 mg capsules and 5 mg/ml or 20 mg/2ml injections (Snyman, 2014:31).

Working mechanism: It acts as a dopamine-2 receptor blocker (Rossiter, 2010:467). This blockade of the dopamine receptors in the mesolimbic dopaminergic system results in a tranquilising and antipsychotic action (Aspen Pharmaceuticals, 2011:2).

Contra-indications: Haloperidol is contra-indicated in patients with Parkinson's disease or who have a history of extrapyramidal effects when using neuroleptics (Rossiter, 2010:467). Haloperidol should also not be administrated in patients who are in a comatose state or who are suffering from severe toxic central nervous system depression (Snyman, 2014:32).

Dosage: The initial dose for adults is 0.5-5.0 mg two to three times a day orally (Rossiter, 2010:467). The maintenance dose for haloperidol is usually 1.5 to 3 mg per day and should be reduced to the lowest effective dose (Snyman, 2014:32). High doses of 20 mg daily in severe cases have been used (Snyman, 2014:32). When used for acute psychoses, 2-5 mg should be given intramuscularly in intervals of four to eight hours and may not exceed 20 mg (Rossiter, 2010:467). Elderly patients should start with small doses, which may increase gradually with increments, and usually start usually with half the dose adults starts with (Snyman, 2014:32). The initial dose for paediatric patients are 0.025-0.05 mg/kg/day orally divided into two to three doses and may be increased to a maximum of 0.15 mg/kg/day if necessary (Rossiter, 2010:467).

Side-effects: Haloperidol is commonly associated with extrapyramidal effects such as akathisia, dystonia and Parkinsonian effects and can cause weight gain and hyperglycaemia (McKean & Monasterio, 2011:17). Using this medication can also cause oligomenorrhea and amenorrhoea (Schellack & Matlala, 2014:30).

2.5.3 Atypical antipsychotics

Atypical antipsychotics are associated with antagonism on the serotonin and dopamine receptors. The pharmacological activity on the serotonin receptors decrease motor side effects that are connected to first-generation antipsychotics (Felmet *et al*., 2010:243).

2.5.3.1 Aripiprazole

Composition: Aripiprazole is available as 5, 10, and 15 mg tablets as well as 7.5 mg/ml intramuscular injections and 9.75 mg/1.3 ml vial solutions for injection (Snyman, 2014:32).

Working mechanism: It is classified as an atypical antipsychotic; acting as an agonist at dopamine D_2 and serotonin type 1 receptors and an antagonist at serotonin type 2 receptors (Taylor *et al.,* 2005:20). It is also used to target both positive and negative symptoms of schizophrenia (Horn *et al*., 2012:79).

Contra-indications: Aripiprazole may not be used in patients with dementia-related psychosis as well as in patients with known hypersensitivity to this product (Otsuka Pharmaceuticals, 2014:1). Use of aripiprazole during pregnancy is classified as a category C risk, where medication may be used if the benefits outweigh the risk; it is also not advised to use medicine during third trimester of pregnancy as the neonate is at risk for developing extrapyramidal- or withdrawal symptoms after being born (Otsuka Pharmaceuticals, 2014:9).

Dosage: The initial dose for adults is 10 to 15 mg per day taken orally; after a period of two weeks the dosage may be increased to a maximum of 30 mg per day (Snyman, 2014:32). The maintenance dose is 15 mg per day taken once orally (Snyman, 2014:32). An intramuscular injection is administrated when the schizophrenic patient is also suffering from agitation, starting with an initial dose of 9.75 mg/1.3ml as a single dose (Snyman, 2014:32). An effective dose range is usually 5.25 to 15 mg as a single injection; a second injection may be administered two hours after the first one and no more than three injections may be administrated in an interval of 24 hours (Snyman, 2014:32). The maximum dose for aripiprazole is 30 mg daily including all other formulations administrated concurrently (Snyman, 2014:32).

Side effects: Aripiprazole may be associated with extrapyramidal effects, sedation, weight gain and orthostatic hypotension (McKean & Monasterio, 2011:17). Using this medication can also cause headaches, anxiety and insomnia (Schellack & Matlala, 2014:32), as well as agitation (Rabin & Siegel, 2012:272).

2.5.3.2 Clozapine

Composition: Clozapine is available in 25 and 100 mg tablets (Snyman, 2014:32).

Working mechanism: It has a unique mechanism of work in that it only binds to D_1 and D_2 receptors and has a weak affinity for D_4, $5HT_3$, α_1 and α_2 adrenergic $AChM_1$ and H_1 receptors Taylor *et al*., 2005:16). It is also used to target the psychosis symptoms of schizophrenia (Horn *et al.,* 2012:79).

Contra-indications: Clozapine is contra-indicated in patients with a history of clozapine-induced agranulycotosis, granulocytopenia and neutropenia (Pharmaplan, 2002:2). It should also not be used in patients with uncontrolled epilepsy, patients in a comatose state, who have glaucoma, are alcoholics or are intoxicated with drugs (Pharmaplan, 2002:2). Clozapine should also not be used by patients with renal, liver or cardiac disorders or patients suffering from impaired bone marrow function (Rossiter, 2010:471). It is also not safe to use during pregnancy or lactation (Pharmaplan, 2002:2).

Dosage: Patients use clozapine as a third-line therapy; the usual dose for clozapine is 200 to 450 mg per day with a maximum dose not exceeding 900 mg daily for a period no more than six months (Schellack & Matlala, 2014:30). The initial dose of clozapine for adults is 12.5 mg once or twice on the first day; on the second day one or two 25 mg to 50 mg tablets may be used (Snyman, 2014:32). An increase of the total dose can be in increments of 25 to 50 mg per day in order to achieve the target dose of 300 mg per day administered in divided doses after two to three weeks of treatment if medicine is well tolerated (Snyman, 2014:32). Thereafter, dosage can be increased in increments of up to a 50 mg or 100 mg once or twice a week if necessary (Snyman, 2014:32). In elderly patients the initial dose should be very low and must start with 12.5 mg on the first day and restrict increments to only 25 mg/day (Snyman, 2014:32). Clozapine may not be used in children under the age of 16 years (Snyman, 2014:32)

Side-effects: Clozapine is commonly associated with sedation, anticholinergic effects such as blurred vision and dryness of the mouth and can also cause postural hypotension, weight gain and a feeling of dizziness (McKean & Monasterio, 2011:16). Patients using clozapine should be closely monitored as it may cause neutropenia which can lead to fatal agranulocytosis (McKean & Monasterio, 2011:18). Constipation is a serious side effect of clozapine that can be life-threatening and it is recommended that a patient should use a laxative concomitantly with the medication (McKean & Monasterio, 2011:18).

2.5.3.3 Risperidone

Composition: Risperidone is available in 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablets, 1 mg/ml oral solutions and fast release tablets available in 0.5 mg, 1 mg, 2 mg and 3 mg tablets (Snyman, 2014:33). It is also available in a prolonged-released suspension for intramuscular injections in strengths of 25 mg, 37.5 mg and 50 mg (Snyman, 2014:39).

Working mechanism: It acts as a potent $5HT_2$ and D_2 antagonist (Taylor *et al*., 2005:18) and is the only atypical antipsychotic of which the official use is indicated for the treatment of behavioural and psychological symptoms of dementia officially (McKean & Monasterio, 2011:19). Risperidone is also used to target both positive and negative symptoms of schizophrenia (Horn *et al*., 2012:79) as well as for acute but also chronic schizophrenia (Schellack & Matlala, 2014:32).

Contra-indications: Patients with known hypersensitivity reactions to risperidone that include anaphylactic or angioedema reactions may not use risperidone (Janssen Pharmaceuticals, 2014:4).

Dosage: The initial dose for adults is 2 mg per day and may be used once or twice a day (Janssen Pharmaceuticals, 2014:3). The dose may be increased in intervals of 24 hours or longer in increments of 1 to 2 mg a dose at doses no greater than 4 to 8 mg per day (Janssen Pharmaceuticals, 2014:3). The usual maintenance dose is 4-6 mg daily with a maximum dose of 16 mg per day (Schellack & Matlala, 2014:32). The initial dose for adolescents (13 to 17 years) is 0.5 mg per day and may only be administrated as a single dose in the morning or evening. The dose may be increased in intervals of 24 hours or longer in increments of 0.5 to 1 mg a dose at doses no greater than 3 mg per day (Janssen Pharmaceuticals, 2014:3).

Side effects: According to the National Alliance on Mental Illness (NAMI) (2013:4), serious side effects of risperidone include: increased levels of prolactin, which may lead to loss of periods in females and the production of breast milk, loss of libido in men, or erectile dysfunction. Risperidone may also cause extrapyramidal effects as well as tardive dyskinesia (NAMI, 2013:4). According to Taylor *et al*. (2005:18), other side effects may include: chest pain, nausea, dyspnoea, dyspepsia and abdominal pain. Low blood pressure, dizziness, sexual dysfunction and an increase appetite are also possible side effects (NAMI, 2013:4). Insomnia, angio-oedema, dysregulation of body temperature and children

developing hyperprolactinaemia can also be caused by using risperidone (Schellack & Matlala, 2014:32).

2.5.3.4 Quetiapine fumarate

Composition: Quetiapine is available in 25 mg, 100 mg, 200 mg and 300 mg tablets and also as extended-release tablets available in 50 mg, 150 mg, 200 mg, 300 mg and 400 mg tablets (Snyman, 2014:41).

Working mechanism: It works more specifically in the mesolimbic area and has a low affinity for D_1, D_2 and $5HT_2$ receptors and a moderate affinity for α_1 and α_2 receptors (Taylor *et al*., 2005:19). Quetiapine fumarate is also used to target both positive and negative symptoms of schizophrenia (Horn *et al*., 2012:79).

Contra-indications: It is not indicated in patients with liver and renal impairments, or in concomitant use with cytochrome P450 and 3A4 inhibitors (Snyman, 2014:33). Safety of quetiapine use in children, adolescents younger than 18 years, during pregnancy or lactation have not been established (Snyman, 2014:33).

Dosage: For the normal quetiapine tablets, adults should start on day one with 25 mg twice daily. At day two and three, the dose should be incremented to 25 mg to 50 mg divided into two or three doses a day. By day four, the dose should range between 300 and 400 mg per day (AstraZeneca Pharmaceuticals, 2013:2). Adolescents (13-17 years) should start with 25 mg two times a day on day one, 100 mg divided twice daily on day two, 200 mg divided twice daily on day three, 300 mg divided twice daily on day four and 400 mg divided twice daily on day five. The recommended dose range is 400-800 mg per day and may be administered three times a day (AstraZeneca Pharmaceuticals, 2013:2). The extended release tablets should be taken one tablet daily preferably in the evening (AstraZeneca Pharmaceuticals, 2012:3). The initial dose recommended per day is 300 mg (AstraZeneca Pharmaceuticals, 2013:3). Depending on the response as well as tolerance of a patient doses should be titrated in a range of 400 to 800 mg per day, in intervals of just as short as one day and in increments of 300 mg per day (AstraZeneca Pharmaceuticals, 2013:3).

Side-effects: Quetiapine is commonly associated with sedation, anticholinergic effects such as a dry mouth feeling, blurred vision and constipation, dizziness, akathisia, restlessness, hyperglycaemia and also postural hypotension (McKean & Monasterio, 2011:16). It may also

cause pain in the chest, back, ear and abdominal area as well as somnolence (Schellack & Matlala, 2014:32).

2.5.3.5 Ziprasidone

Composition: Ziprasidone is available in 20 mg, 40 mg, 60 mg and 80 mg capsules and as an intramuscular injection in strengths of 20 mg/ml (Snyman, 2014:34).

Working mechanism: Ziprasidone acts as a D_2 and $5HT_2$ antagonist with marked agonist activity at $5HT_{1A}$ receptors, while inhibiting monoamine reuptake in a fair amount (Taylor *et al*., 2005:20). It is used during the clinical improvement of acute phases and for maintenance while continuing therapy for schizophrenia (Schellack & Matlala, 2014:32).

Contra-indications: Ziprasidone is contra-indicated in patients who have a history of QT prolongation as well as patients who are treated for dementia-related psychosis, especially the elderly patients (Snyman, 2014:34). Ziprasidone may also not be used by patients who have recently struggled with myocardial infarction or with known uncompensated heart failure or sensitivity to the product (Roerig, 2009:8).

Dosage: The usual dose for ziprasidone is 80 mg per day with a maximum of 160 mg daily (Schellack & Matlala, 2014:32). The initial dose for ziprasidone is 20 mg to be taken twice daily with food orally (Roerig, 2009:26). According to the patient's clinical status, the daily dose may be increased to 80 mg twice daily (Roerig, 2009:26). If dose adjustments are necessary, it should be done in intervals of not less than two days, because steady state is usually reached within one to three days (Roerig, 2009:26). Ziprasidone administrated intramuscularly are only used for acute agitation in schizophrenia and it is not advised to use it for more than three consecutive days (Roerig, 2009:26). It is suggested that 10 to 20 mg may be injected up to a maximum of 40 mg per day (Roerig, 2009:26). A dosage of 10 mg may be injected every two hours and a dosage of 20 mg may be injected every four hours and may not exceed the maximum dose of 40 mg per day (Roerig, 2009:27).

Side-effects: The most common side-effects of ziprasidone are headaches, dizziness, anxiety, drowsiness and an upset stomach (NAMI, 2013:3). Serious side effects include extrapyramidal side effects as well as tardive dyskinesia (NAMI, 2013:3). Ziprasidone may also cause sedation as well as orthostatic hypotension (McKean & Monasterio, 2011:17). Ziprasidone is also associated with nausea and tonic-clonic seizures (Schellack & Matlala, 2014:32).

2.5.3.6 Paliperidone

Composition: Paliperidone is available in 3 mg, 6 mg and 9 mg tablets (Snyman, 2014:34). It is also available as an extended-release intramuscular injectable suspension of paliperidone palmitate in strengths of 50 mg, 75 mg, 100 mg, and 150 mg (Snyman, 2014:42).

Working mechanism: Paliperidone taken orally shares the same compound as risperidone with the exception that it is linked to an innovative delivery system technology in order to achieve smooth drug plasma levels (South African Pharmaceutical Journal, 2011:46). It acts as a D_2 and $5HT_{2A}$ receptor antagonist and also blocks α_1 adrenergic receptors. H_1 histaminergic and α_2 adrenergic receptors also get blocked, but to a lesser degree (South African Pharmaceutical Journal, 2011:46).

Contra-indications: It is not indicated for patients who are hypersensitive to risperidone, with renal impairment, Parkinson's disease, with dementia, pregnancy and for patients under the age of 18 years (Snyman, 2014:42).

Dosage: The initial recommended and target dose for paliperidone is 6 mg taken once daily in the morning (Janicak & Winans, 2007:882). A dosing range of 3-12 mg daily is recommended with dosage adjustments to be done in increments or decrements of 3 mg in intervals of five days or more (Janicak & Winans, 2007:882).

Side-effects: The most common side effects associated with the administration of paliperidone in an injection form include: somnolence, extrapyramidal side effects, akathisia and dizziness (Janssen Pharmaceuticals, 2009:24). Other side-effects related to paliperidone are increased mortality in the elderly patients who are treated for dementia-related psychosis, QT prolongation, orthostatic hypotension and cerebrovascular adverse effects, metabolic changes, disorder in normal body temperature regulation, tardive dyskinesia, priapism, hyperprolactinemia, seizures, neuroleptic malignant syndrome, dysphagia, cognitive and motor impairment and also leukopenia, agranulocytosis and neutropenia (Janssen Pharmaceuticals, 2009:24).

2.5.3.7 Amisulpride

Composition: Amisulpride is available in 50 mg, 100 mg, 200 mg and 400 mg tablets (Medicines and Healthcare Products Regulatory Agency, 2013:6).

Working mechanism: It acts as an antagonist on the D_2 and D_3 receptors with a slight affinity on the D_1- or non-dopaminergic receptors and is used for acute and chronic schizophrenia (Schellack & Matlala, 2014:30).

Contra-indications: Amisulpride is not indicated in patients who use other medication that may enhance torsades de pointes or prolongs QT intervals or in patients who suffer from phaeochromocytoma, who have concomitant prolactin dependent tumours, or during lactation, pregnancy and in children younger than 15 years (Snyman, 2014:42).

Dosage: It should be taken orally 400 mg to 800 mg per day during psychotic episodes (Snyman, 2014:42). During such episodes, doses may be increased to a maximum 1 200 mg per day (Snyman, 2014:42). Patients suffering from predominant negative symptoms should take 50 mg to 100 mg per day orally depending on the patient's response (Snyman, 2014:42).

Side-effects: Amisulpride may cause extrapyramidal effects (McKean & Monasterio, 2011:17), neuroleptic malignancy syndrome (Schellack & Matlala, 2014:32) as well as increase prolactin levels (Leweke *et al.,* 2012:165).

2.5.3.8 Olanzapine

Composition: Olanzapine is available in 2.5, 5 and 10 mg tablets as well as in a 10 ml/vial intramuscular injection (Snyman, 2014:36).

Working mechanism: It acts as a D_2 and $5HT_2$ receptor blocker (Taylor *et al,* 2005:18). Olanzapine is also used to target both positive and negative symptoms of schizophrenia (Horn *et al*., 2012:79).

Contra-indications: Olanzapine may not be used in patients with closed-angle glaucoma as well as patients under the age of 18 years (Pharmacare limited, 2013:2). Olanzapine should be avoided in patients who have a risk of developing diabetes (McKean & Monasterio, 2011:22).

Dosage: The usual dose is 10-20 mg per day with a maximum dose of 20 mg daily (Schellack & Matlala, 2014:32). The initial dose for adults is 5-10 mg once a day orally, with a therapeutic target dose of 10 mg daily reached within several days (Snyman, 2014:43). When administrating the intramuscular injection, 10 mg as a single dose should be injected; after two hours 10 mg may be administrated again (Rossiter, 2010:472). A maximum of three injections may be administrated in 24 hours with a waiting period of at least four hours between the second and third dose (Rossiter, 2010:472).

Side-effects: Olanzapine is commonly associated with metabolic side effects such as weight gain, increased lipid levels (especially triglycerides and LDL cholesterol but decreases the HDL cholesterol), and new-onset of type 2 diabetes as glucose tolerance is impaired (McKean & Monasterio, 2011: 22). Olanzapine can cause one to three kg greater weight gain in patients than other atypical antipsychotics (McKean & Monasterio, 2011:22). It may cause bradycardia, extrapyramidal side effects, weakness and xerostomia (Schellack & Matlala, 2014:32).

2.5.4 Others

2.5.4.1 Sulpiride

Composition: Sulpiride is available in 50 mg and 200 mg capsules and tablets (Snyman, 2014:43).

Working mechanism: It is unique in that it has a dose-related selectivity for pre-synaptic D_4 and post-synaptic D_2 receptors (Taylor *et al*., 2005:17). In doses lower than 800 mg/day sulpiride's main affinity is for D_4 receptors, acting as a dopamine antagonist and leading to more dopamine available in the synaptic cleft (Taylor *et al*., 2005:17). In high doses (above 800 mg/day) sulpiride's main affinity is for D_2 receptors that cause a post-synaptic blockade of D_2 (Taylor *et al*., 2005:17).

Contra-indications: Sulpiride is contra-indicated in patients with phaeochromocytoma, hypomania, renal and hepatic disease (Rossiter, 2010:469). It should also not be used by patients who are sensitive to sulpiride or phenothiazines who have bone-marrow depression and should be used with caution in patients with hypertension (Pharmacare Limited, 1999:1).

Dosage: The usual dose for sulpiride is 200-800 mg daily with a maximum dose of 2400 mg per day (Schellack & Matlala, 2014:30). The maintenance dose of sulpiride is 400- 800 mg daily in divided doses (Snyman, 2014:43). Sulpiride may be used in children (from 6-12

years of age) by administrating 3-5 mg/kg according to their body mass in divided doses per day. When administered to the elderly, dosages should be reduced (Pharmacare Limited, 1999:1).

Side-effects: Sulpiride may cause fatigue, erectile dysfunction as well as weight gain (Schellack & Matlala, 2014:30). It may also cause menstrual abnormalities, an increase in levels of serum prolactin, sedation and galactorrhoea (Rossiter, 2010:469).

2.5.4.2 Zuclopenthixol decanoate

Composition: Zuclopenthixol decanoate is available in 2 and 10 mg tablets as well as in an injection containing 200 mg/ml sterile solution of zuclopenthixol decanoate (Snyman, 2014:43).

Working mechanism: It acts as a neuroleptic and has a high affinity for D_1 and D_2 receptors (Kumar & Stretch, 2005:3). It is used for schizophrenia associated with agitation, hostility, aggressiveness, psychomotor disturbances and suspiciousness (Schellack & Matlala, 2014:30).

Contra-indications: Zuclopenthizol decanoate may not be used in combination with acute alcohol, barbiturates and opiate poisoning (Lundbeck, 2013:5). It is also contra-indicated in patients suffering from or who have a history of hepatic disease and also in patients who are in a comatose state (Snyman, 2014:43). It is also contra-indicated in patients suffering from blood dyscrasias, phaeochromocytoma, leucopenia and agranulocytosis (Lundbeck, 2013:5).

Dosage: In acute phases zuclopenthixol should be administrated intramuscularly in strengths of 50 mg to 150 mg and if necessary may be repeated after two to three days (Department of Health, 2012:15.13). For maintenance therapy zuclopenthixol may be given 200 mg intramuscularly every four weeks (Department of Health, 2012:15.14). The initial dose is 100 mg (0.5 ml) injected into the gluteal region intramuscularly (United Kingdom Psychiatry Pharmacy Group, 2011:1), then a week later or if symptoms reappear a second injection of 100-200 mg (0.5 to 1 ml) should be administered intramuscularly (Lundbeck, 2013:5). The maintenance therapy of this drug is the administration of 100-600 mg (0.5-3 ml) intramuscularly every one to four weeks although it is usually administered as 200 mg (1 ml) every two to four weeks (Lundbeck, 2013:5).

Side-effects: The most common side effects of zuclopenthixol decanoate include: akathisia, movement disorders, weight gain and rising of prolactin levels (United Kingdom Psychiatric Pharmacy Group, 2001:2). Zuclopenthixol may also be associated with insomnia (Schellack & Matlala, 2014:30). Patients using this medication usually need anti-Parkinsonian medication as a result of the movement disorders caused by zuclopenthixol (Kumar & Stretch, 2005:10).

2.5.4.3 Flupenthixol

Composition: Flupenthixol is available in 0.5 mg and 1 mg tablets (Snyman, 2014:44).

Working mechanism: It belongs to the thioxanthene group and is a low dose neuroleptic (Lundbeck, 2000:1). Because it is only administrated in low dosages it acts as an anxiolytic, mood stabiliser, antidepressant and contains certain activating properties (Lundbeck, 2000:1). Flupenthixol blocks the central monoamine receptors particularly in the dopaminergic system (Lundbeck, 2000:1).

Contra-indications: It should not be given to patients who are in a state of excitement, over activity, those who have pre-existing central nervous system depression, coma, phaechromocytoma and bone marrow depression (Snyman, 2014:44). It is also not indicated in patients with severe opiate, alcohol and barbiturate intoxications (Snyman, 2014:44). The use of flupenthixol in pregnant women and during lactation's safety has not yet been determined and is contra-indicated for the use in children (Snyman, 2014:4).

Dosage: The standard initial dose for adults is 1 mg as a single dose in the morning (Snyman, 2014:44). The dose may be increased to 2 mg if the clinical response is inadequate after a week of treatment (Snyman, 2014:44). If the daily dose is more than 2 mg per day, the dosage should be divided and must not exceed 3 mg per day (Snyman, 2014:44). It is advisable to give the last dose of the day not after 16h00 because of the activating properties of the drug (Snyman, 2014:44). Response to flupenthixol is usually within two to three days and the drug should be withdrawn if no response has been observed within a week at the maximum dosage (Snyman, 2014:44).

Side-effects: Insomnia is the most known side-effect of this drug but others may include central depression, antimuscarinic effects and heart effects like tachycardia, hypotension, electrocardiographic changes and cardiac arrhythmias (Lundbeck, 2000:1). A patient may also experience hypersensitivity reactions such as contact sensitivity, urticarial, erythema

multiform and exfoliative dermatitis (Lundbeck, 2000:1). Flupenthixol may also cause delirium, nasal congestion, miosis, catatonic-like states, convulsions, agitation, and alter endocrine functions causing impotence, priapism and inhibition of ejaculation (Lundbeck, 2000:1). A patient may also experience deposition of pigment in the skin as well as in the eyes and also cloudiness of the cornea and lenses when treatment has been used for a duration of time (Lundbeck, 2000:1).

2.5.4.4 Flupenthixol decanoate

Composition: Flupenthixol decanoate consists of a 1 ml ampoule of flupenthixol decanoate that contains 20 mg/ml of active ingredient (Snyman, 2014:44).

Working mechanism: Flupenthixol decanoate is a very strong neuroleptic during the day and does not cause fatigue like other neuroleptics do (Lundbeck, 2000:1). The drug possesses activating properties beneficial to schizophrenic patients which are more co-operative and open during treatment (Lundbeck, 2000:1).

Contra-indications: The drug should not be administered to overactive and excitable patients (Snyman, 2014:44). It is also contra-indicated in concordance with barbiturate, opiate and alcohol poisoning (Snyman, 2014:44). Pregnant women may also not use the medication (Snyman, 2014:44).

Dosage: The usual dose is 40 mg per day with a maximum dose of 400 mg daily (Schellack & Matlala, 2014:30). The maintenance dose for flupenthixol decanoate is 20 mg to 40 mg given intramuscularly every four weeks (Department of Health, 2012:15.14).

Side-effects: Commonly associated with insomnia (Schellack & Matlala, 2014:30) as well as extrapyramidal symptoms and autonomic side-effects (Lundbeck, 2000:1).

2.5.4.5 Clothiapine

Composition: Clothiapine is available in 40 mg tablets and as a 40 mg/4ml injection (Snyman, 2014:44).

Working mechanism: It acts as a $5HT_3$ receptor blocker; it has affinity for $5HT_6$ and $5HT_7$ receptors and is used to down regulate cortical $5HT_2$ receptors (Carpenter *et al*., 2003:12). The injectable form may be used intramuscularly or intravenously (Berk *et al*., 2012:3).

Contra-indications: Clothiapine is contra-indicated in patients with known hypersensitivity to the product, that are in a comatose state, that suffers from central nervous system depression, or in patients that are susceptible to convulsions (Juvise Pharmaceuticals, 2014:2).

Dosage: For acute psychosis, the patient should be administered with a dose between 120 mg and 200 mg per day up to a maximum dose of 360 mg daily (Berk *et al*., 2012:3). The initial dose for adults should be between 120 mg to 160 mg given orally, intravenously or intramuscularly in two to three divided doses daily, the maintenance dose for clothiapine is 40 mg per day (Rossiter, 2010:473).

Side-effects: Patients may experience some of the following side effects: visual disturbances, dry mouth feeling, agitation, oedema, rash, excessive sweating, extrapyramidal side effects, orthostatic hypotension and thrombocytopenia (Snyman, 2014:44).

Antipsychotics have been proven to improve positive symptoms, helping patients to preserve their social role and diminish the stigma around behaviours of psychotic patients (Gordon & Green, 2013:1). However, there are a variety of side effects that need to be taken into account, such as extrapyramidal side effects and some newer effects more often caused by atypical antipsychotics such as weight gain, dyslipidaemia and hyperglycaemia when taking antipsychotics (Miyamoto *et al.,* 2005:79).

2.6 IDENTIFYING FACTORS INFLUENCING TREATMENT GUIDELINES WITH REGARD TO SCHIZOPHRENIA

This section focuses on the prescribing patterns of practitioners, geographical area and access to treatment. It explains the dangers of prescribing antipsychotic treatment for off-label use and offers a brief discussion on the politics associated with treatment for schizophrenia while discussing the guidelines that need to be followed in order to prescribe antipsychotics to schizophrenic patients.

2.6.1 Authorised practitioners prescribing antipsychotic treatment

The most error-prone decisions made by practitioners are diagnostic decisions, leading to a decrease in the quality of medical care (Horn *et al*., 2012:76). The choice regarding diagnoses and treatment of a schizophrenic patient is often influenced by the culture of the

psychiatrist and also the perception of the psychiatrist concerning the race and culture of the patient (Banerjee, 2012:23). However, a large number of patients with psychiatric disorders are also consulting traditional healers acting as psychotherapists (Emsley, 2001:382).

Section 22A of the Medicines and Related Substances Act (101 of 1965) states that schedule 5 medicine that are used for anxiolytic, antidepressant and tranquilising effects may only be prescribed for a period no longer than six months, and should the authorised prescriber wish to repeat the prescription, he/she must first consult with a registered psychiatrist before renewing the prescription. In 1999, research was conducted in order to grant psychologists the right to prescribe psychotropic medication to patients because of the shortage of mental health practitioners in South Africa (Lindegger, 1999:69). It was also argued that with the minimum training in psychotherapy or psychological procedures psychiatrists have, it would be of great advantage to the patient to be treated by a psychologist who has in-depth expertise in behavioural and cognitive assessment (Lindegger, 1999:69). Even though South Africa has a mental health legislation, the Mental Health Care Act 2002, barriers still exist regarding the development in mental health leading to extreme shortages of mental health practitioners and the inability to develop psychiatric services that result in patients being institutionalised and not receiving their rehabilitation in order for them to go back to their communities (Burns, 2010:662).

The median rate of medical professionals working in mental health facilities is six per 100 000 population (WHO, 2011:11). Due to the shortage of psychiatrists, more than 70% of psychotropic medications are prescribed by non-psychiatrists (Foster, 2010:2); whereas the second largest group to prescribe atypical antipsychotics are nurse practitioners (Foster, 2010:5). According to Harrison *et al.* (2012:142), due to the shortage and uneven distribution of trained mental health practitioners in the United States, 40% of children (2 to 17 years) did not receive psychological healthcare or counselling when they needed these services the most, resulting in children and adolescents who have never had psychiatric assessments or non-pharmacological treatments by mental practitioners. However, the number of practicing psychiatrists has been increasing, from 70 registered psychiatrists with the South African Medical Council in 1965, to 400 in 2012, although this is still not sufficient for a population of approximately 50 million individuals (Gillis, 2012:81). The most common reasons for psychiatrists leaving South Africa may include financial considerations, concerns about the crime and violence in the country, uncertainties that arise regarding academic psychiatry as well as private practices and also the social-political insecurities in the country (Emsley, 2001:383). Mental healthcare users go to primary care physicians as their first point of help;

it is therefore important that medical students get first-hand experience with mental healthcare users in order to obtain the necessary knowledge, confidence and skills to help these patients in the best possible way (Du Preez *et al.,* 2015:24).

According to Harrison *et al.* (2012:144), the only way to ensure that prescribing practices are safe is if there is collaboration between primary care providers and qualified mental health providers; unfortunately, collaborations such as these are rare.

2.6.2 Off-label use of antipsychotic treatment

Foster (2010:1) defines off-label prescribing as the issuing of prescriptions by medical professionals of medicine for uses or manners other than what it is authorised by the Food and Drug Administration (FDA). Nearly 50% of all antipsychotic prescriptions are for off-label use (Horn *et al*., 2012:76); this is a cause for concern as second-generation antipsychotics are being prescribed without guidelines for the indication, dosing or monitoring (Horn *et al*., 2012:81), regardless of the fact that these medications may cause harm to the patient (McKean & Monasterio, 2011:15).

Clinicians often have to make difficult decisions regarding the prescribing of antipsychotics for off-label use due to inadequate resources of psychological therapy (Brett, 2015:95). A recent survey conducted in Canterbury, New Zealand, showed that 96% of psychiatrists prescribed antipsychotic medicine for off-label uses, with quetiapine being the most commonly used for indications other than psychotic disorders such as anxiety, sedation and post-traumatic stress disorder (McKean & Monasterio, 2011:20). The use of antipsychotics is associated with the risk of sudden cardiac death and in 2005, the US Food and Drug Administration filed a black box warning because of the increased mortality associated with sudden cardiac death in elderly patients using antipsychotics (Brett, 2015:96).

Not only psychiatrists are responsible for the increase in off-label use of antipsychotics (Harnett, 2013:3). Family doctors and paediatricians are also prescribing this medication for reasons other than its indication (Harnett, 2013:3) For example, general practitioners prescribe antipsychotics to children in order to treat depression or anxiety and paediatricians generally prescribe antipsychotics to treat behavioural and emotional type disorders (Harnett, 2013:3). According to Horn *et al*. (2012:76), nearly one-third of antipsychotic prescriptions are prescribed by general practitioners in primary care settings in British Columbia.

Another problem that is also occurring, are prescribers who issue antipsychotic prescriptions to patients who are not recorded to be diagnosed with psychosis (Marston *et al*., 2014:10). According to Marston *et al*. (2014:10), the reason for this trend may be because of patient preference as they do not want to be labelled with schizophrenia because of its associated stigma, leading to large numbers of individuals not being recorded with psychosis in primary care.

2.6.3 Influence of politics

During apartheid, healthcare personnel were guilty of stigmatising and discriminating against psychiatric patients (Emsley, 2001:382). A report, provided by the American Psychiatric Association in 1978, revealed that apartheid had a negative impact on social institutions, families and even on the mental health of black South Africans that led to unnecessary deaths of black patients (Emsley, 2001:384).

The current condition in South Africa is that resources available for better services in the country are not being used, because of democracy's inefficiencies, lack of accountability, corruption and incompetent management (Dhai, 2012:1). This leads to more problems as patients are not receiving the critical services they need; suffering from preventable morbidity and mortality and it also affects the healthcare professionals, as they are not getting sufficient training for their occupations (Dhai, 2012:2).

2.6.4 Role of geographical area and access to services in treatment guidelines

A study, conducted in 2007 showed that there were only 38 psychiatrists in KwaZulu-Natal, which was only 25% of the required national norm (Burns, 2010:663). In 2001, 24 public psychiatric hospitals were registered in South Africa (Emsley, 2001:382).

Most of the mental health professionals are located in urban areas leading to rural regions without any psychiatric expertise (Burns, 2010:665). More than 50% of psychiatrists have their own private practices, and these practices provide first-world standards of care that only people who are funded by medical insurance or only 20% of the population can afford to utilise these services (Emsley, 2001:383). One reason for psychiatrists opening their own private practices could be that South African psychiatrists are poorly reimbursed, especially when compared to European standards (Emsley, 2001:383). Another possible reason, according to Sukeri *et al*. (2014:160), is that health services in South Africa are located in large urban areas because of the policy of apartheid many years ago. This has led to an

unbalanced health system, especially in the motherlands (homelands); and in the Eastern Cape today, mental health services are disorganised and broken.

The development of psychiatric services on a tertiary level in institutions in South Africa is not funded; advances in this development only occur when clinicians succeed in convincing institutional managers to overspend on their 'equitable share' budgets, which is rarely adequate (Burns, 2010:664). There is also still a shortage in the number of psychiatrists in rural areas, while still losing many psychiatrists due to opportunities overseas (Gillis, 2012:81). According to Emsley (2001:382), psychiatric services are not fully developed in rural areas leading to patients with psychiatric disorders not being identified and not receiving the help they need to be treated.

2.6.5 Guidelines that need to be followed in order to decide whether or not a patient should use medicine

Many disorders mimic the pattern of schizophrenia, and therefore several other disorders must be ruled out first before an individual can be diagnosed with schizophrenia, making this diagnosis very difficult (Versola-Russo, 2006:90). According to Lehman *et al*. (2004:9), planning the treatment for a schizophrenic patient involves three goals: 1) symptoms should be either reduced or eliminated; 2) the patient's quality-of-life and also functioning should be maximised; and 3) recovery of the patient's effects of the illness should be maintained or promoted.

Issuing prescriptions for antipsychotics needs to be done with caution as this medication causes severe side effects (Marston *et al.,* 2014:1). According to Schellack and Matlala (2014:29), each patient should undergo the following investigations before antipsychotic treatment may be started: an electrocardiogram, liver function tests, white cell count, the body mass index, fasting blood glucose and waist-to-hip ratio of the patient. These investigations are necessary as all antipsychotic medication causes to some degree weight gain, elevation in lipid levels and some medication, especially clozapine, causes agranulocytosis (Schellack & Matlala, 2014:29). Monotherapy is usually recommended, as combining antipsychotic medication has no advantage (Schellack & Matlala, 2014:29).

A good guide to approach psychosis according to the KwaZulu-Natal treatment protocols is to take into account the five Ds, namely: diagnosis, drug, dose, duration and depot antipsychotics (Burns *et al*., 2007:12). Before administrating antipsychotic medication to a patient, the patient must first be diagnosed with psychosis; the KwaZulu-Natal treatment

protocols declare that a patient is psychotic when he/she is experiencing any of the following psychotic symptoms: hallucinations, negative symptoms, delusions and disorganised behaviour (Burns *et al*., 2007:12). According to the NICE guidelines (2014:4), before a person can be diagnosed with psychosis, he/she must first undergo an assessment specifically at a specialist mental health service or an early intervention service where a healthcare professional has a meeting with the individual and decides whether or not the person has a mental health condition and what medication would be most appropriate to treat the patient. Professionals such as these only include psychiatrists, psychologists or professionals who specialise in treating psychosis or schizophrenia through psychological therapy (NICE guidelines, 2014:4). The assessment should include a physical examination as well as personal questions about the patient's wellbeing or mental health, after which a care plan must be developed and provided to the patient (NICE guidelines, 2014:4).

Although certain guidelines must be followed, there are some psychiatrists who prescribe antipsychotics surreptitiously (Latha, 2010:99). Surreptitious prescribing can be defined as the provision of a prescription to a healthcare professional or family member of a patient with the knowledge that the medication will most likely be administered to the patient in a disguised form such as food or drinks with the patient taking the medication unknowingly (Latha, 2010:99). This practice is only allowed if the patient refuses or is unable to take his/her medication, due to his/her illness or psychopathology and has the chance of receiving effective treatment outcomes by only taking the medication (Latha, 2010:100).

2.7 FACTORS INFLUENCING SCHIZOPHRENIC PATIENTS

This section focuses on the effect of co-morbidities and addictions concomitant with patients suffering from schizophrenia and how age and gender plays a role in schizophrenia. This section also focuses on the importance of patient adherence towards medication and some factors that may influence the adherence of patients. In addition, the economic burdens the disease places on the patients' families and why generic medication is not always an option are discussed.

2.7.1 The influence of co-morbidities and addictions on the type of treatment guidelines

Schizophrenia patients, when compared to the average population, live an unhealthier lifestyle regarding exercise, diet and consumption of nicotine (Roick *et al*., 2007:275). Schizophrenia patients have an unbalanced diet, eating breakfast less frequently, while

eating more regularly in the evening and consuming instant meals more often while drinking coffee much more than the average population (Roick *et al*., 2007:273).

For patients suffering from schizophrenia, concordant cardiovascular disease, type 2 diabetes and lung diseases associated with smoking are two thirds of the main causes of premature mortality (Smith *et al.,* 2013:1137). Comorbidity is the presence of two illnesses or disorders at the same time in a person and usually implies that there will be interactions between the illnesses affecting the patient's prognosis and course of the illnesses (Volkow, 2010:1). Women with schizophrenia have a higher prevalence of developing diabetes and hyperprolactinemia than men, while men have a higher prevalence of developing hypertension than woman do (Ochoa *et al*., 2012:5). Depressive symptoms are usually observed either during the first stages of psychotic relapse or during the recovery from psychosis (WHO, 1998:10). Although psychotic co-morbidities are common in schizophrenia patients, substance abuse co-morbidities are more predominant (Buckley *et al.,* 2009:383). According to Buckley *et al.* (2009:383), no two schizophrenic patients present with the same pattern of symptoms.

Schizophrenia patients are usually associated with drug use disorders while cannabis is the drug that is misused most commonly (Johns, 2001:118). A study done in 2011 in Australia on the prevalence of men with a lifetime disorder of cannabis or illicit drug use was 63.2%, while for women it was 41.7% (Morgan *et al.,* 2011:48). The effects that cannabis can cause on mentally ill patients include psychological responses (for example depression, panic, psychosis and anxiety), dependency as well as withdrawal effects (Johns, 2001:116). Schizophrenic patients smoke more than four cigarettes per day than the average person (Roick *et al*., 2007:273). Men suffering from schizophrenia have a higher prevalence of smoking cigarettes than women with a proportion of 71.1% compared to 58.8% (Morgan *et al.,* 2011:47).

A long-term study showed that schizophrenic patients struggling with substance abuse had a 16-fold increased conviction rate for crimes associated with violence (Rueve & Welton, 2008:40). The study also showed that 30% of all schizophrenic men suffering from substance abuse have been convicted of a crime of violence (Rueve & Welton., 2008:40). The proportion of alcohol abuse or dependence in patients suffering from schizophrenia are higher for men than for women with 58.3% compared to 38.9%, respectively (Morgan *et al*., 2011:48).

2.7.2 The influence of patient's gender and age on treatment guidelines

Women perform better in numerous areas of schizophrenia treatment than men (Ochoa *et al.,* 2012:5). For example men usually develop schizophrenia between the age of 18 and 25 years, whereas women have two peaks at the age of onset of the disease, developing the illness usually between the age of 25 to 35 years and then also when they are over 40 years reaching their paramenopausal peak (Ochoa *et al*., 2012:2). Because women develop schizophrenia at a later age than men do, they are better adjusted to the illness as they are better accustomed to requirements of the community than what men was at an earlier stage in life (Ochoa *et al.,* 2012:5).

When symptoms experienced by the illness are being compared according to gender, a comprehensive literature review revealed that men present with more negative and disorganisation symptoms and women present with more affective symptoms (Ochoa *et al.,* 2012:2). Haas *et al*. (1990:289) indicated that women with schizophrenia tend to improve during psychosocial treatment in concordance with family-involvement, whereas men usually worsen after such treatment; this might be because encounters with socialisation lead to discouragement of dependency for men and also the inability to talk about feelings.

According to Smith *et al*. (2013:1136), when looking at the mortality of diagnosed schizophrenia patients, men on average die 20 years earlier, and women die 15 years earlier, compared to non-diagnosed mental illness patients. Studies have also shown that in men pre-morbid functioning is worse than in women and have also revealed that for women to develop a psychotic disease they need more exposure to life events such as stress than men; women also perform better in social functioning (for example fertility and marital status) and have fewer basic needs (for example food and accommodation) and also fewer functional needs (for example money and education) (Ochoa *et al*., 2012:3). Men performing poorer might be because social and occupational demands are greater for men than for women, resulting in higher stress and also negative beliefs of males ever readjusting to live in the community again (Haas *et al.,* 1990:289).

Furthermore, when looking at sex-related expectations, it is culturally expected for men to be more independent than women, whereas it is expected for women to be more family dependent than for men. It is therefore easier for women to accept family assistance; women are therefore not experiencing as much stress and pressure from the community as men (Nasser *et al*., 2002:356). Considering cognitive functioning, women perform better than men, for example in language and memory domains (Ochoa *et al.,* 2012:3). According to

Grigoriadis and Seeman (2002:437), female schizophrenic patients suffer more from mood symptoms, for example depression, while men suffer from apathy, lack of speech and flat affect. Studies have also shown that when comparing substance abuse with gender, men have a higher prevalence than women do and this may also be a risk factor for men in developing this illness (Versola-Russo, 2006:95). Women are more likely to experience affective symptoms, while men tend to experience more negative symptoms, which will affect the type of treatment given to different genders (Versola-Russo, 2006:95).

When looking at treatment outcomes, women seem to respond better to typical antipsychotics and olanzapine than men do (Ochoa *et al*., 2012:4). According to Grigoriadis and Seeman (2012:437), women have a second peak onset of schizophrenia that men do not have, due to the 'oestrogen hypotheses'. The presence of the hormone oestrogen in woman delays the onset of severe symptoms of schizophrenia as it has been hypothesised that oestrogen protects women by reducing dopamine concentration that is known to affect psychotic symptoms (Versola-Russo, 2006:95). Studies have shown that oestrogen in women creates protection against schizophrenia, which may explain the differences in sex such as the later stage of onset, better premorbid functioning, response to treatment and course of illness (Grigoriadis & Seeman, 2012:438).

Studies have also shown that low vitamin D levels in men with schizophrenia are associated with increased negative symptoms and a decrease in premorbid adjustment, whereas in women, low levels of vitamin D are associated with increased anti-social aggression, but reduced hallucinations and emotional withdrawal (Cieslak *et al.,* 2014:545).

2.7.3 Effect of patient adherence on treatment outcomes

Non-adherence is very common in schizophrenia patients, leading to relapse, hospitalisation, personal suffering, a decrease in quality-of-life, a loss of income and also costs associated with more healthcare (Barkhof *et al*., 2012:9). According to Versola-Russo (2006:89), approximately half of all people diagnosed with schizophrenia are being treated. Non-adherence to antipsychotic medication is not only associated with reduced treatment outcomes, but also an increase in suicide attempts for these patients (Novick *et al*., 2010:109). Women are more adherent to treatment recommendations and taking medication than men are (Smith *et al*., 1997:73; Beck *et al.,* 2011:42).

Because non-adherence is an immense problem in psychiatric ill patients, clinicians and family members sometimes need to apply the concept of covert medication in order to

improve the care of these severely mentally ill patients (Latha, 2010:98). According to the Mental Welfare Commission for Scotland (2013:2), covert medication is the administration of medication in any disguised form that usually involves giving medication via food or drinks without the knowledge of the individual that he or she is taking medication. Treating patients through depot medication may prevent covert non-adherence (Barkhof *et al.,* 2012:10).

2.7.3.1 Factors influencing adherence of patients towards treatment

According to Versola-Russo (2006:102), practitioners not understanding or respecting the cultural beliefs of patients through incorporating each individual's beliefs into their treatment might play a role in the adherence of patients as they become non-compliant or unwilling to participate.

The following factors may contribute to poor adherence associated with schizophrenia: the misconception of patients of the severity of the degree of their illness, patients diagnosed at an early age of onset with short duration of illness, medication side effects, the route of administration and substance abuse (Barkhof *et al*., 2012:10). According to Novick *et al*. (2010:109), factors influencing poor adherence are categorised in three types, namely illness-related factors such as insight of the severity of the illness and the duration of the illness, treatment-related factors such as side-effects and the difficulty of the treatment and also patient-related factors such as substance as well as alcohol abuse and thirdly the individual's attitude toward his/her illness and treatment. Novick *et al*. (2010:112) also highlights risk factors that might cause future non-adherence to antipsychotic medication, namely alcohol and substance abuse, hospitalisation, self-supporting housing and individuals showing aggression.

According to Baloush-Kleinman *et al.* (2011:179), the attitude of the individual toward medication directly influences the individual's adherence toward the medication. Attitudes toward medication are influenced by the patient's awareness of his/her medication needs, the individual's awareness of the social consequences of the condition, negative symptoms, and also the insight of the patient regarding the patient-physician alliance (Baloush-Kleinman *et al*., 2011:180). Adherence of a patient can be improved by a psychiatrist or designated team member phoning or visiting a patient when he/she is not attending their appointments (Lehman *et al*., 2004:20). Unfortunately, this will not be possible in South Africa due to the shortage of mental health professionals in this country (Burns, 2010:662).

2.7.4 Effect of cost of treatment on patients

Schizophrenia is the most costly illness treated by psychiatrists, as it not only puts great economic burden on patients, but also on their families, society and healthcare systems (Emsley & Booysen, 2004:58). When treatment can no longer be afforded by the patient, it may lead to risks of patient non-adherence and self-medication treatment (Versola-Russo, 2006:8). The National Department of Health's aim is to provide rightful, sufficient, suitable and accessible mental health services for the country; unfortunately, these are not always met due to budgetary constraints (Emsley, 2001:382). Hopefully, the proposed National Health Insurance that will be implemented in 2021 will provide the opportunities and inducements needed in psychiatry as are planned for general medical care in South Africa (Gillis, 2012:82).

In general, patients with schizophrenia are reluctant to change and due to their suspiciousness regarding upcoming change they can develop paranoia or delusions (Treur *et al*., 2009:2). Therefore, generic substitution may reduce drug costs, but may have a negative impact on the compliance of the patients with treatment, resulting in higher hospitalisation costs and also poorer control of symptoms (Treur *et al*., 2009:2). It is advised that such patients be counselled through changing of a brand of a product they are currently using (McKean & Monasterio, 2011:22).

Schizophrenic patients are known to perform worse academically than those without the condition, affecting job opportunities for such patients (Versola-Russo, 2006:8). Schizophrenic patients with a high pre-morbid IQ, experience more affective symptoms but fewer negative symptoms and have better insight and functional outcome than typical schizophrenic patients (Černis *et al.,* 2015:630).

What makes schizophrenia such a costly illness to treat is that it not only includes direct costs such as medication, hospitalisation, special accommodation, care during the day, distinct investigations and disability allowances, but that it also involves indirect costs such as unemployment, idleness, increased family costs for the household, travel costs and unforeseen expenditures (Emsley & Booysen, 2004:58). According to Emsley and Booysen (2004:65), families spend approximately 15 hours a week and nearly R 49 771 ($3 500) per year taking care of an individual in the family with schizophrenia. According to a study conducted in 2003, the cost of treatment for schizophrenia is extremely high; for an individual with re-occurring psychotic symptoms the annual cost of treatment will be approximately R282 131 (AUS$30 000); for most patients and their families this is

unaffordable especially because most of them are not able to return to work (Andrews *et al*., 2003:434). For patients who do not have healthcare insurance, treatment may become unaffordable even if they are using generic medication (Lehman *et al*., 2004:19).

In 1996, South Africa developed a National Drug Policy with the hope of reducing prices of medicine, by enhancing the use of generic medication, and to achieve better dispensing and prescribing practices (Gray, 2009:15). Therefore, in 1997, sections 18A and 22G of the Medicine and Related Substances Act (Act 101 of 1965) were rewritten. Changes made to the Act included the prohibition of bonuses, incentive schemes or rebate systems, and the founding of a pricing committee (Gray, 2009:17). The dispensing fee for pharmacists was established and transparent single exit prices (SEP) were introduced to be used by manufacturers as the only price when selling medication to any person except for the state (Gray, 2009:17). This ensured that no medication would be supplied by any person according to a bonus system, an incentive scheme or rebate system (Mngadi, 2014:49). Three types of adjustments of SEP can be done, namely annual SEP adjustment, permanent SEP reduction and non-permanent SEP reduction (Mngadi, 2014:49). A dispensing fee may be charged additionally from the SEP depending on the medicine price.

The single exit price is set according to a benchmark of other prices internationally that follow more or less the same pricing system regulatory than South Africa (Department of Health, 2015). New Zealand, Australia, Canada and Spain were chosen as benchmarking countries (Department of Health, 2015). The SEP may be applied to products that are priced below the international benchmark and may be increased up to the international benchmark, but the SEP may not exceed the price of the benchmark (Department of Health, 2015).

The annual increase of SEP for 2008 was 6.5%; in 2009 SEP increased with 13.2% and in 2010 SEP increased with 7.4% (Council for Medical Schemes, 2014:4). In 2011, there was no increase in SEP (Government Gazette, 2011:3). An annual adjustment was made in 2012 for the SEP of medicines and scheduled substances where the South African Minister of Health stated that SEP may only be applied to a maximum of 2.14% as last stated on 9 December 2011 (Government Gazette, 2012:3). In 2013, a maximum of 5.8% was applied as last stated in 23 December 2012 (Government Gazette, 2013:3).

2.8 FACTORS INFLUENCING THE DISPENSING OF MEDICINE TO SCHIZOPHRENIA PATIENTS

In this section the influence that cultural beliefs as well as support from families have on the treatment outcomes of patients is discussed. It focuses on the effect that the environment in which the patient is surrounded in have, as well as the violence that is associated with schizophrenic patients. The role the pharmacist play in the treatment of these patients and the effect that antipsychotic treatment as well as polypharmacy have on the treatment outcomes, is also discussed.

2.8.1 Support from families and their cultural beliefs

Family therapy is proven to be an effective intervention for schizophrenia (Asmal *et al*., 2011:367). According to Asmal *et al*. (2011:367), family therapy is a type of treatment model that involves either a single family member or a group of family members of the relative or patient. Benefits from family interventions may include reduced risk of relapse, prevents re-hospitalisation, improves consistency of taking medication and decreases levels of stress and burden on families (Pharoah *et al.,* 2012:27). Family interventions are effective in preventing relapse of schizophrenia symptoms when it includes both the patients and their relatives attending psychiatric therapies (Asmal *et al*., 2011:140).

Unfortunately, family networks gradually break down in developing countries where mental health resources are limited to the public and therefore lack of support for the families results in relatives struggling to take care of the patients with schizophrenia (Asmal *et al*., 2011:369). According to Myers (2011:309), some families are guilty of prolonging the duration of untreated psychosis of their relatives due to their own alternative explanations for psychotic symptoms.

Not only patients are affected by this illness, but also the caregivers influencing their social and mental functioning (Asmal *et al*., 2011:140). Family interventions are developed in order to show relatives how they can support patients with schizophrenia, for example reminding patients to take their medication and also to publish information about the illness so that the stigma associated with schizophrenia can be lessened (Asmal *et al*., 2011:141). Expressed emotion (EE) forms part of the field of family interventions that involves an observation of how families are involved in the lives of the patients with schizophrenia. In South Africa, there are a variety of potential limitations of EE that needs to be considered because of our

cultural diversity (Asmal *et al*., 2011:141). For instance, the indigenous cultural groups in South Africa can blame spiritual forces for psychotic symptoms (Asmal *et al*., 2011:141).

The incidence of schizophrenia, its symptoms, course as well as the outcomes of patients vary across different cultural backgrounds (Myers, 2011:305). In Africa, explanatory models for schizophrenia are often described in themes such as bewitchment, guilt, ancestral calling, jealousy and the 'evil eye' (Asmal *et al*., 2011:368). African patients treated for schizophrenia and who were hospitalised often seek further help from traditional healers in hope of another reason for what is actually causing the disease (Asmal *et al*., 2011:141). Furthermore, the families of these patients may share the same beliefs and help their relatives to seek help from traditional healers (Asmal *et al*., 2011:368). A study was conducted on Xhosa patients and found that of the family members, 67% believed that the onset of the disease was due to spirit possession and/or witchcraft (Asmal *et al*., 2011:368).

2.8.2 Patient's environment

Patients living in ethnic dense areas have an increased risk of developing schizophrenia (Myers, 2011:307). Such areas are associated with an individual residing in a cultural environment that makes him/her feel isolated or different than the majority of the population in which he/she is surrounded (Myers, 2011:308). According to Arajärvi *et al.* (2005:808) individuals born and brought up in urban areas have an increased risk to develop schizophrenia during their adulthood.

An association is drawn between psychotic symptoms and a vitamin D deficiency (Myers, 2011:308). Darker-skinned individuals have increased rates of developing psychosis due to less efficient processing of vitamin D since the northern latitudes have weaker sunlight (Myers, 2011:308). The association between vitamin D and schizophrenia includes the effect the season has in which an individual is born, for example individuals born in late winter or in early spring are less exposed to levels of vitamin D during their prenatal and perinatal periods (Cieslak *et al*., 2014:543). Studies have even predicted that 44% of all schizophrenia cases in Denmark may have been prevented if vitamin D levels were optimised in pregnant mothers (Myers, 2011:308). It has been reported that vitamin D supplementation can reduce symptoms of schizophrenia and even enhance the recovery from this illness (Clelland *et al*., 2014:15).

According to Dean and Murray (2005:69), environmental risk factors associated with schizophrenia can be divided into three stages, namely the early life-, childhood- and later

life stage. The early life stage includes obstetric complications, the season of birth, maternal malnutrition and stress and prenatal or postnatal infection (Dean & Murray, 2005:70). The childhood stage includes head injuries, child abuse and adverse child rearing (Dean & Murray, 2005:70). The later life stage includes drug abuse, social adversity, migration or ethnicity, life events and urbanisation (Dean & Murray, 2005:70).

2.8.3 Violence among schizophrenic patients

Today, mental illness and violence are intricately linked to each other causing consequences in the form of discrimination and isolation from the society (Rueve & Welton, 2008:36). A study conducted in 2009 on violence associated with schizophrenic patients showed that aggressive behaviour is present in patients with schizophrenia regardless of their adherence to antipsychotic medication (Bobes *et al*., 2009:218). Volavka (2013:24) describes violence as aggression among individuals.

Violence among schizophrenic patients is a health problem in the public sector (Volavka, 2012:24). It contributes to several problems such as an increase in cost of treatment, emotional trauma among caregivers and plenty of staff time (Volavka, 2012:24).

Clinicians proposes the following factors that can contribute to schizophrenic patients becoming violent: a patient's age, sex, his/her personality traits, suicidal acts, a history of violent acts, social circumstances and agitation, impulsivity and excitement, substance abuse, suspiciousness and auditory hallucinations (Wehring & Carpenter, 2011:877).

2.8.4 Role of pharmacists in mental healthcare

Pharmacists are often the first healthcare professionals contacted by mental consumers due to their availability and accessibility in the community (Pharmaceutical Society of Australia, 2013:8). Medicinal treatment forms a major part of management of mental illnesses and therefore pharmacists play an intricate role in enhancing mental health services and reducing the burden associated with mental disorders (Rubio-Valera *et al*., 2014:10968). Mental healthcare services provided by pharmacists include a range of settings including community pharmacies, hospital pharmacies and general practice clinics (Pharmaceutical Society of Australia, 2013:6).

As being experts in pharmacotherapy, pharmacists have a broad range of skills that can contribute to the treatment of mental illnesses, these skills include the provision of information to describers about drugs, assisting with strategies to improve medication

adherence and also to communicate and counsel patients regarding their medicine (Rubio-Valera *et al.,* 2014:10979). It is in the scope of practice of pharmacists to ensure safe and effective use of medicines by detecting, preventing and resolving problems related to drugs (Rubio-Valera *et al.,* 2014:10969). It is not in the scope of practice for a pharmacist to diagnose patients; however, they should be able to identify signs and symptoms of a mental illness during verbal or non-verbal signs, during direct requests for herbal sleeping aids and analgesics and also changes in an individual's medical or social history (Pharmaceutical Society of Australia, 2013:11). Pharmacists are in important positions to communicate with patients and emphasise how important medication adherence to antipsychotic treatment is as they are directly involved with the dispensing of the medicine to the patient (Rubio-Valera *et al.,* 2014:10973). A pharmacist also plays an important role in minimising the impact of a mental illness and also maximising the recovery of an episode of a mental illness, by providing information regarding the medicine and advice regarding co-morbidities, encouraging medication adherence and during the supplement of services (Pharmaceutical Society of Australia, 2013:13). A pharmacist can address physical co-morbidities of mentally ill patients by screening tests, blood glucose and blood pressure measurements and assisting patients with advice regarding smoking habits (Pharmaceutical Society of Australia, 2013:15).

There are some barriers to the pharmacist's role in preparing and dispensing medicine and also pharmaceutical care services to patients such as pharmacists' attitudes towards the stigma associated with mental disorders (Rubio-Valera *et al*., 2014:10976). According to the Pharmaceutical Society of Australia (2013:17), stigma and discrimination in a community pharmacy setting towards mental illness are the most essential barrier to the improvement of mental disorders. In Jeddah, Saudi Arabia, a study was done in Saudi community pharmacies regarding the dispensing of medication without prescriptions and found that antipsychotics were given freely to individuals without any prescriptions (Al-Mohamadi *et al*., 2011:15). One of the most common barriers for effective functioning of pharmaceutical services to sensitive mental ill patients is the lack of time to implement services in a busy pharmacy setting (Pharmaceutical Society of Australia, 2013:19).

2.8.5 Influence of antipsychotic polypharmacy

The identification of optimal treatments for schizophrenia remains a challenging goal (Ballon & Stroup, 2013:208). The availability of antipsychotic drugs has grown substantially, but the effective reduction of positive symptoms is still an eluding factor that leaves much to be

desired of antipsychotic drug treatment (Ballon & Stroup, 2013:208). The available schizophrenic guidelines suggest the use of monotherapy with the occasional last resort usage of polypharmacy (Fleischhacker & Uchida, 2014:1083). The NICE guidelines, Algorithm of Texas medication, Guidelines of the World Federation of Societies of Biological Psychiatry and even the Japanese guidelines suggest the use of monotherapy for the treatment of schizophrenia, unless the patient is in a transition period between treatments or when in combination with clozapine (Fleischhacker & Uchida, 2014:1083).

Not only does antipsychotic polypharmacy cause side effects, but it also increases treatment costs and should only be prescribed when patients are difficult to treat (Fleischacker & Uchida, 2014:1090). Discontinuation rates for patients who are using polypharmacy are also higher than for those who are using antipsychotic monotherapy (Cullen *et al*., 2014:7). According to a recent study polypharmacy has shown effective toleration and effectivity, although polypharmacy with benzodiazepines seems to worsen therapeutic outcomes (Làngle *et al.,* 2012:372). Clozapine remains the compound of which the most clinical studies exist with regard to combination therapy (Fleischacker & Uchida, 2014:1084). Common drug combination of clozapine and risperidone studied in schizophrenia showed inconclusive results following double blind tests, thereby adding to the questionable effects of polypharmacy in schizophrenia (Fleischhacker & Uchida, 2012:1084).

A study conducted in 2012 on the effects and treatment outcome of schizophrenic patients using polypharmacy showed that only 21 to 33% of patients over a two-year period had used antipsychotic monotherapy; the rest were all treated with combinations of antipsychotic drugs (Làngle *et al.,* 2012:379). One cause of polypharmacy might be that patients visit several physicians at a time, obtaining a variety of prescriptions without the prescribers being aware of each other, leading to potential medication interactions (Rubio-Valera *et al.,* 2014:10974). Clinicians claim that in long-course psychotic patients, higher doses of antipsychotic treatment are needed in order to achieve the best clinical responses and as such, are using polypharmacy in order to achieve higher doses without using disproportionate amounts of one single drug (Làngle *et al*., 2012:379). These therapeutic considerations supplement the growing use of polypharmacy rather than the enforced monotherapy in unresponsive schizophrenia (Ballon & Stroup, 2013:208).

2.8.6 Effect of treatment for patients and the community

Using antipsychotic treatment when diagnosed with schizophrenia can diminish relapse rates and morbidity (Jobe & Harrow, 2005:893). A study conducted in Australia in 2011 showed that overall, schizophrenic patients using antipsychotic treatment for their condition experienced relief of symptoms, with 57.2% of patients reporting that they experienced a great deal of relief 28.2% reported that they experienced some relief and 9.6% reported they experienced no relief of symptoms (Morgan *et al*., 2011:72). It is important to note that the outcome of patients residing in developed industrialised countries are worse than in those residing in developing countries (Jobe & Harrow, 2005:896). According to Jobe and Harrow (2005:898), a positive side to the outcome of schizophrenia could be seen in the incident rates of patients having periods of recovery as well as that a limited number of patients have been reported to have a progressive downhill in their course of illness.

2.9 CHAPTER SUMMARY

In this chapter, the history and the development of schizophrenia were discussed. Schizophrenia was defined and the causes of the disease were explained leading to a better understanding of the disease.

The next chapter contains the results of the empirical investigation phase of the study including discussion of treatment, factors influencing dispensing and prescribing and costs of treatment.

CHAPTER 3: RESULTS AND DISCUSSION

This chapter focuses on the results and the discussion, found by the objectives stated in the empirical investigation of the study. Two manuscripts are included to present the results and discussion.

Objectives addressed in manuscript one were:

- To determine the prevalence of schizophrenic patients on the database during the study period stratified by gender and age.
- To determine the prescribing and dispensing patterns of schizophrenia treatment during the study period.

Manuscript one was submitted to the *South African Medical Journal*. Author guidelines are inserted in Annexure D and can be viewed by following the link http://www.samj.org.za/index.php/samj/about/submissions (Date of access: 21 Sep. 2015).

Objectives addressed in manuscript two were:

- Conducting a cost analysis on schizophrenia treatment in order to determine possible cost savings due to generic substitution.
- To establish the factors influencing the direct medicine treatment costs of schizophrenia treatment, using database-related variables (medicine-related factors and prescriber speciality).

Manuscript two was submitted to the *Health SA Gesondheid journal*. Author guidelines are inserted in Annexure E and can be viewed by following the link http://www.elsevier.com/journals/health-sa-gesondheid/1025-9848?generatepdf=true (Date of access: 21 Sep. 2015).

3.1 MANUSCRIPT 1

TITLE

Prescribing and dispensing factors concerning schizophrenia treatment in the South African private health sector during the period 2008-2013

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KEYWORDS

Prescriber, compliance, prescribed daily dose, schizophrenia, dispensing, medicine possession ratio

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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Abstract

Background. There is paucity of information with regard to compliance by prescribers and patients alike to antipsychotic treatment in South Africa.

Objective. To determine the prevalence of schizophrenic patients as well as factors influencing both prescribing and dispensing patterns of antipsychotics in the private sector of South Africa, stratified by gender and age.

Method. A retrospective analysis was performed on data for 2008-2013 obtained from a Pharmaceutical Benefit Management Company. Prevalence of schizophrenia was determined by age and gender. Prescribing patterns were determined by comparing prescribed daily doses (PDD) to maximum recommended daily doses (MRDD) and by assessing the prescribing volume of antipsychotics by prescribers. The medicine possession ratio was used as proxy to determine patient compliance with antipsychotics.

Results. Overall women had a higher prevalence of schizophrenia than men, 54.04% *vs.* 45.96%, respectively. Men had a higher prevalence of schizophrenia between ages of 18 to 35 years, whereas women presented with a higher prevalence above the age of 35 years. Psychiatrists generally prescribed most (60.88%) antipsychotics, followed by general practitioners (29.27%). Several antipsychotics were prescribed above their MRDD. Age, gender and co-morbidities had no association with compliance to antipsychotics prescribed; however, type of active ingredient ($p < 0.0001$; Cramer's $V = 0.1287$) and length of treatment period ($p < 0.0001$; Cramer's $V = 0.2477$) played a role.

Conclusion. Type of active ingredient and length of treatment period were predictors of compliance to antipsychotics. In general antipsychotics were prescribed above their maximum recommended daily doses.

Introduction

The global prevalence of schizophrenia is 1%. [1] Men develop schizophrenia at an earlier stage in life, usually between the ages of 18 and 25 years, whereas women have two peaks of onset of developing schizophrenia; the first one between the ages of 25 and 35 years, and the second during their menopausal peak of over 40 years of age. [2]

Although the prevalence of mental illness is high in South Africa, mental health is considered as a low priority [3] and therefore a shortage of psychiatrists is still a problem in this country. [4] According to Burns, only 0.38 psychiatrists were available for every 1 000 individuals in KwaZulu-Natal during 2010, leading to non-psychiatrists prescribing antipsychotics.[4] The Medicine and Related Substances Act 101 of 1965, Section 22 A in South Africa states that physicians may only prescribe schedule 5 medicine used for tranquilising, depression or anxiety for six months and thereafter a registered psychiatrist should be consulted before the renewal of a prescription.[5] Consequently, non-psychiatrists have to work in collaboration with psychiatrists, according to the Medicine Act in South Africa. [5] Schizophrenia is listed as one of the 27 chronic disease list (CDL) conditions in South Africa. [6] A therapeutic algorithm for the treatment of schizophrenia was developed by the Council for Medical Schemes as a guideline for physicians to prescribe antipsychotic treatment to patient members in the private health sector. [6] Medical aid schemes are obliged to cover the costs of treatment and care of the diagnosis, assuming guidelines are followed by physicians according to the algorithms developed. [7]

Patient compliance to antipsychotic treatment for schizophrenia is generally poor; [8] [9] [10] approximately 40% of schizophrenia patients have been found non-compliant to their antipsychotic treatment. [10][9] Non-compliance to medication leads to various difficulties including hospitalisation, [8][9][11] relapse, [8][9][11] reduced quality of life, [8] increase in costs associated with treatment therapy [8] [10] and a loss of income.[8] Non-compliant patients have a threefold greater chance of being hospitalised than those who are adherent. [10] Factors that may contribute to patients being non-compliant are antipsychotic treatment side-effects, [8][9] problem of substance abuse, [8][9] [10] formulation in which the medication is taken, [8] unawareness of the degree of illness severity [8][9] as well as patients diagnosed at a young age with a short duration of illness.[8][9] [10] Patients diagnosed at a young age, usually have a shorter duration of illness and therefore had insufficient time in order to experience the consequences of non-compliance to their antipsychotic medication. [10] In this study, the medicine possession ratio (MPR) calculation was used as proxy to determine patient compliance with antipsychotic treatment. Another study, also determining patient compliance toward antipsychotic medication by using the MPR method, found that patients have a poor compliance towards antipsychotic medication. [9]

Method

A retrospective, quantitative drug utilisation study was performed in order to identify patients registered for schizophrenia treatment on the chronic disease list from 2008 to 2013 by analysing medicine claims data. Data were obtained from a nationally representative South African Pharmaceutical Benefit Management (PBM) company. In 2013, a total of 8.78 million individuals were registered as beneficiary members of medical schemes in South Africa.[12] Data fields used were: patient's date of birth, gender of patient, prescriber

(prescriber speciality), treatment date, day's supply, active ingredients and their quantities as well as ICD-10 codes (F20-F20.9).

Antipsychotics were identified using the Monthly Index of Medical Specialties (MIMS) classification system. Inclusion criteria included all patients with valid ICD-10 codes (F20.0-F20.9) associated with a claim reimbursed from the patient's prescribed minimum benefit (PMB) for one or more of the active ingredients listed in the MIMS categorised under phenothiazines, butyrophenones, atypical antipsychotics and others.

Prescribing patterns were assessed using the prescribed daily dose (PDD) and speciality of the prescriber. The PDD was calculated by dividing the quantity of the product of the dispensed product (number of tablets or volume of suspension) and the strength of the drug (mg or ml), by the number of days the medication was supplied for. General medical practitioners, neurologists and psychiatrists' prescribing patterns were assessed by determining the prescribing volume of active ingredients during the study period. The PDD was compared to the maximum recommended daily dose (MRDD) to assess compliance to prescribing guidelines. Age groups used to assess the comparison between PDD and MRDD were $18 < \text{age} \leq 65$ years and age > 65 years.

Dispensing patterns were assessed using the MPR as proxy for patients' compliance to antipsychotic treatment. The study population included in this calculation consisted of 1 780 patients with at least two paid claims from their PMB. The MPR method has been proven to provide significant comparisons between compliance and patient subgroups.[9] The MPR was determined by the total number of days for which the medicine was supplied, divided by the number of days in the refill interval multiplied by 100. This method makes it possible to determine the number of doses that were dispensed during the dispensing period.[9] The MPR for medicine items claimed by patients was considered compliant if the MPR was between 80 and 110%. [10] An MPR value < 80% indicated an undersupply of medicine; this was when a presence of refill gaps occurred and the possession was considered to be to too low. An MPR value > 110% indicated an oversupply of medicine and the possession was considered to be too high. [10] Compliance of patients was assessed, stratified by age and gender. Age groups used to assess the compliance with antipsychotics prescribed were: $0 < \text{age} \leq 12$, $12 < \text{age} \leq 18$, $18 < \text{age} \leq 35$ years, $35 < \text{age} \leq 65$ years and age > 65 years. The treatment period was divided into three groups, namely $0 > \text{days} \leq 30$ days, $30 < \text{days} \leq 120$ days, days > 120.

Prescribed minimum benefit CDL conditions were identified by their ICD-10 codes of paid claims from patients in order to discuss the comorbidities associated with schizophrenia.

Statistical analyses were performed by using the SAS program version 9. 3 (SAS Institute, Cary, NC, 2008-2013). The variables of the study were expressed through descriptive statistics, including frequency, standard deviations (SD), percentages (%), means and 95% confidence intervals. A probability of $p \leq 0.0001$ was considered statistically significant. Inferential statistics included chi-square distribution models used to determine how the statistics of the population were distributed. Practical significance using Cramer's V with values ≥ 0.1 were regarded as a small effect, ≥ 0.3 as moderate effect and ≥ 0.5 large effects, which were then used to determine the effect size. Analysis of Variance (ANOVAs) with Tukey's HSD post-hoc test was used to compare mean values between more than two independent groups. Cohen's d-value (with a practical significance taken as $d \geq 0.8$) was only considered when the p-value was statistically significant.

This study was approved by the Health Research Ethics Committee of North-West University (NWU-00179-14-A1). Goodwill permission was obtained from the Board of Directors of the PBM Company of South Africa, while the analysis of data was conducted anonymously.

Results

From 2008 to 2013, the prevalence of schizophrenia remained relatively the same ranging between 0.08 and 0.09 % (Table 1). Women had a higher prevalence of schizophrenia than men; however, no statistically or practically significant differences were observed between schizophrenia prevalence and gender ($p = 0.4761$; Cramer's $V = 0.0320$). Patients between the ages of 18 to 35 years had the highest prevalence of schizophrenia over the study period. Age groups had no statistically or practically significant association with schizophrenia prevalence through the study years ($p = 0.8371$; Cramer's $V = 0.0280$) (Table 1).

Hypertension was the most prevalent co-morbid CDL condition associated with schizophrenia. However, a decrease in hypertension, hypothyroidism and type 2 diabetes mellitus of 1.88%, 0.95% and 0.32%, respectively, was observed over the study period. Epilepsy and hyperlipidaemia in schizophrenic patients increased during the study period by 1.25 and 3.92%, respectively (Table 1). No statistical or practical significant differences were observed between average number of chronic diseases and the different study periods (Table 1) ($p = 0.0013$; Cohen's d value = 0.0516).

The number of patients (male *vs.* female) as a function of the study period is shown in Table 2. There was a statistically significant difference ($p < 0.0001$) between the proportions of males *vs.* females in each age group. The size of this effect was moderate (Cramer's $V \geq 0.3$). There were more males in the younger age groups compared to more females in the older age group. Male patients between the ages of 18 to 35 years and between ages 35 to 65 years had a relative increase from 2008 to 2013. A 9.13% decrease was observed from 2008 to 2013 in male patients above 65 years of age. Female patients between the ages of 18 to 35 years and between ages 35 to 65 years, however, had a relative decrease in prevalence with 11.77% and 3.90%, respectively, from 2008 to 2013.

In Table 3, a statistically significant association ($p < 0.0001$) was shown between prescriber speciality and active ingredient; however, this effect was small (Cramer's $V = 0.1836$). The majority of antipsychotics were prescribed by psychiatrists (60.88%), followed by general medical practitioners (29.27%).

In Table 4, prescribed guidelines were assessed by evaluating the most prevalent active ingredients and by comparing the doses prescribed (PDD) to the MRDD allowed for age groups $18 < \text{age} \leq 65$ years and 65 years > age. The PDDs of olanzapine and risperidone exceeded the MRDDs in patients from 18 to 65 years old for the entire study period 2008 to 2013. The PDDs of aripiprazole (years 2008, 2009, 2011, 2012 and 2013), amisulpride (2009), clozapine (2008, 2013), haloperidol (2008, 2011, 2012) and quetiapine (years 2009, 2010, 2012, 2013) exceeded the MRDDs for patients aged 18 to 65 years. The PDDs of olanzapine and risperidone exceeded the MRDDS for patients above 65 years of age for the entire study period 2008 to 2013. The PDDs of clozapine for 2013 also exceeded the MRDD for patients above 65 years. Olanzapine was prescribed during the entire study period (2008-2013), while also exceeding the MRDD allowed for elderly patients.

The compliance status of antipsychotics prescribed was statistically significantly associated with age groups ($p < 0.0001$). However, this association was weak (Cramer's $V = 0.0606$). The majority of items (58.47%) claimed for patients older than 65 years were in the compliant category. A proportion of 46.57% and 51.70%, could be categorised in the compliance group for patients 18 to 35 years and older than 35 to 65 years, respectively (Table 5). Undersupply and oversupply both, were the highest for patients between the ages of 18 to 35 years.

Compliance status was independent of patient's gender ($p < 0.0637$; Cramer's $V = 0.0308$). Men, however, were compliant with 53.34% of items claimed, whereas women were only compliant with 50.50% of items claimed. Prevalence of undersupply of antipsychotic items was the most for women, whereas that of oversupply of antipsychotics was similar for both men and women (Table 5).

Antipsychotics prescribed had a significant association with treatment period ($p < 0.0001$); the association had a moderate effect (Cramer's $V = 0.2477$). Most antipsychotics (54.76%) with a treatment period longer than four months showed a MPR in the compliance category. Only 32.57% and 49.42% of antipsychotics with a treatment period less than 120 days and 30 days, respectively, could be categorised in the compliance group. Within the group of antipsychotics that were oversupplied most could be categorised as taking place during treatment periods of less than 30 days, whereas undersupplied were most categorised in treatment periods longer than 120 days (Table 5).

Table 5 furthermore shows that the compliance status of antipsychotics prescribed had a statistically significant association with active ingredients ($p < 0.0001$); however, the effect is small (Cramer's $V = 0.1287$). For active ingredients, 59.61% of clozapine items claimed were categorised under the compliant group. For all other active ingredients, except aripiprazole and amisulpride, more than 50% of items were categorised under the compliant group.

Compliance status was independent of the number of co-morbidities associated with a schizophrenic patient ($p < 0.0902$) (Table 5). The majority of items claimed (100%) for patients associated with 6 co-morbid conditions were in the compliant category.

Discussion

The study population consisted of significantly more female than male patients, which is similar to the literature reporting on the prevalence of schizophrenia patients. [2] Men in the study population were generally between the ages of 18 and 35 years, whereas women were generally above the age of 35 years. This may be ascribed to the fact that women have a higher prevalence of schizophrenia than men at a later stage in life at their para-menopausal peak, due to the 'oestrogen hypothesis', where oestrogen delays the onset of schizophrenia in women. [2]

When prescribers' speciality were compared to the number of items prescribed, psychiatrists had the highest percentage of items prescribed (60.88%), followed by general practitioners (29.27%) (psychiatrists: general medical practitioners ratio, 1:2.1). The relatively high prevalence of items prescribed by general practitioners could be due to the shortage of mental health professionals, especially psychiatrists, in South Africa. [4] Mental health has a low priority in Africa with 0.38 psychiatrists available for every 1 000 individuals. [3] Reasons for

low priority of mental health in South Africa may be attributable to three categories, namely legitimacy of the problem where severity of the illness and prevalence of patients are misunderstood, feasibility of response where a lack of knowledge for appropriate interventions and socio-cultural beliefs play a role in the cause and treatment and lastly, support for response where a lack in funding and advocacy and stigma related to the disease play a role. [3]

Both clozapine and olanzapine exceeded the MRDD for age group >65 years, which is regarded as potentially harmful in elderly patients.[13] The following conditions may worsen if patients are already suffering from them while using clozapine, namely dementia, seizures, cognitive impairment, delirium and constipation. [13] Elderly patients using olanzapine have the potential to develop the following side-effects: bradycardia and orthostatic hypotension, while delirium, urinary retention, constipation and cognitive impairment may worsen if a patient is already experiencing these effects.[13] Compliance to correct prescribing guidelines for atypical antipsychotics could improve by 1) ensuring that the correct psychiatric diagnosis is made, 2) before treatment is initiated the prescriber should consider target symptoms, indications and degree of functional impairment, 3) patients using atypical antipsychotics should be monitored by protocols already approved, and 4) healthy lifestyles should be encouraged. [14]

No practically significant associations were found between compliance to antipsychotics prescribed and age group. Compliance towards antipsychotics prescribed increased as treatment period prolonged, which could be due to a decrease or low level in patients' clinical symptoms and an increase in patients' function; the longer a patient is taking antipsychotic treatment on a daily basis.[11]

We furthermore showed that the best compliance to antipsychotics prescribed was towards clozapine, followed by haloperidol, olanzapine, risperidone and quetiapine and showed the least compliance towards amisulpride and aripiprazole. Amisulpride causes major increases in prolactin levels and both amisulpride and aripiprazole are associated with weight gain and extrapyramidal side-effects, which could be the cause for the low prevalence of medication compliance percentages. [15] Clozapine is associated with severe side-effects and may only be used if no other antipsychotic offered an effective treatment outcome or adherence during the treatment period. [8] Better compliance to clozapine could be ascribed to increased symptom improvement and cognitive function when compared to other typical antipsychotic drugs prescribed.[10][16] The use of clozapine requires frequent clinical sessions in order to monitor full blood counts. [15][16] Therefore, these clinical visits encourage compliance as many patients are also under the understanding that when white blood cell counts are monitored, blood levels of clozapine medicine are also being monitored. [16] Lastly, patients using clozapine are preselected beforehand as the use of clozapine requires cooperation from the patient in order to obtain necessary monitoring while using this medicine. [16]

The most common comorbidities associated with schizophrenia found in our study support findings from other studies in that hyperlipidaemia, hypertension and diabetes mellitus are generally associated with schizophrenic patients. [2] Clozapine, olanzapine and risperidone are the drugs that are most likely to be associated with causing hypertension, as these are the three antipsychotics that have the highest affinities for α_2 receptors. [15] These drugs were also most prescribed in our study.

Study limitations

Data for this study included only those claims reimbursed by the patient's medical aid scheme; antipsychotics bought through cash transactions were excluded. There was therefore the potential of underreporting of prevalence. There was also a limited external validity for this study as only one database was used for the study.

Conclusion

This study focused on the prevalence of schizophrenic patients as well as the prescribing and dispensing patterns of antipsychotics in South Africa. Medication compliance rates of this study should be taken into consideration during the prescribing of antipsychotic medication according to the therapeutic algorithm developed by the Council of Medical Schemes. [6] In our study, compliance rates of the atypical antipsychotics (aripiprazole, amisulpride and quetiapine) had the lowest percentage in the compliant group for antipsychotics. Prescribers can use this information, by carefully noting negative symptoms of these items beforehand and thereby prevent or monitor potential non-compliance of patients. We showed that age, gender and number of co-morbidities only played a minor role in the compliance of antipsychotics prescribed. In support of similar studies, our study also showed that treatment period and the type of active ingredient prescribed are strong predictors for compliance to antipsychotics prescribed.

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Conflicts of interest

The authors declare no conflict of interest

Table 1 Patient demographics

	2008 *n* (%)	2009 *n* (%)	2010 *n* (%)	2011 *n* (%)	2012 *n* (%)	2013 *n* (%)	*p*-value (Cramer's *V*)
Total number of patients	758 505	1 033 057	968 158	864 977	815 810	809857	
Number of schizophrenic patients	637 (0.08)	834 (0.08)	823 (0.09)	766 (0.09)	713 (0.09)	637 (0.08)	
Gender							
Male	285 (44.74)	363 (43.53)	377 (45.81)	356 (46.48)	338 (47.41)	308 (48.35)	0.4761 (0.0320)
Female	352 (55.26)	471 (56.47)	446 (54.19)	410 (53.52)	375 (52.59)	329 (51.65)	
Age (years)							
> 0 ≤ 18	11 (1.73)	15 (1.80)	6 (0.73)	7 (0.91)	9 (1.26)	5 (0.78)	
> 18 ≤ 35	133 (20.88)	173 (20.74)	181 (21.99)	169 (22.06)	151 (21.18)	148 (23.23)	
> 35 ≤ 65	354 (55.57)	473 (56.71)	452 (54.92)	417 (54.44)	379 (53.16)	350 (54.95)	0.8371 (0.0280)
> = 65	139 (21.82)	173 (20.74)	184 (22.36)	173 (22.58)	174 (24.40)	134 (21.04)	
Co-morbidities per schizophrenic patient							
Hypertension	155 (24.33)	186 (22.30)	193 (23.45)	178 (23.24)	175 (24.54)	143 (22.45)	0.8861 (0.0198)
Hyperlipidaemia	70 (10.99)	90 (10.79)	105 (12.76)	102 (13.32)	108 (15.15)	95 (14.91)	0.0517(0.0499)
Hypothyroidism	71 (11.15)	92 (11.03)	98 (11.91)	91 (11.88)	75 (10.52)	65 (10.20)	0.8811(0.0200)
Epilepsy	58 (9.11)	72 (8.63)	66 (8.02)	69 (9.01)	69 (9.68)	66 (10.36)	0.7146 (0.0257)
Diabetes type 2	54 (8.48)	67 (8.03)	69 (8.38)	58 (7.57)	57 (7.99)	52 (8.16)	0.9915 (0.0108)
Average number of chronic diseases per patient mean ± SD (95% CI)	0.78 ±1.02 (0.70-0.86)	0.74 ±1.05 (0.67-0.81)	0.80 ±1.10 (0.73-0.88)	0.80 ±1.11 (0.72-0.88)	0.85 ±1.14 (0.76-0.93)	0.81 ±1.06 (0.49-0.61)	0.0013 (0.0516)

Table 2 Prevalence of schizophrenia according to gender and age group

	2008		2009		2010		2011		2012		2013	
Total, N	**487**		**646**		**633**		**586**		**530**		**498**	
Age groups	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
(years)	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
18 > age ≤ 35	85	48	114	59	125	56	117	52	108	43	112	36
	(63.91)	(36.09)	(65.90)	(34.10)	(69.06)	(30.94)	(69.23)	(30.77)	(71.52)	(28.48)	(75.68)	(24.32)
35 > age ≤ 65	145	209	189	284	193	259	193	224	176	203	157	193
	(40.96)	(59.04)	(39.96)	(60.04)	(42.70)	(57.30)	(46.28)	(53.72)	(46.44)	(53.56)	(44.86)	(55.14)
> 65 age	49	90	51	122	53	131	40	133	48	126	35	99
	(35.25)	(64.75)	(29.48)	(70.52)	(28.80)	(71.20)	(23.12)	(76.88)	(27.59)	(72.41)	(26.12)	(73.88)
p-value (Cramer's *V*)	<.0001 (0.21)		<.0001 (0.26)		<.0001 (0.29)		<.0001 (0.32)		<.0001 (0.30)		<.0001 (0.34)	

Table 3 Number of antipsychotic items prescribed over the study period according to type of prescribers

Type of active ingredient	Endocrinologist *n* (%)	General medical practitioner *n* (%)	Neurologist *n* (%)	Other *n* (%)	Psychiatrist *n* (%)	*p*-value (Cramer's *V*)
Amisulpride (n=2 559)	12 (0.47)	409 (15.98)	0 (0.0)	131 (0.0)	2 007 (78.43)	
Aripiprazole (n=5 234)	0 (0.00)	687 (13.13)	47 (0.90)	239 (4.57)	4 261 (81.41)	
Chlorpromazine (n=1 081)	0 (0.00)	560 (51.80)	116 (0.00)	116 (10.73)	405 (37.47)	
Clothiapine (n=593)	0 (0.00)	179 (30.19)	61 (0.00)	181 (10.29)	353 (59.53)	
Clozapine (n=5 078)	24 (0.47)	1 476 (29.07)	12 (0.24)	344 (6.77)	3 222 (63.45)	
Flupenthixol (n=2 312)	1 (0.04)	806 (34.86)	0 (0.00)	187 (8.09)	1 318 (57.01)	
Fluphenazine (n=933)	0 (0.00)	561 (60.13)	0 (0.00)	161 (17.26)	211 (22.62)	
Haloperidol (n=2 035)	0 (0.00)	1 071 (52.63)	0 (0.00)	130 (6.39)	834 (40.98)	
Olanzapine (n=10 533)	16 (0.15)	2 963 (28.13)	59 (0.56)	614 (5.83)	6 881 (65.33)	< 0.0001
Paliperidone (n=493)	0 (0.00)	48 (9.74)	14 (2.84)	14 (2.84)	417 (84.58)	(0.1836)
Pimozide (n=480)	0 (0.00)	271 (56.46)	3 (0.63)	32 (6.67)	174 (36.25)	
Quetiapine (n=5 782)	4 (0.07)	1 256 (21.72)	137 (2.37)	509 (8.80)	3 876 (67.04)	
Quetiapine fumurate (n=787)	0 (0.00)	104 (13.21)	16 (2.03)	82 (10.42)	585 (74.33)	
Risperidone (n=13 321)	16 (0.13)	4 146 (33.65)	109 (0.88)	1 091 (8.85)	6 959 (56.48)	
Sulpiride (n=169)	0 (0.00)	101 (59.76)	0 (0.00)	4 (2.37)	64 (37.87)	
Trifluoperazine (n=1 425)	3 (0.21)	800 (56.14)	23 (1.61)	101 (7.09)	498 (34.95)	
Ziprasidone (n=2 266)	0 (0.00)	457 (20.17)	64 (2.82)	117 (5.16)	1 628 (71.84)	
Zuclopenthixol (n=1 439)	0 (0.00)	594 (41.28)	78 (5.42)	679 (6.12)	88 (47.19)	
Total (n = 74 205)	81 (0.11)	21 719 (29.27)	1 802 (2.43)	5 430 (7.32)	45 173 (60.88)	

Table 4 Prescribed daily dosages compared to maximum recommended dosages allowed

	Amisulpride		Aripiprazole		Clozapine		Haloperidol		Olanzapine		Quetiapine		Risperidone	
Age groups (years)	**18 < age ≥ 65**	**65 > age**	**18 < age ≥ 65**	**65 > age**	**18 < age ≥ 65**	**65 > age**	**18 < age ≥ 65**	**65 > age**	**18 < age ≥65**	**65 > age**	**18 < age ≥ 65**	**65 > age**	**18 < age ≥65**	**65 > age**
RDD	1 200	-	30	-	900	450	30	-	20	10	750	-	16	3
2008, *n*	414	80	572	14	654	80	178	141	1 240	281	158	69	1 311	458
PDD, mg(SD)	292 (222)	226 (257)	16 (7)	11 (6)	203 (244)	121 (96)	6 (10)	5 (5)	10 (6)	7 (3)	137 (72)	233 (247)	3 (4)	2 (2)
> Max dose* (%)	-	-	5 (0.87)	-	2 (0.31)	-	1 (0.56)	-	20 (1.61)	9 (3.2)	-	-	13 (1)	49 (10.97)
2009, *n*	400	70	906	40	845	123	275	193	1 599	372	996	222	1 826	603
PDD, mg(SD)	303 (347)	260 (228)	19 (51)	12 (4)	207 (191)	145 (88)	5 (5)	5 (4)	10 (6)	8 (5)	259 (216)	187 (186)	3 (3)	1 (2)
> Max dose (%)	1 (0.25)	-	5 (0.55)	-	-	-	-	-	36 (2.25)	28 (7.53)	37 (3.71)	-	10 (0.55)	56 (9.29)
2010, *n*	435	38	866	75	815	117	236	180	1 564	487	1 022	239	1 542	614
PDD, mg(SD)	323 (220)	226 (175)	16 (7)	13 (7)	207 (187)	125 (87)	7 (7)	5 (5)	10 (6)	8 (4)	269 (214)	198 (192)	3 (4)	2 (5)
> Max dose (%)	-	-	-	-	-	-	-	-	29 (1.85)	28 (5.75)	58 (5.38)	-	20 (1.3)	81 (13.19)
2011, *n*	398	62	856	92	756	97	170	187	1 376	558	790	238	1 498	520
PDD, mg(SD)	301 (201)	142 (50)	17 (29)	10 (3)	294 (802)	119 (82)	7 (11)	6 (5)	10 (6)	8 (5)	272 (212)	230 (209)	3 (5)	2 (4)

	Amisulpride		Aripiprazole		Clozapine		Haloperidol		Olanzapine		Quetiapine		Risperidone	
Age groups (years)	**18 < age ≥ 65**	**65 > age**	**18 < age ≥ 65**	**65 > age**	**18 < age ≥ 65**	**65 > age**	**18 < age ≥ 65**	**65 > age**	**18 < age ≥65**	**65 > age**	**18 < age ≥ 65**	**65 > age**	**18 < age ≥65**	**65 > age**
> Max dose (%)	-	-	2 (0.23)	-	-	-	2 (1.18)	-	24 (1.74)	59 (10.57)	44 (5.57)	-	18 (1.2)	49 (9.42)
2012, *n*	317	58	778	70	715	73	113	160	1 142	458	773	195	1 527	423
PDD, mg(SD)	263 (196)	163 (258)	16 (9)	12 (5)	267 (756)	145 (78)	12 (21)	7 (6)	10 (7)	8 (5)	262 (220)	242 (213)	4 (8)	1 (2)
> Max dose (%)	-	-	3 (0.39)	-	-	-	10 (8.85)	-	30 (2.63)	74 (16.16)	54 (6.99)	-	28 (1.83)	13 (3.07)
2013, *n*	268	18	839	71	683	101	92	97	1 079	349	773	205	1 346	411
PDD, mg(SD)	273 (188)	119 (46)	16 (8)	13 (9)	207 (190)	178 (134)	6 (5)	6 (5)	10 (7)	9 (5)	295 (244)	243 (189)	4 (10)	2 (2)
> Max dose (%)	-	-	5 (0.60)	-	3 (0.44)	9 (8.91)	-	-	36 (3.34)	69 (19.77)	78 (10.09)	-	16 (1.19)	26 (6.33)

* > max dose is the number of times an active ingredient was prescribed above the maximum recommended daily dosage

Table 5 Compliance status of antipsychotics prescribed

	Compliant (≥ 80% or ≤ 110%)	Undersupply (< 80%)	Oversupply (>110%)	Total	*p* value (Cramer's *V*)
Age groups (year), n (% within age group)					
0 < age ≤ 12	4 (80)	1 (20)	0 (0)	5 (100)	
12 < age ≤ 18	44 (54.32)	18 (22.22)	19 (23.46)	81 (100)	
18 < age ≤ 35	658 (46.57)	461 (32.63)	294 (20.81)	1 413 (100)	< 0001
35 < age ≤ 65	1 646 (51.70)	981 (30.81)	557 (17.49)	3 184 (100)	(0.0606)
65 > age	649 (58.47)	297 (26.76)	164 (14.77)	1 110 (100)	
Gender, n (% within gender)					
Male	1 421 (53.34)	771 (28.94)	472 (17.72)	2 664 (100)	< 0.0637
Female	1 580 (50.50)	987 (31.54)	562 (17.96)	3 129 (100)	(0.0308)
Treatment period, n (% within treatment period)					
0 > days ≤ 30	156 (32.57)	38 (7.93)	285 (59.50)	479 (100)	
30 < days ≤ 120	603 (49.42)	341 (27.95)	276 (22.62)	1 220 (100)	< 0001
120 > days	2 242 (54.76)	1 379 (33.68)	473 (11.55)	4 094 (100)	(0.2477)
Most prescribed active ingredients, n (% within ingredients)					
Risperidone	621 (54.33)	327 (28.61)	195 (17.06)	1 143 (100)	
Olanzapine	411 (54.51)	228 (30.24)	115 (15.25)	754 (100)	
Quetiapine	308 (50.99)	171 (28.31)	125 (20.70)	604 (100)	
Aripiprazole	189 (47.73)	125 (31.57)	82 (20.71)	396 (100)	< 0001
Clozapine	183 (59.61)	84 (27.36)	40 (13.03)	307 (100)	(0.1287)
Amisulpride	84 (49.12)	57 (33.33)	30 (17.54)	171 (100)	

	Compliant (≥ 80% or ≤ 110%)	Undersupply (< 80%)	Oversupply (>110%)	Total	*p* value (Cramer's *V*)
Haloperidol	86 (56.95)	46 (30.46)	19 (12.58)	151 (100)	
Number of chronic diseases, n (% within chronic diseases)					
No co-morbidities	1 567 (51.11)	975 (31.80)	524 (17.09)	3 066 (100)	
1 co-morbidities	839 (52.01)	487 (30.19)	287 (17.79)	1 613 (100)	
2 co-morbidities	354 (54.46)	175 (26.92)	121 (18.62)	650 (100)	
3 co-morbidities	170 (50.45)	92 (27.30)	75 (22.26)	337 (100)	< 0.0902 (0.0404)
4 co-morbidities	57 (53.27)	25 (23.36)	25 (23.36)	107 (100)	
5 co-morbidities	12 (66.67)	4 (22.22)	2 (11.11)	18 (100)	
6 co-morbidities	2 (100)	0 (0)	0	2 (100)	

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3.2 MANUSCRIPT 2

Maximum potential cost-savings attributable to generic substitution of antipsychotics 2008 to 2013

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Background: Schizophrenia is a costly illness to treat, especially during a time of escalating medicine inflation costs, putting a large economic strain on patients, their families and the community. Treatment, however, can become more affordable through generic substitution. **Objective:** To determine the maximum potential cost-saving through generic substitution for both originator and more expensive generic items while observing the prescribing patterns of antipsychotics. **Method:** Antipsychotic medicine usage was analysed retrospectively during the study period 2008 to 2013 using data obtained from a nationally representative Pharmaceutical Benefit Management Company. The study population consisted of 4 410 patients with valid ICD-10 codes (F20-F20.9) who all had a paid claim for an antipsychotic from their prescribed minimum benefits. Active ingredients were identified using the MIMS classification system. Maximum potential cost-savings were determined by generically substituting all originator and more expensive generic items with the average cost of the least expensive generic item available. **Result:** Through generic substitution, a total potential cost-saving of R4 642 685.45 could be possible from 2008 to 2013. Average cost per items increased during the study period from R 600.53 ± R 435.00 in 2008 to R 1196.59 ± R 942.16 in 2013 and had a significant effect on patients' contribution which increased with approximately 726.94% during the study period. Psychiatrists prescribed the majority of antipsychotics and although generic items claimed increased with 60.31% during the study period, psychiatrists still favoured non-generic prescribing (40.63%). **Conclusions:** Potential economic benefits can be generated with generic substitution.

Keywords

Generic substitution, potential cost-saving, originator, generic, non-generic, antipsychotics, South Africa

Abbreviations

GDP-	Gross domestic product
PMB-	Prescribed Minimum Benefit
NDP-	National Drug Policy
WHO-	World Health Organization
MIMS-	Monthly Index of Medicine Speciality
SEP-	Single exit price
NRF-	National Research Foundation

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1.1 Introduction

When costs of treatment for psychiatric illnesses are compared, the most costly illness to treat is schizophrenia (Emsley, & Booysen, 2004, p. 58). Without healthcare coverage, treatment for schizophrenia can become unaffordable even if generic medicines are used (Lehman *et al*., p. 19). Irrespective of its economic strain on patients themselves, this disease also puts a large economic burden on families, societies and the healthcare systems (Emsley, & Booysen, 2004, p. 58). For example, according to Emsley and Booysen (2004, p. 65), it costs approximately R 498 771 annually for families to take care of a schizophrenic individual within the family, while spending approximately 15 hours a week taking care of these members.

South Africa spends 8.3% of gross domestic product (GDP) on health which is already relatively higher than the 5% recommended by the World Health Organization (Department of Health, 2011, p. 9). According to the South African National Treasury (2015), a total of R 121 billion was spent on health for 2012/2013 (NHI). Regardless of this relatively high expenditure, health outcomes, compared to more or less the same middle-income companies, remain poor (Department of Health, 2011, p. 9).

In order to control costs in the private health sector of South Africa, the Council of Medical Schemes listed the Prescribed Minimum Benefit (PMB) conditions (Council for Medical Schemes, 2009). Medical aid schemes are obligated to cover diagnosis, medical costs as well as cost of care of patients registered on the chronic disease list of the PMB, provided that the prescribed therapeutic algorithm is followed (Council for Medical Schemes, 2009; Department of Health, 2003). Schizophrenia is listed as one of these 27 chronic disease disorders in South Africa.

Further initiatives to save costs stem from the National Drug Policy (NDP) developed in 1996 in South Africa and the implementation of the single exit price (SEP) strategy (Gray, 2009, p. 15). Generic medicines are drugs of which original patents have expired and that are allowed to be manufactured by companies other than those of the original innovator companies (Dunne *et al*., 2013, p. 1). These generic medicines should be of the same formula (for example, the same amount of active ingredient, same route of administration etc.) while giving the same therapeutic effectiveness than that of the originator medicine (Borgherini, 2003, p. 1578). The single exit price in South Africa is set according to benchmark prices of other international countries that follow pricing systems closest to the system that is used in South Africa (Department of Health, 2015). In 2013, medicine expenditure increased with 2% for cost per item from 2011 (Mediscor, 2013, p. 3). A total of 42.2% of manufacturers that represents approximately 83.3% of products

sold in South Africa took a 4% increase in SEP for the months January to May in 2013 (Mediscor, 2013, p. 3). This increase in cost puts a large economic strain on patients during a time of spiralling medication inflation (Mediscor, 2013, p. 4).

Brand name products have a higher cost than their generic versions, which produces the same therapeutic effect (Fischer, & Avorn, 2003, p. 1052). Costs of originator drugs, especially in low and middle-income countries, are substantially higher than their generic alternatives (WHO, 2010). Typically, generic substitutions are 20 to 90% cheaper than those of originator medicines (Dunne *et al*., 2013, p. 1). In 2013, 20% of overall medicine products costs were for original items for which patents have already expired (Mediscor, 2013, p. 3). This raised concern, as average generic equivalents were only R 96 per item compared to the average cost of original items with expired patents at R 131 (Mediscor, 2013, p. 3).

In this study, we aim to determine the maximum potential cost-saving by substituting the average medicine cost of more expensive generic and originator items with that of the least expensive generic available on the database during the study period. Generic substitution poses the advantage of reducing treatment expenditure for patients while maintaining the same quality of care (Hamann *et al*., 2012, p. 686).

1.2 Method

Medicine usage of antipsychotic treatment was analysed retrospectively for the study period 1 January 2008 to 31 December 2013. Data were obtained from a Pharmaceutical Benefit Management Company (PBM). A total of 8.78 million individuals in South Africa were registered as members of medical schemes in 2013 (Council for Medical Schemes, 2014a) of whom 1.7 million individuals were members of this nationally representative Prescribed Minimum Benefit Management Company. Data fields used from the database included date of treatment, active ingredients, direct medicine cost (SEP, medical scheme contribution and patient contribution), trade names of active ingredients and quantities.

All patients with ICD-10 codes F20-F20.9 with a claim reimbursed from their prescribed minimum benefit for active ingredients included in the MIMS classification system for schizophrenia (N = 4 410) were included in the study (Snyman, 2014, p. 31). Antipsychotics were categorised according to four pharmacological groups: phenothiazines, butyrophenones, atypical antipsychotics and others (Snyman, 2014, p. 31).

Schizophrenia prevalence was determined as percentage of the total population of the database. Total costs of antipsychotics was also determined as a percentage of the total cost of medicine products of the database. Thereafter, the average cost per item per patient was compared to the medical scheme contribution and patient contribution. The influence of the single exit price on the average cost per item was also determined. Average costs per generic status (i.e. generic, non-generic or originator) were also compared, while observing the medical scheme contribution and patient contributions. Prevalence of antipsychotics prescribed based on generic status and prescriber speciality were also determined.

The primary outcome of this study was to determine the maximum potential cost-saving in direct medicine costs for patients per year by generically substituting all originator and more expensive generic drugs with the average cost of the least expensive generic item during the year. The differences in actual and substituted costs per year were then summed to calculate the total potential cost-saving for the study period.

The SAS program version 9.3 (SAS Institute, Cary, NC, 2008-2013) was used for statistical analyses. Descriptive statistics included frequencies, means, standard deviations (SD) and 95% confidence intervals (95% CI). Inferential statistics included Analysis of Variance (ANOVA) with Tukey's HSD post-hoc test used to compare mean values between more than two independent groups. Cohen's *d*-value was used to determine effect sizes and was taken as practically significant if $d \geq 0.8$. This was only considered if there was a practical significance $p \leq 0.0001$. Chi-square distribution models were used to test the distribution of the statistics of the population. Practical significance was then determined by Cramer's *V* and values ≥ 0.1 was regarded as a small effect, ≥ 0.3 as a moderate effect and ≥ 0.5 as large effects.

This study was approved by the Board of Directors of the PBM Company, as well as the Health Research Ethics Committee of the North-West University (NWU-00179-14-A1).

1.3 Results

The prevalence of schizophrenia stayed more or less the same between 0.08% and 0.09% during the study period 2008 to 2013. Table 1 shows a statistically significant association between the generic status of drugs prescribed and the study period; however, the effect was small (Cramer's $V = 0.1725$). The use of non-generic items decreased with 35.21% from 2008 to 2013, whereas the use of originator and generic items increased with 8.08% and 27.12%, respectively.

The majority of antipsychotics were prescribed by psychiatrists (Table 1). Prescribing by general medical practitioners decreased during the study period with 5.43%, whereas prescribing of neurologists and psychiatrists increased with 0.52% and 4.8%, respectively. Although there was an overall increase in the total costs for the treatment of schizophrenia across the study period, ranging from R 6 374 096.29 in 2008 to R 12 278 673.01 in 2013, costs for schizophrenia treatment as percentage of the total cost of the database stayed relatively the same.

An overall increase in the average costs per item occurred from 2008 to 2013 (Table 2). The average cost of SEP per item increased with 77.62% from R24.26 ± R 67.84 (95% CI 18.98-29.53) in 2008 to R 43.09 ± R165.44 (95% CI 555.89 ± 555.89) in 2013. Evidently, the average cost per item also increased with 99.26% from R600.53 ± R 435.00 (95% CI 566.68-634.38) in 2008 to R 1196.59 ± R 942.16 (95% CI 1123.29-1269.90) in 2013 (Cohen's *d*-value = 1.01). Although the average cost covered by medical schemes stayed more or less the same, a practically significant increase of 726.94% occurred in the co-payment of patients from R 77.48 ± R 123.76 (95% CI 67.86-87.11) in 2008 to R 640.71 ± R518.19 (95% CI 600.39-681.02) in 2013 (Cohen's *d*-value = 2.28).

The number of generic items claimed increased with 60.31% from 156 in 2008 to 393 in 2013 (Table 3). The average cost per originator items increased with approximately 136% ($p < 0.0001$; Cohen's *d*-value = 0.77) over the study period, whereas that of the non-generic items increased with ~106% ($p < 0.0001$; Cohen's *d*-value = 0.56). The average cost of generics, however, increased with almost 220% from 2008 to 2013 ($p < 0.0001$; Cohen's *d*-value = 1.02).

The average cost per item consist of a drug's SEP, scheme contribution and patient contribution. The average patient contribution for non-generic and generic drugs increased with more than 700% over the study period (with both $p < 0.0001$; Cohen's *d*-value > 0.8) whereas that of originator drugs increased with 444% ($p < 0.0001$; Cohen's *d*-value = 1.1). The SEP increased with ~163% for non-generic items ($p < 0.0001$; Cohen's *d*-value = 0.18) and ~105% for generic items ($p < 0.0001$; Cohen's *d*-value = 0.89). The scheme contribution increased with ~8% for non-generic; ~38% for originals and ~92% for generics (Table 3).

The prescribing of generic antipsychotics by all prescribers increased with 30.58%, 41.52% and 25.23% for general medical practitioners, neurologists and psychiatrists, respectively, from 2008 to 2013 (Table 4). The prescribing of non-generic items by all prescribers decreased during the study period; however, psychiatrists still favoured prescribing of non-generic items during 2013

(40.63%). The majority of prescriptions by general medical practitioners, neurologists and all other prescribers were for generic items.

Availability of generic alternatives increased within the study period; however, from the 18 antipsychotics currently available in the South African market, only five had generic alternatives on the database during the study period. These included; clozapine, haloperidol, olanzapine, quetiapine and risperidone (Table 5). The total costs for originator and generic items in 2008 amounted to R 281 946.66. If all originator and more expensive generic items were substituted with the average cost of the least expensive generic item available, a potential cost-saving of R 106 855.59 (37.90%) could have been generated during 2008. Similarly, potential annual cost savings of 25.72%, 33.64%, 47.80%, 41.47% and 39.29%, respectively, would have been possible from 2009 to 2013. A total amount of R 4 642 685 could have been potentially saved over the five year study period if all originator and more expensive generic items were substituted with the least expensive generic item available on the database for each year.

1.4 Discussion

Treatment for schizophrenia is extremely costly (Emsley, & Booysen, 2004, p. 58), and therefore patients' health expenditures can be reduced by developing a cost saving plan through generic substitution (Hamann *et al*., 2012, p. 686). By using generic medication, at a lower cost and assured quality of their originator equivalent, health outcomes for both patients and health systems can be achieved at a lower cost.

No generic equivalents were available for the phenothiazines and 'others' (e.g. sulpiride, zuclopenthixol decanoate, flupenthixol and clothiapine) groups on the dataset during the study period. Of the 18 antipsychotics available in South Africa, only five had generic medicines as alternatives claimed on our database during the study period. The low number of generic alternatives for quetiapine and olanzapine could be due to patent protection during our study period. These expired in 2011 for olanzapine (Zyprexa®) and in 2012 for quetiapine (Seroquel®) (DeRuiter, & Holston, 2012).

A potential cost-saving of a quarter to half a billion dollars annually is possible when prescription drugs are substituted with generic brands (Fischer, & Avorn, 2003, p. 1059). Our study showed that approximately R4.6 million could have been saved if antipsychotic drugs were generically substituted. However, schizophrenic patients are reluctant to change and may become suspicious, paranoid, delusional or even hostile when changing their medicine to a generic version, effecting their compliance to medicine (Treur *et al*., 2009, p. 2).

In total, 20% of medicine items claimed during 2013 were original brand name products (Mediscor, 2013, p. 3). Medical aid schemes have a reference drug for each therapeutic class used to determine the maximum price that may be reimbursed (Mcleod, & Ramjee, 2007, p. 65). If the cost of the drug dispensed is higher than the price of the reference drug, then the patient has to pay the difference in price (McLeod, & Ramjee, 2007, p. 65). Psychiatrists are not always willing to consider that medication may be substituted with their generic equivalents (Hamman *et al*., 2013, p. 688). Furthermore, patients themselves are not always willing to use generic equivalents for their drugs. For example a study found that 73% of patients treated with oral antipsychotics would refuse generic substitution when given the chance by a pharmacist (Roman, 2009, p. 693).

Antipsychotics claimed during 2013 were the most expensive, even with generic substitution (Table 5). The national single exit price (SEP) increased initially with 6.5% annually from 2008 then 13.2% (2009), 7.4% (2010), 0% (2011), 2.14% (2012) and 5.8% (2013) respectively, affecting the dispensing fee that directly influenced the average cost per item (Council for Medical Schemes, 2014; Government Gazette, 2011; Government Gazette, 2012; Government Gazette, 2013; Mediscor, 2013, p. 7). A 5.8% increase in the SEP was allowed in 2013, causing an overall 2% increase in the average cost per items, explaining the large increase in total costs for 2013 (Mediscor, 2013, p. 5). Patient contribution also increased significantly from 2008 to 2013; this could be due to additional costs charged by the provider that was in disagreement with the medical scheme rate or dispensing fee for the year (Mediscor, 2013, p. 4).

A rapid increase was observed in the percentage of medical expenditures in association with prescription drugs (Fischer, & Avorn, 2003, p. 1051). In 2011, $12.6 billion was spent on 54 million prescriptions issued for antipsychotics in the United States of America (Leonhauser, 2012, p. 22). For our study, atypical antipsychotics had more generic equivalents (clozapine, olanzapine, quetiapine, risperidone) as opposed to typical antipsychotics (haloperidol), supporting studies from the literature that atypical antipsychotics are leading the market (Leonhauser, 2012, p. 22). By targeting physician prescribing practices, excess spending on the use of brand name products can be reduced (Fischer, & Avorn, 2003, p. 1059). However, physicians have been found to believe that brand name drugs are more effective and have a higher standard of manufacturing than their generic versions (Fischer, & Avorn, 2003, p. 1059). Reasons stated against generic substitution includes that generic items appear differently (different colours, odd shapes etc.) than the originator items, confusing patients, especially the elderly (Dunne *et al*., 2013, p. 14). Therefore, it is encouraged that generic products have the same appearance than their originators (Posner, & Griffin, 2011, 732).

1.5 Conclusion

This study confirmed the potential economic benefits using generics. It can be concluded that if only 45% of claims were dispensed using generic substitution, which, accordingly to Mediscor, is the actual rate for generic substitution in South Africa, then a total of R2 089 208.20 could still have been saved during the study period. Due to patent protection on drugs, there is the probability that the number of generic alternatives will increase for antipsychotics in the future. However, with the enormous increase in patient contribution towards antipsychotics, it is clear that even generic drugs may soon be unaffordable to patients which can also affect patients' compliance. It is therefore necessary that alternative and innovative cost-savings methods be investigated.

1.6 Conflicts of interests

The authors have no conflicts of interest to declare in this manuscript.

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Table 1 Basic characteristics of the study population

	2008	2009	2010	2011	2012	2013	*p*- value (Cramer 's *V*)
Database							
Number of patients	758 505	1 033 057	968 158	864 977	815 810	809 857	
Database cost (R)	1 782 920 908.9	2 505 739 217.5	2 457 045 952.7	2 008 943 287.0	1 838 950 559.0	3 604 278 997.0	
Schizophrenia patients							
Number of schizophrenic patients	637 (0.08)	834 (0.08)	823 (0.09)	766 (0.09)	713 (0.09)	637 (0.08)	
Cost for schizophrenia patients R (%)	6 374 096.29 (0.36)	8 926 490.81 (0.36)	9 477 421.93 (0.39)	8 534 989.46 (0.42)	7 055 848.88 (0.38)	12 278 673.01 (0.34)	
Average cost (R) per item per patient ±SD and (95% CI)	600.53 ± 435.00 (566.68-634.38)	665.72 ± 513.66 (630.80-700.62)	696.91 ± 558.92 (658.67-735.16)	698.29 ± 527.35 (660.89-735.70)	628.76 ± 484.63 (593.13-664.40)	1 196.59±942.16 (1123.29-1269.90)	
Antipsychotics by generic status							
Non-generic *n* (%)	8 002 (73.24)	8 562 (59.22)	8 684 (61.69)	6 121 (48.14)	4 743 (41.55)	4 038 (38.03)	<0.0001
Originator *n* (%)	1 625 (14.87)	2 490 (17.22)	1 905 (13.53)	2 864 (22.52)	2 526 (22.13)	2 437 (22.95)	(0.1725)
Generic *n* (%)	1 299 (11.89)	3 405 (23.55)	3 487 (24.77)	3 730 (29.34)	4 145 (36.32)	4 142 (39.01)	
Antipsychotics prescribed by prescriber speciality							
General medical practitioner *n* (%)	3 371 (30.85)	4 302 (29.76)	4 326 (30.73)	3 876 (30.48)	3 145 (27.55)	2 699 (25.42)	
Neurologist *n* (%)	299 (2.74)	258 (1.78)	248 (1.76)	259 (2.04)	392 (3.43)	346 (3.26)	
Other *n* (%)	804 (7.36)	1 195 (8.26)	1 127 (8.01)	768 (6.04)	824 (7.22)	793 (7.47)	
Psychiatrist *n* (%)	6 452 (59.05)	8 702 (60.19)	8 375 (59.50)	7 812 (61.44)	7 053 (61.79)	6 779 (63.85)	

Table 2 Total cost per item per patient per year

		Cost per item (R)		SEP (R)		Medical Scheme amount (R)		Patient contribution (R)		Total costs
Year	**N**	**Mean ± SD**	**95% CI**	**Mean ± SD**	**95% CI**	**Mean ± SD**	**95% CI**	**Mean ± SD**	**95% CI**	
2008	637	600.53 ±435.00	566.68-634.38	24.26 ±67.84	18.98-29.53	523.05 ±403.05	491.69-554.41	77.48 ±123.76	67.86-87.11	6 374 096.29
2009	834	665.72 ±513.66	630.80-700.62	30.20 ±102.89	23.21-37.18	560.85 ± 560.84	528.59-593.09	104.87± 174.52	93.00-116.73	8 926 490.81
2010	823	696.91 ±558.92	658.67-735.16	33.39 ±105.75	26.16-40.63	591.24 ± 591.24	556.48-626.01	105.67 ±185.84	92.96-118.39	9 477 421.93
2011	766	698.29 ± 527.35	660.89-735.70	35.49 ±117.55	27.16-43.83	607.73 ± 607.73	572.92-642.54	90.57 ±154.46	79.61-101.52	8 584 989.46
2012	713	628.76 ±484.63	593.13-664.40	33.85 ±118.04	25.17-42.52	541.56 ± 541.56	509.71-573.41	87.20 ±150.32	76.15-98.26	7 055 848.88
2013	637	1196.59 ± 942.16	1123.29-1269.90	43.09 ±165.44	30.22-55.96	555.89 ± 555.89	521.61-590.16	640.71 ±518.19	600.39-681.02	12278673.01

Table 3 Average cost per antipsychotic according to generic status

		Cost per item		SEP		Scheme amount		Patient contribution		*p*-value
	N	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	
2008										
Non-generic	573	689.80±487.20	649.80-729.80	30.07 ±84.73	23.12-37.03	602.27 ±462.74	564.29-640.23	87.51 ±143.27	75.76-99.27	
Originator	191	412.70±353.40	362.30-463.20	12.68 ±16.17	10.37-14.99	312.33 ±268.52	274.01-350.66	100.41 ±223.58	68.50-132.32	<.0001
Generic	156	267.54±258.30	226.70-308.40	4.42 ±4.81	3.66-5.18	219.22 ±216.94	184.91-253.53	48.32 ±141.35	25.97-70.68	
2009										
Non-generic	641	779.90 ±618.50	731.90-618.40	43.78 ± 139.77	32.94-54.62	666.02 ±577.08	621.26-710.78	113.91 ±208.92	97.70-130.11	
Originator	297	442.70 ±363.20	401.20-363.20	14.42 ± 17.41	12.43-16.41	305.77 ±279.83	273.81-337.72	136.94 ±169.20	117.62-156.26	<.0001
Generic	343	418.10 ±324.20	383.70-324.20	8.02 ± 6.15	7.37-8.68	361.03 ±304.01	328.74-393.31	57.09 ±113.65	45.02-69.16	
2010										
Non-generic	623	812.40 ±633.31	762.60-862.26	47.42 ±146.94	35.86-58.98	691.39 ±584.12	645.44-737.35	121.04 ±227.90	103.11-138.97	
Originator	256	581.0 ±587.26	508.74-653.31	17.06 ±19.87	14.62-19.51	436.09 ±537.97	369.88-502.31	144.93 ±214.75	118.50-171.36	<.0001
Generic	357	410.90 ±339.70	375.60-	7.85 ±5.83	7.25-8.46	356.28 ±309.37	324.08-	54.68 ±104.21	43.84-	

		Cost per item		SEP		Scheme amount		Patient contribution		*p*-value
	N	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	
			446.31				388.48		65.53	
2011										
Non-generic	552	812.35 ±640.53	758.80-865.90	50.69 ±151.97	37.99-63.40	714.18 ±603.72	663.71-764.66	98.17 ±182.35	82.92-113.41	
Originator	337	830.90 ±659.29	760.26-901.55	22.79 ±18.15	20.84-24.73	690.75 ±610.50	625.33-756.16	140.16 ±197.98	118.94-161.37	<.0001
Generic	379	457.69 ±317.91	425.58-489.80	9.53 ±5.88	8.94-10.12	422.59 ±299.28	392.36-452.82	35.10 ±60.61	28.98-41.23	
2012										
Non-generic	414	717.89 ±682.45	651.96-783.82	61.48 ±196.36	42.51-80.44	613.87 ±605.70	555.35-672.39	104.02 ±198.15	84.88-123.17	
Originator	275	620.76 ±512.91	559.87-681.64	16.58 ±14.47	14.86-18.29	465.55 ±405.01	417.47-513.63	155.21 ±217.18	129.42-180.99	<.0001
Generic	415	442.93 ±309.30	413.08-472.77	9.15 ±5.46	8.63-9.68	412.96 ±297.57	384.25-441.67	29.97 ±29.97	25.09-34.84	
2013										
Non-generic	378	1424.06 ±1303.76	1 292.20-1 555.91	79.19 ±266.22	52.26-106.11	650.32 ±619.99	587.62-713.02	773.74 ±704.78	702.46-845.01	
Originator	267	976.80 ±733.79	888.38-1 065.21	12.69 ±12.70	11.16-14.22	429.64 ±336.11	389.14-470.14	547.16 ±421.51	496.37-597.95	<.0001
Generic	393	854.85 ±576.13	797.71-911.99	9.09 ±5.41	8.56-9.63	420.56 ±286.90	392.15-448.97	434.29 ±294.11	405.12-463.46	

Generic status: generic; non-generic; originator

Table 4 Prevalence of antipsychotics prescribed by generic status and prescriber speciality

	General medical practitioner			Neurologist			Psychiatry			Other		
Years	**Non-generic**	**Originator**	**Generic**	**Non-generic**	**Originator**	**Generic**	**Non-generic**	**Originator**	**Generic**	**Non-generic**	**Originator**	**Generic**
2008	2 391	542	438	123	142	34	4 882	846	724	606	95	103
	(70.93)	(16.08)	(12.99)	(41.14)	(47.49)	(11.37)	(75.67)	(13.11)	(11.22)	(75.38)	(11.81)	(12.81)
2009	2 311	795	1 196	109	68	81	5 540	1 320	1 842	602	307	286
	(53.72)	(26.36)	(31.40)	(42.25)	(26.36)	(31.40)	(63.66)	(15.17)	(21.17)	(50.38)	(25.69)	(23.93)
2010	2 361	646	1319	137	57	54	5 549	951	1 875	637	251	239
	(54.58)	(14.93)	(30.49)	(55.24)	(22.98)	(21.77)	(66.26)	(11.36)	(22.39)	(56.52)	(22.27)	(21.21)
2011	1633	857	1 386	97	83	79	4 076	1 700	2 036	315	224	229
	(42.13)	(22.11)	(35.76)	(37.45)	(32.05)	(30.50)	(52.18)	(21.76)	(26.06)	(41.02)	(29.17)	(29.82)
2012	1 166	738	1 241	118	90	184	3 107	1 519	2 427	352	179	293
	(37.07)	(23.47)	(39.46)	(30.10)	(22.96)	(46.94)	(44.05)	(21.54)	(34.41)	(42.72)	(21.72)	(35.56)
2013	915	608	1 176	62	101	183	2 754	1 554	2 471	307	174	312
	(33.90)	(22.53)	(43.57)	(17.92)	(29.19)	(52.89)	(40.63)	(22.92)	(36.45)	(38.71)	(21.94)	(39.34)

Generic status: generic; non-generic; originator

Table 5 Average maximum potential cost-savings through generic substitution

	2008		2009		2010		2011		2012		2013	
	Total cost (R), *n*	**Potential cost save (R) (%)**	**Total cost, (R)*n***	**Potential cost save (R) (%)**	**Total cost, (R) *n***	**Potential cost save (R) (%)**	**Total cost, (R) *n***	**Potential cost save (R) (%)**	**Total cost, (R) *n***	**Potential cost save (R) (%)**	**Total cost,(R) *n***	**Potential cost save (R) (%)**
Cloza-pine	113 167.57 (201)	32 916.31 29.09%	159 148.45 (249)	44 045.71 27.68%	177 826.18 (219)	71 411.89 40.16%	191 209.42 (211)	72 068.27 37.69%	403292.65 (661)	261 891.53 64.94%	408 437.66 (363)	132 594.46 32.46%
Halo-peridol	1 031.97 (5)	706.37 68.45%	2 199.43 (15)	1 091.23 49.61%	3 138.88 (25)	1 418.63 45.20%	1 481.66 (10)	769.96 51.97%	5854.48 (24)	4 118.08 70.34%	12 171.93 (43)	4 049.66 33.27%
Olan-zapine	-	-	-	-	-	-	1 299 877.83 (1082)	710 044.10 5.46%	826591.08 (1084)	28 9141.70 34.98%	1 004 361.17 (752)	200 917.80 20%
Que-tiapine	-	-	-	-	-	-	-	-	351164.33 (721)	177 121.20 50.44%	607 153.41 (720)	274 303.70 45.19%
Rispe-ridone	167 747.12 (224)	73 232.91 43.66%	1 326 960.99 (389)	337 699.40 25.45%	1 152 382.69 (1927)	375 693.30 32.60%	1 068 857.11 (1792)	441 389.50 41.30%	921614.13 (1483)	308 024.20 33.42%	1 632 547.04 (1487)	828 035 50.72%
Total	281 946.66	106 855.59 37.90%	1 488 308.87	382 836.34 25.72%	1 333 347.70	448 523.82 33.64%	2 561 426.10	1 224 272.20 47.80%	2 508 516.70	1 040 297 41.47%	3 664 671.20	1 439 900.50 39.29%

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3.3 CHAPTER SUMMARY

This section discussed the results achieved from the empirical objectives stated in the study in the two manuscripts. The following chapter provides a brief overview of the results found in the literature and empirical study, and discuss the limitations, strengths and recommendations.

CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS

4.1 INTRODUCTION

In this section, the conclusions with regard to the literature and empirical objectives stated in Chapter 1 will be discussed. It identifies the limitations encountered and describes the strengths of the study. The chapter concludes with recommendations for future studies.

4.2 LITERATURE STUDY OBJECTIVES

Objectives stated to be obtained from the literature review:

- Review treatment of schizophrenia.
- Identify factors influencing treatment guidelines with regard to schizophrenia.
- Determine the effect of treatment for schizophrenic patients.
- Determine factors influencing the dispensing of schizophrenic patients.
- Determine factors influencing schizophrenic patients, for example adherence.
- Determine optimal direct medicine treatment cost (using the single exit price and generic substitution) associated with schizophrenia treatment.

The conclusions reached with regard to these objectives will be addressed in paragraphs 4.2.1 to 4.2.6.

4.2.1 Review of treatment of schizophrenia

This literature objective was achieved in sections 2.4, 2.5 and 2.8. From these sections, it can be concluded that schizophrenia is treated by antipsychotic medication, typical antipsychotics (first generation) and atypical (second generation) antipsychotics.

All antipsychotics have a similar mechanism of action and that is to block D_2 receptors in the nigrostriatal and mesolimbic pathways of the brain (section 2.4). From the literature, it was found that atypical antipsychotics are regarded as having an advantage over typical antipsychotics, as they cause fewer severe side effects and presents with a better tolerance.

Antipsychotics are associated with a variety of side effects. Typical antipsychotics are more associated with causing extrapyramidal side effects, whereas atypical antipsychotics usually cause weight gain, diabetes mellitus, hyperlipidaemia etc. (section 2.5).

International and national guidelines have been developed for the prescribing of antipsychotic medication (section 2.4). The availability of antipsychotics has increased over the years; however, no new treatments are available that address the positive symptoms associated with schizophrenia (paragraph 2.8.5).

4.2.2 Identify factors influencing treatment guidelines with regard to schizophrenia

This objective was achieved in section 2.6. From this section, it can be concluded that the following factors played a role in treatment guidelines of schizophrenia:

- Authorised practitioners
- Off-label use
- Politics
- Geographical area
- Medicine

From the literature, it was revealed that there is a shortage of **authorised practitioners** in South Africa. This shortage leads to more than 70% of non-psychiatrists prescribing antipsychotics. The Medicines and Related Substances Act, section 22A, states that no prescriber except for a registered psychiatrist may repeat a prescription for schedule 5 medicine when it is used as an anxiolytic (Act 101 of 1965) (paragraph 2.6.1).

Prescribers also prescribe antipsychotics **off-label use**; as many patients are using antipsychotics without being diagnosed with psychosis (paragraph 2.6.2). Antipsychotic off-label uses are generally for post-traumatic stress disorders, anxiety and sedation (Mckean & Monasterio, 2011:20). Children often use antipsychotic medication to treat conditions other than psychotic disorders for depression and anxiety, whereas paediatricians prescribe it in order to treat emotional and behavioural type disorders (Harnett, 2013:3). Paediatricians often prescribe antipsychotics to children in order to treat conditions other than psychotic disorders such as emotional and behavioural type disorders, psychotic disorders and depression.

Available resources in South Africa are not used for the provision of better services, due to this country's **politics**. The democracy's inefficiencies cause corruption, incompetent management and a lack of accountability influencing the quality of treatment of schizophrenic patients as physicians are not receiving appropriate training and patients are not receiving services (paragraph 2.6.3).

Geographical area influences schizophrenia patients as psychiatrists practising in South Africa are not spread evenly across the country, but are more focused in urban than rural areas. More than 50% of psychiatrists in South Africa have their own private practices, thereby limiting their services to only those who can afford these services. Furthermore, psychiatric services available in the rural areas are not of the same standard as urban areas, leading to untreated patients and even unidentified patients suffering from psychiatric disorders (paragraph 2.6.4).

The diagnosis of schizophrenia is very difficult as a variety of disorders imitate the pattern of disease of schizophrenia. A patient must first undergo a number of physical examinations before a psychiatrist should prescribe antipsychotic **medication,** as treatment is coupled with a number of severe side effects (paragraph 2.6.5). These investigations include an electrocardiogram, waist-to-hip ratio of a patient, liver function tests, fasting blood glucose, liver function tests, body mass index measurements and white blood cell counts.

4.2.3 Determine the effect of treatment for schizophrenic patients

This objective was achieved in section 2.8 and concluded that, overall it could be accepted that most patients experience positive treatment outcomes using antipsychotic medication (paragraph 2.8.6). Effective treatment outcomes can be measured by a decrease in morbidity and relapse rates and an increase in periods of recovery (paragraph 2.8.6). A worse treatment outcome is also associated with schizophrenic patients residing in developed, industrialised countries compared to those residing in developing countries (paragraph 2.8.6).

4.2.4 Determine factors influencing the dispensing of antipsychotic treatment of schizophrenic patients

This objective was achieved in section 2.8. From this section, it can be concluded that the following factors played a role in the dispensing of treatment for schizophrenic patients:

- Support from families and cultural beliefs
- Environment
- Violence
- Pharmacists
- Polypharmacy

From the literature, it was found that **family** therapy can be effective interventions for schizophrenia by preventing relapse of the disease's symptoms. **Cultural beliefs** also play a

role in the diagnoses of schizophrenia in South Africa, as 67% of Xhosa family members believe that the onset of schizophrenia is caused by spiritual possession and witchcraft and therefore seek help from traditional healers instead of registered psychiatrists (paragraph 2.8.1).

It was also revealed from the literature that there are three stages in an individual's life influenced by **environmental** risk factors that can cause schizophrenia, including 1) early life stage, for example obstetric complications and season of birth., 2) the childhood stage, for example head injuries and abuse, and 3) the later life stage for example drug abuse, ethnicity and life events. Where a patient resides can also play a role in developing schizophrenia, for example patients residing in urban areas have increased risk of developing schizophrenia. Furthermore, darker-skinned individuals residing in the northern latitudes also have an increased risk of developing schizophrenia as vitamin D is insufficiently processed due to weaker sunlight (paragraph 2.8.2).

Violence among patients with schizophrenia in the form of aggression is present, regardless of how adherent a patient is, leading to an increase in their treatment cost and adding emotional trauma while requiring more staff time (paragraph 2.8.3).

Pharmacists, being experts in pharmacotherapy, play an important role in the treatment of the disease as medication is an essential part of the treatment of schizophrenia (paragraph 2.8.4). Pharmacists not only dispense this medication, but can also assist in strategies improving the adherence to the medication and are also qualified to counsel patients (paragraph 2.8.4). Mental healthcare is provided by pharmacists through a variety of settings such as community, hospital and general practice pharmacies (paragraph 2.8.4). Barriers exist in services provided by pharmacists in the improvement of mental disorders through their attitudes, discrimination and stigma they have associated with mental illnesses and time available in busy settings to treat these patients with special care (paragraph 2.8.4).

Although various guidelines such as the National Institute for Health and Care Excellence (NICE) guidelines, Japanese guidelines, Guidelines of the World Federation of Societies of Biological Psychiatry, and Algorithm of Texas medication, to name a few, all support monotherapy of schizophrenia treatment, **polypharmacy** regarding the treatment of schizophrenic is still significantly present. Polypharmacy not only increases a patient's treatment costs, but the discontinuation rates are also higher for patients using more than one antipsychotic at a time (paragraph 2.8.5).

4.2.5 Determine factors influencing schizophrenic patients

This objective was achieved in section 2.7. From this section it can be concluded that the following factors may influence schizophrenic patients:

- Co-morbidities
- Gender and age
- Adherence
- Cost of treatment

From the literature, it was concluded that schizophrenia is associated with a variety of **co-morbidities** (paragraph 2.7.1), for example, women diagnosed with schizophrenia have a higher prevalence of developing diabetes and hyperprolactinaemia, whereas men present with a higher prevalence of hypertension (paragraph 2.7.1). Concordance of type 2 diabetes mellitus, cardiovascular diseases or lung diseases causes two thirds of premature mortality in schizophrenic patients (Smith *et al*., 2013:1137).

Gender and age also play a significant role in the development of the disease, where men develop schizophrenia at an earlier stage in life, whereas women have two peaks of onset — one between the ages of 25 and 35 years and the other at their para-menopausal peak (paragraph 2.7.2). It has been found that women are better adjusted to requirements set by this disease. Men present with more negative and disorganisation symptoms of schizophrenia, whereas women present with more affective symptoms (paragraph 2.7.2)

In the literature, it was revealed that patient **adherence** toward antipsychotic medication is generally poor (paragraph 2.7.8). There are a variety of factors influencing non-adherence that may include unawareness of the severity of the disease, side-effects of medication and substance abuse (paragraph 2.7.3).

When treatment of schizophrenia becomes unaffordable to patients, they may become less adherent and also start to treat themselves. It is concluded from the study that **cost of treatment** not only influences the patient, but it also puts an economic burden on their families, healthcare systems as well as society (paragraph 2.7.4). The literature revealed that not only direct costs such as medicine, disability allowances, hospitalisation, etc. are involved in the treatment of schizophrenia, but also indirect costs, for example unemployment, travel costs, etc., making this illness very expensive.

4.2.6 Determine optimal direct medicine treatment cost (using the single exit price and generic substitution) associated with schizophrenia treatment

This literature objective was achieved in section 2.7. From this section, it was concluded that schizophrenia is a costly illness to treat and that it is the most expensive of all psychiatric illnesses treated by mental health professionals in South Africa (paragraph 2.7.4).

In South Africa, the National Drug Policy was implemented to ensure an adequate and reliable supply of safe, cost-effective medicines of acceptable quality to all citizens of South Africa and the rational use of medicines by prescribers, dispensers and consumers (NDP, 1996:3). From the literature, it was found that although generic substitution reduces cost of treatment, schizophrenic patients are hesitant to change and may become delusional and paranoid when their medicine is changed, affecting their adherence to treatment (paragraph 2.7.4).

The single exit price is determined annually in accordance with similar price systems used internationally in order for manufacturers to set their prices when selling medicine products (paragraph 2.7.4). The single exit price increased between 2.14 and 13.2%, annually from 2008 to 2013 (paragraph 2.7.4). From the literature, it was concluded that an increase in SEP directly influenced the dispensing fee of medicine products causing treatments costs to increase (paragraph 2.7.4).

4.3 EMPIRICAL STUDY OBJECTIVES

Objectives stated to be obtained from the empirical investigation phase of the study:

- To determine the prevalence of schizophrenic patients on the database during the study period stratified by gender and age.
- To determine the prescribing and dispensing patterns of schizophrenia treatment during the study period.
- Conducting a cost analysis on schizophrenia treatment in order to determine possible cost savings due to generic substitution.
- To establish the factors influencing the direct medicine treatment costs of schizophrenia treatment, using database-related variables (demographic, chronic diseases and medicine related factors).

Conclusions of these objectives were reached in the form of two manuscripts and are discussed in paragraphs 4.3.1 to 4.3.4.

4.3.1 To determine the prevalence of schizophrenic patients on the database during the study period stratified by gender and age

This empirical objective was achieved in manuscript one. Schizophrenia has a worldwide prevalence of 1% (Millier *et al*., 2014:85). The population in this study consisted of 4 410 patients (0.09%) diagnosed with schizophrenia during the study period (Table 1). It was concluded that, overall, the prevalence of schizophrenia was higher in female patients, (N = 2 383) than in males (N = 2 027) (Table 1). Schizophrenia was furthermore more prevalent in patients between the ages of 35 and 65 years (N = 2 425) (Table 1). Men, in general, had a higher prevalence of schizophrenia between the ages of 18 and 35 years, whereas women presented with a higher prevalence of schizophrenia above 35 years. This may be ascribed to the protection provided by oestrogen in women before reaching their para-menopausal peak (Table 2).

4.3.2 To determine the prescribing and dispensing patterns of schizophrenia treatment during the study period

This empirical objective was achieved in manuscript one. Prescribing patterns were determined by analysing the prescriber speciality with the number of active ingredients prescribed. It was concluded that, overall, psychiatrists prescribed the highest percentage of prescribing antipsychotics compared to neurologists and general medical practitioners (Table 3).

Prescribing patterns were also determined by comparing doses of active ingredients prescribed (PDDs) to maximum recommended daily doses (MRDDs) (Table 4). It was concluded that olanzapine and risperidone were the most common active ingredients prescribed above their maximum recommended daily doses during the study period 2008 to 2013 (Table 4). Olanzapine is listed as a potentially inappropriate drug in elderly patients based on the 2012 Beers Criteria list (Campanelli, 2012:30). This antipsychotic was prescribed above its maximum recommended daily dose to approximately 20% of elderly patients in 2013.

Dispensing patterns were determined by observing the compliance status to antipsychotics prescribed through various factors, namely age groups, gender, treatment period, active ingredients and number of chronic diseases (Table 5). As treatment period lengthened, compliance of patients towards antipsychotics prescribed increased. Therefore, it can be

concluded that treatment period had a direct influence on compliance, supporting findings from an earlier study, showing that lengthened treatment periods increase compliance to antipsychotics due to an increase in patient functioning and a decrease in clinical symptoms associated with schizophrenia (Morken *et al*., 2008:4). Clozapine showed the best compliance out of the antipsychotics that were prescribed (Table 5). Other studies have also showed that compliance to clozapine is generally higher than to other antipsychotics due to frequent obligated clinical visits, encouraging patients to take their medication (Gilmer *et al*., 2004:693; Weiss *et al*., 2002:342). Patients using clozapine are selected beforehand, as this medication requires cooperation from the patient to frequently attend their clinical visits for obligated monitoring of white blood cell counts (Weiss *et al*., 2002:342).

4.3.3 Conducting a cost-analysis on schizophrenia treatment in order to determine possible cost-savings due to generic substitution

This empirical objective was achieved in manuscript two. In the South African market, 18 antipsychotics were available during the study period where only five of these active ingredients were prescribed in generic versions on the database, namely clozapine, quetiapine, risperidone, olanzapine and haloperidol (Table 5).

Total direct medicine cost of schizophrenia treatment for patients on the database for the study period amounted to R 52 647 520.38. It was concluded that if originator and more expensive generic items were substituted with the average cost of the least expensive generic item, potential annual cost-savings of 37.90%, 25.72%, 33.64%, 47.80%, 41.47% and 39.29% could have been generated from 2008 to 2013, respectively (Table 5). A study conducted in the United States of America showed that potential cost-savings of a quarter to half a billion dollars could have been generated annually when all drugs were substituted with generic items (Fischer & Avorn, 2003:1059).

A total cost of R4 642 685 (39.21%) could thus have been potentially saved during the study period 2008 to 2013 (Table 5). Therefore, it is concluded that generic substitution contributes to potential economic benefits.

4.3.4 To establish the factors influencing the direct medicine treatment costs of schizophrenia treatment, using database-related variables

This empirical objective was achieved in manuscript two. From this manuscript, it can be concluded that the following factors can influence the direct medicine treatment costs of schizophrenic patients:

- Prescriber
- Cost per items
- Single exit price
- Patient contribution
- Scheme contribution

It was concluded that over the study period, a decrease in the **prescribing** of antipsychotics was observed for general medical practitioners with 5.43%, whereas antipsychotics prescribed by neurologists and psychiatrists increased with 0.52% and 4.8%, respectively (Table 4). Because general medical practitioners are not authorised to issue prescriptions for antipsychotics for more than six months without consulting a psychiatrist, this result supports the fact that the Medicine Act in South Africa is being followed (Medicines and Related Substances Act 101 of 1965).

It was furthermore concluded that psychiatrists favoured the use of non-generic items (40.63%). This leads to higher medical expenditures for patients as the original items or non-generic items are often more expensive than the reference drug price agreed upon by the medical scheme and therefore generating a higher patient contribution (726.94%) (Table 4).

It was concluded that all factors influencing the direct medicine cost increased over the study period, including the **cost per item** with 99.26%, the **SEP** with 77.62%, **medical scheme** contribution with 6.28% and patient **contribution** with 726.94% (Table 2).

Use of **generic items** increased with 60.31% during the study period (Table 3). The average cost of generic items increased with approximately 220%. Aspects influencing the cost of these generic items includes SEP, scheme contribution and patient contribution, which all increased with ~105%, ~92% and ~700%, respectively over the study period.

4.4 STUDY LIMITATIONS AND STRENGHTS

A number of limitations presented itself during the study. The following limitations applied overall during the study:

- When patients used varying providers, all the necessary claims were not captured (e.g. 'out-of-pocket' payments, hospitalisation etc.) as these claims data was lost to the database and therefore not available for analyses.
- The first record of patient on the database was not necessarily the first time the patient received treatment for schizophrenia, and consequently this study could not determine incidence of schizophrenia in the study population.
- External validity was also limited as only one database was used for analyses and was therefore not representative of the South African market as a whole.

Strengths of the study included the use of data obtained from a Pharmaceutical Benefit Management Company that is nationally representative in South Africa containing more than 1.5 million members and has more than 20 medical schemes registered. Automated validation processes were applied in-house by the PBM ensuring clinical management and eligibility services, real-time benefit and pricing management are done on a regular basis ensuring that the integrity of the data is valid. It is therefore safe to assume that the database used for the study is trustworthy.

This research study will benefit i) prescribed minimum benefit companies, ii) medical schemes, iii) schizophrenic patients, and iv) healthcare professionals (clinicians, pharmacists and nurses). Benefits include:

- This research project helped to increase the understanding of healthcare delivery of a schizophrenic patient.
- The study helped to improve the awareness of clinicians to prescribe antipsychotics according to the therapeutic algorithm of the Council of Medical Schemes (Medical Schemes Act 131:1998) in order for patients to experience medical benefits at a cost-affordable price and improve patient adherence.
- Brought factors forward to clinicians of the effects of prescribing antipsychotics not according to the therapeutic algorithm of the Council of Medical Schemes.

4.5 RECOMMENDATIONS

This study highlighted the compliance to antipsychotic treatment as well as the potential economic burden of schizophrenia on patients and the healthcare system. Suggestions for future research therefore include:

- To determine the factors influencing prescribers' choice of antipsychotic drugs in the private health sector of South Africa.
- Factors influencing compliance to antipsychotics from the patient's point of view.
- To determine the potential impact of schizophrenia on a future National Health Insurance for South Africa.

4.6 CHAPTER SUMMARY

This chapter is a summary of all the achievements reached of the specific objectives stated in the literature review and empirical investigation. Strengths of the study were discussed as well as the limitations found in the study. Recommendations for future studies are also mentioned. Hereby, all objectives stated in the study were achieved.

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ANNEXURE A: ALGORITHM FOR THE TREATMENT OF SCHIZOPHRENIA

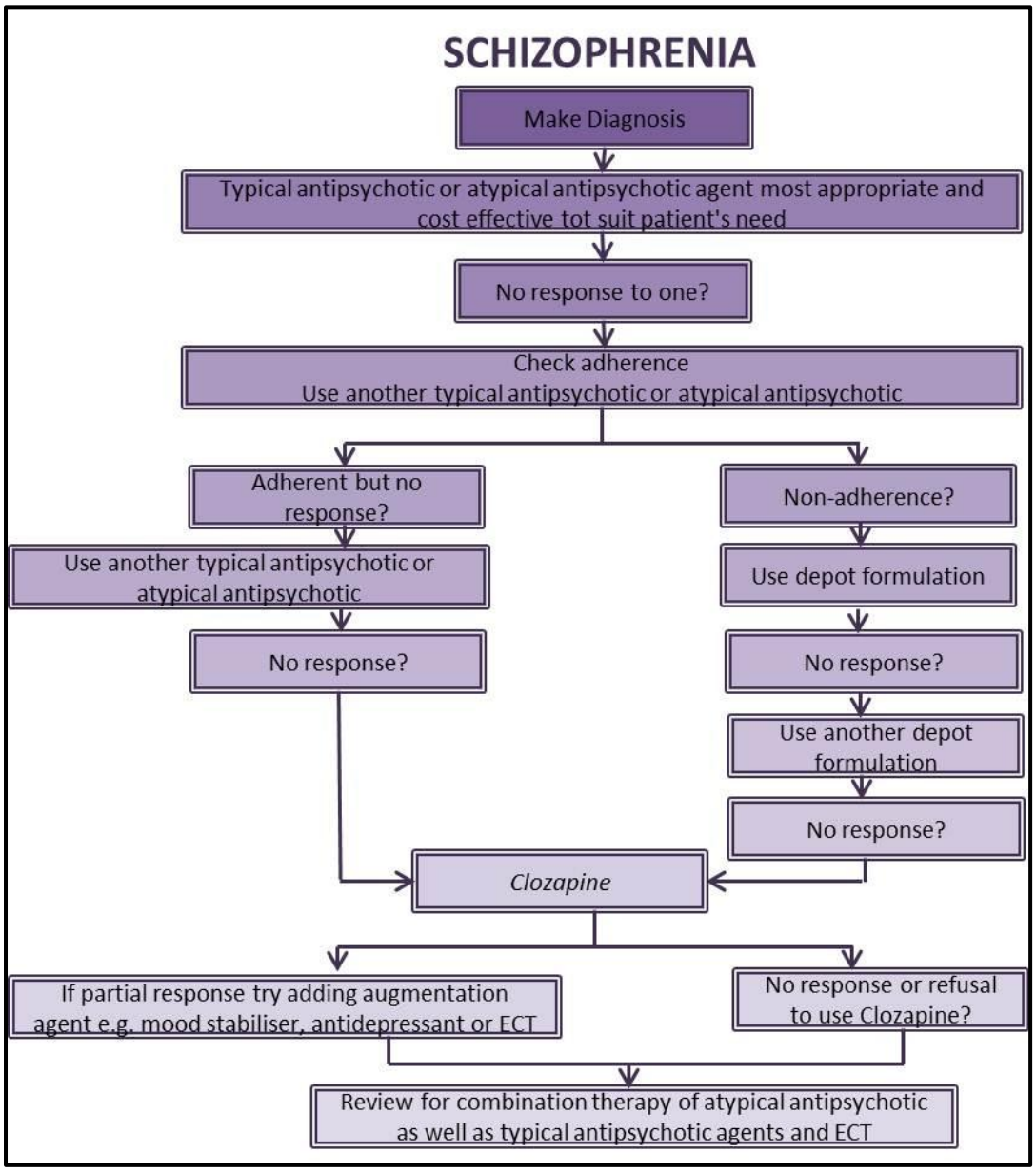

Figure 2: Therapeutic algorithm for the treatment of schizophrenia (Department of Health, 2003)

ANNEXURE B: VALIDATION PROCESS TO ENSURE THE VALIDITY AND RELIABILITY OF DATA EMPLOYED BY THE PBM

Validation processes	Examples
Data integrity validation and eligibility management.	Claim field format checks Provider validation checks Member validation checks Verify dependant code Waiting period check Duplicate check
Medicine utilisation management (checked at active ingredient level against patient history)	Refill limits (e.g. 12 fills per year for chronic medication) Fill limitations per period (e.g. 1 fill per 26 days) Product quantity limits (e.g. 200 analgesics/365 days) Products requiring pre-authorisation (e.g. immune-modulating agents) Patient specific exclusions (e.g. for pre-existing conditions and general waiting periods) Pre-existing conditions (e.g. patient specific as advised by scheme) Drug to age range limitations (e.g. RitalinTM and generics will pay for patients 16 years and younger) Drug to gender limitations (e.g. hormone replacement therapy in women) Invalid prescriber specialty (e.g. DianeTM prescribed by dermatologists) Broad category exclusions (e.g. soaps/shampoos excluded) Specific products excluded (e.g. urinary antiseptics) Waiting periods (e.g. patient specific as advised by scheme)

Validation processes	Examples
Clinical management	Ingredient duplication Maximum daily dose exceeded Therapeutic duplication Drug-drug interactions Drug-allergy interactions Drug-age interactions Drug-gender interactions Drug-disease interactions Drug-inferred health state interactions
Pricing management	Continuous price file maintenance Apply reference pricing e.g. generic reference pricing and therapeutic reference pricing (i.e. formulary based pricing for chronic diseases)
Formulary management	Management of Chronic disease List prescribed minimum benefits and non-chronic disease list conditions Daily real-time benefit validation

ANNEXURE C: CHECKLIST FOR THE ASSESSMENT OF QUALITY OF DATA

This checklist has been developed from the following sources:

BMJ 2004:1102; Clemens *et al*. 1995: 173; CRD 2009: Centre for review and dissemination; Sacristan *et al*. 1993: 1130; Siegel *et al*. 1996; Russel *et al.* 1996; Weinstein *et al*. 1996.

Aspect	Checklist item	Approach followed
Framework	Background of the problem. General framing and design of the analysis. Research question is stated. Target population for intervention. Statement of the perspective of the analysis.	
Data and methods	Critique of data quality. Statement of year of costs. Statement of type of currency.	
Discussion	Summary of reference case results. Summary of sensitivity of results to assumptions and uncertainties in the analysis. Limitations of the study. Relevance of study results for specific policy questions or decisions.	
Data collection	Methods for the estimation of quantities and unit costs are described. Currency and price data are recorded. Details of currency of price adjustments for inflation or currency conversion are given. Details of any model used are given.	

Aspect	Checklist item	Approach followed
Measurement of costs	Is the measurement of costs suitable for the perspective? Are the costs up to date and the prices those of the market? Is an adjustment of future costs and benefits performed?	
Cost analysis	Which costs were evaluated in the study? Measurement of the associated resource quantities. Valuation (cost) of those resources. Time horizon of costs and benefits is stated. The discount rate(s) is(are) stated. The choice of rate(s) is(are) justified.	
Cost categories	Costs relevant to the study question. Costs associated with the analysis that is undertaken. Direct medical, direct nonmedical and indirect costs are estimated.	
Measurement of resource data: Resource use is measured in physical units: drugs	Issues to consider: Methods for the estimation of quantities and unit costs are described Quality of the database should be documented. Any assumptions in the measurement of resources should be explicitly reported and justified If an expert was consulted to estimate some of the resources, the methods used should be described. The source(s) and methods of deriving the costs/charges should be clearly stated and validated.	

Aspect	Checklist item	Approach followed
Valuation of resource data	Issues to consider: All the sources used to obtain unit costs should be reported and be relevant for the specific study setting. All costs should be adjusted to a specific price year so that the effects of inflation are removed from the cost estimation. If the time horizon for estimating costs was longer than one year, discounting should have been performed in order to reflect time preferences. If prices were used instead of costs and cost-to-charge ratios calculated, these should reflect the true opportunity costs of the strategies compared.	

ANNEXURE D: AUTHOR GUIDELINES SOUTH AFRICAN MEDICAL JOURNAL

Author Guidelines OF SOUTH AFRICAN MEDICAL JOURNAL

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

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Provide evidence of Research Ethics Committee approval of the research where relevant.

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Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to www.icmje.org.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields. References should be limited to no more than 15. Please provide a structured abstract not exceeding 250 words, with the following recommended headings: Background, Objectives, Methods, Results, and Conclusion.

Scientific letters will be considered for publication as shorter ***Research articles***.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the *SAMJ* peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Forum articles must be accompanied by a short description (50 words) of the affiliation details/interests of the author(s). Refer to recent forum articles for guidance. Please provide an accompanying abstract not exceeding 150 words.

Book reviews should be about 400 words and must be accompanied by the publication details of the book.

Obituaries should be about 400 words and may be accompanied by a photograph.

Guidelines must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed. A structured abstract not exceeding 250 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents. References, appendices, figures and tables must be kept to a minimum.

Guidelines exceeding 8 000 words will only be considered for publication as a supplement to the SAMJ; the costs of which must be covered by sponsorship or advertising. The Editor

reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - www.icmje.org. Manuscripts must be provided in UK English.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'). The same applies to ± and º, i.e. '35±6' and '19ºC'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting: The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as 'supplementary files'. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings.

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Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

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Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

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ANNEXURE E: AUTHOR GUIDELINES FOR HEALTH SA GESONDHEID JOURNAL

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

DESCRIPTION

Health SA Gesondheid - Journal of Interdisciplinary Health Sciences is an open access, peer-reviewed interdisciplinary and inter professional scholarly journal that aims to promote communication, collaboration and teamwork between professions and disciplines within the health sciences to address problems that cross and affect disciplinary boundaries.

Health SA Gesondheid - Journal of Interdisciplinary Health Sciences publishes original articles on issues related to public health, including implications for practical applications and service delivery that are of concern and relevance to Africa and other developing countries. It facilitates the gathering and critical testing of insights and viewpoints on knowledge from different disciplines involved in health service delivery.

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- Purpose (aims) and objectives
- Definitions of key concepts

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Results and Findings Results should be clear and concise

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ANNEXURE F: AVERAGE MAXIMUM POTENTIAL COST SAVINGS THROUGH GENERIC SUBSTITUTION

Cost saving analyses for 2008

Active ingredient by trade name (mg)	GI	N	Mean ±SD	Cost of originator items R	Cost if substituted with generic R	Potential cost save R (%)
Clozapine						
Leponex (100 mg)	O	201	520.33 ±390.11	113 167.57	80 251.26	32 916.31
Cloment (100 mg)	G	357	399.26 ±253.90			
Haloperidol						
Serenace (5 mg)	O	5	204.40 ±68.02	1031.97	325.60	706.37
Sandoz haloperidol (5 mg)	G	128	65.12 ±50.07			
Risperidone						
Risperdal (1 mg)	O	72	602.24 ±422.99	40772.24	20 756.16	20 016.08
Risperidone hexal (1 mg)	G	5	288.28 ±8.34			
Risperdal (2 mg)	O	107	787.93 ±295.55	93405.67	49 027.40	44 378.27
Risperidone hexal (2 mg)	G	4	458.20±0.00			
Risperdal (3 mg)	O	35	993.26 ±226.60	33569.21	24 730.65	8 838.56
Risperidone hexal (3 mg)	G	6	706.59 ±391.23			
Total (R)				281 946.66	175 091.07	106 855.59 (37.90)

Cost saving analyses 2009

Active ingredient by trade name	GI	N	Mean ±SD	Cost of original items (R)	Cost of generic items (R)	Potential cost save (R)
Clozapine						
Leponex (100 mg)	O	249	595.46 ±490.11	159 148.45	115 102.74	44 045.71
Cloment (100 mg)	G	530	462.26 ±303.33			
Haloperidol						

Active ingredient by trade name	GI	N	Mean ±SD	Cost of original items (R)	Cost of generic items (R)	Potential cost save (R)
Serenace (5 mg)	O	15	173.09 ±137.88	2 199.43	1 108.20	1 091.23
Sandoz haloperidol (5 mg)	G	185	73.88 ±39.38			
Risperidone						
Risperdal (0.5 mg)	O	259	292.99 ±129.20	75 980.02	53 641.49	22 338.53
Aspen risperidone (0.5 mg)	G	39	207.11 ±99.62			
Risperdal quicklet (0.5 mg)	G	62	265.01 ±90.66	18 680.42	12 840.82	5 839.60
Risperidone hexal (0.5 mg)	G	9	324.81 ±0.01	2 923.28	1 863.99	1 059.29
Risperlet (0.5 mg)	G	52	236.88 ±84.77	12 501.23	10 769.72	1 731.51
Zoxadon (0.5 mg)	G	7	255.28 ±135.77	2 187.76	1 449.77	737.99
Risperdal (1 mg)	O	245	507.93 ±246.53	126 303.08	83 282.85	43 020.23
Aspen risperidone (1 mg)	G	41	353.91 ±168.03	13 086.14	13 937.13	
Mylan risperidone (1 mg)	G	1	339.93±0.00			
Risperdal quicklet (1 mg)	G	100	397.80 ±142.69	35 205.23	33 993.00	1 215.23
Risperidone hexal (1 mg)	G	172	356.27 ±147.59	63 580.76	58 467.96	5 112.80
Risperlet (1 mg)	G	71	422.40 ±161.03	27 073.31	24 135.03	2 938.28
Zoxadon (1 mg)	G	49	391.81 ±186.78	17 172.70	16 656.57	516.13
Risperdal (2 mg)	O	236	726.46 ±361.06	189 564.46	139 034.68	50 529.78
Aspen risperidone (2 mg)	G	40	644.20 ±280.55	21 703.88	23 565.20	
DRL risperidone (2 mg)	G	2	1277.46 ±0.00	2 554.92	1 178.26	1 376.66
Risperdal quicklet (2 mg)	G	111	745.51 ±402.26	94 233.11	65 393.43	28 839.68
Risperidone hexal (2 mg)	G	156	589.13 ±244.49			
Risperlet (2 mg)	G	80	750.98 ±397.03	65 165.19	47 130.40	18 034.79
Zoxadon (2 mg)	G	65	590.04 ±307.30	39 400.21	38 293.45	1 106.76
Risperdal (3 mg)	O	87	987.90 ±342.64	91 626.32	56 463.00	35 163.32
Aspen risperdone (3 mg)	G	37	763.29 ±220.39	31 015.07	24 013.00	7 002.07
DRL risperidone (3 mg)	G	3	649.00±0.00			
Risperdal quicklet (3 mg)	G	116	1011.80±431.88	122 185.14	75 284.00	46 901.14
Risperidone hexal (3 mg)	G	129	733.21 ±296.99	99 494.41	83 721.00	15 773.41
Risperdal (4 mg)	O	54	1373.28±348.51	74 120.78	46 680.30	27 440.48
Aspen risperidone (4 mg)	G	105	966.20 ±247.97	104 111.31	90 767.25	13 344.06

Active ingredient by trade name	GI	N	Mean ±SD	Cost of original items (R)	Cost of generic items (R)	Potential cost save (R)
Risperdal quicklet (4 mg)	G	28	1226.67±384.85	31 882.28	24 204.60	7 677.68
Risponz (4 mg)	G	1	864.45±0.00			
Total (R)				1 488 308.87	1 105 476	382 836.36 (25.72)

Cost saving analyses for 2010

Active ingredient by trade name	GI	N	Mean ±SD	Cost of original items (R)	Cost of generic items (R)	Potential cost save (R)
Clozapine						
Leponex (100 mg)	O	219	714.17 ±577.80	177 826.18	106 414.29	71 411.89
Cloment (100 mg)	G	524	485.91 ±316.93			
Haloperidol						
Serenace (5 mg)	O	25	164.99 ±123.89	3 138.88	1720.25	1 418.63
Sandoz haloperidol(5 mg)	G	210	68.81 ±41.01			
Risperidone						
Risperdal (0.5 mg)	O	175	265.08 ±120.59	48 312.36	29 254.75	19 057.61
Aspen risperidone (0.5 mg)	G	50	249.85 ±186.98	10 390.81	8 358.50	2 032.31
DRL risperidone (0.5 mg)	G	1	167.17 ±0.00			
Mylan risperidone (0.5 mg)	G	3	261.96 ±119.81	701.15	501.51	199.64
Risperdal quicklet (0.5 mg)	G	48	315.58 ±161.02	15 819.19	8 024.16	7 795.03
Risperidone hexal (0.5 mg)	G	25	331.55 ±237.27	10 964.92	4 179.25	6 785.67
Risperlet (0.5 mg)	G	93	223.26 ±103.93	22 804.80	15 546.81	7 257.99
Zoxadon (0.5 mg)	G	14	230.74 ±92.41	3 870.03	2 340.38	1 529.65
Risperdal (1 mg)	O	111	520.46 ±252.47	56 445.45	32 867.10	23 578.35
Aspen risperidone (1 mg)	G	30	301.64 ±172.12	8 944.22	8 883.00	61.22
DRL risperidone (1 mg)	G	13	523.59±0.00	6 806.63	3 849.30	2 957.33
Mylan risperidone (1 mg)	G	1	576.25±0.00	576.25	296.10	280.15
Risperdal quicklet (1 mg)	G	43	372.66 ±200.48	19 673.84	12 732.30	6 941.54
Risperidone hexal (1 mg)	G	105	387.51 ±334.84	41 043.50	31 091.55	9 951.95
Risperlet (1 mg)	G	128	387.49 ±164.90	53 595.44	37 900.80	15 694.64
Risponz (1 mg)	G	1	296.10 ±0.00			

Active ingredient by trade name	GI	N	Mean ±SD	Cost of original items (R)	Cost of generic items (R)	Potential cost save (R)
Zoxadon (1 mg)	G	94	314.47 ±140.31	30 773.95	27 833.40	2 940.55
Risperdal (2 mg)	O	145	839.41 ±487.89	126 897.35	71 643.05	55 254.30
Aspen risperidone (2 mg)	G	99	702.35 ±278.82	71 810.85	48 914.91	22 895.94
DRL risperidone (2 mg)	G	4	806.96 ±121.66	3 309.66	1 976.36	1 333.30
Mylan risperidone (2 mg)	G	9	682.63 ±233.39	5 834.35	4 446.81	1 387.54
Risperdal quicklet (2 mg)	G	95	860.36 ±448.91	89 868.08	46 938.55	42 929.53
Risperidone hexal (2 mg)	G	48	555.09 ±237.81	27 824.55	23 716.32	4 108.23
Risperlet (2 mg)	G	120	679.22 ±422.90	94 930.61	59 290.80	35 639.81
Risponz (2 mg)	G	10	494.09 ±0.00			
Zoxadon (2 mg)	G	128	566.74 ±217.20	73 985.72	63 243.52	10 742.20
Risperdal (3 mg)	O	46	1079.51±355.25	49 956.80	29 854.00	20 102.80
Aspen risperidone (3 mg)	G	54	952.88 ±355.55	44 094.18	35 046.00	9 048.18
DRL risperidone (3 mg)	G	1	649.00 ±0.00			
Risperdal quicklet (3 mg)	G	91	988.12 ±469.57	91 728.61	59 059.00	32 669.61
Risperidone hexal (3 mg)	G	117	899.61 ±395.69	93 795.27	75 933.00	17 862.27
Risponz (3 mg)	G	4	733.60 ±0.00	2 934.40	2 596.00	338.40
Risperdal (4 mg)	O	21	1453.32 ±21.40	30 301.74	18 759.30	11 542.44
Aspen risperidone (4 mg)	G	56	893.30 ±358.52			
Risperdal quicklet (4 mg)	G	12	1088.16 ±45.34	13 466.34	10 719.60	2 746.74
Risponz (4 mg)	G	1	921.64 ±0.00	921.64	893.30	28.34
Total (R)				1 333 347.75	884.823.97	448 523.78 (33.97)

Cost saving analyses for 2011

Active ingredient by trade name	GI	N	Mean ±SD	Cost per original item (R)	Cost per generic item (R)	Potential cost save(R)
Clozapine						
Leponex (100 mg)	O	211	828.00 ±610.7	191 209.42	119 141.15	72 068.27
Cloment (100 mg)	G	475	564.65 ±357.16			
Haloperidol						

Active ingredient by trade name	GI	N	Mean ±SD	Cost per original item (R)	Cost per generic item (R)	Potential cost save(R)
Serenace (5 mg)	O	10	140.17 ±126.99	1 481.66	711.70	769.96
Sandoz haloperidol (5 mg)	G	183	71.17 ±38.89			
Olanzapine						
Zyprexa (10 mg)	O	445	1744.18±711.86	826 471.45	293 499.75	532 971.70
Olexar (10 mg)	G	137	659.55 ±254.74			
Redilanz (10 mg)	G	96	663.45 ±259.21	67 895.49	63 316.80	4 578.69
Zyprexa (2.5 mg)	O	143	596.75 ±209.64	87 915.87	51 459.98	36 455.89
Olexar (2.5 mg)	G	43	428.98 ±222.03	19 135.11	15 473.98	3 661.13
Redilanz (2.5 mg)	G	13	359.86 ±283.59			
Zyprexa (5 mg)	O	273	936.21 ±522.36	247 436.52	127 720.32	119 716.20
Olexar (5 mg)	G	82	561.61 ± 298.89	51 023.39	38 362.88	12 660.51
Redilanz (5 mg)	G	24	467.84 ±105.94			
Risperidone						
Risperdal (0.5 mg)	O	178	301.98 ±133.61	53 660.44	27 743.08	25 917.36
Aspen risperidone (0.5 mg)	G	34	200.74 ±79.93	6 545.65	5 299.24	1 246.41
DRL risperidone (0.5 mg)	G	14	191.19 ±19.58	2 842.83	2 182.04	660.79
Mylan risperidone (0.5 mg)	G	3	354.65 ±0.00	1 063.95	467.58	596.37
Risperdal quicklet (0.5 mg)	G	16	297.88 ±191.73	4 816.64	2 493.76	2 322.88
Risperidone hexal (0.5 mg)	G	31	228.13 ±234.05	12 311.43	4 831.66	7 479.77
Risperlet (0.5 mg)	G	102	242.07 ±99.25	25 301.16	15 897.72	9 403.44
Schizorol (0.5 mg)	G	1	155.86 ±0.00			
Zoxadon (0.5 mg)	G	50	228.79 ±88.33	11 445.40	7 793.00	3 652.40
Risperdal (1 mg)	O	61	368.38 ±177.36	27 717.48	13 549.93	14 167.55
Aspen risperidone (1 mg)	G	35	222.13 ±135.15			
DRL risperidone (1 mg)	G	7	539.81 ±0.00	3 778.67	1 554.91	2 223.76
Mylan risperidone (1 mg)	G	12	407.62 ±155.69	4 829.96	2 665.56	2 164.40
Risperdal quicklet (1 mg)	G	29	290.05 ±217.79	8 293.09	6 441.77	1 851.32
Risperidone hexal (1 mg)	G	68	313.08 ±123.02	20 324.33	15 104.84	5 219.49
Risperlet (1 mg)	G	127	346.64 ±136.31	46 313.84	28 210.51	18 103.33
Zoxadon (1 mg)	G	76	372.74 ±194.79	28 830.31	16 881.88	11 948.43

Active ingredient by trade name	GI	N	Mean ±SD	Cost per original item (R)	Cost per generic item (R)	Potential cost save(R)
Risperdal (2 mg)	O	128	888.07 ±502.52	134 908.59	45 054.72	89 853.87
Aspen risperidone (2 mg)	G	100	585.81 ±271.56	56 719.64	35 199.00	21 520.64
DRL risperidone (2 mg)	G	30	588.29 ±588.29	19 152.94	10 559.70	8 593.24
Mylan risperidone (2 mg)	G	8	351.99 ±497.79			
Risperdal quicklet (2 mg)	G	77	810.13 ±458.49	67 220.45	27 103.23	40 117.22
Risperidone hexal (2 mg)	G	19	517.82 ±178.96	8 942.15	6 687.81	2 254.34
Risperlet (2 mg)	G	130	676.79 ±462.63	108 429.02	45 758.70	62 670.32
Risponz (2 mg)	G	5	489.92±0.00	2 449.60	1 759.95	689.65
Schizorol (2 mg)	G	2	456.05 ±0.00	912.10	703.98	208.12
Zoxadon (2 mg)	G	127	492.11 ±189.23	65 669.30	44 604.94	21 064.36
Risperdal (3 mg)	O	8	915.28 ±457.44	8 402.07	5 245.92	3 156.15
Aspen risperidone (3 mg)	G	80	881.31 ±312.66	78 483.73	52 459.20	26 024.53
DRL risperidone (3 mg)	G	1	702.18 ±0.00	702.180	655.74	46.44
Rispacor (3 mg)	G	2	655.74 ±0.00			
Risperdal quicklet (3 mg)	G	70	984.90 ±278.54	70 967.22	45 901.80	25 065.42
Risperidone hexal (3 mg)	G	84	722.75 ±324.10	62 609.52	55 082.16	7 527.36
Risponz (3 mg)	G	24	1039.81±474.84	25 626.97	15 737.76	9 889.21
Risperdal (4 mg)	O	7	1056.59±709.84	5 511.05	6 448.89	(-937.84)
Aspen risperidone (4 mg)	G	85	1008.01±305.90	93 058.03	78 307.95	14 750.08
Risperdal quicklet (4 mg)	G	6	1088.07 ±0.00	6 528.42	5 527.62	1000.80
Risponz (4 mg)	G	2	921.27 ±0.53			
Total (R)				2561426.05	1337153.86	1224272.19 (47.78)

Cost saving analyses for 2012

Active ingredient by trade name	GI	N	Mean ±SD	Cost per original item (R)	Cost er generic item(R)	Potential cost saving
Clozapine						
Leponex (100 mg)	O	230	738.68 ±617.98	178 914.71	49 201.60	129 713.11
Aspen clozapine (100 mg)	G	1	213.92 ±0.00			
Cloment (100 mg)	G	431	526.67 ±323.85	224 377.94	92 199.52	132 178.42

Active ingredient by trade name	GI	N	Mean ±SD	Cost per original item (R)	Cost er generic item(R)	Potential cost saving
Leviteracetam						
Kepra (250 mg)	O	28	425.73 ±216.78	10 049.74	5 458.32	4 591.42
Redilev (250 mg)	G	10	194.94 ±8.06			
Kepra (750 mg)	O	4	750.56 ±338.77	3 481.31	1 696.68	1 784.63
Redilev (750 mg)	G	21	424.17 ±129.89			
Haloperidol						
Serenace (5 mg)	O	24	282.76 ±184.67	5 854.48	1 736.40	4 118.08
Sandoz haloperidol (5 mg)	G	107	72.35 ±54.50			
Olanzapine						
Zyprexa (10 mg)	O	219	1250.74±924.25	281 188.43	140 037.36	141 151.07
Olexar (10 mg)	G	281	767.07 ±287.45	228976.60	179 682.64	49 291.96
Redilanz (10 mg)	G	120	639.44 ±211.85			
Zyprexa (2.5 mg)	O	76	407.44 ±129.47	33 223.83	21 935.12	11 288.71
Olexar (2.5 mg)	G	93	395.97 ±395.97	33561.76	26 841.66	6 720.10
Redilanz (2.5 mg)	G	7	288.62 ±6.55			
Zyprexa (5 mg)	O	170	731.48 ±400.95	115 766.50	69 208.70	46 557.80
Olexar (5 mg)	G	245	530.73 ±279.28	133873.96	99 741.95	34 132.01
Redilanz (5 mg)	G	16	407.11 ±82.53			
Quetiapine						
Seroquel (100 mg)	O	49	538.69 ±204.15	24 466.31	9 842.14	14 624.17
Dopaquel (100 mg)	G	82	247.02 ±157.80	20 454.38	16 470.52	3 983.86
Quetoser (100 mg)	G	2	261.06 ±0.00	522.12	401.72	120.40
Serez (100 mg)	G	11	203.66 ±166.17	3 243.49	2 209.46	1 034.03
Truvalin (100 mg)	G	21	200.86 ±0.00			
Seroquel (200 mg)	O	76	683.95 ±389.32	51 596.99	22 049.88	29 547.11
Dopaquel (200 mg)	G	125	378.01 ±139.58	53 987.31	36 266.25	17 721.06
Quetoser (200 mg)	G	6	290.13 ±1.61			

Active ingredient by trade name	GI	N	Mean ±SD	Cost per original item (R)	Cost er generic item(R)	Potential cost saving
Serez (200 mg)	G	23	350.95 ±144.34	6 965.04	6 672.99	292.05
Truvalin (200 mg)	G	1	339.24 ±0.00	339.24	290.13	49.11
Seroquel (25 mg)	O	86	406.70 ±227.10	37 012.90	7 943.82	29 069.08
Dopaquel (25 mg)	G	63	199.61 ±84.08	12 897.49	5 819.31	7 078.18
Quetoser (25 mg)	G	2	92.37 ±26.13			
Serez (25 mg)	G	30	198.98 ±83.08	5 809.00	2 771.10	3 037.90
Truvalin (25 mg)	G	1	234.12 ±0.00	234.12	92.37	141.75
Seroquel (300 mg)	O	74	1181.71±582.03	86 385.12	27 196.48	59 188.64
Dopaquel (300 mg)	G	76	449.75 ±146.13	35260.04	27 931.52	7 328.52
Mylan quetiapine (300 mg)	G	2	505.12 ±224.15	1 010.23	735.04	275.19
Quetoser (300 mg)	G	8	647.11 ±23.61	5 277.06	2 940.16	2 336.90
Serez (300 mg)	G	12	425.82 ±168.12	5 703.49	4 410.24	1 293.25
Truvalin (300 mg)	G	2	367.52 ±21.10			
Risperidone						
Risperdal (0.5 mg)	O	88	346.94 ±289.03	29 611.01	17 953.76	11 657.25
Aspen risperidone (0.5 mg)	G	26	217.83 ±72.18	4 943.54	5 304.52	
DRL risperidone (0.5 mg)	G	19	208.24 ±30.42	3 806.00	3 876.38	
Mylan risperidone (0.5 mg)	G	1	361.45 ±0.00	361.45	204.02	157.43
Risperdal quicklet (0.5 mg)	G	24	363.68 ±129.64	8 944.98	4 896.48	4048.50
Risperidone hexal (0.5 mg)	G	15	273.92 ±328.63	4 387.60	3 060.30	1 327.30
Risperlet (0.5 mg)	G	68	237.95 ±122.56	15 202.86	13 873.36	1 329.50
Zoxadon (0.5 mg)	G	111	204.02 ±121.75			
Risperdal (1 mg)	O	79	476.49 ±234.79	36 486.25	19 449.80	17 036.45
Aspen risperidone (1 mg)	G	36	356.79 ±177.05	14 925.86	8 863.20	6 062.66
DRL risperidone (1 mg)	G	30	399.56 ±107.79	11 496.79	7 386.00	3660.79
Mylan risperidone (1 mg)	G	7	338.74 ±50.63	2 478.57	1 723.40	755.17
Risperdal quicklet (1 mg)	G	50	307.24 ±114.75	17 536.90	12 310.00	5 226.90
Risperidone hexal (1 mg)	G	46	246.20 ±123.59			
Risperlet (1 mg)	G	128	337.29 ±136.71	44986.73	31 513.60	13 473.13
Zoxadon (1 mg)	G	76	338.03 ±206.26	30336.20	18 711.20	11 625

Active ingredient by trade name	GI	N	Mean ±SD	Cost per original item (R)	Cost er generic item(R)	Potential cost saving
Risperdal (2 mg)	O	147	918.81 ±405.36	148 829.18	74 218.83	74 610.35
Aspen risperidone (2 mg)	G	71	571.53 ±143.75	38 645.61	35 847.19	2 798.42
DRL risperidone (2 mg)	G	50	610.82 ±252.47	31 834.06	25 244.50	6 859.56
Mylan risperidone (2 mg)	G	7	505.35 ±0.00	3 537.46	3 534.23	3.23
Risperdal quicklet (2 mg)	G	51	740.25 ±509.80	40 400.21	25 749.39	14 651.07
Risperidone hexal (2 mg)	G	26	864.74 ±495.92	26 560.35	13 127.14	13 433.21
Risperlet (2 mg)	G	111	700.56 ±500.64	84 576.41	56 042.79	28 533.62
Risponz (2 mg)	G	4	504.89 ±4.03			
Zoxadon (2 mg)	G	162	674.07 ±341.22	107 113.12	81 792.18	25 320.94
Risperdal (3 mg)	O	10	1494.23±1051.59	12 309.72	4 765.20	7 544.52
Aspen risperidone (3 mg)	G	95	750.04 ±336.18	78 385.61	45 269.40	33 116.21
Auroperdal (3 mg)	G	4	717.35 ±0.00	2 869.40	1 906.08	963.32
DRL risperidone (3 mg)	G	8	714.05 ±8.31	5 707.60	3 812.16	1 895.44
Rispacor (3 mg)	G	2	686.97 ±0.00	1 373.94	953.04	420.90
Risperdal quicklet (3 mg)	G	49	476.52±1248.40			
Risperidone hexal (3 mg)	G	56	681.09 ± 2.89	38 167.86	26 685.12	11 482.74
Risponz (3 mg)	G	4	698.77 ±16.69	2 771.45	1 906.08	865.37
Risperdal (4 mg)	O	2	1501.69 ±0.00	3 003.38	1 886.02	1 117.36
Aspen risperidone (4 mg)	G	75	1024.51±270.51	78773.57	70 725.75	8 047.82
Risponz (4 mg)	G	4	943.01 ±0.00			
Total (R)				2522047.72	1475193.30	1046854.40 (41.52)

Cost saving analyses for 2013

Active ingredient by trade name	GI	N	Mean ±SD	Cost per original item (R)	Cost per generic item (R)	Potential cost save (R)
Clozapine						
Leponex (100 mg)	O	244	1358.22 ±1063.04	366 294.58	235 530.76	130 763.82
Cloment (100 mg)	G	312	1011.88±629.17	282 077.77	301 170.48	
Aspen clozapine (100 mg)	G	92	965.29 ±565.73			

Active ingredient by trade name	GI	N	Mean ±SD	Cost per original item (R)	Cost per generic item (R)	Potential cost save (R)
Leponex (25 mg)	O	119	370.32 ±169.85	42 143.08	40 312.44	1 830.64
Aspen clozapine (25 mg)	G	17	338.76 ±297.07			
Haloperidol						
Serenace (5 mg)	O	43	262.32 ±114.06	12 171.93	8 122.27	4 049.66
Sandoz haloperidol (5 mg)	G	12	188.89 ±88.06			
Leviteracetam						
Kepra (250 mg)	O	25	961.38 ±414.30	23 155.65	8 500.25	14 655.40
Redilev (250 mg)	G	10	340.01 ±29.33			
Olanzapine						
Zyprexa (10 mg)	O	245	1582.39 ±909.61	471 838.10	341 922.00	129 916.10
Olexar (10 mg)	G	291	1395.60 ±536.64			
Redilanz (10 mg)	G	116	1587.87 ±548.04	180 340.32	161889.60	18450.72
Zyprexa (5 mg)	O	110	1044.70 ±327.28	112 345.19	89 157.20	23 187.99
Olexar (5 mg)	G	184	964.48 ±282.25	172 984.31	149 135.68	23 848.63
Redilanz (5 mg)	G	22	810.52 ±121.15			
Zyprexa (2.5 mg)	O	89	647.41 ±47.46	58 521.24	56 280.04	2 241.20
Olexar (2.5 mg)	G	71	632.36 ±353.511			
Redilanz (2.5 mg)	G	8	1041.50 ±geen	8332.01	5 058.88	3273.13
Quetiapine						
Seroquel (300 mg)	O	38	1913.63 ±1316.71	92 259.49	18 583.14	73 676.35
Truvalin (300 mg)	G	27	658.44 ±14.73	17939.96	13 203.81	4736.15
Serez (300 mg)	G	12	1009.42 ±339.31	10936.39	5 868.36	5095.03
Quetoser (300 mg)	G	48	901.22 ±485.46	49591.61	23 473.44	26 118.17
Dopaquel (300 mg)	G	47	675.64 ±228.51	35125.47	22 984.41	12 141.06
Mylan quetiapine (300 mg)	G	14	489.03 ± geen			
Seroquel (100 mg)	O	10	615.13 ±15.03	6 272.50	3 198.50	3 074.00
Serez (100 mg)	G	40	319.85 ±30.55			
Truvalin (100 mg)	G	21	354.76 ±22.80	7172.35	6 716.85	455.50

Active ingredient by trade name	GI	N	Mean ±SD	Cost per original item (R)	Cost per generic item (R)	Potential cost save (R)
Dopaquel (100 mg)	G	81	525.35 ±337.07	45989.97	25 907.85	20 082.12
Psyquet (100 mg)	G	5	1286.54 ±geen	6432.69	1 599.25	4833.44
Quetoser (100 mg)	G	23	408.59 ±258.94	7933.07	7 356.55	576.52
Seroquel (200 mg)	O	50	1070.50 ±763.45	75 767.55	35 866.00	39 901.55
Serez (200 mg)	G	60	806.37 ±688.42	50420.42	43 039.20	7 381.22
Truvalin (200 mg)	G	27	1279.72 ±590.95	31322.06	19 367.64	11 954.42
Dopaquel (200 mg)	G	92	759.04 ±540.36	94432.60	65 993.44	28 439.16
Quetoser (200 mg)	G	37	717.32 ±411.59			
Seroquel (25 mg)	O	35	604.36 ±407.50	30 589.77	7 766.15	22 823.62
Serez (25 mg)	G	44	320.28 ±115.84	12110.48	9 763.16	2347.32
Truvalin (25 mg)	G	1	221.89 ±geen			
Dopaquel (25 mg)	G	57	273.85 ±125.76	16431.02	12 647.73	3783.29
Mylan quetiapine (25 mg)	G	14	494.11 ± geen	6917.50	3 106.46	3811.04
Quetoser (25 mg)	G	29	321.81 ±411.59	9508.51	6 434.81	3073.7
Risperidone						
Risperdal (0.5 mg)	O	35	619.71 ±463.60	22 591.54	8 203.65	14 387.89
Mylan risperidone (0.5 mg)	G	2	700.58 ± geen	1401.15	468.78	932.37
Aspen risperidone (0.5 mg)	G	8	234.39 ±109.26			
DRL risperidone (0.5 mg)	G	18	453.67 ±192.18	8667.98	4 219.02	4448.96
Risperdal quicklet (0.5 mg)	G	14	608.35 ±201.56	8503.17	3 281.46	5221.71
Risperidone hexal (0.5 mg)	G	14	255.71 ±87.13	3667.84	3 281.46	386.38
Risperlet (0.5 mg)	G	79	454.51 ±218.37	36665.95	18 516.81	18149.14
Schizorol (0.5 mg)	G	4	432.00 ±geen	1727.98	937.56	790.42
Zoxadon (0.5 mg)	G	145	403.63 ±143.03	53467.18	33 986.55	19 480.63
Risperdal (1 mg)	O	57	1025.22 ±364.64	50 964.06	12 680.79	38 283.27
Risperdal quicklet (1 mg)	G	38	647.71 ±65.36	24952.37	8 453.86	16 498.51
Risperidone hexal (1 mg)	G	42	705.59 ±325.35	26081.34	9 343.74	16737.60
Risperlet (1 mg)	G	111	671.56 ±149.92	74374.83	24 694.17	49 680.66
Zoxadon (1 mg)	G	76	619.96 ±281.38	50153.20	16 907.72	33 245.48
Mylan risperidone (1 mg)	G	7	574.74 ±47.91	3853.77	1 557.29	2296.48
Risnia (1 mg)	G	6	353.12 ±18.90	2099.88	1 334.82	765.06

Active ingredient by trade name	GI	N	Mean ±SD	Cost per original item (R)	Cost per generic item (R)	Potential cost save (R)
Rispacor (1 mg)	G	2	222.47 ±geen			
Aspen risperidone (1 mg)	G	18	697.95 ±524.22	13382.58	4 004.46	9378.12
DRL risperidone (1 mg)	G	51	593.32 ±244.52	29634.43	11 345.97	18288.46
Risperdal (2 mg)	O	136	1631.28 ±551.08	240 552.40	105 148.40	135 404.00
Aspen risperidone (2 mg)	G	59	937.27 ±106.43	54910.32	45 615.85	9294.47
DRL risperidone (2 mg)	G	34	1245.09 ±680.41	47610.54	26 287.10	21 323.44
Mylan risperidone (2 mg)	G	5	982.99 ±geen	4914.96	3 865.75	1049.21
Risnia (2 mg)	G	12	773.15 ±124.58			
Rispacor (2 mg)	G	7	978.28 ±geen	6847.96	5412.05	1435.91
Risperdal quicklet (2 mg)	G	30	1146.53 ±601.69	43259.54	23 194.50	20065.04
Risperdal hexal (2 mg)	G	17	1394.89 ±413.71	26488.08	13 143.55	13344.53
Risperlet (2 mg)	G	106	1563.94 ±932.33	150859.73	81 953.90	68 905.83
Risponz (2 mg)	G	1	968.53 ±geen	968.53	773.15	195.38
Zoxadon (2 mg)	G	174	1451.29 ±797.27	259882.98	134 528.10	125 354.88
Risperdal (3 mg)	O	23	1686.69 ±295.35	41 343.11	20 100.39	21 242.71
Aspen risperidone (3 mg)	G	76	1529.84 ±546.66	135690.37	66 418.68	69271.69
Auroperdal (3 mg)	G	4	1426.09 ±0	5704.37	3 495.72	2208.65
DRL risperidone (3 mg)	G	27	1322.34 ±206.10	36625.96	23 596.11	13029.85
Risnia (3 mg)	G	22	873.93 ±445.05			
Rispacor (3 mg)	G	3	1154.02 ±174.95	3338.36	2621.79	716.57
Risperdal quicklet (3 mg)	G	4	3176.12 ±151.44	12490.29	3495.72	8994.57
Risperdal hexal (3 mg)	G	22	1783.75 ±697.53	32185.33	19 226.46	12 958.87
Risponz (3 mg)	G	7	1407.17 ±2.50	9841.35	6 117.51	3723.84
Risperdal (4 mg)	O	23	3625.63 ±1612.22	106 843.61	56 299.17	50 544.44
Aspen risperidone (4 mg)	G	63	2447.79 ±1225.05			
Total (R)				3687826.86	2233298.0	1454555.97 (39.44)

ANNEXURE G: MANUSCRIPT 1 SUBMISSION CONFIRMATION

>>> "Professor Janet Seggie" <janet.seggie@hmpg.co.za> 2015/10/05 02:13 PM >>>
Dear Dr Rianda Joubert,

Thank you for submitting the manuscript, "Prescribing and dispensing factors concerning schizophrenia treatment in the South African private health sector during the period 2008-2013" to the South African Medical Journal. With the online journal management system that we are using, you will be able to track its progress through the editorial process by logging in to the journal web site:

Manuscript URL:
http://www.samj.org.za/index.php/samj/author/submission/10167
Username: rianda01

If you have any questions, please contact me. Thank you for considering this journal as a venue for your work.

Kind regards

Professor Janet Seggie
South African Medical Journal

_____

South African Medical Journal
Website: www.samj.org.za
Email: publishing@hmpg.co.za
Twitter: @samj_online
Phone: +27 (0)21 681 7200

ANNEXURE H: MANUSCRIPT 2 SUBMISSION CONFIRMATION

>>> "Health SA Gesondheid" <healthsa@uj.ac.za> 2015/10/06 10:08 AM >>>
Dear Dr. Joubert,

We have received your article "Maximum potential cost-savings attributable to generic substitution of antipsychotics 2008 to 2013" for consideration for publication in Health SA Gesondheid-Journal of Interdisciplinary Health Sciences.

Your manuscript will be given a reference number once an editor has been assigned.

To track the status of your paper, please do the following:

1. Go to this URL: http://ees.elsevier.com/hsag/

2. Log in as an Author

3. Click [Submissions Being Processed]

Thank you for submitting your work to this journal.

Kind regards,

Elsevier Editorial System
Health SA Gesondheid-Journal of Interdisciplinary Health Sciences

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Please note that the editorial process varies considerably from journal to journal. For more information about the submission-to-publication lifecycle, click here:
http://help.elsevier.com/app/answers/detail/p/7923/a_id/160

For further assistance, please visit our customer support site at http://help.elsevier.com/app/answers/list/p/7923. Here you can search for solutions on a range of topics, find answers to frequently asked questions and learn more about EES via interactive tutorials. You will also find our 24/7 support contact details should you need any further assistance from one of our customer support representatives.

ANNEXURE I: LANGUAGE EDITOR'S LETTER

To whom it may concern

Cecile van Zyl Language editing and translation
Cell: 072 389 3450
Email: Cecile.vanZyl@nwu.ac.za

30 September 2015

Dear Mr / Ms

Re: Language editing of dissertation: **Factors associated with the prescribing and dispensing of schizophrenia treatment in the private health sector of South Africa**

I hereby declare that I language edited the above-mentioned dissertation by Ms D Husselmann (student number: 22224904) on 28 September 2015.

Please feel free to contact me should you have any enquiries.

Kind regards

Cecile van Zyl

Language practitioner

BA (PU for CHE); BA honours (PU for CHE); MA (NWU)

ANNEXURE J: ETHICAL APPROVAL LETTER

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
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Private Bag X6001, Potchefstroom
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Tel: 018 299-1111/2222
Web: http://www.nwu.ac.za

Faculty of Health Sciences
Tel: 018-299 2092
Fax: 018-299 2088
Email: Minrie.Greeff@nwu.ac.za

20 May 2015

Dr R Joubert
Pharmacy Practice

Dear Dr Joubert

APPROVAL: ETHICS APPLICATION: NWU-00179-14-A1 (R JOUBERT-D HUSSELMAN) "MEDICINE PRESCRIBING PATTERNS IN A SECTION OF THE PRIVATE HEALTH SECTOR UTILISING DATA FROM A PHARMACEUTICAL BENEFIT MANAGEMENT COMPANY IN SOUTH AFRICA"

Thank you for amending your sub-study application, entitled "Factors associated with prescribing and dispensing of schizophrenia treatment in the private health sector of South Africa". All ethical concerns have now been addressed and ethical approval is granted until 31/07/2017.

Please note that any changes to the approved application must be submitted to the Health Research Ethics Committee for approval before implementation.

Yours sincerely

Prof Minrie Greeff
HREC Chairperson

Current details: (13210572) C:\Users\13210572\Documents\HREC\HREC - Applications\HREC - Applications 01 - 10 February 2015\NWU-00179-14-A1 (R Joubert-D Husselman)\NWU-00179-14-A1 (R Joubert-D Husselman) - Approval letter\NWU-00179-14-A1 (R Joubert-D Husselman) - Approval letter.docm
20 May 2015

File reference: 9.1.5.3