A DRUG UTILISATION REVIEW OF LITHIUM AT A PUBLIC SECTOR PSYCHIATRIC HOSPITAL

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A drug utilisation review of lithium at a public sector psychiatric hospital

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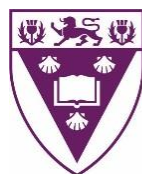
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DECLARATION

I, Charlotte Mapfumo (Rhodes University Student Number G13M5468), hereby declare that all the experimental work, planning, literature search, data capturing and interpretation, as well as writing the initial version of this dissertation was conducted by myself. My supervisor (Prof Johannes Bodenstein) and co-supervisors (Mrs Marisan Bodenstein and Prof Martie S. Lubbe) assisted in the interpretation of the results of the experimental work and proof read the dissertation in preparation for its final version. The work on which this dissertation is based is original (except where acknowledgements indicate otherwise) and that neither the whole work, nor any part thereof, has been or is being submitted for another degree at this or any other university.

_____   _____
Signature   **Date**

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ABSTRACT

A drug utilisation review on lithium at a public sector psychiatric hospital

Key words: Bipolar disorder, drug utilisation review, lithium, narrow therapeutic index, toxicity, therapeutic drug monitoring.

Introduction: Bipolar disorder (BD) is a common mental condition that affects about 60 million people globally. Lithium is among the drugs of choice used to treat BD and other affective disorders such as schizoaffective disorder (SD). Lithium is a mood stabiliser with antimanic, antidepressant and anti-suicidal properties.

Lithium has complex mechanisms of action and a narrow therapeutic index (NTI). Therapeutic drug monitoring (TDM) is a vital component of lithium therapy due to its NTI. Lithium toxicity can occur at therapeutic levels and is characterised by symptoms such as blurred vision and convulsions.

Lithium interacts with a number of drugs resulting in lithium toxicity or diminished effects of lithium. Symptoms of lithium toxicity range from abdominal pain, convulsions and death. Lithium use is associated with serious adverse effects on renal and thyroid function. Other adverse effects include tremor and weight gain. Monitoring of lithium serum levels, renal and thyroid function are therefore recommended for patients on lithium therapy. Monitoring of these parameters assists in the early detection of any problems associated with lithium use.

The metabolic monitoring of lithium is vital due to the adverse effect profile of lithium and the current South African Standard Treatment Guidelines Hospital level: Adults, do not have any recommendations for the monitoring of metabolic parameters. The National Institute for Health and Care Excellence (NICE) may be used and adapted for the South African setting.

Aim and Objectives: The general aim of the study was to conduct a drug utilisation review (DUR) on lithium through investigating its prescribing and monitoring patterns in both inpatients and outpatients at Fort England Hospital.

Methodology: The study was in the form of a retrospective DUR. Data was collected from 40 files (n=40) of patients who were on treatment with lithium between 1 January 2017-31 December 2017 at Fort England Hospital. The data was collected retrospectively for both in- and outpatients. Compliance of the monitoring requirements with both South African and international guidelines was analysed.

Results and Discussion: In 87.50% (n=37) of the cases, patients had been on lithium therapy before 2017 with most patients (n=13; 37.50%) being maintained on 500 mg of lithium. Non-compliance with the South African and NICE guidelines for renal baseline monitoring was 65.00% (n=26) in both guidelines. Non-compliance for baseline thyroid monitoring was 70.00% (n=28) for both guidelines.

There was non-compliance in 45.00% (n=18) of the cases for lithium serum level monitoring for both guidelines. Non-compliance with follow-up renal monitoring was 47.50% (n=19) for both guidelines. Compliance with the NICE guidelines for follow-up metabolic monitoring was 67.50% (n=27).

Conclusion: There was non-compliance in most cases leaving room for clinical improvement in the monitoring of lithium. Healthcare professionals should be educated on the recommended monitoring guidelines to promote the rational use of lithium in South Africa. Pharmacists should be more involved in the TDM of lithium to promote its safe and effective use.

LIST OF ABBREVIATIONS

#

5-HIAAA   5-hydroxyindoleacetic acid

5HT   Serotonin

5HT-1A   Serotonin 1A

5HT-2A   Serotonin 2A

A

AC   Adenylate Cyclase

ACE   Angiotensin Converting Enzymes

ADH   Antidiuretic Hormone

ADR   Adverse Drug Reaction

AIDS   Acquired Immuno Deficiency Syndrome

AIP   Amphetamine Induced Psychosis

AMI   Acute Myocardial Infarction

AMPA   Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid

ANK 3   Ankyrin 3

ARB   Angiotensin Receptor Blockers

ARNTL   Aryl Hydrocarbon Receptor Nuclear Translocator-Like

ATC   Anatomical Therapeutic Chemical

ATP   Adenosine Triphosphate

ATPase   Adenosine Triphosphatase

B

BALANCE   Bipolar Affective disorder: Lithium/Anticonvulsant Evaluation

BAP   British Association of Psychopharmacology

Bcl-2	B-cell lymphoma 2
BD	Bipolar Disorder
BDDCS	Biopharmaceutics Drug Disposition Classification System
BMI	Body Mass Index
BNDF	Brain-Derived Neurotrophic Factor
BNF	British National Formulary
BTS	Bradycardia-Tachycardia Syndrome
BUN	Blood Urea Nitrogen

C

CA1	Cornu Ammonis 1
CACNA1C	Voltage-Dependent L-Type Calcium Channel Subunit Alpha-1C
cAMP	Cyclic Adenosine Monophosphate
CBT	Cognitive Behavioural Therapy
CGI	Clinical Global Impression
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CKD	Chronic Kidney Disease
CLOCK	Circadian Locomotor Output Cycles Kaput
CNS	Central Nervous System
COX	Cyclooxygenase
CREB	cAMP Response Element Binding Protein
CRF	Controlled Release Formulation

D

D_1	Dopamine 1 receptor

D₂   Dopamine 2 receptor

DA   Dopamine

DALY   Disability-Adjusted Life Year

DBSA   Depression and Bipolar Support Alliance

DDD   Defined Daily Dose

DDI   Drug-Drug Interactions

DIP   Drug Induced Psychosis

DISC1   Disrupted in schizophrenia 1

DNA   Deoxyribonucleic Acid

DOPAC   Dihydroxyphenylacetic Acid

DRPs   Drug Related Problems

DSM   Diagnostic and Statistical Manual

DTB   Drugs and Therapeutics Bulletin

DU   Drug Utilisation

DUR   Drug Utilisation Review

E

ECG   Electrocardiogram

ECT   Electroconvulsive Therapy

EEG   Electroencephalogram

eGFR   Estimated Glomerular Filtration Rate

EML   Essential Medicines List

EPSE   Extrapyramidal Adverse effects

ESRD   End Stage Renal Disease

Euro-DURG European Drug Utilisation Research Group

F

FBC   Full Blood Count

FDA   United States Food and Drug Administration

FFT   Family Focused Therapy

FGA   First-generation Antipsychotics

G

GABA   Gamma-Aminobutyric Acid

GFR   Glomerular Filtration Rate

GIT   Gastrointestinal

GSK3   Glycogen Synthase Kinase 3

GSK3α   Glycogen Synthase Kinase 3 Alpha

GSK3β   Glycogen Synthase Kinase 3 Beta

H

H⁺   Hydrogen ion

He   Helium

HHS-FDA   The Department of Human Health: Federal Drug Agency, United States of America

HIV   Human Immunodeficiency Virus

I

ICD   International Classification of Diseases

IMPase   Inositol Monophosphatase

IMSN   Irish Medication Safety Network

IPP-1   Inositol Polyphosphatase 1-Phosphatase

IRF   Immediate Release Formulation

ISBD   International Society for Bipolar Disorders

ISPE   International Society for Pharmacoepidemiology

K

K⁺   Potassium

KIT   Ketamine Induced Psychosis

L

Li⁺   Lithium ion

LIH   Lithium-induced Hyperparathyroidism

LSD   Lysergic Acid Diethylamide

M

MAO   Monoamine Oxidase

MCC   Medicines Control Council

MDD   Major Depressive Disorder

Mg²⁺   Magnesium

MHaPP   Mental Health and Poverty Project

MOA   Mechanism of Action

N

Na⁺   Sodium ion

NAMI   National Alliance on Mental Illness

NAS   Neonatal Adaptation Syndrome

Ndel1   Nuclear Distribution protein nudE-like 1

NDI   Nephrogenic Diabetes Insipidus

NICE   National Institute for Health and Care Excellence

NMDA   N-Methyl-D-aspartate

NMHPFSP   National Mental Health Policy Framework and Strategic Plan

NMR   Nuclear Magnetic Resonance

NMS   Neuroleptic Malignant Syndrome

NR1D1   Nuclear Receptor Subfamily 1, Group D, Member 1

NTI   Narrow Therapeutic Index

NSAIDs   Non-Steroidal Anti-Inflammatory Drugs

P

PCP   Phencyclidine

PDE4B   Phosphodiesterase 4B

PIP   Phencyclidine Induced Psychosis

PKA   Protein Kinase A

R

RDC   Research Diagnostic Criteria

RNA   Ribonucleic acid

S

SAHPRA   South African Health Products Regulatory Authority

SAS   Statistical Analysis System

SASH   South African Stress and Health

SASOP   South African Society of Psychiatrists

SCD   Sudden Cardiac Death

SD   Schizoaffective Disorder

SDV   Standard Deviation

SGA   Second Generation Antipsychotics

SPC   Summary of Product Characteristics

SRF	Sustained Release Formulations
SRT	Social Rhythm Therapy
SSRI	Selective Serotonin Reuptake Inhibitor
SS	Serotonin Syndrome
SSS	Sick Sinus Syndrome
SST	Social Skills Training
STGs	Standard Treatment Guidelines
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

T

T_3	Tri-iodothyronine
T_4	Thyroxine
TDM	Therapeutic Drug Monitoring
THC	Tetrahydrocannabinol
TPO	Thyroperoxidase
TRD	Treatment Resistant Depression
TRH	Thyrotropin-releasing Hormone
TSH	Thyroid Stimulating Hormone

W

WHO	World Health Organization
WHODURG	WHO European Drug Utilization Research Group
Wnt	Wingless/Integrated

LIST OF DEFINITIONS

Agoraphobia: Agoraphobia is defined as the morbid fear of being in public and or in open spaces (Oxford University, 2015:16).

Arrhythmia: This is defined by the Oxford medical dictionary as any deviation from the normal rhythm of the heart. Arrhythmias may be a result of disturbances in the generation or conduction of impulses generated by the sinoatrial node (Oxford University, 2015:81).

Ataxia: Shaky movements and unsteady gait resulting from the brains failure to regulate the body's posture and strength and direction of limb movements (Oxford University, 2015:59). Ataxia can be a result of disorders involving the cerebellum, spinal cord, brain stem cerebral white matter and peripheral sensory nerves (Brunberg, 2008:1420).

Akathisia: Defined as "*a movement disorder characterised by subjective feelings of internal restlessness or jitteriness with a compelling urge to move leading to the observation of repetitive movements, such as leg crossing, swinging or persistent shifting from one foot to another*" (Salem *et al.*, 2017:789).

Bipolar disorder (BD): Bipolar disorder is a manic-depressive illness that affects about 1% of the population. This severe mental disorder causes repeated unusual shifts in mood, energy, activity and diminished ability to perform daily tasks. Mood episodes occur during BD and may include symptoms of both manic and depressive episodes (Oxford University, 2015:87).

Bradycardia: A condition where the heart rate is slower than 50 beats per minute (Williams *et al.*, 2012:210)**.**

Bradycardia-tachycardia syndrome (BTS): A complication of sick sinus syndrome characterised by bradycardia and tachycardia (Tse *et al.*, 2017:519).

Brugada syndrome: Brugada syndrome is an inherited cardiac life threatening problem that causes increased risk for sudden cardiac death (SCD) and ST-segment elevation in the electrocardiogram (ECG) (Sieira & Brugada, 2017:3029).

Cardiac syncope: Syncope is a syndrome characterised by brief self-limited episodes of loss of consciousness occurring as a result of a transient interruption of oxygen supply to the brain. Cardiac syncope is primarily caused by arrhythmias (Puppala *et al.*, 2014:172).

Catalepsy: This is described as the passive adoption of a posture and is usually a symptom of catatonia (Wilcox & Reid Duffy, 2015:578).

Cirrhosis: This is the end stage of any condition in which the liver becomes progressively scarred (Punnoose, 2012:874).

Cystic fibrosis: Cystic fibrosis is an autosomal recessive disorder characterised by abnormally viscous secretions in the lungs and ducts of the pancreas causing inflammation, tissue damage and the destruction of both organ systems (Cutting, 2015:45).

Depression: Also known as major depressive disorder, is a mental disorder that negatively affects thinking and feelings. Depression is typically characterised by feelings of sadness, suicidal ideation, loss of enthusiasm, loss of self-worth, feeling guilty and challenges in thinking, concentrating or making decisions. These symptoms should last for a minimum period of two weeks in order for it to be diagnosed as depression (American Psychiatric Association, 2017).

Drug utilisation review (DUR): Defined by the World Health Organization as "*the marketing, distribution, prescription and use of drugs in a society with special emphasis on the resulting economic, medical and social consequences*" (Sachdeva & Patel, 2010:11).

Dystonia: This is a diverse movement disorder that is characterised by involuntary muscle contractions (Sadnicka et al., 2018:1).

Ebstein anomaly: A rare congenital heart disorder characterised by malformation of the tricuspid valve and right ventricle (Healy *et al.*, 2015:368).

Echolalia: This a condition characterised by the repetition of words or utterances spoken by another individual and is common in people with autism (Berthier *et al.*, 2017:1).

Echopraxia: A condition where a patient spontaneously copies the examiner's movements or is unable to refrain from copying the examiner's test movements, despite instruction to the contrary (Enterman & Van Dijk, 2011:236).

Folliculitis: This is the inflammation of a hair follicle clinically characterised by a pustule with a hair at the centre and commonly caused by bacteria (Bachet *et al*., 2012:556).

Glomerulosclerosis: A condition characterised by scarring of the glomeruli that affects part of the glomerular tuft (Oxford University, 2015:285).

Hyperkalaemia: This is a life threatening electrolyte disturbance characterised by increased extracellular potassium concentrations (Montford & Linas, 2017:3155).

Hyperthermia: Exceptionally high body temperature above 41°C or a therapeutic procedure of raising the body or an organ to temperatures up to 45°C to treat a cancer (Rybiński *et al*., 2013:1).

Hyperprolactinaemia: This is a condition of elevated prolactin levels in blood which could be of physiological, pathological, or idiopathic origin (Majumdar & Mangal, 2013:168).

Interstitial nephritis: This is a condition affecting the kidneys characterised by the presence of infiltrates and swelling (oedema) in between the interstitium. It is associated with acute renal injury (Praga & Gonzalez, 2010:956).

Leucocytosis: Leucocytosis is an elevated white blood cell count based on the patients age e.g. a white blood cell count of 30×10^9/L is completely normal in the first days of life but elevated in adults (George, 2012:475).

Mania: This is an abnormally elated mental state with euphoric mood and that can easily change to irritability. It is characterised by lack of sleep, being talkative, feelings of self-importance, racing thoughts and inflated self-esteem. Mania usually occurs as a symptom of BD (Oxford University, 2015:493).

Myocarditis: Defined as the inflammation of the heart muscle which can be caused by viruses. It can be identified clinically or using histopathologic criteria (Schultz *et al.*, 2009:1001).

Myoclonus: A sudden, brief involuntary muscle jerk (Kojovic *et al.*, 2011:47).

Natriuresis: The excretion of an excessively large amount of sodium in the urine (Oxford University, 2015:488).

Nephrogenic diabetes insipidus (NDI): A clinical syndrome characterised by impaired arginine vasopressin- induced water reabsorption. NDI is acquired and occurs as a complication of medication treatment (e.g. lithium) and conditions such as electrolyte imbalances (Moeller *et al.*, 2013:283).

Neuroleptic Malignant Syndrome (NMS): This is a severe disorder caused by an adverse reaction to medications with dopamine receptor antagonist properties or the rapid withdrawal of dopaminergic medications (Berman, 2011:41).

Nystagmus: This is the involuntary rhythmic oscillation of the eyes that can be easily observed by direct observation of eye movements (Papageorgiou *et al.*, 2014:342).

Oedema: Oedema occurs when fluid builds up in the tissues and may be local or generalised. Oedema is frequently a result of harmless conditions but can occasionally be caused by more serious underlying health problems (Evans & Ratchford, 2016:562).

Pharmacovigilance: Pharmacovigilance is the activities and science involved in the detection, assessment, understanding and prevention of any drug-related problems or adverse effects (Langlitz, 2009:396).

Polydipsia: Excessive thirst as a symptom of disease or psychological disturbance resulting in consumption of more than 3 litres of water a day (Adam & Sunil, 2013:6672).

Polyuria: Defined as the daily urine output in excess of 3.0 to 3.5 litres a day that occurs as a result of solute or water diuresis (Bhasin & Velez, 2016:507).

Pyelonephritis: This is a condition characterised by bacterial and fungal infection of the parenchyma tissue and collecting system (Venkatesh & Hanumegowda, 2017:15).

Retrospective drug utilisation review: A study that reviews drug therapy after its administration to a patient. Patient charts or computerised records are screened in order to determine if drug therapy was successful or not. It detects patterns in prescribing, dispensing and administration of drugs to avoid abuse or misuse of drugs. This type of review serves as a means of developing target interventions and prospective standards (Town, 2014:1).

Sick sinus syndrome (SSS): A variety of cardiac arrhythmias that occur predominantly in elderly people as a result of a senescent sinus node. SSS is characterised by sinus node malfunction and inappropriate tachycardia and bradycardia (Ewy, 2014:539).

Tachycardia: Is conventionally defined as an atrial and/or ventricular rate greater than 100 beats per minute (bpm) (Gopinathannair & Olshansky, 2015:3).

Tardive dyskinesia: This is a neurological disorder that results in repetitive, involuntary movements such as abnormal tongue and lip movements, foot tapping, shoulder shrugging and swaying movements. It is usually a result of antipsychotic use for treating schizophrenia, BD and other mental conditions (Voelker, 2017:1942).

Tinnitus: Tinnitus is the sensation of sounds commonly called "ringing of the ears" associated with hearing impairment (Roberts *et al.*, 2010:14972).

Tubular atrophy: Tubular atrophy is defined by the presence of tubular epithelial thinning, tubular dilation, with or without protein casts. Tubular atrophy is significantly associated with serum creatinine, creatinine clearance and the ability to concentrate and acidify urine (Schelling, 2017:6772).

Ventricular fibrillation (VF): This is a life-threatening cardiac arrhythmia in which the coordinated contraction of the ventricular myocardium is replaced by high-frequency, disorganised excitation that results in failure of the heart to pump blood (Goyal, 2018).

Waxy flexibility: This is described as resistance to being moved and is a common symptom of catatonia (Wilcox & Reid Duffy, 2015:578).

Wilson's disease: This is an autosomal recessive disorder caused by abnormal copper metabolism. This then results in the accumulation of copper in target organs thus impairing their normal functioning. It is also known as hepatolenticular degeneration (Wu *et al.*, 2015:6420).

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CHAPTER 1.
INTRODUCTION AND PROBLEM STATEMENT

1.1 Introduction

Mental health is defined as "*a state of well-being where one can cope with the normal stresses that life presents and has the ability of realising their personal potential*" (WHO, 2014a). Mental health also involves the capability to work productively and make a meaningful contribution to the community (WHO, 2014a). Bipolar disorder (BD) is a mental disorder that affects about 60 million people worldwide (WHO, 2017b).

A study that offers assessments of the utilisation and effects of drugs in people will be conducted. It takes into account the demographic characteristics and health status within the general population. Analysis of prescribing patterns, determinants and implementation of data form part of this study. The description and analysis of drugs, economics and recommendations to healthcare professionals are all aspects that are inclusive of this type of study (Evans, 2012:974).

This study is a descriptive cross-sectional drug utilisation review (DUR) on the use of lithium in BD and other affective disorders at a public sector psychiatric hospital. The prescribing and monitoring patterns of lithium were analysed. The common adverse effects associated with the use of lithium were investigated. Other factors such as comorbid disease states and frequency of lithium toxicity were assessed. The recommended monitoring guidelines for patients on lithium therapy were evaluated against the current practices.

This chapter will provide an overview of the study background, problem statement, aim, research objectives, methodology and dissertation layout.

1.2 Research background

Mental health is as vital as physical health in contributing to the wellbeing of individuals. About 450 million people suffer from mental conditions worldwide and only a minority of these individuals receive treatment (WHO, 2014a). Mental and behavioural disorders result from interaction of biological, psychological and social factors as seen from advances in neuroscience (WHO, 2014a).

According to the Mental Health and Poverty Project (MHaPP) at the Department of Psychiatry and Mental Health at the University of Cape Town, psychiatric conditions

are third after HIV and AIDS, in contributing to the burden of diseases in South Africa. In 2006, 16.50% of the South African population suffered from mental conditions such as depression and anxiety (The South African Depression and Anxiety Group, 2009).

The South African Stress and Health (SASH) study was the first study that focused on mental illnesses in the country on a large scale population base. Results from the study showed that major depressive disorder (MDD) was one of the most prevalent lifetime disorders with a prevalence of 9.80% (Herman *et al.*, 2009:341).

The research focuses on the prescribing, dispensing and monitoring patterns of lithium. According to the South African Health Products Regulatory Authority (SAHPRA) formerly known as the Medicines Control Council (MCC), lithium is a schedule 5 (S5) medicine (Osman, 2015:MAE140). In South Africa, lithium is indicated for the following conditions (Department of Health, 2015:15.1; Rossiter, 2016:484):

- Treatment of BD.
- Prophylaxis of manic and hypomanic episodes.
- Treatment of acute manic and hypomanic episodes.
- Augmentation of antidepressants in the treatment of resistant or recurrent (unipolar) depression.
- Treatment of aggressive or self-mutilating behaviour.

Lithium is a monovalent cation that was discovered in 1817 by Johan August Arfwedson. The name lithium is derived from the Greek word "lithos" which translates to "stone" as it is unlike most alkali metals that were discovered from plant material. Lithium was discovered from a mineral (Oruch *et al.*, 2014:465).

The use of lithium to treat BD took many years to be implemented after its discovery in the treatment of mania and depression. The effectiveness of lithium in the treatment of BD was established after careful consideration of the blood concentration and dosages. The Food and Drug Administration (FDA) approved its use to treat mania in 1970 (Johnson, 1984:2).

One of the common complications associated with lithium use is acute lithium toxicity. This is more common in patients that are on chronic lithium therapy. Lithium toxicity remains prevalent due to its narrow therapeutic index (NTI). Some of the methods

recommended for lithium removal by the kidneys include bicarbonate, as well as continuous arteriovenous and peritoneal dialysis. However, haemodialysis remains the basis for the treatment of acute lithium toxicity (Okusa & Jovita, 1994:383).

- International clinical guidelines exist for the treatment of mental disorders. The Irish Medication Safety Network (IMSN) and the National Institute for Health and Care Excellence (NICE) formerly known as the National Institute for Health and Clinical Excellence (NICE) are some institutions that have best guidelines for the monitoring and prescribing of lithium therapy (Collins *et al.*, 2010:1; Irish Medication Safety Network, 2012). The Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) for adults at hospital level in South Africa provide the relevant doses to be prescribed and the monitoring that is required for patients on lithium therapy (Department of Health, 2015:15.3). The South African Medicines Formulary (SAMF) also contains monitoring guidelines for patients on lithium therapy. Although the SAMF provides information on the prescribing and monitoring requirements of different drugs, it was not utilised in the study as it is a medicines formulary rather than a treatment guideline.

Lithium is available for medicinal use as lithium carbonate immediate release formulations (IRFs) in South Africa (Rossiter, 2016:484). It is also available internationally as prolonged release (PRF) formulations that potentially have advantages over IR formulations and lesser adverse effects (Girardi *et al.*, 2016:295).

1.3 Problem statement

BD affects about 60 million people globally and is characterised by both manic and depressive phases that are separated by a normal mood (WHO, 2017a). The manic phases of BD include symptoms such as increased self-esteem, reduced sleep, over activity and elevated mood. People who only experience manic episodes are classified as having BD. There is effective treatment that is used to alleviate the symptoms of BD and prevent relapse. These drugs are called mood stabilisers (WHO, 2017b).

Lithium is the drug of choice to treat BD. It is regarded as a mood stabiliser, anti-manic drug, a suicidal protector and an antidepressant (Stafford, 2011:25). Lithium has a NTI which means that the difference between therapeutic and toxic doses is small (Blix *et al.*, 2010:50).

Lithium has a recommended therapeutic range of 0.8-1.2 mmol/L and a steady state maintenance concentration of 0.6-1.0 mmol/L (Rossiter, 2016:485). Lithium toxicity is common and occurs when lithium levels rise above 1.5 mmol/L. Therefore, it is vital to monitor lithium levels and adjust lithium doses as necessary (Gitlin, 2016:6).

Lithium has many drug related problems (DRPs) as a result of its NTI. DRPs are associated with increased mortality, health costs and morbidity (Hege *et al.,* 2010:52). There are monitoring tests that should be conducted before initiating lithium therapy and during the course of treatment. Some of these tests include thyroid function and renal function tests (Rossiter, 2016:484).

Therapeutic drug monitoring (TDM) is necessary for patients on lithium. However, lithium can become more toxic when combined with certain drugs such as angiotensin converting enzyme (ACE) inhibitors, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs). As a result, the patient's medical history in terms of other drugs then becomes important to ensure efficacy of lithium and prevention of toxicity (Department of Health, 2015:15.3; Rossiter, 2016:484).

Certain parameters need to be considered when it comes to lithium toxicity. Drug interactions, drug-disease interactions, contraindications, cautions and adverse effects should be considered when conducting TDM for lithium. The age and weight of the patient are critical as lithium dosing is dependent on the weight (Rossiter, 2016:485).

There is a need to improve TDM utilisation for lithium therapy as many studies have shown that TDM for lithium is very low despite it being strongly recommended by guidelines. Warnings and interventions at hospital or national level may be useful in improving TDM. Risk communication, which involves the direct communication between the pharmacist and doctor, can improve TDM. Reports have shown that pharmacist interventions have resulted in improved TDM of lithium (Ooba *et al.*, 2018:255).

This study was an observational pharmacoepidemiological investigation of the descriptive, cross-sectional (coupled to a period in terms of the patient files and

prescriptions) type. Data on the prescribing and monitoring of lithium was retrospectively analysed.

1.4 Motivation for conducting the study

According to the World Health Organization (WHO), there is a global inequity in the distribution of skilled human resources for mental health. One of the barriers that exist in low and middle income countries is the shortage of psychiatrists, psychiatric nurses, psychologists, pharmacists and social workers to assist with the treatment and care of mental patients. Low income countries have 0.05 psychiatrists and 0.42 nurse per 100 000 people. High income countries have 170 and 70 times more psychiatrists and nurses respectively (WHO, 2014b). South Africa is considered an upper-middle income country according to the classification by the World Bank and therefore has a shortage of psychiatric health care professionals (World Bank, 2018).

South Africa carries a huge burden of mental illnesses with depression, anxiety disorders, substance abuse disorders and mood disorders being the most prevalent. Most people with mental disorders face neglect in the healthcare system including discrimination and stigma which has resulted in higher suicide rates, isolation and poor health outcomes. The South African government adopted the National Mental Health Policy Framework and Strategic Plan (NMHPFSP) 2013-2020 in 2013. This was in an effort to integrate mental health into the health system and reduce the mental health treatment gap and burden. The NMHPFSP has specific recommendations for the monitoring and evaluation n of psychotropic medication and drug interactions in the treatment of mental disorders. This therefore underscores the importance of the study as lithium has a NTI and a severe toxicity profile (Department of Health, 2013:19).

The therapeutic and toxic blood levels of lithium do not differ greatly therefore the patients should be monitored closely. TDM is a clinically important aspect of the safety and efficacy of lithium therapy. The Standard Treatment Guidelines (STGs) for hospital adult level recommend that lithium is the drug of choice in treating BD (Department of Health, 2015:15.2).

There are strict guidelines for the monitoring of lithium parameters both internationally and nationally. The NICE in the UK recommends that renal and thyroid function must be tested before initiation of lithium therapy. On-going checks of renal and thyroid

function as well as serum lithium levels must be performed (National Institute of Health and Care Excellence, 2014).

The STGs of South Africa for adults at hospital level and SAMF recommend that thyroid stimulating hormone (TSH) tests be conducted to check for hypothyroidism as well as serum calcium levels to check for hyperparathyroidism. These tests must be conducted before therapy initiation and annually thereafter. Renal function, thyroid function and electrolyte levels must be monitored regularly (Department of Health, 2015:15.3; Rossiter, 2016:484).

Clinical toxicity of lithium may occur even within the therapeutic range of lithium. As a result, patients are more susceptible to suffering from the adverse effects associated with lithium use (Rossiter, 2016:484).

Lithium toxicity is common due to its NTI. Lithium toxicity can be classified as acute, acute-on-chronic and chronic toxicity. Acute toxicity involves a small tissue body burden and therefore symptoms are mild. Acute-on-chronic toxicity occurs in patients that regularly take lithium and have ingested a high dose recently. As a result, the adverse effect profile is more severe. In chronic toxicity, the tissue body burden is significantly high and much more difficult to treat (Haussmann *et al.*, 2015:23).

The adverse effects associated with lithium toxicity are summarised in Table 1-1 (Haussmann *et al.*, 2015:24).

Table 1-1. Adverse effects of lithium toxicity (Haussmann *et al.*, 2015:24).

Classification		**Adverse Effects**
Acute toxicity	Gastrointestinal	Nausea, vomiting, cramping and diarrhoea.
	Neurological	Tremor, dystonia and ataxia.
	Cardiac	Cardiac arrhythmias and T wave flattening.
Acute-on-toxicity	Gastrointestinal	Stomach cramps, diarrhoea and vomiting.
	Neurological	Muscle twitches, slurred speech and seizures.
	Cardiac	Cardiac arrhythmias and T wave flattening.
Chronic toxicity	Neurological	Coma, seizures and convulsions.

Regular monitoring of lithium serum levels, renal and thyroid function and electrolyte levels is important to ensure patient safety. Conducting these tests regularly will assist with the early detection of adverse effects associated with the use of lithium. Monitoring renal and thyroid function is important as the plasma serum levels of lithium are dependent on renal function. Lithium potentially interferes with renal and thyroid function and tests become imperative (National Patient Safety Agency, 2009).

The chemical pathology monitoring requirements of lithium therapy are outlined in Table 1-2 (Rossiter 2016:485; Department of Health 2015:15.2; Katzung 2012:516).

Table 1-2. Chemical pathology monitoring requirements of lithium (Rossiter 2016:485; Department of Health 2015:15.2; Katzung 2012:516).

Classification	Interval
Renal tests (estimated glomerular filtration rate, blood urea nitrogen (BUN), urea, creatinine clearance)	Before initiation, 6 monthly then 12 monthly
Thyroid tests (Thyroid stimulating hormone, TSH)	Before initiation, 6 monthly then 12 monthly
Cardiac tests	An electrocardiogram (ECG) should be performed (if there is a history of cardiac conditions)
Serum lithium levels	Trough levels after 5 days Target dose: 0.6-1.0mmol/L After dose increment: 5 days or 1 week, then after 1 month, then 3 months, then six-monthly during maintenance therapy
Haematology	Full blood count (FBC) must be conducted (if indicated before therapy initiation)
Electrolytes, e.g. sodium and calcium	Before initiation, then annually

There are some metabolic monitoring requirements for patients on lithium therapy. Bipolar patients are at a greater risk of developing more physical co-morbidities and mortality than the general population. Therefore it is important to monitor weight gain

as lithium is known to increase weight (National Institute of Health and Care Excellence, 2014).

The metabolic parameters that require monitoring are outlined in Table 1-3. Metabolic monitoring requirements of lithium (Irish Medication Safety Network, 2012:8).(Irish Medication Safety Network, 2012:8).

Table 1-3. Metabolic monitoring requirements of lithium (Irish Medication Safety Network, 2012:8).

Classification	Interval
Weight	Before initiation, after one month, after three months, after 6 months then annually
Body Mass Index (BMI)	Before initiation, after one month, after three months, after 6 months then annually
Blood pressure	Monthly
Pulse	Monthly

Patients with BD have a life expectancy that is reduced by 11 to 20 years. This conclusion was based on data gathered from patients that are 15 years of age. However, this could be misleading as most bipolar patients have a late onset of illness (Kessing *et al*., 2015:543).

A study conducted showed that there is greater reduction in life expectancy in men than women. Women showed a reduced life expectancy of between 8.3 to 10.6 years while men showed a reduction between 8.7 to 12 years (News Medical Life Sciences, 2015). 15-year-old female and male bipolar patients had a reduced life expectancy of 10.4 and 12.8 years respectively. In general, the life expectancy of bipolar patients decreases with age (News Medical Life Sciences, 2015).

Physical health of patients that suffer from mental illnesses is important even though it remains a challenge. Inadequate monitoring of patients by healthcare professionals often contributes to the physical health challenges associated with mental illnesses. It is important that these patients are given special care so as to improve their quality of

life. There should be increased screening for patients such as the older underweight males as they are more prone to respiratory infections (Krüger, 2012:176).

The toxicity of lithium and its adverse effects are critical motivation for the study. A pharmacoepidemiological investigation on the prescribing, dispensing, toxicity and monitoring patterns of lithium was performed in a public sector psychiatric hospital. Assessment of the safe and effective use of lithium is the motivation for this research project.

1.5 Study questions

This research project was designed to address the following research questions:

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

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

1.6 Primary aim and research objectives

The general aim of this study was to conduct a DUR on the psycholeptic drug lithium, through investigating its prescribing and monitoring patterns in both inpatients and outpatients at a public sector psychiatric hospital in Grahamstown (Cacadu District Municipality, Makana Local Municipality, Eastern Cape Province, South Africa).

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

1.6.1 Specific objectives of the literature study

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

- To describe psychiatric disorders in general and their prevalence in South Africa.
- To discuss the pathophysiology of BD and other affective disorders in general.
- To determine the medicine treatment guidelines of schizoaffective disorder (SD) and specifically BD.
- To describe the history of the development of lithium.
- To discuss the pharmacological properties of lithium (pharmacokinetics and pharmacodynamics) and compare it to other psycholeptics.
- To discuss the toxicological properties of lithium (adverse effects, interactions, safety in pregnancy and lactation, use in specific patient populations) and compare it to other psycholeptics.
- To determine what constitutes a DUR and discuss the components thereof.
- To discuss DURs on psycholeptics in general and specifically on lithium in the public and private sectors, locally and internationally.
- To conceptualise the most appropriate parameters to conduct a DUR on lithium by investigating patient files.
- To explain statistical terminologies that will be used to analyse the data obtained from the empirical study.

1.6.2 Specific objectives of the empirical investigation

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

- To determine the prescribing patterns of lithium and compliance with the recommended treatment guidelines which are the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) of South Africa hospital level adults and the National Institute of Health and Care Excellence (NICE) international guidelines.
- Pharmacovigilance: To identify medication problems (interactions and adverse effects) associated with the use of lithium, with the emphasis on its NTI.

1.7 Justification for study

Currently there is no data regarding the treatment of BD or other affective disorders with lithium in a public sector hospital in South Africa, so the findings of the research project may add new knowledge to the field.

1.8 Research methodology

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

1.8.1 Literature review

The literature and research articles (books, review and research journal articles, websites and dissertations) that were included in the literature survey were selected through a comprehensive Internet search.

Appropriate data bases such as Google Scholar, PubMed, Science Direct, EBSCO. Publication Finder and OPAC (The Online Catalogue) with emphasis on medical and psychiatric journals were utilised.

The following key words or combinations thereof were used in the Internet search to identify the literature related to the research objectives of the study:

- "Psychiatric disorders".
- "Definition of bipolar and schizoaffective disorders".
- "Pathophysiology of bipolar and schizoaffective disorders".
- "Hypotheses of bipolar and schizoaffective disorders".
- "Treatment of bipolar and schizoaffective disorders".
- "Bipolar affective disorder".
- "Lithium".
- "History of lithium".
- "Pharmacology of lithium".
- "Toxicology of lithium".
- "Drug utilisation review".
- "Pharmacovigilance".
- "Prescribing and monitoring patterns".

- "Public health sector".
- "Makana local municipality".
- "Cacadu district municipality".
- "Eastern Cape province".
- "Private health sector".
- "Descriptive statistics".
- "Inferential statistics".

The most appropriate and current literature was used to answer the research questions.

1.8.2 Empirical investigation

The empirical investigation will be discussed under the headings of study design, study setting, target and study population, data source and data analysis. Ethical considerations for the study are discussed separately in more detail.

1.8.2.1 Study design

A descriptive, cross-sectional research approach on lithium was applied to analyse the retrospective data obtained from a structured data collection form. Cross-sectional research can be categorised as exploratory or descriptive with a descriptive design being the most dependable. Correlations among variables in a data set can be detected and periodic data can be analysed in a cross-sectional research study (Neuman, 2014:38).

Existing difficulties in prescribing, validation of current practices, development of theories and determination of how others are practising can be identified in a descriptive research design (Grove & Gray, 2018:31). Lithium prescribing and monitoring patterns are examples of variables that can be determined in a descriptive study. Retrospective data was collected from the documented data from patient files using the data collection form.

1.8.2.2 Study setting

The research was conducted at Fort England Hospital in Grahamstown. It was the first mental health hospital in South Africa established in 1875. Fort England Hospital is a

tertiary specialist psychiatric hospital with 313 beds and various healthcare teams that care for both inpatients and outpatients.

1.8.2.3 Study population

The study population consisted of in- and outpatients older than 18 years and who were on treatment with lithium between 1 January 2017-31 December 2017 at Fort England Hospital.

1.8.2.4 Data source

The data source was clinical information from the patient files.

1.8.2.5 Data collection

Data was collected retrospectively using data collection forms. Patient information obtained from the patient files at Fort England Hospital was recorded onto the data collection forms. The primary investigator of the study collected data from the patients' files.

1.8.2.6 Study variables

Age, gender, race and family history were some of the study variables included in the study.

1.8.2.7 Study measurements

Study measurements investigated in the study included diagnosis, co-morbid disease states and compliance with the monitoring requirements of lithium.

1.8.2.8 Data analysis

The data recorded on the data collection forms was captured in a spreadsheet using the Microsoft Office Excel® 2016. Frequency tables were prepared and the percentages, averages and standard deviations (SDV) calculated. The Statistical Analysis System® (SAS Institute Inc.) software was used to analyse the data. The chi square test, probability values and Cramér's V value were calculated where comparisons of parameters were made.

1.8.2.9 Ethical considerations

Approval to conduct the study was granted by the Rhodes University Faculty of Pharmacy Higher Degrees Committee, the Rhodes University Faculty of Pharmacy Ethics Committee **(PHARM-2018-06)**, the Fort England Hospital Research Committee **(PHARM-2018-06)** as well as the Eastern Cape Department of Health Research Committee **(EC_201808_008)**. The nature of the research collection was discreet and non-invasive. Ethical standards were applied at all times during the study, inclusive of the conceptualisation, research and development phase, implementation and data collection phase as well as analysis of the results.

1.9 Dissertation layout

- **Chapter 2** serves as a literature review. Lithium characteristics and background of lithium use are identified. The clinical indications, mechanism of action and adverse effects of lithium are reported. The aetiology of BD and the types of the BD that exist are outlined. A DUR is described and the types discussed.
- **Chapter 3** outlines the methods employed to collect data for the research. The research design is stated in this chapter. The methods of data collection, analysis and interpretation of results are outlined. The ethical considerations involved with this DUR study are discussed.
- **Chapter 4** focuses on the results that were obtained in the study. The relevant discussions of the results obtained from the study are included.
- **Chapter 5** lists the recommendations and therapeutic interventions suggested after analysis of the results obtained. The limitations of the research are clearly stated and it is the concluding and final chapter of this dissertation.
- All sources used to obtain information used in this dissertation are documented in the **References** section. References in the Harvard style were used with the assistance of Mendeley reference manager software (Mendeley Ltd) and listed in-between the last chapter and the annexures.
- Other information such as the data collection forms used and ethical approval letters obtained are documented in the **Annexures** section.

1.10 Chapter 1 summary

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

CHAPTER 2.
LITERATURE REVIEW

2.1 History of lithium

Mania and depression were thought to be caused by urate imbalances, hence the discovery of lithium carbonate to dissolve the urate crystals (Johnson, 1984:5). In 1871 lithium was used to treat mania, followed by its use in the treatment of depression in 1886 (Johnson, 1984:5). The Australian psychiatrist John Cade started using lithium to treat mania in 1948 after the adverse effects of the drug had become apparent. He injected guinea pigs with lithium urate which resulted in the pigs becoming placid and tranquilised. This then led him to the conclusion that the calming effect was from the lithium and not the urate (Johnson, 1984:5).

In 1952, Erik Strömgren, the head of the Aarhus University psychiatric clinic in Risskov, began the breakthrough in lithium treatment for mania and prophylaxis of manic-depressive illness. Strömgren had read the Cade article and suggested to Mogens Schou who was a psychiatrist at the hospital that he would undertake a randomly controlled trial of lithium in mania. Random controls were newly introduced in psychiatric drug trials in those years. The flip of a coin was used by Schou to randomize the mania patients with lithium or placebo. The results were then published in 1954. Schou concluded that lithium therapy is a useful alternative to electroconvulsive therapy (ECT), since many patients could be kept in a normal state by administration of a maintenance dose of lithium (Schou *et al.*, 1954:255-257).

In another study, 205 patients that were diagnosed with manic-depressive illness were treated with lithium carbonate or placebo for two years. Results showed that lithium was more effective in preventing relapse when compared to the placebo. The difference in treatment outcomes between lithium carbonate and the placebo was due to lower incidences of manic relapses on lithium carbonate. Depressive relapses also reduced significantly in patients that were on lithium when compared to the placebo. Therefore, it was concluded that lithium is safe and effective for use in the prevention of relapse of manic-depressive illnesses (Prien *et al.*, 1973:337).

The use of lithium to treat bipolar disorder (BD) took many years to be implemented after its discovery in the treatment of mania and depression. This was because according to Cade, the discovery was made by an unknown psychiatrist with no research training while working in a chronic hospital using primitive techniques and

negligible equipment. The effectiveness of lithium in the treatment of BD was established after careful consideration of the blood concentration and dosages. The Food and Drug Administration (FDA) approved its use to treat mania in 1970 (Johnson, 1984:2).

2.2 Physicochemical properties of lithium

2.2.1 Description of lithium

The lithium salt, lithium carbonate has a chemical formula of Li_2CO_3. It is a white or almost white powder that is sparingly soluble in water (British Pharmacopoeia, 2018).

2.2.2 Structure of lithium carbonate

The structure of lithium carbonate is depicted in Figure 2–1 below.
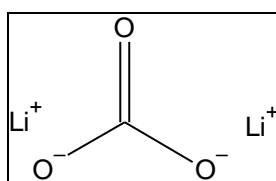
Figure 2–2. The chemical structure of lithium carbonate.

2.2.3 Periodicity

Lithium (Li) is in group one and period three of the periodic table, following hydrogen (H) and helium (He). It has an atomic number of three and is the lightest solid element with a small atomic radius (Wietelmann & Klett, 2018:194).

2.2.4 Biopharmaceutics drug disposition classification system

Lithium carbonate is a class III drug according to the Wu and Benet biopharmaceutics drug disposition classification system (BDDCS). This classification system suggests a strong association between the extent of metabolism and permeability rate of the intestines. Lithium has high solubility and a poor metabolism. High solubility drugs are those that are soluble in 250 ml of water at the highest marketed dose strength over a pH range of 1-7.5 at 37 °C. Class II drugs have poor permeability and therefore uptake transporters are important for intestinal absorption (Benet *et al.*, 2011:519-522).

2.3 Clinical pharmacology

2.3.1 Clinical indications

Lithium is a United States Food and Drug Administration (FDA)-approved drug for use as a mood stabiliser (Oruch *et al.,* 2014:466). Therefore, lithium is used to treat BD, mania and depression. Lithium is also used to augment other antidepressants for the treatment of resistant depression (Rossiter, 2016:484). Lithium decreases the risk of suicide or suicide attempts among patients with affective disorders over the long term course (Lewitzka *et al.*, 2015:14). Table 2-1 summarises the clinical indications for lithium in psychotic disorders (Malhi *et al.*, 2013:19).

Table 2-1. Lithium use in psychotic disorders (Malhi *et al.*, 2013:19).

Indication	Use of lithium
BD	
Acute mania	- First line option is lithium monotherapy - Onset of antimanic action is between 6-10 days - Usually used in combination with benzodiazepines or neuroleptics in practice to achieve a rapid effect
Acute Depression	- Lithium monotherapy is not as effective - Onset of antidepressant effect is between 6-8 weeks - Lithium is used often to augment antidepressant or mood stabiliser therapy
Prophylaxis/maintenance	- Neuroleptics and anticonvulsant are less effective in treating BD when compared to lithium - Outcome of therapy is better when initiated early
Rapid cycling/mixed states	Lithium reduces morbidity and severity of symptoms

Indication	Use of lithium
	• Remission of symptoms and recovery is less likely
Major depression	
Acute episode	• Lithium monotherapy rarely used though effective • Patients with BD family history have greater chances of efficacy
Chronic/treatment resistant	• Lithium used as an augmentation strategy • Prescribed adjunctively with treatment modalities • Effective when used in combination with other antidepressants

2.3.2 Route of administration

In South Africa, lithium is available as an oral dosage form in the form of tablets. The trade name of the lithium carbonate available in South Africa is Camcolit® and Quilonum® (Rossiter, 2016:485). Lithium is also available internationally as lithium capsules or liquid (Roxane Laboratories, 2011:1).

2.3.3 Pharmacological class

Lithium is considered an antimanic, mood stabiliser and antidepressant (Stafford, 2011:25).

2.3.4 Scheduling status

Lithium carbonate is a schedule 5 medicine according to the Drugs and Related Substances Act 101 of 1965. It is considered a schedule 5 medicine as it has low to moderate potential of abuse or dependence (Osman, 2015:MAE140).

2.3.5 Mechanism of action

The active component of the lithium carbonate salt is the lithium ion (Li^+) which is small enough to displace Na^+ and K^+ in the neuronal enzymes. The clinical effects of lithium include mood stabilisation, anti-manic effects, suicidal protection and antidepressant

effects. The exact mechanism of action of lithium in mood disorders is not known. However, some proposed mechanisms of action may act together to exert an effect (McInnis *et al.*, 2014:40).

Some of the proposed mechanisms of action of lithium are explained below.

2.3.5.1 Lithium and serotonin levels

Serotonin (5-HT) is an important neurotransmitter that modulates various neuronal activities that consequently result in the control of behaviour and physiological functions. These functions include the control of suicidal tendencies, aggressiveness and impulses. Therefore, a lack of 5-HT results in abnormalities such as stress, aggressiveness and depression that are common in BD (Carhart-harris & Nutt, 2017:1095).

The abnormal binding and functioning of the 5-HT type 1A (5-HT1A) receptor has been implicated in mood disorders, namely BD and major depressive disorder (MDD). Lithium has an effect on the neuroendocrine function or 5-HT metabolites which suggests that it increases serotonergic neurotransmission (Nugent *et al.*, 2013:1).

Patients with mood disorders treated with lithium have been seen to have enhanced plasma prolactin response to L-tryptophan as well as plasma cortisol response to fenfluramine. All this suggests that lithium causes increased 5-HT neurotransmission. The main metabolite of 5-HT, called 5-hydroxyindoleacetic acid (5-HIAAA), increased in the plasma in patients with MDD after the addition of lithium to their antidepressant treatment. This suggested a turnover in 5-HT even though there was no change in the plasma and platelet 5-HT (Nugent *et al.*, 2013:2).

2.3.5.2 Lithium and glutamate levels

Glutamate is the most abundant neurotransmitter and is excitatory in nature. It is important for the regulation of synaptic plasticity and strength that are vital for the neurobiology of general cognition, memory and learning. Individuals with mood disorders have been observed to have altered levels of glutamate and its metabolites in the cerebrospinal fluid, plasma and serum. Nuclear magnetic resonance (NMR) spectroscopy of bipolar patients has shown altered glutamate levels in different

regions of the brain and glutamate is fundamental for synaptic transmission in brain circuitry (Schloesser *et al.*, 2012:37).

Evidence has shown that lithium causes an increase in the levels of glutamate by increasing glutamatergic neural transmission. Lithium increases excitatory postsynaptic potentials by altering the neuronal excitability at hippocampal cornu ammonis 1 (CA1) synapses. Chronic upregulation of transport activity is caused by lithium as it causes a sharp increase in levels of synaptic glutamate concentrations. A recent report has also shown that lithium's effect on synaptic enhancement at the CA1 synapses may be a result of its ability to potentiate currents through the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype of ionotropic glutamate receptors. This is thought to happen by its ability to selectively increase the probability of channel opening (Schloesser *et al.*, 2012:37).

2.3.5.3 Lithium and dopamine receptors

The neurotransmitter that is involved in movement regulation and reward is dopamine (DA). DA has many vital roles in the brain including the modulation of behaviour and cognition, voluntary movement, motivation, punishment and reward, sleep, mood, attention, working memory and learning. DA is also a precursor in the biosynthesis of neurotransmitters such as noradrenaline and adrenaline (Olguín *et al.*, 2016:1).

The DA hypothesis of BD was proposed in the 1970s with early incarnations focusing on mania. The parallels that existed between the behavioural consequences of ingesting amphetamines and antimanic actions of antidopaminergic drugs were also focused on in this theory. If the manic symptoms development has underlying hyperdopaminergia then the depressive phase might have underlying hypodopaminergia. The opposite changes in the function of DA were hypothesised to underlie the opposing affective poles of BD (Ashok *et al.*, 2017:666).

However, this theory did not specify the origin of the hyper- or hypodopaminergia, resulting in the addition of an intrinsic dysregulation component to the subsequent theories. The addition suggested an intrinsic dysregulation in the homoeostatic regulation of dopaminergic function that leads to cyclical changes in dopaminergic neurotransmission. This would further differentiate the DA hypothesis of bipolar from theories of schizophrenia. Therefore, any faulty mechanism that involve homeostasis

that responds to hyperdopaminergia in the manic phase of BD will cause a decrease in dopaminergic function. This then leads to a hypodopaminergic state and depression (Ashok *et al.*, 2017:668).

Lithium works by modulating the turnover of DA though this occurs via an indirect pathway that involves DA receptors. Lithium decreases the sensitivity of the pre- and post-synaptic DA receptors. This suggests that lithium still exerts clinical action by the modulation of DA neurotransmission (Beaulieu, 2016:521).

2.3.5.4 Lithium and catecholamine receptors

Adenosine triphosphate (ATP) is a nucleotide triphosphate that is converted to cyclic adenosine monophosphate (cAMP) by an enzyme called adenylate cyclase (AC). The AC system is a second messenger system that is activated by monoaminergic neurotransmission. AC is coupled with G-proteins such as the Gs and Gi proteins. cAMP is a second messenger and the Gs protein is the one that is involved in the stimulation of cAMP while the Gi protein inhibits cAMP production. The receptors that regulate cAMP do so through the Gs or Gi proteins and cAMP activates the protein kinase A (PKA). PKA is an enzyme that regulates ionic channels, cytoskeleton elements and transcription factors resulting in its constitution of a critical factor in lasting neurobiological changes (Coulston *et al.*, 2013:142).

PKA regulates and phosphorylates ion channels and the transcription factor cAMP responsive element binding protein (CREB). CREB is of interest as it affects genes that cause neuronal plasticity. Lithium balances the transduction of the AC system by inhibiting stimulated activity and enhancing basal activity at concentrations of 2 mmol/L. Lithium therefore acutely increases basal AC and cAMP levels by Gi protein inhibition. Lithium also reduces Gs protein activity causing minimal fluctuations of cAMP (Coulston *et al.*, 2013:142).

Pharmacological studies have shown that lithium has a regulatory action in the cAMP-PKA pathway. Lithium upregulates the signalling of cAMP by inhibiting glycogen synthase kinase-3 beta (GSK-3β) which is a negative regulator of PKA (Choi *et al.*, 2016:2).

2.3.5.5 Lithium and glycogen synthase kinase 3

Glycogen synthase kinase 3 (GSK-3) is a threonine or serine kinase with two isoenzymes or paralogous proteins, namely GSK-3α and GSK-3β, that regulate cell apoptosis (cell death) and other diverse cellular processes. This kinase is important in numerous central functions such as gene transcription, circadian cycle and apoptosis and these functions are significantly affected in the pathophysiology of recurrent severe mood disorders. GSK-3β activation inhibits CREB and other survival-promoting transcription factors. GSK-3β is regulated by a number of signals that originate from a number of signalling pathways such as PKA (Machado-Vieira *et al.*, 2009:4).

Lithium can directly or indirectly inhibit GSK-3 in order to exert an effect. Lithium has been shown to be a direct and irreversible inhibitor of GSK-3β as it acts as a competitive inhibitor of magnesium (Mg^{2+}). GSK-3 is inhibited by the phosphorylation of a serine in its N terminal region. Lithium indirectly inhibits GSK-3 by increasing the phosphorylation of the inhibitory serine of GSK-3. It is thought that the direct and indirect inhibition work together to cause a cumulative inhibition of GSK-3. The inhibition of GSK-3 causes anti-apoptotic effects, improved cell structural stability and gene transcription (Machado-Vieira *et al.*, 2009:4).

The circadian rhythm is a vital regulatory factor in the cells throughout the body. This circadian rhythm affects processes such as behaviour and physiology (sleep, blood pressure and body temperature). Rev-Erbα also known as NR1D1 (nuclear receptor subfamily 1, group D, member 1) is a nuclear receptor that regulates circadian rhythm and metabolism and is a secondary regulator of the cell-autonomous clock (Bugge *et al.*, 2012:657).

Lithium blocks the GSK3β enzyme that is responsible for phosphorylating the Rev-Erbα (intracellular transcription factor protein). This results in an increase in the expression of ARNTL (Aryl hydrocarbon Receptor Nuclear Translocator-Like) which dampens the circadian cycle. This blocks the body's natural cycle as the hypothalamus is blocked. This results in many biological functions controlled by the brain being affected. Some of these processes include metabolism, body temperature and sleep cycle. The brain then resettles in a more harmonised way (Yin *et al.*, 2006:1003).

2.3.5.6 Lithium and the phosphoinositol cycle

Phospholipids are the precursors for most signalling molecules with inositol phospholipids playing an important role in receptor-mediated signal-transduction pathways. Some of the diverse functions that constitute inositol phosphates are cell division, secretion, neuronal excitability, and responsiveness (Machado-Vieira *et al.*, 2009:5).

About 40 years ago, the effect of lithium on brain inositol levels was demonstrated with lithium inhibiting two enzymes in the inositol pathway, namely inositol poly phosphate 1-phosphatase (IPP-1) and inositol monophosphatase (IMPase) through uncompetitive inhibition. The function of the IMPase enzyme is to regenerate myo-inositol from inositol monophosphates to synthesise phosphatidylinositol. Therapeutically effective concentrations of lithium inhibit IMPase (Brown & Tracy, 2013:164).

Lithium blocks IMPase and the recycling of inositol into inositol lipids causing a decrease in the ability of the cell to respond to stimuli and a decrease in phosphatidylinositol bisphosphate (PIP_2). This results in a decrease in neuronal excitability normalising the mood (Katzung, 2012:515).

2.3.5.7 Lithium and gene expression regulation and neuroprotection

Lithium has been linked to the expression of hundreds of genes. The regulation of genes by lithium results in the interference of a large number of cellular functions. Though the mechanisms by which lithium regulates gene expression are not completely understood, transcription factors and micro ribonucleic acids (RNAs) are thought to be the key targets for lithium (Squassina *et al.*, 2016:77).

Brain derived neurotrophic factor (BDNF) and B-cell lymphoma 2 (bcl-2) are neuroprotective proteins activated by CREB which is a downstream target of AC and cAMP. BDNF and bcl-2 levels are reduced in BD and lithium increases the levels of both BDNF and bcl-2. This happens due to the activation of CREB by lithium (Coulston *et al.*, 2013:143).

2.3.5.8 Lithium and brain chemicals

It is believed that lithium directly affects brain chemicals, thus affecting how cells send messages amongst themselves. This consequently changes the level of brain hormones responsible for stimulating cell growth. The five mechanisms of action of lithium on the brain electronics are brain chemicals, cell messengers, brain fertiliser, repairing or protecting and repair of damaged deoxyribonucleic acid (DNA) (Stafford, 2011:31).

Figure 2–3 depicts the ways in which lithium is thought to have an effect on the brain (Stafford, 2011:31).
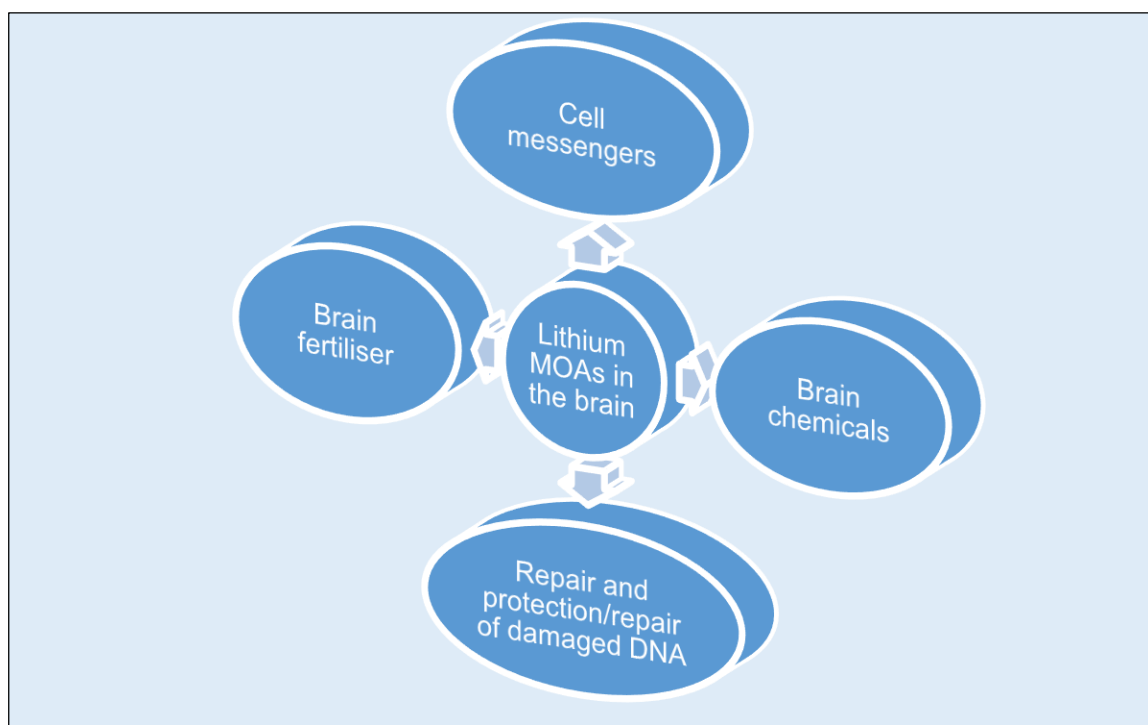
Figure 2–3. Mechanisms of action of lithium on the brain (Stafford, 2011:31).

2.3.5.8.1 Effect of lithium on the cell messenger system

In order for brain cells to live, grow and divide, they require chemicals to facilitate their communication both amongst and within themselves. The brain cells have a number of ways of communicating within themselves and the use of chemical switches called messengers is one of them. Lithium is believed to affect the important communication

messengers, thus affecting processes such as cell resilience and regeneration. Brain cell plasticity is the term given collectively for these processes (Stafford, 2011:32).

2.3.5.8.2 The effect of lithium on brain fertilisers

One of the known brain fertilisers in the brain is called brain derived neurotrophic factor (BDNF) which is responsible for brain cell growth. Lithium is believed to increase the levels of the BDNF. In BD, the mood thermostat circuit that exists between the amygdala (which is the emotional powerhouse) and the prefrontal cortex (which is the main controller of the amygdala) are damaged. The BDNF repairs this damage on this part of the brain and thus as lithium increases BDNF levels it results in improving BD (Stafford 2011:33).

2.3.5.8.3 The effect of lithium on repair of damaged DNA

Lithium has an effect on how genes are read and consequently how proteins are made. Genes are the blueprints of how proteins are made and they differ from individual to individual. When other proteins are being manufactured, special proteins are used to read the genes and process them. Lithium interferes with a number of proteins involved in this process. This then results in lithium changing the expression of some genes leading to more resilience in brain cells during times of stress and an increase in their longevity (Stafford, 2011:34-35).

2.3.5.8.4 The effect of lithium on brain chemicals

The monoamine theory of depression suggests that the pathophysiological basis of depression is a result of low levels of noradrenaline, 5-HT and/or DA in the central nervous system. This hypothesis has been supported via the use of antidepressants that then alleviate the symptoms of depression by increasing neurotransmitter levels (Liu *et al.*, 2017:2). 5-HT is thought to be a 'happy hormone' and thus lithium is thought to increase the levels of the 'happy hormones' such as 5-HT, thus alleviating the symptoms of BD (Stafford, 2011:32).

2.3.5.8.5 The effect of lithium on the repairing and protecting structures of the brain

The amygdala is an important part of the brain that forms the core of the neural circuit that is responsible for the generation of emotions. It is also responsible for other cognitive processes such as modulating memory and regulating attention. The amygdala processes any fearful or threatening stimuli (Baxter & Croxson, 2012:21180).

Brain scans can be used to view the brain of people affected by BD. Most of the scans that have been performed have shown the prefrontal cortex to be small and an enlarged amygdala. A small prefrontal cortex means that the ability of the regulating strong impulses that are a result of raw emotions is reduced. Special brain scans can show problems with the circuit that connects the amygdala and the prefrontal cortex. Lithium is involved in the protection and correction of this brain circuit. This circuit is a mood thermostat that moderates the intensity, sensitivity and fluctuation of moods based on the environment. Thus when the thermostat is faulty, the mood it controls becomes erratic (Stafford, 2011:33-34).

2.3.6 Bioavailability

The oral bioavailability of lithium is considered to be between 80% and 100%. However, the bioavailability of lithium carbonate varies depending on the formulation. An immediate release formulation (IRF) and a controlled release formulation (CRF) will have different bioavailabilities due to differences in dosing frequency and dose (Girardi *et al.*, 2016:295).

According to Ware *et al.*, the bioavailability of lithium's IRF versus sustained release formulations (SRF) varies widely, from 95% to 100% and 60% to 90%, respectively (Ware *et al.*, 2016:57). The SRFs of lithium have been designed in order to reduce the related adverse effects, improve patient adherence and for more consistent serum lithium concentrations (Girardi *et al.*, 2016:293).

2.3.7 Absorption

Lithium is completely and rapidly absorbed by the gastrointestinal tract after oral administration. The blood peak (maximum) concentration of lithium is reached within two to four hours of a single oral dose for IRFs (Rossiter, 2016:484).

Peak serum concentrations of lithium in SRFs occurs in four to four and half hours. The therapeutic range of lithium is between 0.5-0.8 mmol/L. Lower concentrations of lithium are regarded ineffective and concentrations above 0.8 mmol/L cause adverse effects and toxicity. However, lithium has a NTI which means that there is a small difference between the therapeutic and toxic dose and requires TDM. In clinical practice, lithium blood levels are measured after eight hours in order to avoid sampling during peaks (Blix *et al.*, 2010:52).

The rapid absorption of lithium has resulted in SRFs in order to maintain constant blood levels. This reduces the frequency of lithium induced adverse effects and toxicity. SRFs reduce the rate of absorption and therefore the peak plasma level (Giusti *et al.*, 2012:154).

2.3.8 Peak plasma time

Lithium peaks in the plasma between two and four hours after oral administration. Lithium reaches the extracellular fluid and gradually accumulates in the tissues once it has been absorbed (Giusti *et al.*, 2012:154).

2.3.9 Half life

Lithium has a plasma half-life of 24 hours with up to 36 hours in the elderly (Rossiter, 2016:484).

2.3.10 Elimination half life

Lithium has an elimination half-life of 18-24 hours in young adults. The elimination half-life is prolonged in the elderly and is shorter in children. The elimination half-life can be up to 60 hours in patients on chronic lithium therapy (Stafford, 2011:1513).

2.3.11 Volume of distribution

Lithium is distributed in total body water though there is slow entry into the intracellular compartment. The initial volume of distribution of lithium is 0.5 L/kg (extracellular space) which eventually rises to 0.7-0.9 L/kg (intracellular space). There is some sequestration of lithium in the bones and it is not bound to plasma proteins (Katzung, 2012:514). Elderly patients are considered to have a reduced volume of distribution and therefore require lower doses (Durakovic & Vitezic, 2013:518).

2.3.12 Metabolism

About 95% of ingested lithium is released unchanged in the urine as it does not undergo biotransformation (Giusti *et al.*, 2012:154).

2.3.13 Clearance

The clearance of lithium varies proportionally to the glomerular filtration rate (GFR) and is usually between 20-30% of GFR. The clearance of lithium is 0.2 times that of creatinine, thus dose adjustment is necessary if factors such as renal impairment exist. Renal blood flow and the GFR decrease as the age increases. Since lithium bypasses hepatic or intestinal metabolism, its clearance is directly proportional to the GFR (Chiu *et al.*, 2007:270).

A decrease in total body water, fat-free mass and an increase in body fat occurs as an individual ages and this is due to changes in the composition of the human body. Drug clearance is reduced in the elderly. Consequently, the clearance of lithium decreases with an increase in age as the GFR decreases (Durakovic & Vitezic, 2013:518).

2.3.14 Target plasma concentration

The target plasma concentration of lithium is between 0.6-1.4 mmol/L (Katzung, 2012:514).

2.3.15 Contraindications

Though the use of lithium is effective in treating mental conditions, it is contraindicated in a number of conditions.

2.3.15.1 Renal insufficiency

The use of lithium in patients that have existing renal damage is contraindicated. Lithium is associated with an increased diagnostic incidence of renal impairment. About 20% of patients on long term lithium therapy develop chronic kidney disease (CKD) (Kerckhoffs *et al.*, 2018:1). The risk of developing end stage renal disease (ESRD) for patients on lithium is six times greater than that of the general population. Lithium also causes lithium-induced nephropathy and it is becoming a common adverse effect (Gupta & Khastgir, 2012:217). Therefore, it should not be used in patients that have pre-existing renal insufficiency.

2.3.15.2 Cardiovascular disease

Lithium at therapeutic levels can cause the flattening of the T wave and inversion on the electrocardiogram (ECG). Lithium use in the bradycardia-tachycardia syndrome (BTS) "sick sinus" is completely contraindicated. This is because lithium further depresses the sinus node. When lithium is used in cardiovascular diseases, it increases the risk of toxicity and therefore may only be used if the dose is adjusted to the rate of lithium excretion (Katzung, 2012:517).

2.3.15.3 Severe dehydration

Lithium can enter the collecting duct of the kidney via highly selective lithium and sodium channels. These channels are located in the apical membrane and thus there is increased excretion of sodium. Increased excretion of sodium causes decreased renal tubule responsiveness to antidiuretic hormone (ADH) and aldosterone. This then causes dehydration as there is increased excretion of fluids, leading to lithium toxicity. Therefore the use of lithium in dehydration is contraindicated as there is a higher risk of lithium toxicity which could potentially lead to death (Giusti, 2012:156).

2.3.15.4 Urinary retention

Urinary retention is one common urological emergency and is defined as impaired emptying of the bladder that leads to postvoidal residual urine. Micturition (urination) has a complex mechanism of action and therefore many drugs can interact with this pathway. Most drugs that have some anticholinergic effects are associated with

urinary retention. Lithium has some mild anticholinergic effects (Verhamme *et al.*, 2008:376).

Lithium however is not metabolised by the liver and is therefore excreted unchanged via urine. If lithium is used in a patient with urinary retention, lithium toxicity will occur as it is not excreted in the urine. Characteristics of lithium toxicity such as abdominal pain, vomiting, tremor and nausea can be noticed (Portes, 2012:154).

2.3.16 Considerations in special populations

The use of lithium in special populations is explained below.

2.3.16.1 Pregnancy

Lithium has teratogenic effects which means that it can cause abnormalities in the development of the foetus. In pregnancy, lithium can cause congenital cardiovascular abnormalities such as the Ebstein anomaly and overall cardiac effects. The Ebstein anomaly was first described by Wilhelm Ebstein in 1866 as a rare congenital heart disorder that affects approximately 1 in every 200 000 births. Malformation of the tricuspid valve and right ventricle are characteristics of the Ebstein anomaly (Healy *et al.*, 2015:368).

Lithium is a category D classification drug in pregnancy (The Pharmaceutical Society of South Africa, 2010:465). Category D in pregnancy means that there is positive evidence of risk on the unborn human foetus. This is established from adverse drug reactions observed in humans even though the risks can be outweighed by the benefits. Positive evidence may be from investigational or marketing experience or studies done in humans. Therefore, the use of category D drugs in pregnant women is deemed acceptable when the potential benefits outweigh the potential risks (Wood, 2013:78).

Though there is evidence of human foetal harm, its potential benefits may warrant its use in pregnant women. The teratogenicity potential of lithium has caused some women to terminate their pregnancies or discontinue lithium therapy during pregnancy. Women of child bearing age with BD planning on getting pregnant should therefore balance the benefits and risks of continuing treatment given its teratogenic potential (Patorno *et al.*, 2017:2246).

2.3.16.2 Lactating women

Lithium use is contraindicated in breastfeeding. Despite limited data, current practice guidelines do not encourage lithium use while breastfeeding. Lithium is excreted in breast milk in significantly high concentrations, thus breastfeeding is not recommended if the nursing mother is on lithium (Rossiter 2016:484).

Drugs enter milk by passive diffusion and the extent to which drugs are bound by maternal plasma proteins influences the transfer of drugs. Free unbound drugs diffuse readily in the milk and lithium is unbound. Neonates and premature babies have a lower capacity to metabolise and excrete drugs. (Hotham, 2015:156-157). Lithium toxicity in new-borns can be observed as lethargy, poor suckling, tachycardia and respiratory distress syndrome (Lugt *et al.*, 2012:375).

2.3.16.3 Paediatrics and adolescents

The use of lithium is not recommended in children below the age of 12 (Rossiter, 2016:485). Lithium was approved for use in youths with mania between the age of 12 and 17 in the early 21st century based on adult trials. The FDA has requested for collaborative lithium trials to determine the safety and efficacy of lithium in paediatric BD. One study conducted reported that lithium is safe and effective in treating acute mania in children and adolescents with BD (Rosen, 2010:3).

2.3.16.4 Geriatric patients

Lithium is the treatment of choice for BD in elderly patients. The physiological changes, comorbid physical and psychiatric illnesses that are associated with age increase the vulnerability to adverse effects. This means that the dose has to be decreased, thus potentially lowering the benefits of the drug therapy (De Fazio *et al.*, 2017:756). Lower doses (0.4 to 0.7 mmol/L serum levels) of lithium should be administered to the elderly as they have decreased renal function and consequently decreased clearance of lithium (Rossiter, 2016:485).

2.3.16.5 Surgery

There are risk factors that should be considered in the perioperative stage as there is potential of interaction between anaesthetic drugs and lithium. Some of the risks

include extent of surgery, physical state of patient, direct and indirect effects of psychotropics, anaesthesia, withdrawal symptoms and risk of psychiatric recurrence and relapse (Attri *et al.*, 2012:8).

Lithium effects can be hazardous in surgery if there is haemodynamic instability and renal function obstruction. Sodium and potassium metabolism interference can impede renal function. Lithium should therefore be discontinued 72 hours before surgery due to its half-life of 24-36 hours. The anaesthetic requirements in patients on lithium are reduced as lithium has some sedative effects (Attri *et al.*, 2012:10).

The factors that should be considered when deciding if lithium should be used or discontinued in the perioperative stage or in surgery include (Irish Medication Safety Network 2012:8):

- Use of lithium in surgery increases the risk of arrhythmias.
- Dehydration precipitates lithium toxicity so patient must be adequately hydrated.
- Decreased renal function and surgery related electrolyte imbalance may precipitate toxicity.
- The action of depolarising and non-depolarising muscle relaxants is prolonged by lithium.
- NSAIDs must be avoided as they affect renal function and lithium excretion.

Lithium is safe for use in minor surgery. Electrolyte imbalances and reduced renal function may however precipitate lithium toxicity (Blood, 2012:1).

2.3.16.6 Sodium depletion

Lithium is transported into the cells by the sodium (Na^+)/hydrogen (H^+) exchange protein, making it a facilitated transport process. Lithium transport out of the cells requires active transport with the assistance of the Na^+-potassium (K^+) adenosine triphosphatase (ATPase) pump. The elimination pathways of lithium are limited, causing intracellular build-up of lithium. The transport of lithium into cells is two times slower than that of sodium and is present in many cells of the body such as the proximal tubule in the kidney. These mechanisms are evidence that hyponatraemia (low sodium levels in the blood) facilitates lithium intoxication. Long term use of lithium may influence sodium levels in patients and cause lithium intoxication. Renal

absorption and increased serum levels of lithium may be influenced by volume depletion (Dilmen *et al.*, 2016:220).

2.3.17 Drug interactions

2.3.17.1 Lithium, angiotensin converting enzyme inhibitors and angiotensin receptor blockers

The concomitant use of lithium and angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) leads to the reduced clearance of lithium, resulting in lithium toxicity (Smith, 2011:342).

ARBs block the reabsorption of water and sodium by the proximal tubules. This process is normally mediated by angiotensin II and this also inhibits aldosterone secretion. As a result, there is increased loss of sodium at the distal tube, causing natriuresis. This natriuresis causes lithium reabsorption into the circulation and therefore toxicity (Jann *et al.*, 2016:440).

ACE inhibitors can decrease thirst levels which then leads to mild dehydration. They also increase the levels of renal sodium loss, causing an increase in the renal absorption of sodium. Consequently, the lithium plasma levels are increased causing toxicity. Risks for this adverse effect include dehydration, cardiac failure and renal impairment (Moinhos & Sul, 2018:39).

2.3.17.2 Lithium and diuretics

The renal clearance of lithium is reduced by about 25% when there is concomitant use of lithium and diuretics (Katzung, 2012:516). The interaction pattern varies according to the class of diuretic and its corresponding pharmacokinetics. Thiazide diuretics cause lithium toxicity as they act on the proximal convoluted tubule of the kidney where lithium absorption is higher. Loop and potassium sparing diuretics should be used to replace thiazide diuretics as they are considered safer (Moinhos & Sul, 2018:40).

Carbonic anhydrase inhibitor diuretics such as acetazolamide increase lithium excretion, causing decreased plasma levels. These diuretics block the reabsorption of sodium in the proximal and distal renal tubules (Jann *et al.*, 2016:440).

Loop diuretics such as furosemide increase sodium loss and the subsequent renal absorption of sodium. Therefore patients on loop diuretics should restrict their salt intake as this may precipitate lithium toxicity (Moinhos & Sul, 2018:39).

A summary of drug interactions between lithium and diuretics is outlined in Table 2-2 (Moinhos & Sul, 2018:39).

Table 2-2. Drug interactions between lithium and diuretics (Moinhos & Sul, 2018:39).

Class of diuretic	Example of diuretic	Effect on lithium concentration
Carbonic anhydrase inhibitors	Acetazolamide	Decrease
Loop diuretics	Furosemide	No change or slight increase
Osmotic	Mannitol, Urea	Decrease
Potassium sparing	Amiloride, Spironolactone	No change or slight increase
Thiazide diuretics and analogues	Hydrochlorothiazide, Indapamide	Severe increase

2.3.17.3 Lithium and antithyroid drugs

The concomitant use of antithyroid drugs or iodides with lithium results in hypothyroid effects being increased (The Pharmaceutical Society of South Africa, 2010:465). Lithium is thought to be goitrogenic when used in BD. The *in vivo* response of cultured cells to thyrotropin-releasing hormone (TRH) can be altered by lithium. The thyroid then concentrates lithium, causing the inhibition of thyroidal iodine uptake (Lazarus, 2009:909).

Lithium also results in the inhibition of thyroid hormone secretion and coupling of iodotyrosines. Alteration of the thyroglobulin structure is also caused by lithium use. If the thyroid hormone secretion is inhibited, hypothyroidism and goitre result (Lazarus, 2009:910).

The symptoms of hypothyroidism include weakness, dry skin, fatigue, weight gain and menstrual changes. Levels of thyroid stimulating hormone (TSH) and thyroxine (T$_4$) should be monitored to diagnose hypothyroidism (Pearce *et al.*, 2012:2).

2.3.17.4 Lithium and non-steroidal anti-inflammatory drugs

Lithium use with nephrotoxic medications such as cyclooxygenase (COX) 2 inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs) can affect the pharmacokinetics of lithium and lead to serious adverse effects (Hassan *et al.*, 2013:1).

Renal function may be altered by the use of all NSAIDS as they inhibit COX-1 and/or COX-2 that is expressed in the kidneys. COX-1 regulates glomerular filtration and renal haemodynamics and COX-2 mediates water and salt excretion. Some renal syndromes that may be caused by nonselective NSAIDs include weight gain, sodium retention, peripheral oedema, hyperkalaemia, increased blood pressure and acute renal failure (Moore *et al.*, 2015:1064).

NSAIDs such as indomethacin result in decreased renal excretion of lithium. This leads to toxicity as there is an increased serum concentration of lithium. This is common in NSAIDs that block the synthesis of prostaglandins. However, these interactions have not been reported for aspirin and paracetamol (Katzung, 2012:516). These NSAIDs inhibit the synthesis of renal prostaglandins, leading to decreased renal blood flow and a possibility of increasing sodium reabsorption. This results in the reabsorption of lithium, causing plasma level monitoring to be essential (Taylor *et al.*, 2009:132).

A study by Moore *et al.,* showed that drug-drug interactions (DDI) were present between lithium and rofecoxib with increased lithium concentration. Celecoxib also had DDIs with lithium, causing an increase in lithium concentration. This increase in lithium concentration resulted in clinical adverse effects such tremor, nausea, vomiting, renal insufficiency, weakness, ataxia, increased muscle tone, dysarthria, slurred speech, lethargy, sedation and disorientation (Moore *et al.*, 2015:1068-69).

A summary of the drug interactions between lithium and NSAIDs is outlined in Table 2-3 (Moinhos & Sul, 2018:39).

Table 2-3. Drug interactions between lithium and non-steroidal anti-inflammatory drugs (Moinhos & Sul, 2018:39).

NSAID	Effect on lithium concentration
Aspirin	None
Ibuprofen	Increase
Indomethacin	Increase
Mefenamic acid	Increase
Naproxen	Increase

2.3.17.5 Lithium and xanthines

Xanthines such as theophylline and aminophylline can interact with lithium. This interaction results in increased renal clearance of lithium and decreased serum concentrations of lithium (Hoeft, 2014:120). The direct blockade of sodium reabsorption at the proximal tubule is responsible for the increase in lithium clearance. Adverse effects that result from the concurrent use of lithium and theophylline include polyuria, fatigue and polydipsia. However, care should be taken when xanthines are stopped in order to avoid lithium toxicity (Jann *et al.*, 2016:440).

2.3.17.6 Lithium and antipsychotics

Lithium is often co-administered with antipsychotics for the management of manic or mixed manic episodes associated with BD. Early studies suggested that the combination of lithium and conventional antipsychotics resulted in acute irreversible toxicity. Recent studies have concluded that the interaction between lithium and antipsychotics is rare and that it is safe to use the combination (Finley, 2016:935). However, concomitant administration of lithium and antipsychotics has worsened tremor in patients (English *et al.*, 2015:386).

2.3.17.7 Lithium and antidepressants

Lithium is often used to augment antidepressant treatment for refractory depression. Antidepressants such as selective serotonin re-uptake inhibitors (SSRIs) interact with lithium (Jann *et al.*, 2016:440). This interaction leads to increased lithium levels as well as a risk of developing serotonin syndrome (SS). Patients and their lithium levels should be monitored carefully (The Pharmaceutical Society of South Africa, 2010:465).

SS is one of the most common adverse effects associated with the use of 5-HT active medications. It is a life threatening condition that can be caused by a number of drug combinations. It occurs as a result of increased 5-HT levels in the central nervous system (CNS) and causes autonomic, neuromuscular and mental changes. The symptoms of SS may range from mild to severe and include hyperthermia, tremor, akathisia and agitation. The use of lithium as an adjuvant concomitantly with antidepressants increases the risk of developing this adverse effect. Studies have shown that SS occurs when lithium is used together with venlafaxine which has a dual reuptake inhibition mechanism (Volpi-abadie *et al.*, 2013:534-536).

2.3.17.8 Lithium and anticonvulsants

Some of the anticonvulsants used to treat BD are carbamazepine, valproate and lamotrigine. Studies have shown that concomitant administration of lithium and carbamazepine increases lithium levels, resulting in toxicity (English *et al.*, 2015:386). This is thought to be a result of carbamazepine increasing lithium levels in unspecified compartments of the CNS or intracellularly. The combination of lithium and carbamazepine has resulted in adverse effects such as ataxia, tremors and nystagmus. These symptoms have been seen to resolve once carbamazepine is discontinued (Finley, 2016:935).

There have been no reports of lithium toxicity when lithium is concomitantly used with lamotrigine. The combination of valproate and lithium has been well tolerated and is recommended for patients that do not respond to the first line treatment. However, some studies have shown that concomitant use of lithium and valproate leads to increased valproate concentrations and unchanged lithium concentrations. Any adverse effects reported from the combination are thought to be a result of cumulative toxicities of either drug, rather than potential interactions (Finley, 2016:935).

2.3.17.9 Lithium and muscle relaxants

The concurrent use of lithium and muscle relaxants such as pancuronium results in prolonged depolarising and non-depolarising muscle blockade. The action of lithium and non-depolarising drugs is synergistic while its action with depolarising drugs is additive. Succinylcholine administration and use of lithium has been seen to potentiate neuromuscular blocking. Lithium enhances the myoneuronal blocking effects of

pancuronium and suxamethonium. It is therefore important to monitor neuromuscular activity for patients on lithium undergoing anaesthesia with neuromuscular blocking drugs (Flood & Bodenham, 2010:79).

2.3.17.10 Summary of the most clinically relevant drug interactions

Some of the most clinically relevant drug interactions and their effects are outlined in Table 2-4 (Taylor *et al.*, 2009:133).

Table 2-4. Clinically relevant drug interactions of lithium (Taylor *et al.*, 2009:133).

Drug group	Extent of effect	Time lapse of effect	Additional information
ACE Inhibitors	Lithium concentration increased up to 4-fold, usually unpredictable	Develops over weeks	7-fold increased risk of hospitalisation for lithium toxicity in the elderly
NSAIDS	Increases lithium concentration by greater than 4-fold, usually unpredictable	Varies from days to several months	Can be bought without a prescription, used on a "when required" basis
Thiazide diuretics	Increases lithium concentration by up to 4-fold	Occurs within first 10 days	Effects will be visible in the first month, loop diuretics are the safer option

2.3.18 Adverse effects

Lithium has its advantages and is clinically effective which is why its use has increased fairly over the years. Lithium serum levels can be monitored and the patient outcomes and adverse effects can be observed. There must be a balance between the adverse

effects and the efficacy of the lithium. The adverse effects may appear almost immediately, even though the efficacy may not be immediate (Oruch *et al*., 2014:468).

Lithium carries a 'black box' warning which implies its potential to cause lethal adverse effects. It is important that the dose be started as low as possible and then titrated upwards based on efficacy. An initial plasma level of 0.4-1.2 mmol/L is desired with the lower range (0.4 mmol/L) being the maintenance dose. Most of the adverse effects of lithium are dose dependent and thus the lowest effective dose is recommended. All systems of the body may exhibit adverse effects associated with the use of lithium (Oruch *et al*., 2014:468).

Adverse effects are an important variable in both prescription patterns and adherence. Lithium adverse effects can be managed to ensure that patients remain comfortable while on treatment (Gitlin, 2016:2).

The overall strategies that are implemented to manage lithium adverse effects are outlined below (Gitlin, 2016:2):

- Use of antidotes for specific adverse effects.
- Changing the time of administration.
- Switching to a different formulation of lithium.
- Lower doses of lithium.
- Switching to a different mood stabiliser.
- Watchful waiting.

2.3.18.1 Adverse effects on thyroid function

Lithium has shown to decrease thyroid function in most patients. The use of lithium is associated with an increased risk of developing clinical hypothyroidism. However, this phenomenon is reversible and non-progressive. A few patients present with frank thyroid enlargement while fewer present with hypothyroidism. The TSH levels must be measured every 6-12 months if a patient is on lithium therapy (Katzung, 2012:516).

2.3.18.2 Adverse effects on cardiac function

Lithium causes a wide range of cardiac adverse effects, ranging from ventricular fibrillation to nonspecific T-wave changes. Reports have described interactions

between the Brugada syndrome and lithium with clinical consequences ranging from isolated ECG changes to cardiac syncope to sudden cardiac death (Wright & Salehian, 2010:418). The Brugada syndrome is an inherited cardiac life threatening problem that is infrequently revealed by lithium use. Most people are not aware that they have this condition which causes increased risk for sudden cardiac death (SCD) and ST-segment elevation in the ECG (Sieira & Brugada, 2017:3029).

A definite contraindication to the use of lithium is the BTS, also known as the "sick-sinus syndrome". The sick-sinus syndrome (SSS) is a group of disorders where the heart is unable to perform its pace making function due to acquired or genetic causes. BTS is a complication of SSS that is characterised by bradycardia and tachycardia (Tse *et al.*, 2017:519). This is because the lithium ion depresses the pace making activity of the sinus node, causing sinus arrhythmias, syncope episodes and heart block. Lithium causes this by interacting with pacemaker channels and/or the sodium-calcium exchanger (Oudit *et al.*, 2007:230).

An ECG also reveals the flattening of the T wave. This change is benign and disappears once lithium is excreted from the body (Katzung, 2012:516). Therefore, it is important to know any cardiovascular problems that a patient has before lithium is administered.

2.3.18.3 Adverse effects on weight

Weight gain is an adverse effect commonly associated with the use of lithium. This is thought to be due to the effect that lithium has on carbohydrate metabolism. However, lithium-induced hypothyroidism and lithium-induced oedema can cause the weight gain. This lithium-induced weight gain contributes to non-adherence in patients (Dent *et al.*, 2012:1). A study conducted proved that lithium causes weight gain in patients compared to patients taking other antipsychotics such as olanzapine (Adida *et al.*, 2012:721).

2.3.18.4 Adverse effects on neurology

The precise mode of action of lithium on the CNS is still not clear but electroencephalogram (EEG) findings suggest that lithium has cortical and subcortical

effects on the CNS. Neurological adverse effects are experienced both at normal serum levels and at toxic levels (Ozdin & Sarisoy, 2013:119).

One of the most common lithium induced adverse effects is tremor. This adverse effect occurs at therapeutic levels (Katzung, 2012:516). Tremor can be reduced by dividing the daily dose, reducing the caffeine intake and reassessing the concomitant use of lithium and other drugs. Propranolol and atenolol which are commonly used in essential tremor are also used to alleviate lithium-induced tremors. If a patient has hypokalaemia, potassium supplements must be given to improve the tremor (Canning *et al.*, 2012:174).

Mild Parkinsonism tremors are one neurological effect caused by lithium though they are uncommon. Rarely is the use of lithium linked to increased seizures and peripheral neuropathy. Some of the factors that increase the risk of lithium tremor include high serum lithium levels, male gender, increased age, concurrent antidepressant medications and neuroleptic medications (Canning *et al.*, 2012:174).

2.3.18.5 Adverse effects on dermatology

The incidence of lithium-induced skin conditions ranges from 3% to 45%. The dermatological conditions caused by lithium include acne, eczema, psoriasis and hair loss. Acneiform usually occurs within the first 6 months of lithium therapy as lithium increases circulating neutrophil chemotaxis and induces follicular hyperkeratosis. Acneiform eruptions have been seen to subside when lithium is discontinued. Folliculitis is more common in patients even though it is considered a less severe adverse effect (Katzung, 2012:517; Scarfi & Arunachalam, 2013:1525).

The clinical manifestations of lithium induced psoriasis are listed (Jafferany, 2008:435):

- Exfoliative (erythrodermic) psoriasis.
- Generalised psoriasis.
- Nail psoriasis.
- Plaque-type psoriasis.
- Pustular psoriasis.
- Scalp psoriasis.

2.3.18.6 Adverse effects on renal function

A study conducted showed that lithium reduces the GFR by 6.22 ml/min. Lithium increases the risk of developing reduced urinary concentrating ability. On average lithium can reduce the urinary concentrating ability by 15% of the normal maximum. Lithium may increase the risk of developing renal failure, though the risk is small (Adida *et al.*, 2012:721).

Oedema is a common adverse effect of lithium use. This is a result of the sodium retention potential that lithium possesses. Weight gain may be expected in patients that end up with oedema though water retention does not account for weight gain in up to 30% of the patients on lithium therapy (Katzung, 2012:517).

Polyuria (which is the passage of abnormally large volumes of dilute urine) with secondary polydipsia (which is excessive thirst) are common adverse effects of lithium use that occur at the therapeutic levels of lithium (Katzung, 2012:516).

Nephrogenic diabetic insipidus (NDI), end stage renal disease (ESRD), tubular dilation, tubular atrophy and glomerulosclerosis can be caused by lithium use. NDI occurs as a result of the collecting tubule of the kidneys losing its ability to conserve water under the influence of the ADH. Consequently, there is an excessive water clearance (Alsady *et al.*, 2016:1588).

Lithium-induced diabetes insipidus responds to amiloride and not vasopressin as with diabetes insipidus. Patients on lithium should avoid dehydration and have regular renal function tests conducted (Alsady *et al.*, 2016:1587; Katzung, 2012:516).

The toxic effects of lithium on renal function and the proposed mechanisms of action are outlined in Table 2-5 (Alsady *et al.*, 2016:1588). The adverse effects appear in order in the table based on how frequently they occur in patients.

Table 2-5. Toxic effects of lithium on renal function and proposed mechanisms of action (Alsady *et al.*, 2016:1588).

Adverse effect	Section of kidney affected	Proposed mechanism of action
NDI[1]	Collecting duct and distal tubule	Down regulation and loss of principal cells causing decreased water uptake
Cellular remodelling (increase of intercalated versus principal cells)	Collecting duct and distal tubule	Possibly due to lithium-induced metabolic acidosis or arrest of collecting duct principal cells
Interstitial fibrosis	Throughout the kidney	Possibly due to Wingless/Integrated (Wnt) signalling pathway prolongation
Tubular atrophy	Proximal tubule	Not known but is usually linked with interstitial fibrosis in many renal diseases
Tubular dilation	Collecting duct	Not exactly known but suggested mechanism is increased cell proliferation
Microcysts	Collecting duct and distal tubule	Not exactly known but suggested mechanism is increased cell proliferation
Glomerulosclerosis	Glomerulus	Not exactly known but suggested mechanism is a progressive renal damage consequence

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[1] NDI refers to Nephrogenic Diabetes Insipidus

2.3.18.7 Adverse effects on the gastrointestinal tract

The common gastrointestinal (GIT) adverse effects associated with lithium use include nausea, vomiting and diarrhoea. Nausea is usually present during the early treatment phase and is rare during long term therapy. Nausea affects between 10% and 20% of patients that are treated with lithium. Taking lithium after meals has been shown to diminish nausea. Diarrhoea is present in about 10% of patients on lithium therapy and is usually present during the first 6 months of treatment (Gitlin, 2016:3).

2.3.18.8 Adverse effects on the parathyroid gland

The parathyroid gland is responsible for regulating extracellular calcium homeostasis. Calcium is important for physiological processes such as blood coagulation, muscle contraction and synaptic activity (Okabe & Graham, 2004:17716). A study showed that the use of lithium causes hyperparathyroidism and therefore calcium levels should be monitored before and during treatment (Adida *et al.*, 2012:721).

The common adverse effects caused by lithium are summarised in Table 2-6 (Rossiter, 2016:485; Katzung, 2012:516-517; The Pharmaceutical Society of South Africa, 2010:465).

Table 2-6. Common adverse effects of lithium (Rossiter, 2016:485; Katzung, 2012:516-517; The Pharmaceutical Society of South Africa, 2010:465).

Classification	Adverse effects
Renal	Polydipsia, nephrogenic diabetes insipidus, electrolyte imbalance, increased aldosterone secretion causing oedema
Metabolic	Weight gain
Thyroid	Goitre, hypothyroidism
Gastrointestinal	Nausea, vomiting, diarrhoea
Cholinergic	Polyuria
Parathyroid	Hyperparathyroidism due to increased calcium levels
Dermatological	Acne, rash, psoriasis

2.3.19 Lithium toxicity

Lithium is a drug that has a greater toxicity index and thus overdose should be avoided. Toxicity usually results from accumulative high levels during on-going therapy. Lithium toxicity occurs when the plasma levels are above 1.5 mmol/L (Haussmann *et al.*, 2015:24). A plasma concentration of above 2.5 mmol/L is fatal and thus must be treated immediately. Signs of acute toxicity include nausea, diarrhoea, abdominal pain, vomiting, tremor, convulsions, confusion, light headedness and renal insufficiency (Haussmann *et al.*, 2015:24).

Lithium toxicity is an emergency that could possibly cause death or neuronal damage. Signs and symptoms of severe lithium toxicity include impaired consciousness, seizures, myoclonus, muscle twitches, blurred vision, coma and death. Some of the risk factors of developing lithium toxicity are exceeding the recommended dose, dehydration, low sodium diet, renal impairment and possible drug interactions. Lithium toxicity is common in the elderly as they have decreased renal function (Flood & Bodenham, 2010:78).

Patients that become unconscious due to lithium toxicity should be monitored for airway patency and it should be ensured that they have adequate ventilation. Blood levels of lithium must be taken immediately, after 6 hours and every 6-12 hours. Gastric lavage must be considered for patients that ingested more than 4 g of lithium and present within 1 hour after ingestion. It is also important to ensure that the patient is adequately hydrated and to correct any electrolyte imbalances (Flood & Bodenham, 2010:78)

Haemodialysis should be used in a case of severe lithium poisoning. Stopping haemodialysis may cause a significant increase in the blood lithium levels (Flood & Bodenham, 2010:79).

The indications for haemodialysis in lithium toxicity are outlined (Flood & Bodenham, 2010:79):

- Plasma lithium levels greater than 7.5 mmol/L in acute overdose.
- Plasma lithium greater than 4.0 mmol/L in acute on chronic overdose.
- Neurological signs and symptoms.

A summary of the clinical symptoms associated with lithium toxicity are outlined in Table 2-7 (Gitlin, 2016:6).

Table 2-7. Clinical symptoms associated with lithium toxicity (Gitlin, 2016:6).

Organ System	Acute toxicity	Chronic toxicity
Endocrine	None	Hypothyroidism
Gastrointestinal	Nausea, vomiting	-
Heart	Prolonged QT interval, ST and T wave changes	Myocarditis
Haematological	Leucocytosis	Anaemia
Neurological		
Mild	Fine tremor, light headedness, weakness	Fine tremor, light headedness, weakness
Moderate	Drowsiness, muscle twitching, slurred speech, tinnitus	Drowsiness, muscle twitching, slurred speech, tinnitus
Severe	Coma, confusion, seizures	Memory deficits, Parkinson's disease, psychosis
Neuromuscular	Peripheral neuropathy	Peripheral neuropathy
Renal	Urine concentrating defect	Chronic interstitial nephritis, nephrogenic diabetes insipidus, renal failure
Skin	None	Dermatitis, localised oedema, ulcers

2.3.19.1 Risk factors for lithium toxicity

Risk factors for lithium intoxication include drugs that alter renal function and other conditions. Drugs such as thiazides can increase serum lithium levels by increasing the renal reabsorption in the proximal tubules (Haussmann *et al.*, 2015:24).

Table 2-8 outlines these factors in detail (Haussmann *et al.*, 2015:24).

Table 2-8. Risk factors for lithium intoxication (Haussmann *et al*., 2015:24).

Category of risk	Conditions
Alterations in sodium and potassium levels	Volume depletion, decreased dietary sodium intake, decreased effective circulating volume
Illnesses	Cystic fibrosis, cirrhosis, congestive heart failure, diabetes insipidus, diabetes mellitus, infections and renal insufficiency
Medications	ACE[2] inhibitors, cyclosporine, diuretics (loop diuretics and thiazides) and NSAIDs[3]

2.3.20 Initiation of lithium therapy

Lithium has variations in its renal clearance and response to treatment as these parameters depend on the individual patient. This means that the dose needs to be determined for each patient with regular monitoring of blood levels. Lithium is usually started on a clinical titration method, meaning that it is started on low doses and serum levels are measured after steady state has been reached. This is a 12-hour serum level that is taken after a week of lithium initiation. The daily dose of lithium is then adjusted to suit the patient's need with gradual increments to reach the desired serum level (Sienaert *et al*., 2013:13).

2.3.21 Dosage forms and preparations

The following immediate release preparations are available in South Africa (Rossiter 2016:485):

- Camcolit® (Norgine) tablets 250 mg and 400 mg.
- Quilonum® (GlaxoSmithKline) tablets 450 mg.

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[2] ACE refers to Angiotensin Converting Enzyme
[3] NSAIDs refers to Non-Steroidal Anti-inflammatory Drugs

2.3.22 Dosing

The dosing of lithium carbonate is dependent on the body weight of the patient, age and renal function (Oruch *et al.*, 2014:467). Dosing frequency affects compliance which decreases as the frequency increases.

The *Keck* method for calculating the lithium dose is as follows (Chiu et al., 2007:270):

Dose (mg/day) = 20 x weight, where weight is total body weight in kilograms.

Adult dosing: The dose is initially 20 mg/kg/day with a usual range of 750 mg-1000 mg/day. This dose is to be given in divided doses for a duration of 5-7 days. The dose of lithium should be adjusted when necessary to achieve plasma concentrations of 0.8-1.2 mmol/L in acute manic episodes (Rossiter, 2016:485).

The dose may be given once a day at night if the dose has been stabilised. The dose must be reduced and monitored if renal impairment exists as well as in geriatric patients (Rossiter, 2016:485).

2.3.22.1 Dose increment

Lithium is usually started in low, divided doses to minimise adverse effects (e.g. 300 mg three times a day or less, depending on the patient's weight and age). The dose of lithium is usually titrated upwards (generally to serum concentrations of 0.5-1.2 mmol/L) based on response and adverse effects (American Psychiatric Association, 2016:3).

Lithium levels should be checked before and after each dose increment. Steady-state levels are likely to be reached approximately 5 days after dose adjustment, but levels may need to be checked sooner if a rapid increase is necessary, such as in the treatment of acute mania, or if toxicity is suspected. Lithium levels should be checked at shorter intervals after each dose increment to minimise the risk of toxicity as levels approach the upper therapeutic range limits (1 mmol/L) (American Psychiatric Association, 2016:3).

2.3.22.2 Maintenance dose

The frequency and severity of previous episodes, pattern of appearance and the extent to which a patient is willing to follow a program of maintenance treatment determine the use of lithium as a prophylactic. Candidates for use of lithium as maintenance treatment are those that have had one or more episodes of illness per year. Serum levels higher than 0.9 mmol/L have shown the best results, though patients can be maintained with serum concentrations as low as 0.6 mmol/L (Katzung, 2012:516).

2.3.22.3 Withdrawal of lithium

Lithium must never be stopped suddenly unless the individual is suffering from signs of toxicity or has a serum level greater than 1.5 mmol/L. It is recommended to reduce the dose gradually to minimise risks of manic and depressive episodes (National Health Services, 2017:10).

Lithium should be gradually stopped with the dose being gradually decreased over a period of at least 4 weeks. This should be done preferably for up to 3 months especially if a history of manic episodes is known for the patient (Irish Medication Safety Network 2012:6).

2.3.22.4 Adherence

Studies have shown that patients with chronic diseases such as BD adhere with medication regimens that have a once a day dosing compared to more frequent regimens. Adherence has been seen to be significantly lower in regimens that are dosed twice, three or four times a day (Coleman, 2012:534).

The results of the correlation of dosing frequency and adherence are tabulated in Table 2-9 (Coleman, 2012:535).

Table 2-9. Correlation of dosing frequency and adherence (Coleman, 2012:535).

Dosing frequency	Percentage adherence
Once a day	79%
Twice a day	69%
Three times a day	65%
Four times a day	51%

SRFs of lithium are available internationally but are currently unavailable in South Africa. The standard dosing for lithium is three times a day and this reduces adherence significantly. SRFs extend the half-life of the drug consequently reducing the dosing frequency. This then results in an increase in adherence. SRFs decrease the peak serum concentration, causing reduced dose dependant adverse effects. The increased serum trough concentrations allow for the better management of symptoms (Girardi *et al.*, 2016:298).

2.3.22.5 Lithium overdose

Overdose of lithium with SRFs delays the onset of lithium toxicity and prolongs the duration of toxicity. This should be taken into consideration in decisions about the need for initial or repeat haemodialysis (American Psychiatric Association, 2016:2).

The following steps must be employed in the management of lithium overdose (National Health Services, 2017:9):

1. A doctor should be contacted or visit an emergency division at a hospital.
2. Discontinue lithium.
3. Vital signs and a full assessment of mental state must be conducted.
4. Lithium serum levels, renal electrolytes, renal function tests and ECG tests must be performed.
5. Gastric lavage, emesis and absorption using activated charcoal must be employed.
6. Ensure hydration and maintain electrolyte balance.
7. Haemodialysis should be performed for patients with serum levels greater than 4.0 mmol/L.

2.3.23 Monitoring requirements

A general medical history and physical examination are recommended before initiation of lithium therapy. Renal (BUN and creatinine level tests) and thyroid function tests must be conducted before lithium therapy is initiated. Patients with a history of cardiac disease must have an ECG performed before lithium administration. Patients on lithium therapy require regular monitoring of the serum concentrations (American Psychiatric Association, 2016:3).

The SAMF recommends that renal and thyroid function tests should be conducted every 6-12 months and more frequently in the elderly. Serum concentrations of lithium must be observed every week after dose increments. Eventually lithium levels have to be monitored once a month, then at three months and then at a six month intervals while on maintenance therapy (Rossiter, 2016:485).

Lithium trough levels are best measured before the next dose. Since lithium is given in divided doses, trough levels are measured 12 hours after the preceding dose. This is usually done in the morning (Reddy & Reddy, 2014:346).

Electrolytes such as sodium, potassium and chloride should be monitored before treatment and every 12 months after treatment initiation. Urea and electrolyte tests must be conducted regularly if lithium is co-prescribed with interacting drugs. These tests are important as they establish the baseline measures of the functioning of certain body systems (Prescribing Observatory for Mental Health, 2010:4).

Table 2-10 outlines the recommended monitoring requirements for patients on lithium. If mood changes are observed and there are any clinical indications, more frequent monitoring may be required (International Society for BDs 2009:68-69).

Table 2-10. Recommended monitoring guidelines for lithium therapy (International Society for BDs 2009:68-69).

Parameter	Investigation	When to monitor
Lithium	Plasma lithium concentration	Monitor closely after 1 week then at one month Monitor every 3-6 months for long term use
Thyroid function	Thyroid stimulating hormone levels (TSH) Free thyroxine (T_4)	Baseline then at 6 months Annually for long-term use of lithium
Renal function	Electrolytes Urea and creatinine Estimated glomerular filtration rate (eGFR)	Baseline, then annually Baseline, then at 6 months Baseline, then at 6 months
Weight	Body mass index (BMI), weight, body waist circumference	Baseline, then annually
Parathyroid function	Calcium concentrations	Baseline, then annually
Cardiac function	ECG[4] function	Baseline, then annually

The Drugs and Therapeutics Bulletin (DTB 2005), the Summary of Product Characteristics (SPC) for Priadel® and the British National Formulary (BNF 2007), NICE and British Association for Psychopharmacology (BAP) guidelines for BD 2003 have recommendations for monitoring patients receiving lithium therapy (Prescribing Observatory for Mental Health, 2010:3).

The respective recommendations are summarised in Table 2-11 (Prescribing Observatory for Mental Health, 2010:3).

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[4] ECG refers to Electrocardiogram

Table 2-11. Monitoring recommendations for lithium therapy (Prescribing Observatory for Mental Health, 2010:3).

Source	Serum lithium	Target range (mmol/L)	Urea and electrolytes and thyroid function tests
BAP guideline for BD 2003	Every 3-6 months	0.5-1.0 (up to 1.5mmol/L in acute mania)	Every 12 months
BNF 2007	Every 3 months	0.4-1.0	Every 6-12 months
DTB 2005	Every 3 months	0.4-1.0	Every 6 months
NICE guideline for BD 2006	Every 3 months	0.7-1.0	Every 6 months (Urea and electrolytes more often if interacting drugs are co-prescribed)
Priadel® SPC	Every 3 months	0.6-0.8	Requires periodic assessment

2.3.23.1 Laboratory tests

The following laboratory tests must be conducted for patients on lithium therapy.

2.3.23.1.1 Thyroid function

The necessary thyroid function tests that must be conducted are as follows (Schneider *et al.*, 2018:2):

- **TSH test:** This test will measure the amount of thyroid stimulating hormone levels. Elevated levels of TSH show hypothyroidism.
- **Free thyroxine (T$_4$):** This test will measure the free thyroxine in the body. Decreased levels of T$_4$ indicate hypothyroidism.

Interpretation of results

The interpretation of the results obtained is as follows (Schneider *et al.*, 2018:2):

- Elevated TSH and decreased T_4 levels indicated hypothyroidism.
- Elevated TSH levels and normal T_4 levels indicate subclinical hypothyroidism.

2.3.23.1.2 Renal function

Prolonged use of lithium affects renal function and therefore it is important to conduct tests. The necessary renal function tests that must be carried out are:

- **Creatinine:** This test is done to evaluate the efficiency of the kidneys. Creatinine is a product of creatine that is filtered by the kidneys. This test measures the amount of creatinine in the urine or blood. The normal creatinine clearance value is usually 100-130 ml/min in females and 110-150 ml/min in men. Raised creatinine levels above the upper limit of the normal range indicate kidney damage (Gowda *et al.*, 2010:170).

According to the National Kidney Disease Education Program, results from creatinine tests can be used to calculate the estimated glomerular filtration rate (eGFR) (Gowda *et al.*, 2010:170). The eGFR can be calculated using the patient's age, weight, gender along with the blood creatinine levels. The eGFR is recorded in ml/min/1.73m^2 and screens for early kidney damage (Michels *et al.*, 2010:1003).

The reference ranges for eGFR are depicted below in Table 2-12 (Gouden & Jialal, 2018:2).

Table 2-12. The eGFRs and their descriptions (Gouden & Jialal, 2018:2).

Kidney damage stage	Estimated GFR[5] (ml/min/1.73m^2)	Description
1	90+	Normal or minimal kidney damage with normal GFR
2	60-89	Mild decrease in GFR
3	30-59	Moderate GFR decrease
4	15-29	Severe GFR decrease
5	<15	Kidney failure

[5] GFR refers to Glomerular Filtration Rate

The Cockcroft-Gault equation for creatinine clearance is shown below (Michels *et al.*, 2010:1003).

$$\text{Creatinine clearance (ml/min)} = \frac{F \times \big(140 - \text{age} \times \text{weight (kg)}\big)}{\text{serum creatinine (mg/dL)} \times 72}$$

Where F = 1 for males and 0.85 for females.

- **Blood urea nitrogen (BUN):** This test is done to evaluate the health state of the kidneys and measures the amount of urea in the blood. Urea is formed when proteins are broken down by the liver. Raised BUN levels are an indication of kidney disease or failure. Elevated BUN levels could also be due to shock, fever, dehydration, congestive heart failure or blockage of the urinary tract by a kidney stone. BUN levels that exceed 100 mg/dl indicate severe renal damage. Decreased BUN levels are normally seen in fluid excess, though they can be a result of trauma, malnutrition, surgery or opioids (Gowda *et al.*, 2010:170).

The reference ranges of the BUN are depicted below in Table 2-13 (American Association for Clinical Chemistry, 2017).

Table 2-13. Reference ranges for BUN (American Association for Clinical Chemistry, 2017).

Age	Reference range
0-18 years	not available due to wide variability
Adult	2.1-7.1 mmol/L
>60 years	2.9-8.2 mmol/L

2.3.23.1.3 Sodium

This test indicates the amount of sodium in the blood. Sodium is an electrolyte that is usually affected by lithium administration. Lithium can affect the levels of sodium in the body and hyponatraemia can cause lithium toxicity. Therefore, serum sodium levels should be regularly checked for patients on lithium therapy (Dilmen *et al.*, 2016:220).

2.3.23.1.4 Potassium

Potassium is an electrolyte that is important for nerve and muscle communication. Potassium is the most conclusive electrolyte marker for renal failure. Decreased

secretion and filtration of potassium during renal failure results in increased potassium levels. The most life threatening complication in renal failure is therefore hyperkalaemia (Gowda *et al.*, 2010:171).

2.3.23.1.5 Calcium

Lithium has been hypothesised to alter the homeostasis of calcium by several mechanisms. Lithium causes hypercalcaemia by stimulating calcium reabsorption and it acts on the renal tubules and intestine. Lithium is known to stimulate the release of the parathyroid hormone which regulates calcium homeostasis. Hypercalcaemia is characterised by renal dysfunction, delirium and mood and behavioural changes (Shapiro & Davis, 2015:13).

Lithium-induced hyperparathyroidism (LIH) is a common and often overlooked complication of lithium therapy. Some symptoms of LIH such as fatigue and depression resemble symptoms of the mood disorder resulting in a delay in the diagnosis of LIH. It is therefore recommended to perform regular monitoring of parathyroid hormone and serum calcium levels by the International Society for BDs (ISBD) (Twigt *et al.*, 2013:1).

2.3.23.1.6 Lithium serum concentrations

This test measures the lithium levels in the blood to determine if they are in the therapeutic range. Lithium requires close monitoring of serum levels to avoid toxicity. It may also be done in order to assist with dose adjustment and to determine if additional drug therapy has an effect on lithium levels (Reddy & Reddy, 2014:346).

The therapeutic range of lithium is 0.8-1.2 mmol/L where patients will respond to lithium without experiencing toxicity. The recommended maintenance range of lithium is 0.6-1.0 mmol/L (Rossiter, 2016:485).

2.3.23.1.7 Glucose monitoring

Glucose is the main substrate for tissue energy production. Glucose tests must be conducted in order to identify any problems in glucose metabolism. Normal blood glucose levels are maintained by factors that control glucose utilisation and production.

Hormones such as insulin and glucagon are involved in glucose homeostasis (Güemes *et al.*, 2016:569).

The reference values for glucose in normal and diabetic patients are summarised in Table 2-14 (Goldenberg & Punthakee, 2013:9).

Table 2-14. Glucose reference values (Goldenberg & Punthakee, 2013:9).

Target levels of glucose				
Type	Random	Fasting	Pre-prandial (before meals)	Post-prandial (2 hours after meal)
Normal	<11.1 mmol/L	<6.1 mmol/L	4-5.9 mmol/L	<7.8 mmol/L
Prediabetes	N/A	6.1-6.9 mmol/L	N/A	7.8-11 mmol/L
Diabetes	≥11.1 mmol/L	≥7 mmol/L	4-7 mmol/L	<8.5 mmol/L

2.3.23.2 Physical examination

It is important that appropriate physical health monitoring is undertaken to ensure safe and effective use of drugs and to identify any new or worsening physical symptoms. The monitoring of lithium optimises its safety and effectiveness as it is a potentially toxic drug. Baseline monitoring identifies patients that are not suitable to be treated with lithium. On-going monitoring allows for the prompt identification of problems, thus allowing for the dose of lithium to be adjusted properly and for treatment optimisation (National Health Services, 2017:4).

2.3.23.3 Weight

Lithium can cause weight gain, therefore the weight and body mass index (BMI) of the patient is important. BMI can be defined as the measure of body fat based on the weight and height of an individual. BMI does not account for differences in body composition and body fat contribution to the overall body weight. BMI is however dependent on gender, age, ethnic group and leg length. Women usually have a lower BMI than men. The unit for BMI is kg/m^2 and the formula is as follows (Pasco *et al.*, 2014:1; Nuttall, 2015:120):

$$BMI \ (kg/m^2) = \frac{(weight \ (kg))}{height \ (m^2)}$$

There are reference values for BMI that indicate the weight status in different population groups and any problems related to weight in individuals. The reference values for BMI for adults are outlined in Table 2-15 (Nuttall, 2015:120).

Table 2-15. Reference values for BMI (Nuttall, 2015:120).

BMI value(kg/m^2)	Weight status
<18.5	Underweight
18.5-24.9	Normal
25-29.9	Overweight
≥30	Obese

2.3.23.4 Lifestyle review

It is important to assess the smoking, diet and physical activity of patients on lithium.

2.3.23.4.1 Smoking

Tobacco smoke contains polycyclic aromatic hydrocarbons that induce liver enzymes that metabolise clinically important drugs such as antipsychotics. Smoking induces the enzyme CYP1A2 and the activity of this enzyme is higher in smokers. This is clinically relevant for drugs with a NTI such as lithium. Smokers have been noted to have an increased clearance of drugs (Lucas & Martin, 2013:102).

Smoking cessation presents a risk of developing depression in patients. Therefore drugs such as bupropion and nicotine replacement therapy should be employed in order to aid the smoking cessation (Delva, 2008:480).

2.3.23.4.2 Diet

It is important to maintain therapeutic levels of lithium as there is potential for toxicity. The following dietary guidelines help maintain the required therapeutic levels of lithium.

- **Drink 8 to 10 glasses of water daily:** It is vital to keep hydrated as dehydration leads to increased levels of lithium. Hot days and exercise require a significantly higher intake of water. Drinking water and non-caloric beverages will avoid weight gain (National Institutes of Health, 2011:1).

- **Keep salt intake the same everyday:** Salt intake must be maintained daily as a high salt intake results in decreased levels of lithium. A low salt diet results in increased levels of lithium which will result in toxicity. It is important to avoid foods that have high sodium content such as processed meats (fish, ham, and bacon), processed cheese and tomato juice (Fairview Health Services, 2011:1).

- **Keep caffeine intake the same daily:** It is important to keep levels of caffeine consumed from tea, coffee or cola the same daily. A lower caffeine intake results in increased lithium levels and lithium levels are reduced by increased caffeine intake (National Institutes of Health, 2011:1).

- **Take lithium with food or milk:** This will reduce gastrointestinal adverse effects such as vomiting, diarrhoea and nausea (National Institutes of Health, 2011:1).

2.3.23.4.3 Alcohol

Alcohol should be avoided when on lithium therapy. It increases the incidence of nervous system adverse effects such as dizziness and sedation. Concurrent use of lithium and alcohol may impair judgement and thinking (National Alliance on Mental Illness, 2012).

2.4 Psychiatric disorders

2.4.1 Introduction

Mental, physical and social health are a vital component of life and are all interdependent. Therefore, with this understanding it is apparent that mental health is important for the well-being of individuals, societies and countries. People with mental disorders have a higher rate of mortality and disability (WHO, 2017a).

The World Health Organization (WHO), reports that people with schizophrenia and major depression have a 40% to 60% higher chance of dying prematurely when compared to the general population (WHO, 2013a). There is an association between mental disorders and substance use disorders. The combination of neurological, mental and substance disorders accounted for 13% of the global burden of disease in 2004. Depression accounts for 4.3% of the global burden of disease and is one of the leading causes of disability (WHO, 2013a:08).

Mental disorders have large economic consequences with a recent study estimating that between 2011 and 2030, US$16.3 million of economic output will be lost as a result of the global impact of mental disorders (WHO, 2013a:8). There is a large gap between the need and provision for treatment with between 76% and 85% of people with severe mental disorders in low-income and middle-income countries not receiving treatment for their disorder. Between 35% and 50% of people in high-income countries with severe mental disorders do not receive treatment (WHO, 2013a:8).

The WHO has proposed a Mental Health Action Plan 2013-2020 with a vision of creating a world where mental health is promoted, valued and protected. The overall goal of this plan is to encourage well-being, improve recovery, provide care and reduce mortality, disability and morbidity in people with mental disorders. The 4 objectives of the action plan are as follows (WHO, 2013a:9-10):

1. Implement strategies that will promote mental health and for prevention.
2. Provision of comprehensive, integrated and responsive mental health and social care services in community-based settings.
3. Strengthening an effective governance and leadership for mental health.
4. Strengthening the research, information and evidence for mental health.

The National Mental Health Policy Framework and Strategic Plan 2013-2020 was implemented by the South African government in 2013 with the aim of integrating mental health into the health system. This was a result of the huge burden of mental illness that South Africa has and the stigma and discrimination that people with mental illnesses encounter. The NMHPFSP specifies the recommendations for the careful monitoring and evaluation of psychotropic medication as well as the specific drug interactions in the treatment of mental disorders. This was all implemented in line with the broader quality improvement mechanisms in the Department of Health (Department of Health, 2013:19).

Biological, psychological and social factors influence mental illnesses. The relationship of these factors and the development of mental disorders is illustrated in Figure 2–4 (WHO, 2014b).
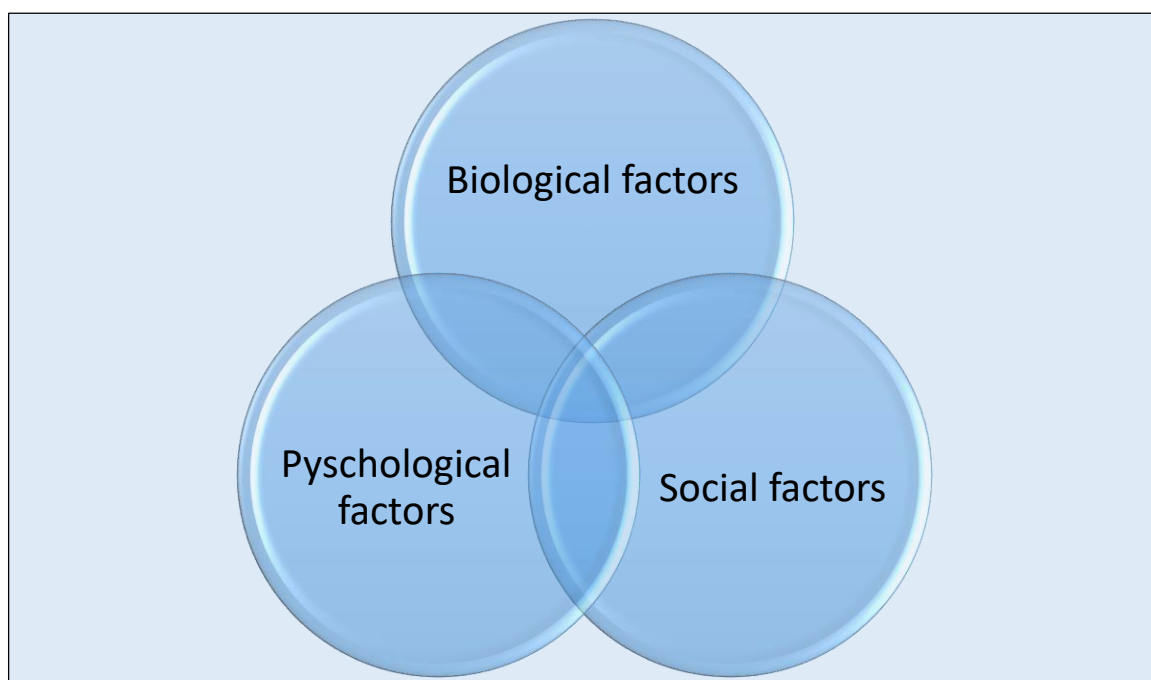
Figure 2–4. Factors that influence the development of mental disorders (WHO, 2014b).

2.4.2 Prevalence of psychiatric conditions

According to the WHO, about 60 million people suffer from BD, 50 million from dementia and 23 million from schizophrenia and psychoses globally (WHO, 2017a). In 2015, over 300 million (4.4%) people were estimated to have suffered from depression (WHO, 2017a:5). It was also seen that almost the same number of people suffers from anxiety and therefore it is impossible to add these numbers and reach a total for common mental disorders as they happen concurrently. The health loss due to these disorders is huge. (WHO, 2017a:5).

The WHO ranked depression as the largest contributor of disability with 7.5% of the world living with disabilities in 2015. It affects women more than men, occurring in 5.1% and 3.6% of women and men respectively. About 800 000 people commit suicide due to depression and anxiety disorders are ranked the 6th largest contributor to global disability (WHO, 2017a:5, 2017b).

The prevalence rate of depression varies by age with more numbers seen in adulthood. Depression can occur in children under the age of 15 although the frequency is lower than adults. More than 7.5% of females aged between 55-74 and 5.5% of men suffer from depression (WHO, 2017a:8).

Between 2005 and 2015, there was a 18.4% increase in the number of people living with depression. Anxiety disorders commonly occur more in women (4.6%) than in men (2.6%). About 246 million people have anxiety disorders and there was a 14.9% increase from 2005 due to growth and ageing of the population (WHO, 2017a:10).

The prevalence of depression varies depending on the WHO region. The different estimates according to regions are summarised in Figure 2–5 (WHO, 2017a:8,10).
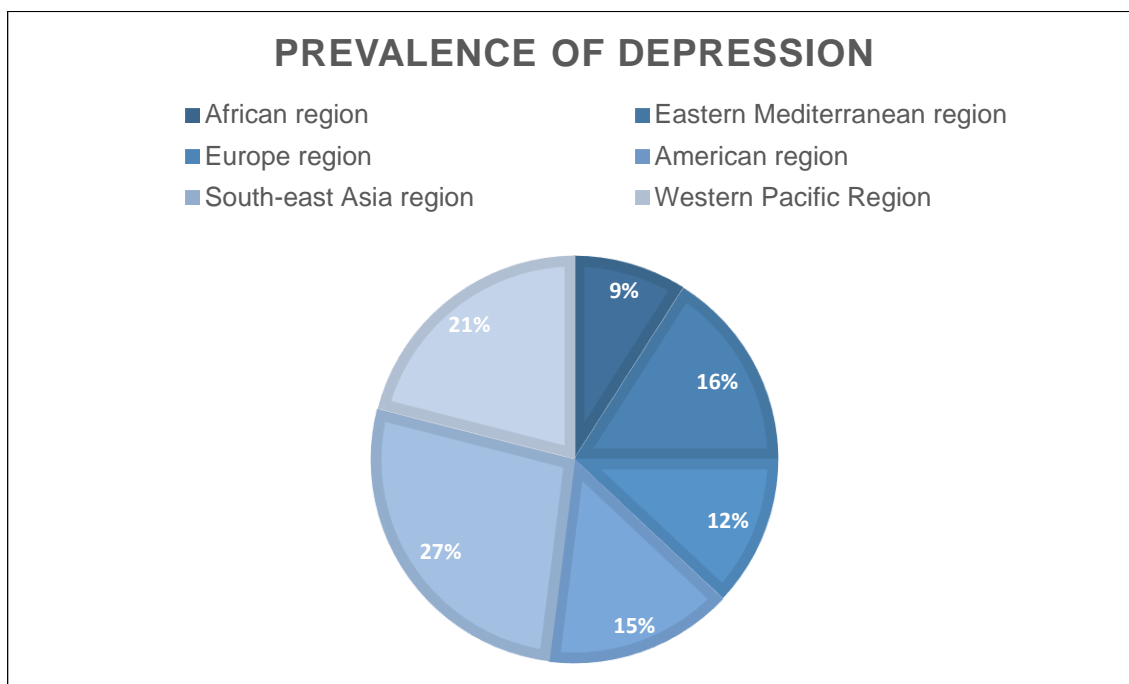
Figure 2–5. Prevalence of depression globally (WHO, 2017a:8,10).

Diagnoses were made based on the Composite International Diagnostic Interview (CIDI) by the WHO for the Diagnostic and Statistical Manual, 4th edition (DSM-IV) disorders. The common psychiatric conditions in South Africa according to the DSM-IV/CIDI criteria were documented. The most prevalent disorders were alcohol abuse, major depression and agoraphobia with 11.4%, 9.8% and 9.8% respectively (Stein *et al.*, 2009:114) . Anxiety disorders (15.8%) were the most common class of disorders followed by substance use (13.3%) and mood disorders (9.8%). The lifetime estimate of any disorder was 30.3% with 11.2% having two disorders and 3.5% having three or more disorders (Stein *et al.,* 2009:114). However, there is lack of nationally representative data on the prevalence of psychiatric conditions in South Africa.

2.4.3 The diagnostic and statistical manual of mental disorders

The American Psychiatric Association published this system of classification for recognised mental disorders, dividing them into clearly defined categories based on sets of objective criteria. DSM is widely recognised as a diagnostic standard globally used for assessing and categorising mental disorders (Kawa & Giordano, 2012:3).

The first edition (DSM-I) was in published 1952. The 102 construed diagnostic categories in this edition were based on psychodynamic aetiological explanations. The theories of Adolf-Meyer were reflected in the nomenclature and included terms such as depressive reaction. The second edition (DSM-II) was published in 1968. One of the major changes in DSM-II was the further expansion of the definitions of mental illness that were arguably in line with a broadening of psychodynamic theory. This was done to include milder conditions that were observed in the general population. In the 1980 DSM-III edition, an explicit definition of the criteria and multiaxial system where the different components of a patient's condition could be accessed separately was introduced (Kawa & Giordano, 2012:4).

Clarifications and improvements were in the revised third edition of the DSM (DSM-IIIR) in 1987. The fourth edition (DSM-IV) of 1994 was based on ICD9 and the Organic Mental Syndromes and Disorders section was renamed to Delirium, Dementia, and Other Cognitive Disorder. This was done to eliminate the assumption that other mental disorders that were not in this category were not organic (Kawa & Giordano, 2012:6).

The fifth edition (DSM-V) was published in 2013, though there is controversy associated with its use. Reliability and validity are the two key feature of a diagnostic system. According to Peter (2008), DSM-V has failed to provide the validity that is expected from it. Validity in this context is defined as any additional information about the aetiology and/or prognosis of an individual's clinical state that is beyond description. DSM-III and DSM-IV provided reliability and increased research and the time that was taken to produce the DSM-V criteria was too short to develop an agenda that would provide a valid diagnostic system (Peter, 2008:853).

According to Van Heugten-Van der Kloet and Van Heugten *et al.*, one of the problems associated with the use of DSM-V is that it is a categorical system. In this system, the

individual conditions are regarded as discrete units which are either you have it or you don't. This presents a problem as most psychiatric disorders that have been analysed thus far by taxometric means are dimensional in nature. The categorical approach is the core of DSM-V even though it took a modest step in employing a dimensional approach (Van Heugten-Van der Kloet & Van Heugten, 2015:1).

A comparison of the advantages of a dimensional and categorical system approach are outlined in Table 2-16 (Van Heugten-Van der Kloet & Van Heugten, 2015:3).

Table 2-16. Advantages of dimensional and categorical classification system (Van Heugten-Van der Kloet & Van Heugten, 2015:3).

Dimensional	Categorical
• Avoids misleading, unstable and illusory effects • Better ability to recognise subthreshold conditions • Criteria to assess is less with smaller set of underlying dimensions of functioning • Decisions with regards to hospitalisation or medication has many different cut-off points • More specific and complex and precise information • Potential to facilitate the development of distinctions between normal and abnormal functioning • Valid internally to describe specific patient's psychopathology.	• Causes confusion as minor changes in a diagnostic criterion causes significant changes in prevalence rates. This further complicates the public health policy and scientific theories • Decisions regarding hospitalisation and medication is categorical with specific distinctions required to guide clinical decisions • Frequent use of "Not Otherwise Specified" causes lack of clinical utility with inadequate diagnostic coverage • Misleading and inaccurate descriptions • Numerous valid categorical distinctions • Presents useful information in a concise manner with one diagnosis.

The ICD10 is used worldwide, reflecting the views and needs of the international psychiatric community. DSM-IV and ICD10 have similar classification systems

although there are differences. They differ in the nomenclature such as 'antisocial' or 'dissocial'. The ICD10 includes borderline and impulsive disorder as subtypes of being emotionally unstable (Loranger *et al.*, 2007:115).

The ICD10 has different categories for defining and diagnosing psychiatric conditions. The criteria for diagnosing schizoaffective disorder (SD), BD and MDD are summarised in Table 2-17 (WHO, 2013:89-109).

Table 2-17. Criteria for diagnosing schizoaffective disorder (WHO, 2013:89-109).

Disorder	Category
SD	F25.0 SD, manic type
	F25.1 SD, depressive type
	F25.2 SD, mixed type
	F25.8 Other SDs
	F25.9 SD, unspecified
BD	F31.0 BD, current episode hypomanic
	F31.1 BD, current episode manic without psychotic symptoms
	F31.2 BD, current episode manic with psychotic symptoms
	F31.3 BD, current episode mild or moderate depression
	.30 Without somatic syndrome
	.31 With somatic syndrome
	F31.4 BD, current episode severe depression without psychotic symptoms
	F31.5 BD, current episode severe depression with psychotic symptoms
	F31.6 BD, current episode mixed
	F31.7 SD, currently in remission
	F31.8 Other BDs
	F31.9 BD, unspecified
MDD	F32.0 Mild depressive episode

Disorder	Category
	.00 Without somatic syndrome
	.01 With somatic syndrome
	F32.1 Moderate depressive episode
	.10 Without somatic syndrome
	.11 With somatic syndrome
	F32.2 Severe depressive episodes without psychotic symptoms
	F32.3 Severe depressive episodes with psychotic symptoms
	F32.8 Other depressive episodes
	F32.9 Depressive episode, unspecified
Persistent mood (affective) disorders	F34.0 Cyclothymia

2.4.4 Schizoaffective disorders

Schizophrenic and affective symptoms occur simultaneously either within the same episode or in episodes that are a few days apart. The relationship of these disorders between typical mood and schizophrenic disorders is uncertain. Patients who suffer from recurrent schizoaffective episodes that are manic in nature usually go through a full recovery (WHO, 2013:91).

There are different diagnostic guidelines for the different categories of SD and are outlined in Table 2-18 (WHO, 2013:91).

Table 2-18. Diagnostic guidelines for schizoaffective disorder (WHO, 2013:91).

Condition	Description	Diagnostic criteria
SD	Episodic disorders where affective and schizophrenic symptoms are prominent within the same episode of illness, preferably simultaneously, but at least within a few days of each other	When definite schizophrenic and affective symptoms are prominent simultaneously with a few days of each other or the same episode
SD, manic type	A disorder which involves the prominent presence of schizophrenic and manic symptoms in the same episode of illness	At least one schizophrenic symptom in an episode An elevation of mood paired with increased excitement or irritability
SD, depressive type	A disorder which involves the prominent presence of schizophrenic and depressive symptoms in the same episode of illness	Prominent depression associated with at least two symptoms of depression in the same episode At least one typical schizophrenic symptom should be clearly present
SD, mixed type	Disorders where the symptoms of schizophrenia coexist with those of a mixed bipolar affective disorder	Includes cyclic schizophrenia, mixed schizophrenic and affective psychosis

2.4.5 Bipolar disorder

This condition involves at least two episodes where the patient's mood is significantly disturbed with episodes of mania (elevated mood) and depression (decreased mood) (WHO, 2013:97).

Some of the diagnostic criteria of BD are outlined in Table 2-19 (WHO, 2013:97-99).

Table 2-19. Diagnostic criteria for bipolar disorder (WHO, 2013:97-99).

Disorder	Description	Diagnostic criteria
BD	At least two episodes consisting of mania or hypomania and depression.	• Manic episodes usually begin abruptly and last for between 2 weeks and 4-5 months • Depression occurs for about 6 months
BD, current episode mixed	At least one manic, hypomanic, or mixed affective episode has been experienced in the past by the patient and currently exhibits either a mixture or a rapid alternation of manic, hypomanic, and depressive symptoms	Manic and depressive symptoms should be present
BD, currently in remission	A disorder between alternating episodes of mania and depression but patient is not currently suffering from any significant mood disturbance, and has not done so for several months	• The patient has had at least one manic, hypomanic, or mixed affective episode in the past • Patients should have suffered in addition at least one other affective episode of hypomanic, manic, depressive, or mixed type

2.4.6 Depressive episodes

Depressed mood, loss of interest and decreased energy are clinical symptoms of all forms of depression, namely mild, moderate and severe depression. A duration of at least 2 weeks is usually required for diagnosis for all the three different types of depression but shorter periods may be reasonable if symptoms are unusually severe and of rapid onset (Mccormick *et al.*, 2015:532).

2.4.7 Cyclothymia

This is a disorder characterised by persistent instability of mood, involving numerous periods of mild depression and mild elation. Establishment of the diagnosis is difficult if there is no observation over a prolonged period or an account of the patient's past behaviour (WHO, 2013:106).

The diagnostic criteria for cyclothymia is outlined in Table 2-20 (WHO, 2013:106-107).

Table 2-20. Diagnostic criteria for cyclothymia (WHO, 2013:106-107).

Disorder	Description	Diagnostic criteria
Cyclothymia	This disorder is common in the relatives of patients with bipolar affective disorder	• Persistent instability of mood, involving numerous periods of mild depression and mild elation • These characteristics shouldn't be sufficiently prolonged to fulfil the criteria for BD or recurrent depressive disorder

2.4.8 Bipolar disorder

BD is a brain disorder that is characterised by recurrent phases of depressive, hypomanic and manic symptoms. These phases are described as the mood episodes.

Patients affected by BD also have intervening periods that are symptom free. BD affects the patient's quality of life, health status and functioning (Jann, 2014:489).

According to the Depression and Bipolar Support Alliance (2018), BD is common in all ages, races and ethnic groups. BD affects equal numbers of men and women though research has indicated that three times as many women than men experience rapid cycling (Depression and Bipolar Support Alliance, 2018).

2.4.8.1 Aetiology of bipolar disorder

Several factors have been identified as risk factors for developing BD. These include genetics, perinatal, neuroanatomic and neurochemical abnormalities.

2.4.8.1.1 Genetics

High genetic transmission risks have been associated with BD. Studies have shown that people that have a first degree relative with BD is 7 times likely to develop BD. Studies between monozygotic and dizygotic twins have indicated that there is a 33.90% concordance for BD in identical twins. This is due to the fact that identical twins share 100% of their DNA. BD also has a major genetic component that affects the ankyrin 3 (ANK3), calcium channel, voltage-dependent, L type, alpha 1C subunit (CACNA1C), and Circadian Locomotor Output Cycles Kaput (CLOCK) genes (Ayano, 2016:2).

2.4.8.1.2 Perinatal factors

Numerous investigations have reported the link between obstetric complications and the early onset of BD. BD has been associated with increased risks of perinatal birth complications. However, the significance of these findings in causing BD are still unclear (Ayano, 2016:2).

2.4.8.1.3 Neurochemical factors

Multiple pathways have been implicated in BD. The catecholamine hypothesis indicates that a decrease in adrenaline and noradrenaline causes depression and an increase causes mania. Increased levels of glutamate also contribute to the development of BD. Other neurotransmitters implicated in its aetiology are 5-HT and DA that can trigger mania (Ayano, 2016:2).

2.4.8.1.4 Environmental factors

Studies have shown that people with BD experience recurrent stressful events prior to their first mood episode. Negative life events have been linked with the manic or hypomanic and depressive episodes of BD (Ayano, 2016:3).

2.4.8.2 Manic phase of bipolar disorder

The manic phase of BD is mainly a phase where the individual feels high spirited with more energy than usual and occurs at least once a week. At least one lifetime manic episode is required to make a diagnosis of BD. This phase may involve three or more of the following symptoms (Maurel *et al.*, 2010:24; Mccormick *et al.*, 2015:532).

- Increased indulgence in risky behaviour such as reckless driving.
- Exaggerated self-esteem.
- Reduced need for sleep.
- Decreased attention.
- Elevated mood.
- Increased goal-directed activities.
- Racing thoughts.
- Excessive irritability.
- Risk taking behaviour.

2.4.8.3 Depressive phase of bipolar disorder

For a diagnosis of BD to be made, at least one past or current hypomanic and one past or current major depressive episode are required. The depressive phase of BD occurs in a period of two weeks and the patient has at least five symptoms. This phase usually has a negative impact on the social wellbeing of the patients and is characterised by the following (Mccormick *et al.*, 2015:532):

- Suicidal ideation.
- Low self-esteem.
- Loss of interest or pleasure.
- Intense feeling of worthlessness, sadness and despair.
- Fatigue and lethargy.

- Agitation.
- Sleeping problems (insomnia or hypersomnia).
- Feeling guilty.
- Negative thoughts regarding the future.
- Eating excessively.
- Trouble with concentration.

2.4.8.4 Hypomanic phase of bipolar disorder

A diagnosis of BD can be made if there has been at least one past or current hypomanic and at least one past or current major depressive episode. Abnormal and persistent elevated or irritable mood along with increased energy are characteristic of hypomania. The hypomanic phase is similar to the manic phase but the symptoms are less severe when compared to those in a manic phase. The hypomanic phase can last for four days in a row but does not affect function like mania and the mood disturbances can be observed by others (Mccormick *et al.*, 2015:532).

2.4.8.5 Bipolar I disorder

Bipolar I, bipolar II and cyclothymic disorder are the three conditions that fall under the BD category. Bipolar I disorder is characterised by manic and depressive episodes. The manic episode in bipolar I disorder is severe and may lead to hospitalisation as it causes functional impairment. This disorder is diagnosed when a person has a manic episode (Jann, 2014:489).

2.4.8.6 Bipolar II disorder

Bipolar II disorder is defined by depressive and hypomanic episodes that are major. The depressive symptoms can be severe and these individual usually have co-existing mental illnesses such as anxiety. The main difference between bipolar I and bipolar II is the severity of the manic episodes with full mania causing severe functional impairment and hospitalisation. Hypomania on the other hand is not severe enough to cause remarkable functional impairment or to necessitate hospitalisation (Jann, 2014:489).

2.4.8.7 Cyclothymic bipolar disorder

The core features of cyclothymic disorder are extreme mood instability and reactivity associated with emotional dysregulation. It has an early onset that presents as a complex clinical picture due to the impulsive behaviours and reactive mood fluctuations. Intense mood changes of all polarities, over reacting to stimuli, changes in motivation and energy are experienced in the emotional dysregulation (Perugi *et al.*, 2017:372).

The diagnostic features of cyclothymic disorder include a number of depressive and hypomanic episodes for a period greater than 2 years, not meeting the diagnostic criteria for hypomania and major depressive episodes and no symptom free period that is longer than 8 weeks during the 2-year period (Bobo, 2017:1536).

2.4.8.8 Rapid cycling

This is a specifier for diagnosing BD and involves four or more episodes of manic, hypomanic, or major depressive episodes during a 12-month period (Mccormick *et al.*, 2015:532). It is often a severe and refractory form of BD. Rapid cycling is associated with a higher risk for suicide attempt and alcohol abuse and less favourable outcomes with more pronounced effects (Backlund *et al.*, 2010:1).

The pharmacological treatment that has been used to treat rapid cycling bipolar I or bipolar II disorder include lithium, quetiapine, carbamazepine, aripiprazole, olanzapine, lamotrigine and valproate. The use of one these drugs or in combination is recommended for rapid cycling with psychosis. Risk factors for rapid cycling include thyroid disorder, substance use disorders and antidepressant drug use. It is therefore recommended to screen for substance abuse, discontinue antidepressants and treat thyroid diseases when managing patients with rapid cycling BD (Bobo, 2017:1546).

The exact causes of this condition are unknown but three overlapping theories have been suggested. These theories are:

1. **Sensitization or kindling:** According to this theory, episodes are triggered by the anticipation of life events or actual life events such as death of a loved one. As a result, the patient becomes more sensitive to minor triggers or stressors over time, causing an episode in response to the triggers. Eventually, episodes may occur without triggers, increasing the frequency of episodes and the chances of rapid or ultra-rapid cycling (Depression and Bipolar Support Alliance, 2016).

2. **Circadian rhythm abnormalities:** This theory suggests that people with rapid cycling have daily biological rhythms that don't match the normal cycle. Sleep disturbances that are characteristic of mania and depression seem to be accounted for by this theory. There is a possibility that the abnormal daily biological rhythms can prolong the duration and contribute to the seriousness of the illness and not necessarily cause it (Depression and Bipolar Support Alliance, 2016).

3. **Hypothyroidism:** According to this theory, inadequate amounts of thyroid hormone in the brain can cause rapid cycling. Most patients with rapid cycling have normal thyroid levels but respond well to treatment with thyroid hormone regardless of their blood levels (Depression and Bipolar Support Alliance, 2016).

A summary of the diagnostic criteria of BD according to DSM-V is outlined in Table 2-21 (Mccormick *et al.*, 2015:532).

Table 2-21. Diagnostic criteria of BD according to DSM-V (Mccormick *et al.*, 2015:532).

Episode	Description
Hypomanic episode • At least one past or current hypomanic episode and a past or current major depressive episode are required for diagnosis of BD	• Abnormal and persistent mood that is elevated or irritable with increased activity that last for at least four days • Others can observe the mood disturbances • Symptoms are the same as those for mania • Symptoms are less severe to cause any marked impairment

Episode	Description
Major depressive episode • Criteria is the same for MDD and depressive episodes of BD • At least one past or current hypomanic episode and a past or current major depressive episode are required for diagnosis of BD	Five or more of the following symptoms should be present over a 2-week period with depressed mood or loss of interest nearly on a daily basis: • Agitation • Depressed mood • Difficulty concentrating • Fatigue • Feeling of worthlessness • Insomnia or hyper insomnia • Loss of interest or pleasure • Suicidal ideation • Weight gain or loss

Manic episode
A diagnosis of BD requires at least one lifetime manic episode
	• Abnormal and persistent mood that elevated or irritable mood and increased activity that last for at least one week
	• Three or more of the following symptoms or four if the mood is irritable:
	  • Decreased sleep
	  • Goal agitation
	  • Increased self esteem
	  • Increase in risk taking behaviours
	  • Racing thoughts
	  • Talking too much
	• Symptoms are severe to cause marked impairment

Episode	Description
Specifiers	**Description**
Anxious distress	At least two of the following symptoms must appear during the most recent mood episode on most days: • Trouble concentrating • Fear that something bad may happen • Individual may feel like they may lose control • Tense • Abnormally restless
Mixed features • Depressive episode with mixed features • Hypomanic or manic episode with mixed features	• Meets criteria for depressive episode with at least three hypomanic or manic symptoms • Meets criteria for a hypomanic or manic episode with at least three depressive symptoms
Rapid cycling	Four or more episodes of hypomanic, major depressive or manic episode in a period of 12 months

2.4.8.9 Prophylaxis

The BALANCE (Bipolar Affective disorder: Lithium/Anticonvulsant Evaluation) study demonstrated the efficacy of lithium and valproate in BD prophylaxis. Lithium is the only drug that has proven to have prophylactic activity in BD. Combination therapy of lithium and valproate has been shown to be effective in prophylaxis compared to valproate monotherapy. Lithium monotherapy is more effective than valproate monotherapy (Allan, 2012:389).

2.4.8.10 Maintenance

Treatments that should be used in maintaining bipolar patients are those that are effective in the acute phase of BD. The combination of pharmacotherapy is often superior to monotherapy in preventing relapses. Mood stabilisers and atypical

antipsychotics are effective in preventing manic episodes of BD. Lithium, lamotrigine, olanzapine and quetiapine are some of the pharmacological treatments that can be used in the maintenance phase of BD. Lithium is generally more effective than the other treatments (Bobo, 2017:1542).

2.4.8.11 Other treatment options for bipolar disorder

2.4.8.11.1 Introduction

There have been recent developments in the treatment of acute and long term BD. However, these advances have remained quite modest with antipsychotics such as quetiapine and anticonvulsants such as lamotrigine being used in the treatment of BD. Psychosocial interventions have been used adjunctively to drugs and these have proven to be of benefit (Geddes & Miklowitz, 2013:1).

2.4.8.11.2 Antipsychotics

Antipsychotics are usually used as adjunctive therapy to lithium as lithium is superior in mood stabilisation and ideation. Atypical antipsychotics are generally used as they are considered to have lower extrapyramidal effects. The most commonly used atypical antipsychotics include quetiapine and olanzapine (Geddes & Miklowitz, 2013:1).

Antipsychotics are effective in the treatment of acute mania with variable efficacy in the treatment of depression. However, quetiapine has shown the clearest evidence in the treatment of depression. Better symptomatic improvements in patients with bipolar depression have been noted in patients that are on quetiapine therapy. Patients that continue to take quetiapine and have responded to the acute phase treatment have been shown to have a reduced risk of recurrence based on some evidence. Quetiapine has a fast onset of action which is clinically useful because it can be initiated early in the course of worsening depression (Geddes & Miklowitz, 2013:1,3).

Olanzapine is effective in the treatment of BD but studies have shown that it is more effective when combined with fluoxetine. The olanzapine-fluoxetine combination offers more symptomatic relief of depressive symptoms. This evidence suggests that the combination of fluoxetine and olanzapine is synergistic or that fluoxetine can be used

in the treatment of bipolar depression (Derry & Moore, 2007:40; Geddes & Miklowitz, 2013:1,3).

2.4.8.11.3 Anticonvulsants

Anticonvulsants are used in the treatment of psychiatric conditions such as alcohol and benzodiazepine withdrawal symptoms, panic and anxiety disorders and BD. The anticonvulsants recognised as mood stabilisers are carbamazepine, sodium valproate and lamotrigine. These anticonvulsants are heterogeneous in their mechanisms of action and their efficacy varies in the various mood states of BD (Grunze, 2010:127).

2.4.8.11.3.1 Carbamazepine

This drug is generally used in the treatment of acute mania or mixed bipolar episodes, though it is not indicated to treat BD. However, lithium, valproate and other atypical antipsychotics are preferred over carbamazepine. This is due to lack of data supporting its use in depressive phase of BD or in the maintenance phase. Carbamazepine is associated with complications in dosing due to its burden of adverse effects, drug interactions and enzyme induction. The adverse effects commonly associated with its use include dizziness, nausea, vomiting and somnolence. Carbamazepine is usually used when other treatments have failed (Nierenberg, 2010:24; Khoo, 2012:166).

2.4.8.11.3.2 Lamotrigine

Lamotrigine has been proven to be effective in the treatment of the depressive phase of BD though it lacks acute antimanic efficacy. It has prophylactic efficacy against manic and depressive relapse. Lamotrigine has been associated with minimal adverse effects when compared to lithium. It is associated with minimal to no weight gain and sedation. Severe dermatological reactions such as Stevens Johnson syndrome may occur. Lamotrigine appears to be well tolerated and compatible when used concurrently with lithium, valproate, antipsychotic and antidepressant drugs (Nierenberg, 2010:26; Khoo, 2012:166).

2.4.8.11.3.3 Valproate

Valproate is used in the treatment of acute mania and is more effective than lithium in the treatment of mania associated with depressive symptoms or mixed mania. It is therefore a recommended first line treatment in mixed manic patients or acute mania. There is limited data, however, regarding its efficacy in depression or prevention (Khoo, 2012:165).

Valproate usually causes sedation as an adverse effect with weight gain being at least as common as with lithium. Pancreatitis and hepatotoxicity are rare adverse effects of valproate. Combination treatment of lithium and sodium valproate has shown greater rates of clinical improvement when compared to lithium monotherapy, though there is the risk of toxicity (Khoo, 2012:165; Del Grande *et al.*, 2014:9).

2.4.8.11.4 Psychosocial interventions

An integration of pharmacotherapy and targeted psychotherapy has been recommended in various treatment guidelines for optimum treatment of BD. Some models of evidence-based psychotherapy include cognitive-behavioural therapy, family-focused therapy, interpersonal and social rhythm therapy as well as group psychoeducation. These models all have common goals, though they differ in their assumptions, structure and methods (Geddes & Miklowitz, 2013:5). The common goals of psychosocial interventions for BD treatment are outlined (Geddes & Miklowitz, 2013:16):

- Decrease alcohol and drug use.
- Enhance adherence to drug therapy.
- Increase awareness and acceptance of the illness.

2.4.8.11.4.1 Cognitive behavioural therapy

The recognition that manic episodes are often linked to excessive optimistic thinking has led to the adaptation of cognitive behavioural therapy (CBT) in the treatment of the depressive phase of BD. The assumption of CBT is that the recurrences of mood disorders are determined by negative thinking in response to life events and fundamental beliefs that are dysfunctional about the world or oneself. However, the

use of CBT in the adjunctive prevention of relapse is inconclusive (Geddes & Miklowitz, 2013:6).

2.4.8.11.4.2 Family-focused therapy

Family focused therapy (FFT) is considered time limited and modularised treatment that comprises of communication enhancement training, psychoeducation and problem solving skills. This family approach offers patients an opportunity to gain control over simultaneous episodes while building skills that might prevent or decrease the impact of future episodes. The effectiveness of FFT in adjunction to pharmacotherapy has been proven in numerous researches. The combination of other promising methods and FFT can provide a strong base for special populations based on age of onset, family organisation, severity of symptoms and comorbid features (Morris *et al.*, 2007:11).

2.4.8.11.4.3 Interpersonal and social rhythm therapy

Social rhythm therapy (SRT) was developed by Ellen Frank for outpatients that had BD. It is based on the social hypothesis theory of depression that integrates research in the areas of sleep or circadian rhythm and life events. SRT improves the stability of daily activities such as the sleep-wake cycle in order to minimise the impact of disrupting the circadian cycle (Haynes *et al.*, 2016:1).

Social rhythms refer to the pattern by which daily activities occur such as eating supper at 07:00 p.m. rather than the frequency (eating supper everyday) or type (e.g. pleasurable or routine) of behaviours. SRT involves elements of scheduling activities and activation of behaviour. SRT therefore encourages patients with dysregulated mood to develop and maintain moderately active and consistent routines as social rhythm instability is a risk factor for mood disruption (Haynes *et al.*, 2016:2).

2.4.8.11.4.4 Group psychoeducation

The use of group approaches that follow a predetermined curriculum has been suggested. Emphasis on the awareness of the illness, adherence to medication, sleep and wake regularity and early detection of recurrences is set in the Barcelona approach. A trial of patients with BD types I and II in the euthymic phase of BD was conducted. 21 sessions of structured group psychoeducation and pharmacotherapy

as well as 21 unstructured sessions were randomly assigned to patients. Results showed that after 5 years of treatment, there were fewer relapses in patients who were involved in the structured groups when compared to those that were in unstructured groups (Geddes & Miklowitz, 2013:7).

2.4.9 Major depression

One of the most common psychiatric conditions is MDD. It is characterised by dysregulation of mood and affect. Other abnormalities such as sleep and appetite disturbances, cognitive dysfunction and fatigue are associated with this condition. Unipolar depressive disorder is the term that is usually used to differentiate MDD from depression that alternates with episodes of mania (Villanueva, 2013:1).

MDD is not a condition that is limited to adults and the elderly. It has been shown to have onset in childhood and adolescents. MDD occurs in older adolescents at levels that can be compared to adults. The point prevalence of MDD is 2% in childhood and between 5% and 8% in adolescents and adults (Rohde *et al.*, 2013:42). Patients that experience this early onset of MDD continue to suffer from depression in their adulthood. It is a lifelong disorder characterised by multiple recurrences, averaging from one episode in every 5 years in about 70% of child and adolescent patients. Reports have shown that the risk of suicide increases with age from adolescence to childhood or in recurrent MDD cases (Rohde *et al.*, 2013:42).

For one to be diagnosed with MDD, they need to meet the criteria as stated in the DSM. A person with MDD must have five or more of the symptoms stated and must experience them at least once a day for a period longer than two weeks. According to the DSM-IV-TR, the symptoms must not meet the criteria for a mixed episode and should cause clinical distress or impairment in the normal functioning of an individual. The symptoms must not be due to a medical condition or direct psychological effects of a substance, e.g. a drug of abuse. The symptoms must not be due to bereavement and should persist for more than two weeks and characterised by suicidal ideation, marked functional impairment and psychotic symptoms (Reynolds & Kamphaus, 2013:1).

The criteria for MDD according to DSM-IV-TR requires that 5 of the following must be present continuously for a 2-week period with at least 1 being depressed mood or lack of interest (Soleimani & Lapidus, 2011:178):

- Depressed mood or irritable most of the day, nearly every day.
- Fatigue or loss of energy on a daily basis.
- Diminished ability to think, concentrate or indecisiveness nearly every day.
- Significant weight change or a change in appetite.
- Recurrent suicidal ideation, thoughts of suicide and death and having a suicide plan.
- Changes in sleep pattern (insomnia or hypersomnia).
- Psychomotor agitation or retardation nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt.
- Decreased interest or pleasure in most activities, most of each day.
- No history of BD.
- Symptoms not accounted for by bereavement.
- Symptoms should cause clinically significant impairment.

2.4.9.1 Treatment resistant depression

Treatment resistant depression (TRD) is a common clinical condition among patients being treated for major depressive disorder. Patients with TRD do not respond to the first line treatment of depression or combinations of the newer generation antidepressants and adjunctive therapy with atypical antipsychotics (Thase, 2017:42).

Unipolar major depressive disorder is being considered refractory or resistant when two antidepressants of different pharmacological classes fail to produce a clinically significant improvement at least twice. The two classes of antidepressants should have been administered according to their respective guidelines with regards to dose, duration and compliance. Patients should be assessed for accuracy of diagnosis, medical adherence and for other factors that can exacerbate depression such as coexisting psychiatric, medical or psychosocial disorders (Souery *et al.*, 2006:21).

There are many organic causes of depression and Table 2-22 summarises some of these causes (Ebert *et al.*, 2008:312-313).

Table 2-22. Some organic causes of depression (Ebert *et al.*, 2008:312-313).

Category of causes	Conditions
Infectious diseases	• Tuberculosis • Influenza • Encephalitis • Human immunodeficiency virus (HIV) • Infectious hepatitis
Cardiovascular disorders	• Hypoxia • Chronic heart failure • Post myocardial infarction
Metabolic and endocrine disorders	• Diabetes mellitus • Hypokalaemia • Cushing's syndrome • Anaemia • Addison disease
Collagen- vascular conditions	• Rheumatoid arthritis • Systemic lupus erythematosus
Medications	• Antibiotics • Analgesics, e.g. indomethacin • Antihypertensives with catecholamine effects, e.g. propranolol • Sedative hypnotics, e.g. barbiturates • Oral contraceptives
Neurological diseases	• Dementia • Migraine • Parkinson disease • Stroke • Wilson disease
Neoplasm	• Bronchogenic carcinoma • Lymphoma • Pancreatic cancer

Category of causes	Conditions
Commonly abused substances	• Alcohol • Cocaine withdrawal • Opiates
Other conditions	• Chronic pyelonephritis • Pancreatitis

A variety of psychotherapeutic techniques can be used to treat depression. However, there is limited evidence of the effectiveness of psychotherapeutic techniques used to treat TRD. There is a clinical approach that is being used to treat TRD and is depicted in Figure 2–6 below (Souery *et al.*, 2006:21).
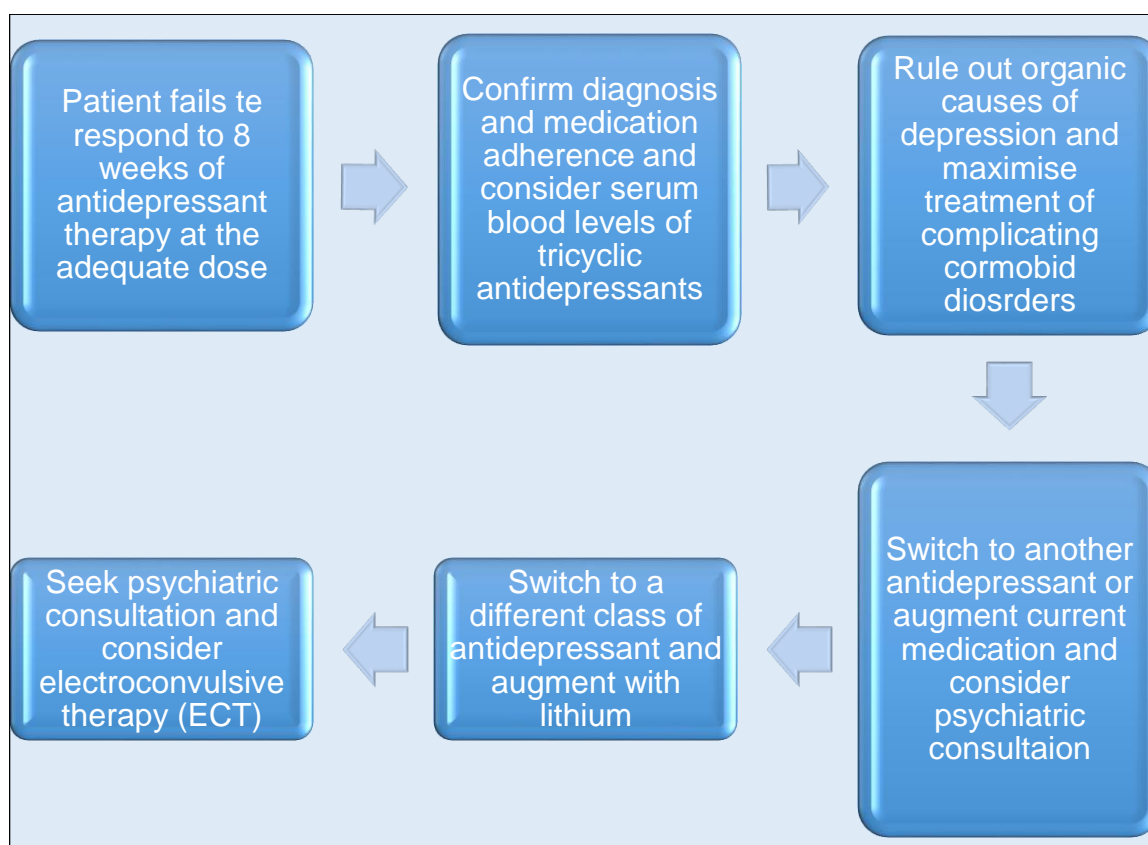
Figure 2–6. Approach used to treat treatment resistant depression (Souery *et al.*, 2006:21).

2.4.10 Other psychotic disorders

2.4.10.1 Schizoaffective disorder

Schizoaffective disorder (SD) is a chronic mental disorder that is primarily characterised by symptoms of schizophrenia, such as delusions and hallucinations. It also presents with symptoms of a mood disorder such as mania and depression. In this case the SD reflects as a co-occurrence of schizophrenia and a mood disorder (bipolar or major depressive disorder). When the SD reflects as a severe form of either major depressive or BD, there is failure of episode-related psychotic symptoms to remit between mood episodes. SD usually overlaps between BD and schizophrenia and as a result most people are misdiagnosed with either BD or schizophrenia (Abrams *et al.*, 2008:1089; National Alliance on Mental Illness, 2018).

SD was regarded as a subtype of schizophrenia by the first (1952) and second (1968) edition of the DSM. Differentiating between schizoaffective, schizophrenia and BDs can be difficult as they have overlapping symptoms. The DSM-V is used as a basic tool in diagnosing mood disorders (Abrams *et al*; 2008:1090; Yogeswary, 2014:13).

The research diagnostic criteria (RDC) attempted to differentiate SD from psychotic mood disorders. The RDC defines SD as "the acute occurrence of a full mood syndrome (depression and/ or mania) and one of a set of "core schizophrenic" symptoms such as bizarre delusions, first-rank symptoms or nearly continuous hallucinations at the same time" The International Statistical Classification of Disease and Related Health Problems simply known as the International Classification for Diseases (ICD-10) defines SD as a distinct unit and can be used in patients with co-occurring mood symptoms and schizophrenic-like mood-incongruent psychosis (Yogeswary, 2014:11).

2.4.10.1.1 Aetiology of schizoaffective disorder

The exact aetiology of SD remains unknown to this date. However, a combination of factors has been suggested to cause this condition. These factors include age, gender, genetics, stress, brain structure and chemicals and drug use (Abrams *et al.*, 2008:12).

2.4.10.1.1.1 Gender

According to the DSM-IV-TR criteria, SD affects more women than men. Disturbances in emotional regulation that are clinically significant are more common in women and hence a greater frequency of SD. As a result, women are more prone to other affective disorders than men (Abrams *et al.*, 2008:12; Yogeswary, 2014:1094).

2.4.10.1.1.2 Genetics

Studies have been conducted in order to determine if there is a pattern in family history of people that suffer from SD compared to those that have schizophrenia or BD. As with other neurobiological studies, these studies have failed to distinguish SD and schizophrenia or BD based on their genetics (Abrams *et al.*, 2008; Yogeswary, 2014:1100).

Hodgkin and colleagues reported that abnormalities in the Disrupted-In-Schizophrenia-1 (DISC1) is associated with SD. The DISC1 is thought to play a role in neurodevelopment and is expressed in the forebrain. Several forms of this protein are produced during post translational modification and it is expressed in multiple intracellular compartments such as the nucleus, mitochondria, centrosome, microtubule fractions, actin cytoskeletal fractions, and postsynaptic densities (Abrams *et al.*, 2008:1100).

cAMP signalling and mediation of the centrosome-dynein cascade are part of the functions of this protein. The DISC1 also interacts with other proteins that affect neurobehavioral function such as the nuclear distribution protein nudE-like 1 (Ndel1) and phosphodiesterase 4B (PDE4B). The PDE4B is a phosphodiesterase that regulates the signalling of adenosine monophosphate while Ndel1 makes use of endo-oligo peptidase activity to regulate neuronal migration. PDE4B is linked to both the processing of information and emotional regulation and is of particular interest (Abrams *et al.*, 2008:1100).

Potential genetic risk factors for BD and schizophrenia are the abnormalities in the DISC1. The results from Hodgkinson and colleagues suggest that abnormalities in this protein or the way in which its product undergoes post-translational modification can produce dysfunctions in emotional regulation and information processing. Information

processing may be affected more than emotional regulation, producing the schizophrenic phenotype with insignificant mood disturbances. BD results when the emotional regulation is affected and disturbances in both these neurobehavioral domains result in SD (Abrams *et al.*, 2008:1100,1104).

According to the National Alliance on Mental Illness (NAMI), it was found that in general there is a greater chance of developing SD if first degree relatives have either BD or schizophrenia (National Alliance on Mental Illness, 2018).

2.4.10.1.1.3 Stress

Stressful events such as the death of a loved one or a car accident can contribute to the start of SD. Traumatic episodes in childhood often increase the chances of developing SD in adulthood (Royal College of Psychiatrists, 2015).

2.4.10.1.1.4 Brain structure and function

There are classic neurotransmitters and neuropeptides that act on specific receptors in the brain. If these neurotransmitters and neuropeptides are altered, the schizophrenic and affective symptoms of SD become apparent. Neurotransmitters are brain chemicals used for communication throughout the brain and body. The schizophrenic symptoms of this condition involve the alteration of the postsynaptic excitatory neurotransmitters 5-HT and DA. There is decreased activity in the mesolimbic system, hippocampus and prefrontal cortex of glutamate and the presynaptic inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (Mental Iillness Research Education and Clinical Centre, 2016:2; Werner *et al.*, 2016:16).

There are neuropeptides that act as modulators and these include substance P, neurotensin and cholecystokinin. The brainstem, hippocampus and hypothalamus are the regions of the brain involved in depression with glutamate, 5-HT, DA and noradrenaline playing an important role in depression. The pathophysiology of affective symptoms involves neuropeptides such as substance P, neuropeptide Y and galanin. The hypothalamic-adrenal axis and its connections to the brainstem and hippocampus are considered in SD as schizophrenic and affective symptoms can be enhanced by traumatic events or stress. Therefore, the recommended

pharmacotherapy must interfere with the neurotransmitters and neuropeptides that cause SD (Werner *et al.,* 2016:16).

2.4.10.1.1.5 Drug use

Drug induced psychosis (DIP) is common in drug users as they may present with symptoms that are similar to those of SD. Drugs such as cocaine, cannabis and hallucinogens such as lysergic acid diethylamide (LSD) can cause mental health problems, especially in the presence of pre-existing mental illnesses. Psychotic symptoms indicative of schizophrenia or BD can manifest after frequent long use of drugs. These drugs interfere with the absorption and release of brain chemicals such as serotonin and DA. Heavy, long-term use of any drug can cause symptoms of psychosis in the user. A few drugs, however, tend to be more closely correlated with DIP than others such as amphetamines, cannabis and LSD (Paparelli *et al.*, 2011:1).

2.4.10.1.2 Symptoms of schizoaffective disorder

Symptoms of SD can be severe and therefore require close monitoring. Symptoms will be based on the type of mood disorder diagnosed and psychotic symptoms represent the inability to differentiate between reality and imagination. The psychotic symptoms of schizophrenia include hallucinations, delusions, slow movement, poor motivation and disorganised thinking. Symptoms of depression include poor appetite, change in sleeping patterns, weight loss or gain, guilt or self-blame, feeling of worthlessness, suicidal thoughts or death and inability to think or concentrate. Symptoms of mania include increased activity such as social and sexual activity, racing thoughts, exaggerated self-esteem, agitation and increased talking may be present in SD (Yogeswary, 2014:13; National Alliance on Mental Illness, 2018).

2.4.10.1.3 Diagnosis of schizoaffective disorder

It may be difficult to diagnose SD as it has overlapping symptoms between schizophrenia and BD. A thorough physical examination and full medical history must be conducted by the doctor if there are symptoms of SD. X rays and blood tests may be done to rule out any physical illness that may be the cause of the symptoms. If no physical illness is found, the DSM-V or ICD-10 criteria can be used to diagnose schizoaffective disorder (Abrams *et al.*, 2008:1090; Yogeswary, 2014:13).

Table 2-23 summarises the DSM-V criteria for diagnosing SD (Abrams *et al.*, 2008:1090; Yogeswary, 2014:13).

Table 2-23. DSM-V criteria for schizoaffective disorder diagnosis (Abrams *et al.*, 2008:1090; Yogeswary, 2014:13).

Category	Criteria
A	Uninterrupted periods of illness where there is a Major depressive episode (Major depressive or manic) concurrent with criterion A of schizophrenia (hallucinations, disorganised speech, delusions, catatonic behaviour or negative effects such as mild emotional effect)
B	Depressed mood with delusions or hallucinations for more than 2 weeks in the absence of a major mood episode (depressive or manic) during the lifetime duration of the illness
C	Presence of symptoms that meet the criteria for a major mood episode during the majority of the active and residual portions of the illness
D	The effects of a substance or medical condition can't be attributed to the disturbance

Specify whether

Bipolar type: Applies if the presentation of a major depressive episode includes a manic episode

Depressive type: Only applies if the presentation is a major depressive episode

With catatonia: This specifier applies to both SD with prominent depressive symptoms and SD with prominent manic episodes may be used to specify a current episode with at least three of the following: Catalepsy, waxy flexibility, echolalia and echopraxia

The research diagnostic criteria (RDC) attempted to differentiate SD from psychotic mood disorders. The RDC defines SD as "the acute occurrence of a full mood syndrome (depression and/or mania) and one of a set of "core schizophrenic" symptoms such as bizarre delusions, first-rank symptoms or nearly continuous hallucinations at the same time" The ICD-10 defines SD as a distinct unit and can be used in patients with co-occurring mood symptoms and schizophrenic-like mood-incongruent psychosis (Yogeswary, 2014:11).

The ICD-10 has a criterion for diagnosing SD. Table 2-24 shows the diagnostic criteria for SD according to the ICD-10 (Yogeswary, 2014:12).

Table 2-24. ICD-10 diagnostic criteria for schizoaffective disorder (Yogeswary, 2014:12).

Diagnosis depends on the approximate balance between the number, severity and duration of schizophrenic and affective symptoms

G1: Disorder meets the criteria for one of the affective disorders of moderate or severe degree, as specified for each category

G2: Symptoms from at least one of the groups listed below must be clearly present for most of the time during a period of at least 2 weeks (these groups are almost the same as for schizophrenia):

1. Delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations (Criterion G1a for paranoid, hebephrenic (disorganised), or catatonic schizophrenia)

2. Hallucinatory voices giving a running commentary on the patient's behaviour or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body (Criterion G1b for paranoid, hebephrenic, or catatonic schizophrenia)

3. Persistent delusions of other kinds that are culturally inappropriate and completely impossible, but not merely grandiose or persecutory (Criterion

G1c for paranoid, hebephrenic, or catatonic schizophrenia), e.g. has visited other worlds or can communicate with plants or animals without speaking

4. Thought echo, thought insertion or withdrawal, thought broadcasting (Criterion G1d for paranoid, hebephrenic, or catatonic schizophrenia)

5. Intermittent but frequent appearance of some forms of catatonic behaviour, such as posturing, waxy flexibility, and negativism (Criterion G1b for paranoid, hebephrenic, or catatonic schizophrenia)

6. Grossly irrelevant or incoherent speech, or frequent use of neologisms (a marked form of Criterion G1a for paranoid, hebephrenic, or catatonic schizophrenia)

G3: Criteria G1 and G2 above must be met within the same episode of the disorder, and concurrently for at least part of the episode. Symptoms from both G1 and G2 must be prominent in the clinical picture.

G4: Most commonly used exclusion clause. The disorder is not attributable to organic mental disorder, or to psychoactive substance-related intoxication, dependence, or withdrawal

Schizoaffective disorder, manic type

A. The general criteria for SD must be met

B. Criteria for a manic disorder must be met.

Other schizoaffective disorders; Schizoaffective disorder, unspecified

Comments: If desired, further subtypes of SD may be specified. This may be done according to the longitudinal development of the disorder, as follows: Concurrent affective and schizophrenic symptoms only, symptoms as defined in Criterion G2 for SDs, concurrent affective and schizophrenic symptoms beyond the duration of affective symptoms.

2.4.10.1.4 Treatment of schizoaffective disorder

Despite SD being categorised in the DSM-V criteria, there are no treatments specific for this condition. It is important, however, to be able to distinguish between the two types of SDs so as to maximise treatment. The treatment doesn't cure the condition but helps patients manage the condition, minimise symptoms and improve patient's social life (quality of life). Medications, psychotherapy and self-education can be used to successfully treat SD (Abrams *et al.*, 2008:1103; Yogeswary, 2014:13).

2.4.10.1.4.1 Pharmacological treatment

There are several pharmacological preparations that may be used to treat SD, namely antidepressants, antipsychotics and mood stabilisers (National Alliance on Mental Illness, 2018).

Antidepressants: The best antidepressants for this condition are SSRIs. There is improved compliance with the use of SSRIs as they have a less complicated adverse effect profile when compared to other antidepressants. Antidepressants should be discontinued if the psychosis worsens of if there is no improvement. The benefits associated with the use of antidepressants outweighs the adverse effects risk as they alleviate the depressive symptoms associated with SD. The success or failure rate of any previously used antidepressants should be taken into account (Yogeswary, 2014:14).

Antipsychotics: The effect of atypical antipsychotics on the two types of SD have been conducted in many studies. Patients with schizophrenia with depression and schizoaffective disorder with acute exacerbation are best treated with antipsychotics. Clozapine was shown to improve SD that is bipolar in nature when compared to the depressive type in three studies. One study showed a decrease in suicidal ideation when treated with clozapine. Risperidone has been shown to be effective in schizoaffective patients with the depressive type (Yogeswary, 2014:14).

Mood stabilisers: Lithium and carbamazepine are the most commonly used mood stabilisers in treating SD. Carbamazepine has been shown to be more efficient than lithium in treating SD of the depressive type (Abrams *et al.,* 2008:1104; Yogeswary, 2014:14).

2.4.10.1.4.2 Non-pharmacological treatment

Psychotherapy such as CBT or FFT may be used. The psychotherapy treatments of SD are summarised below.

Psychotherapy and counselling: Better understanding of the condition and hope for the future in patients living with schizoaffective disorder can be introduced by building a relationship with the patients during therapy. Effective sessions should focus on real life plans, problems and relationships and new skills and behavioural aspects specific to the patient's settings can be introduced (Yogeswary, 2014:14).

Cognitive behavioural therapy (CBT): CBT is a blend of cognitive and behavioural therapy. Conducting CBT can be challenging but it has been shown to have positive effects in assisting the patient in coping with their condition. This can be done on a personal basis or in a group setting. Cognitive therapy involves the person's thoughts and beliefs and how these influence their mood and actions. This type of therapy aims at making a person's thoughts more adaptive and healthy. Behavioural therapy is aimed at an individual's actions and it is aimed to change unhealthy behaviour patterns. Skills related to daily functioning, social skills and problem solving are taught to patients during CBT (Mental Illness Research Education and Clinical Centre, 2016:6).

Family focused therapy: Family therapy can assist the families to deal better with their loved ones. Patients should be educated on their illness, medication and problems associated with their condition. Treatment can be more effective if patients are able to discuss their problems with others. Social isolation can be reduced by using support groups (Yogeswary, 2014:14).

2.4.10.2 Schizophrenia

Schizophrenia is a chronic mental disorder that involves a spectrum of symptoms such as delusion, paranoia, hallucinations, deficiencies in cognition, social withdrawal and lack of motivation when it is active. Psychosis is a major defining characteristic in diagnosing schizophrenia and is characterised by the failure of logic, intent and organisation that comes with normal human thought. It usually stars during the young adulthood years (20 to 35 years) and lasts for a lifetime and has a detrimental effect

on social relationships, education and even career opportunities (Lakhan & Vieira, 2009:1; Aleman, 2014:1).

2.4.10.2.1 Hypotheses of schizophrenia

2.4.10.2.1.1 Dopamine

DA is an inhibitory catecholamine neurotransmitter that is thought to play a key role in schizophrenia. Adrenaline and noradrenaline are some neurotransmitters that belong to the catecholamine family. Its excessive transmission in the brain's mesolimbic system and prefrontal cortex causes schizophrenia. The DA receptor blockade by haloperidol and chlorpromazine proposed by Arvid Carlsson and Margit Lindqvist in 1963 was a significant cornerstone in psychiatry (Brisch *et al.*, 2014:1).

According to the "original DA hypothesis", positive symptoms of schizophrenia such as hallucinations that resulted from DA increase are thought to be due to cortical pathway disturbance through the nucleus accumbens. A reduction in D_1 dopamine receptor activation and decreased activity of the nucleus caudatus cause the negative symptoms of schizophrenia, such as poverty of speech according to the "original DA hypothesis". However, the "revised DA hypothesis" suggests DA dysregulation in the amygdala and prefrontal cortex which are important regions of the brain for emotional processing. This hypothesis also suggests the over activity of the hippocampus in patients with schizophrenia (Brisch *et al.*, 2014:1).

2.4.10.2.1.2 N-Methyl-D-aspartic acid and glutamate

The correlation between the clinical potencies of the antipsychotic drugs and their affinity for the D_2 dopamine receptor supports the DA theory of schizophrenia, though there are inconsistencies. The N-methyl-D-aspartic acid (NMDA) receptor hypofunction hypothesis was developed in part to explain some of these inconsistencies, including why schizophrenia is associated with subtle structural brain changes and the prominence of negative symptoms and cognitive impairment. New treatment that has been recommended for schizophrenia are signalling enhancers of NMDA receptors (Picchioni & Murray, 2008:4135; Brisch *et al.*, 2014:3).

Psychotomimetic drugs such as phencyclidine (PCP) and ketamine have been observed to cause psychotic symptoms and neurocognitive disturbances similar to

those in schizophrenia. They cause these effects by blocking the neurotransmission at the NMDA-type glutamate receptors. Glutamate and NMDA receptors are located throughout the brain and therefore glutamatergic models have predicted general cortical dysfunction in the brain due to the involvement of NMDA receptors. Dopaminergic deficits that are common in schizophrenia could be secondary due to underlying problems in the glutamatergic function as NMDA receptors are located in brain circuits that regulate the release of DA (Javitt, 2010:4).

2.4.10.2.2 Aetiology of schizophrenia

Schizophrenia is a heterogeneous syndrome considered a neurodevelopmental disorder. The exact causes of schizophrenia are unknown but there is a combination of multiple factors that have been thought to contribute to the development of this condition. These factors include environmental influences and genetic susceptibility (Patel *et al.*, 2014:638).

2.4.10.2.2.1 Genes

The genetic framework of schizophrenia involves common, *de novo* and rare alleles that are distributed among a number of genes. Specific allelic inheritance may contribute to the development of schizophrenia, therefore a risk for schizophrenia is inherited. Alleles not inherited (arising de novo mutations) also contribute to the risk of developing schizophrenia. A risk of developing schizophrenia may be due to increased paternal age at conception which is associated to the number of de novo mutations noted in an individual (Rees *et al.*, 2015:8).

The genetic risks of contracting schizophrenia based on prevalence estimates are outlined in Table 2-25 below (Patel *et al.*, 2014:638; Royal College of Psychiatrists, 2018).

Table 2-25. Genetic risks of contracting schizophrenia based on prevalence estimates (Patel *et al.*, 2014:638; Royal College of Psychiatrists, 2018).

Relatives with schizophrenia	Chance of developing schizophrenia
None or general population	1.0%
Parent	3.8%
Sibling	8.7%
Child with 1 parent with schizophrenia	12.0%
Child with both parents with schizophrenia	30-40.0%
Twins (monozygotic)	40-50.0%
Twins (dizygotic)	12-14.0%

Studies of twins and adoption studies have proven the link between genetics and schizophrenia. Monozygotic twins have an increased concordance than dizygotic twins because monozygotic twins share all of their genes unlike dizygotic twins that are believed to share about 50.0% of their genes. A strong association between schizophrenia and susceptible alleles has been identified. The concordance rate for schizophrenia in monozygotic twins is about 50-60.0%, indicating that the environment plays an important role in schizophrenia (Brown *et al.*, 2011:1).

Another study by Foley and colleagues suggested that schizophrenia may be a complex multigene trait. The alleles of schizophrenia are believed to be present on the population producing a weak effect when individually expressed or interacting synergistically when expressed together. Many vulnerability genes have been identified, but none have been conclusively linked to schizophrenia to date (Lakhan & Vieira, 2009:3).

2.4.10.2.2.2 Environment

Epidemiological studies and studies from discordant twins have shown that there is a major environmental risk of schizophrenia which exert pronounced effects on early brain development. Early environmental hazards such as being born in winter and early spring can subtly deviate early brain development (Picchioni & Murray, 2008; Lakhan & Vieira, 2009:2).

Ecological studies have shown that there is a relationship between prenatal infection and schizophrenia. These infections may all act in a common pathway such as the cytokine response, unique pathways or a combination of pathways that increase susceptibility to schizophrenia (Brown *et al.*, 2011:3).

Prenatal exposure to viruses such as influenza and poliovirus, poor prenatal nutrition, adverse obstetric events and cannabis (dagga) smoking during adolescence are all examples of environmental factors that can cause schizophrenia. Schizophrenia manifestation has been suggested to be a result of environmental factors and genetic predisposition (Lakhan & Vieira, 2009:2).

2.4.10.2.2.3 Drug and alcohol abuse

Psychosis can be instigated by factors such as maternal stress, traumatic brain injury and drug abuse. Drug abuse can induce psychosis independent of genetic factors and drug induced psychosis (DIP) can be caused by drugs such as amphetamine, dagga, lysergic acid diethylamide (LSD), phencyclidine (PCP) and ketamine. Important factors in DIP for drugs like LSD and ketamine include varying doses and regimen of administration (Ham *et al.*, 2017:11).

LSD was synthesised in 1938 by Albert Hoffman and discovered its hallucinatory properties. LSD is a drug of weak addictive properties, yet it is the most potent hallucinogen. It was proposed by Glennon that serotonin 2 (5HT-2) receptor subtypes are the target for hallucinogens like LSD. Subsequent studies proved this theory, showing 5HT-2 receptor abnormalities in schizophrenic brains post-mortem. Other studies showed that there was 5HT-2 receptor mediation in the production of psychotomimetic effects in healthy humans (Paparelli *et al.*, 2011:2; Ham *et al.*, 2017:18).

Dagga is the most used illicit recreational drug with more than 160 million people using it every day. Studies have shown that the risk for schizophrenia is 2.4 times greater in dagga smokers compared to non-users. The main psychoactive ingredient in dagga is delta-9-tetrahydrocannabinol (THC) which causes transient psychotic symptoms and impaired memory at sufficient doses. This occurs through cannabinoid (CB1) receptor stimulation and these receptors are present in the hippocampus, amygdala, cerebellum, basal ganglia, and pre-frontal cortex regions of the CNS. When these

receptors are stimulated, they cause an increase in DA release, resulting in psychotic symptoms (Paparelli *et al.*, 2011:4).

Amphetamine was synthesised in 1887 and the number of people with amphetamine induced psychosis (AIP) has increased. Amphetamine psychosis (positive and cognitive symptoms) similarity to schizophrenia was initially described in the 1950s. Amphetamines stimulate DA outflow and antipsychotics block DA receptors in the brain. Amphetamines inhibit DA reuptake into the presynaptic neuron and facilitate the release of DA vesicles, resulting in DA increase in the synaptic cleft (Paparelli *et al.*, 2011:2; Ham *et al.*, 2017:13).

PCP and ketamine are psychotogenic drugs that act as NMDA receptor antagonists. PCP adverse effects include hallucinations, depression and delirium. PCP induced psychosis (PIP) and ketamine induced psychosis (KIP) can be caused by acute administration. PCP and ketamine cause excessive glutamate in the glutamatergic neuron of the pre-frontal cortex, thus providing a neurobiological explanation for the negative symptoms (Ham *et al.*, 2017:16).

2.4.10.2.2.4 Life events

Critical reviews of the relationship between schizophrenia and stressful life events have been conducted. These reviews have supported clinical observations that suggest that stressful life events contribute to the development of psychotic symptoms and possibly exacerbate symptoms. This evidence also supports the stress-diathesis model of schizophrenia that assumes that psychosocial stress is one of the several factors that contributes to the onset and relapse of psychotic symptoms (Tessner *et al.*, 2011:432).

2.4.10.2.3 Types of schizophrenia

The classical subtypes of schizophrenia are namely paranoid, hebephrenic, undifferentiated and residual, catatonic. However, all these subtypes of schizophrenia have been removed in the most recent DSM-V diagnostic criteria. They were removed due to their limited diagnostic stability, low reliability and validity (Ziso & Marsden, 2014:62).

2.4.10.2.3.1 Paranoid schizophrenia

This type of schizophrenia is characterised as stable paranoid delusions, auditory hallucinations and perceptual disturbances by the ICD-10. Catatonic symptoms and speech disturbance may be absent or relatively inconspicuous (WHO, 2013:80).

2.4.10.2.3.2 Hebephrenic schizophrenia

According to the ICD-10 diagnostic criteria, a confident diagnosis of hebephrenia requires a period of 2 or 3 months of continuous observation in order to ensure that the characteristic behaviours are sustained. It has been characterised by prominent affective changes, fleeting and fragmentary hallucinations, shallow and inappropriate mood and disorganised speech (WHO, 2013:81).

The conditions that need to be met for hebephrenic schizophrenia are outlined in Table 2-26 (WHO, 2013:80-81).

Table 2-26. ICD-10 diagnostic criteria for hebephrenic schizophrenia (WHO, 2013:80-81).

A. The general criteria for schizophrenia must be met

B. Either of the following must be present:

1. Definite and sustained flattening or shallowness affect

2. Definite and sustained incongruity or inappropriateness of affect

C. Either of the following must be present:

1. Behaviour that is aimless and disjointed rather than goal oriented

2. Definite thought disorder manifesting as incoherent speech

D. Hallucinations or delusions may be present to a mild degree, though they shouldn't dominate the clinical picture

2.4.10.2.3.3 Undifferentiated schizophrenia

According to the ICD-10, this is a subtype of schizophrenia that is characterised by symptoms of schizophrenia though the overall picture is neither the catatonic, paranoid nor disorganised type (WHO, 2013:82).

2.4.10.2.3.4 Residual schizophrenia

According to the ICD-10 criteria, a clear progression from an early stage (comprising one or more episodes with psychotic symptoms meeting the general criteria for schizophrenia) to a later stage is present in this chronic stage of development of schizophrenia. This type is characterised by long-term, though not necessarily irreversible, "negative" symptoms (WHO, 2013:83).

The diagnostic criteria for residual schizophrenia is outlined in Table 2-27 (WHO, 2013:82-83).

Table 2-27. ICD-10 criteria for residual schizophrenia (WHO, 2013:82-83).

The following requirements should be met for a definite diagnosis of residual schizophrenia:

1. Prominent "negative" schizophrenic symptoms such as psychomotor slowing, underactivity, blunting of affect, passivity and lack of initiative, poverty of quantity or content of speech, poor nonverbal communication by facial expression, eye contact, voice modulation, posture, poor self-care and social performance

2. Evidence in the past of at least one clear-cut psychotic episode meeting the diagnostic criteria for schizophrenia

3. A period of at least 1 year where the intensity and frequency of hallucinations and delusions has been minimal and the negative schizophrenic syndrome has been present

4. Absence of dementia or other organic brain disease or disorder, and of chronic depression or institutionalism sufficient to explain the negative impairments

2.4.10.2.3.5 Catatonic schizophrenia

The ICD-10 regards catatonic schizophrenia as a prominent psychomotor disturbance alternating between automatic obedience and negativism or stupor and hyperkinesis. A person with catatonic schizophrenia may maintain constrained attitudes and postures over long periods and present with episodes of violent excitement (WHO, 2013:81).

2.4.10.2.4 Symptoms of schizophrenia

Symptoms of schizophrenia are classified as positive, negative, impaired cognition and disorganisation (neurophysiological changes). Positive symptoms are psychotic experiences that are not generally seen in healthy individuals. Negative symptoms represent a "loss" of functions or abilities that individuals without schizophrenia

normally possess. The relative symptoms of each category are (Aleman, 2014:1; Patel *et al.*, 2015:1):

- **Positive symptoms**: Hallucinations, delusions, exaggerated or distorted perceptions or beliefs, agitation.
- **Negative symptoms**: Lack of motivation, social withdrawal, flattening emotional responses and reduced speech and activity.
- **Cognitive deficits**: Difficulties in paying attention, concentration, problem solving memory and decline in normal functioning.
- **Neurophysiological changes:** Abnormal eye movements, disordered and confused thinking and speech and difficulties with logical thinking.

2.4.10.2.5 Pharmacological treatment of schizophrenia

Antipsychotics are the primary treatment for schizophrenia and other psychotic disorders and have been categorised as either first generation (typical) or second generation (atypical) antipsychotics (Patel *et al.*, 2014:641).

2.4.10.2.5.1 First generation antipsychotics

First generation antipsychotics (FGAs) are effective for the positive symptoms of schizophrenia. Extrapyramidal motor effects and tardive dyskinesia are common with their use. Examples of FGAs include haloperidol, chlorpromazine and fluphenazine (Patel *et al.*, 2014:642).

2.4.10.2.5.1.1 Mechanism of action

The exact mechanism of antipsychotic drugs remains unknown, but is based on the DA hypothesis of schizophrenia. FGAs work by causing the postsynaptic blockade of the DA_2 receptors. These drugs lower the dopaminergic neurotransmission in the four DA pathways. FGAs can also block other receptors such as the histamine-1, muscarinic-1 and alpha-1 types (Reynolds, 2011:198; Guzman, 2017).

2.4.10.2.5.1.2 Adverse effects

The DA_2 receptor blockade caused by FGAs causes unwanted or debilitating adverse effects such as extrapyramidal adverse effects (EPSEs) (Sykes *et al.*, 2017:1).

The adverse effects of FGAs are summarised in Table 2-28 (Patel *et al.*, 2014:642-643).

Table 2-28. Adverse effects of first generation antipsychotics (Patel *et al.*, 2014:642-643).

Class of adverse effects	Adverse effects
Extrapyramidal adverse effects	• Dystonia • Pseudo parkinsonism • Tardive dyskinesia • Akathisia (feeling of restlessness and an urgent need to move)
Anticholinergic effects	• Blurred vision • Dry mouth • Urinary retention
Cardiac effects	Cardiotoxicity, including prolonged QT intervals
Weight effects	Weight gain
Sexual effects	Sexual dysfunction
Neuronal	Neuroleptic malignant syndrome
Other	• Sedation • Postural hypotension • Reduced seizure threshold • Hyperprolactinaemia

2.4.10.2.5.2 Second generation antipsychotics

Second generation antipsychotics (SGAs) are also known as atypical antipsychotics. These drugs have a lower risk of EPSE and tardive dyskinesia when compared to FGAs. SGAs are, however, associated with a higher risk of weight gain, cardio metabolic abnormalities, glucose dysregulation and dyslipidaemia. Examples of SGAs include risperidone, quetiapine, olanzapine and amisulpride. Clozapine is a unique antipsychotic that has shown efficacy in treatment resistant schizophrenia. (Lally & MacCabe, 2015:170).

2.4.10.2.5.2.1 Mechanism of action

SGAs are serotonin antagonists as they have the ability to block serotonin receptors. Most of the SGAs are 5-HT2A antagonists while some are 5-HT1A antagonists. The 5-HT2A antagonists increase DA neurotransmission in the nigrostriatal pathway, reducing the risks of EPSE. This antagonism also increases the release of DA in the prefrontal cortex, thus improving the negative and cognitive symptoms of schizophrenia. SGAs such as quetiapine and clozapine are 5-HT1A antagonists that increase DA release in the prefrontal cortex and reduce the release of glutamate. SGAs are thought to dissociate rapidly from the DA_2 receptors, thus lowering the risks of EPSE (Reynolds, 2011:198; Guzman, 2017).

2.4.10.2.5.2.2 Adverse effects

SGAs cause a number of adverse effects such as weight gain and drowsiness. The adverse effects of SGAs and clozapine are outlined in Table 2-29 (Raffin *et al.*, 2014:87-90).

Table 2-29. Adverse effects of second generation antipsychotics (Raffin *et al.*, 2014:87-90).

Name of drug	Adverse effects
Amisulpride	- Insomnia - Hyperprolactinaemia - Extrapyramidal effects
Aripiprazole	- Weight gain - Somnolence - Sedation - Fatigue
Clozapine	- Constipation - Hypersalivation - Hypo and hypertension - Nocturnal enuresis - Increased triglycerides - Fatigue - Sedation

Name of drug	Adverse effects
	• Weight gain • Rare adverse effects include • Agranulocytosis • Aspiration pneumonia • Cardiomyopathy • Myocarditis • Neutropenia • Thromboembolism
Olanzapine	• Increased glucose levels • Increased appetite • Sedation • Weight gain
Risperidone	• Extrapyramidal effects at high doses • Weight gain • Somnolence • Sedation • Fatigue • Gastrointestinal irritation
Quetiapine	• Weight gain • Increased triglycerides • Hypotension

2.4.10.2.5.3 Lithium

Many schizophrenic patients do not achieve a satisfactory treatment response with ordinary antipsychotic drug treatment. Augmentation with other drugs and lithium is sometimes needed. There has not been randomised trial-based evidence that shows the effectiveness of lithium as monotherapy for schizophrenia. Lithium use with other antipsychotics has noted to be effective in treating schizophrenia (Leucht *et al.*, 2015:7).

2.4.10.2.6 Non-pharmacological treatment of schizophrenia

Societal influences and understandings of behavioural, cognitive and social research have promoted an increase in appreciation of the importance of cognitive and psychological factors required to understand and treat psychotic symptoms. Outcomes achieved through the sole use of antipsychotic medication have simultaneously caused growing discontent, particularly when functional recovery is concerned. This, combined with the high reported rates of medication non-adherence, has led to a major improvement in the development of non-pharmacological interventions for schizophrenia (Andreou & Moritz, 2016:1).

2.4.10.2.6.1 Cognitive behavioural therapy

This is one of the non-pharmacological interventions that has been included in treatment guidelines. CBT is concerned with the influence of beliefs, thoughts and self-statements on behaviour. CBT has a long-lasting positive effect on delusions compared to standard care (Andreou & Moritz, 2016:1; Pandarakalam, 2016:4).

The goals of CBT are outlined as follows (Andreou & Moritz, 2016:1; Pandarakalam, 2016:4):

1. Address negative self-evaluation.
2. Build and maintain treatment plans.
3. Change false beliefs about auditory verbal hallucinations.
4. Challenge unreasonable understandings.
5. Develop cognitive behavioural strategies.
6. Develop newer understanding of hallucinatory experience.
7. Use distraction techniques to divert attention.
8. Modify maladaptive behaviour, e.g. fear of the voices or hiding from them.

2.4.10.2.6.2 Family and patient education

One predictor of outcome is the family environment. Patients with schizophrenia and their families usually face problems in relationships, inability to fulfil marital or family roles and inability to care for themselves. Therefore, patients with schizophrenia and their families require emotional and social support, education and skills training (Gümüş, 2009:156).

Patient education aims to provide patients with better insight about their illness and what behaviours they can employ in their lives to improve their health. Health education given to patients and their families based on their needs has notably increased their ability to cope with the illness. Often patients and their relatives require information about the medication, adverse effects and the illness. Health education has improved the quality of life and enables patients to be more productive as both the patient and family will be supported (Gümüş, 2009:157).

2.4.10.2.6.3 Individual therapy

Accounts of meaningful engaging in some form of psychoanalytic psychotherapy in patients with schizophrenia was described in some reports by 1940. It was also noted that schizophrenic patients were receptive to this treatment and attain a form of recovery. Psychoanalytic psychotherapy then emerged as a treatment with the aim of aiding schizophrenic patients to develop a healthier sense of self. Individual psychotherapy helps people with schizophrenia to navigate interpersonal contexts, develop and maintain meaningful relationships and understand other people they encounter (Hasson-ohayon *et al.*, 2013:2).

2.4.10.2.6.4 Social skills training

Social skills training (SST) can be defined as treatment approaches that aim to address deficits in social cognition and competence that cause a deterioration in social functioning. SST improves interpersonal dysfunction that leads to failed social behaviour linked to interpersonal stress and isolation. SST focuses on the following factors (Rus-calafell *et al.*, 2014:466):

- Expressive behaviours such as body movements, speech content and gestures.
- Responsive behaviours such as attention, emotion and social perception.
- Interactive behaviours such as conversational turns and response and reaction times.
- Situational factors such as knowledge of cultural factors.

SST can therefore improve treatment outcomes and the patient's recovery process in schizophrenia (Rus-calafell *et al.*, 2014;472).

2.4.10.2.6.5 Vocational rehabilitation

Comprehensive vocational rehabilitation in schizophrenic patients has been seen to produce better neuropsychological performance. Present studies suggest that cognitive abilities are important in employment outcomes. Vocational rehabilitation reduces the negative impacts caused by cognitive deficits in schizophrenic patients. However, for patients with schizophrenia to succeed in vocational training, they require professional support to attain jobs and appropriate work behaviour and the necessary skills to maintain a competitive employment level (Evans *et al.*, 2004:340).

2.5 Drug utilisation reviews

2.5.1 Introduction

In 1977 the WHO defined drug utilisation research as the prescribing, marketing, distribution and use of drugs in society with special emphasis on the health and social consequences (Sachdeva & Patel, 2010:11). Therefore, a drug utilisation review (DUR) is an authorised, on-going review on the prescribing, dispensing and use of medicine. Comprehensive analysis of patient's prescription and medication data before, during and after dispensing forms a major part of the review. This is done in order to ensure positive patient outcomes as well as appropriate medication decision making. DURs serve as a quality assurance measure that provides prescriber feedback, corrective action as well as other necessary therapeutic interventions (Navarro 2008:217).

The three classes of a DUR are retrospective, prospective and concurrent (Navarro 2008:215):

All three methods work in order to maintain effective and appropriate use of drugs. This can then have a positive impact on the patient's quality of life and overall drug effectiveness. A DUR is important as it assists the managed health care systems by understanding, interpreting, evaluating and improving the use of drugs as well as their prescribing. This is a key role as it facilitates the effective use of resources that may be scarce (Academy of Managed Care Pharmacy, 2009:1).

Pharmacoepidemiology is defined as "*the study of use and effects of drugs in large populations of people.*" (Thaker *et al.*, 2015:53). It quantifies drug adverse effects and

drug use patterns. It combines clinical pharmacology and epidemiology and aims at promoting rational and cost-effective drug use. Several factors of drug research involved in pharmacoepidemiology include benefits, risks and utilisation of drugs (Thaker *et al.*, 2015:53). On the other hand, pharmacovigilance is the activities and science involved in the detection, assessment, understanding and prevention of any drug-related problems or adverse effects (Langlitz, 2009:396).

Pharmacoepidemiological studies may be drug oriented with emphasis on the use and effectiveness of drugs. Sophisticated utilisation-oriented pharmacoepidemiological studies may focus on the drug (such as dose-effect), prescriber (such as quantity issued to a patient) and the patient (such as renal function of patient). The outcomes of such a study are health related as well as have economic consequences. DURs are an important part of pharmacoepidemiological studies as it defines the extent and determinants of drug exposure (WHO, 2003a).

DURs in pharmacoepidemiology have become significant as they are closely linked to other specialities such as public health, pharmacovigilance, pharmacoeconomics and pharmacogenetics.

DURs facilitate the rational use of drugs in different populations. It is impossible to suggest measures that will improve prescribing and rational drug use if there is no information with regards to how drugs are being prescribed and used. The rational use of a drug with the respect to a patient implies that the drug is affordable, is the correct one and administration of the drug is at optimal doses (WHO, 2003a).

2.5.2 History

Interest in drug utilisation studies began in the early 1960s and this initiative was sparked by the United Kingdom and Northern Europe. The WHO organised a symposium in 1964 in Moscow on drug toxicology which led to serious consideration on the need for it (Truter, 2008:92; Sachdeva & Patel, 2010:11).

Drug utilisation studies were spawned by the thalidomide disaster. It became evident that without the knowledge of the ways in which such dangerous products had been employed, it would be difficult to assess the frequency and location of the risks involved (Truter, 2008:92; Sachdeva & Patel, 2010:11).

A study was conducted after the Moscow meeting on drug consumption between 1966 and 1967.The importance of comparing drug use between countries and regions was a result of the hard work of Pieter Siderius of Holland and Arthur Engel of Sweden. They managed to demonstrate the significant difference in the sales of antibiotics between 1966 and 1967 in six different European countries, prompting the WHO to organise its first "consumption of drugs" symposium in Oslo in 1969. The WHO Drug Utilization Research Group (WHO-DURG) and European Drug Utilization Research Group (Euro-DURG) were formed following this symposium (Truter, 2008:92).

During this 1969 symposium, a classification system of drugs was developed, namely the defined daily dose (DDD) and anatomical therapeutic chemical (ATC). These were designed as a comparative unit of drug use and a WHO collaborating centre was established in Oslo to maintain and develop the ATC/DDD system. Before the DDD, it was difficult to compare data obtained from different countries as the source and form of information varied. The DDD was developed to overcome this difficulty as it was a new unit of measurement that could be compared (Wettermark *et al.*, 2016:4).

The former Czechoslovakia was one of the first countries to implement the DDD methodology with the first comprehensive DDD list being published in Norway in 1975. The International Society for Pharmacoepidemiology (ISPE) has been part of the meetings with the Euro-DURG in Europe since 1994. The main focus then was to improve drug utilisation by cross national studies based on the ATC/DDD method. This was a result of significant differences between countries and within them that couldn't be explained solely by morbidity differences. Consequently, there has been an expansion in this area with more focus on social, economic and qualitative methods with a greater focus on public health (Wettermark *et al.*, 2016:4).

The pioneers of this research understood that investigations of drug use at patient level are important in interpreting drug utilisation data correctly. It then became apparent that the following questions had to be answered (Wettermark *et al.*, 2016:5):

- Why are drugs prescribed?
- Who are the drugs prescribed for?
- Who prescribes the drugs?
- Do patients take their medicine correctly?

- What are the risks and benefits of the drug?

Drug utilisation programs have been developed mainly at individual patient level and local health programs in the United States. Scandinavia and Europe have implemented drug utilisation studies at national and international levels. Most drug utilisation studies in Europe have been based on quantitative data, describing and comparing trends in drug use based on geographic location and time period (Truter, 2008:92; Sachdeva & Patel, 2010:11).

2.5.3 Definitions

The WHO first defined drug utilisation reviews in 1977 as *"the marketing, distribution, prescription and use of drugs in a society with special emphasis on the medical, social and economic consequences"* (Wettermark *et al.*, 2016:7).

The Academy of Managed Care Pharmacy defines a DUR as an authorised, structured, ongoing review of prescribing, dispensing and use of medication. A DUR involves a comprehensive review of patients' prescription and medication data before, during and after dispensing to ensure appropriate medication decision-making and positive patient outcomes (Academy of Managed Care Pharmacy, 2009:1).

The current definition of a DUR implies that it is a bridge between pharmacoepidemiology and health services. DURs may also involve both qualitative and quantitative studies (Wettermark *et al.*, 2016:8).

2.5.4 Consequences

Drug utilisation reviews focus on various medical, social and economic aspects of drug use. The risks and benefits of drug therapy are examples of the medical aspects while cost of treatment is part of the social aspects. Table 2-30 demonstrates the consequences associated with the use of drug utilisation reviews (Lubbe, 2012:10).

Table 2-30. Consequences of drug utilisation reviews (Lubbe, 2012:10).

Category	Consequence
Economic	• Pricing of drugs • Resource allocation to drug and health budgets • Treatment and cost of drugs
Medical	• Determination of benefit-risk ratio • Risk associated with diseases
Social	• Drug regulations • Drug abuse and dependence • Inappropriate use of drug • Patterns in drug use

2.5.5 Rational use of drugs

DURs became a necessity after the early signs of irrational use of drugs. Rational use of drugs can be defined as a process where patients receive medications that are appropriate for their medical needs, in doses that meet their personal requirements, for an adequate period of time, at the lowest cost both for them and the community. When one or more of these conditions is not met the use of drugs is considered irrational (Kar *et al.*, 2010:12).

There are different aspects involved in the irrational use of drugs and these include diagnosis, prescribing, dispensing and patient adherence (Ofori-Asenso & Agyeman, 2016:2):

- **Diagnosis:** Insufficient medical history, inadequate examination of the patient and inadequate laboratory resources contribute to the irrational use of drugs.
- **Prescribing:** Under and over prescribing, multiple prescribers and prescribing and incorrect prescribing contribute to the irrational use of drugs.
- **Dispensing:** Incorrect interpretation of results, incorrect labelling, incorrect counting, compounding or pouring of drugs promotes irrational drug use.
- **Patient adherence:** Insufficient counselling to promote adherence, poor labelling and insufficient oral instructions to the patients are part of irrational drug use.

Some strategies and interventions have been developed to encourage the more rational use of drugs. The main interventions that have been advocated by WHO are (Kar *et al.*, 2010:12-13):

- Training medical students about the different levels of rational use of drugs.
- Use of clinical guidelines.
- Compilation and use of an essential drugs list.
- Formation of drugs and therapeutics committees at district and hospital level.
- Training of undergraduate students in problem-based pharmacotherapy.
- Continuing in-service medical education as a licensure requirement.
- Independent information on drugs should be used, such as drug information centres.
- Educating the public about drugs.
- Prevention of financial incentives.
- Use of appropriate and imposed regulations.
- Adequate government expenses should be available to ensure accessibility of drugs.

2.5.6 Classification

A DUR can be either quantitative or qualitative (Truter, 2008:92).

2.5.7 Types

A DUR is categorised into three different types, namely (Carver & Anderson, 2018:2):

- **Prospective:** This type of DUR evaluates a patient's medication therapy before the medicine is dispensed.
- **Concurrent:** This type of DUR involves the ongoing monitoring of drug therapy during the course of the treatment.
- **Retrospective:** This type of DUR reviews drug therapy after the patient has received the medication (after prescribing, dispensing and use of medicine).

Drug utilisation reviews can be further classified into cross-sectional, longitudinal and continuous longitudinal studies.

2.5.7.1 Prospective

Evaluation of a patient's drug therapy before it is dispensed is involved in a prospective DUR (Carver & Anderson, 2018). A prospective DUR also involves comparing drug orders with criteria before the patient receives the drug. This type of evaluation is ideal for its preventive potential and its individual patient-centred interventions. This allows for pharmacists to identify and resolve problems before the patient starts taking their medicine. Typically, this is done on a daily basis by the assessment of prescriptions, medicine dosages and directions. This allows to identify any duplicate therapy or possible drug interactions (Academy of Managed Care Pharmacy, 2009:3).

- This type of DUR addresses issues or criteria such as (Shailaja, 2016:3):
- Adverse drug reactions
- Clinical abuse or misuse
- Dosage form and route of administration
- Drug interactions (when two or more different drugs interact and alter their intended effects, often causing adverse events)
- Drug-disease modifications.
- Drug-disease contraindications (when usage of a particular drug is contraindicated in a certain condition).
- Drug-patient precautions (such as allergies, pregnancy or age etc.).
- Formulary substitutions (e.g. generic substitution or therapeutic interchange).
- Indications.
- Inappropriate duration of drug treatment.
- Therapeutic outcome.

2.5.7.2 Concurrent

A concurrent DUR involves the continuous review of pharmacotherapy while the patient is receiving the drug. This type of evaluation is ideal where adjustments to drug therapy may be necessary, based on ongoing diagnostic and laboratory tests. It allows for pharmacists to alert prescribers of potential problems and intervene in areas of concern, such as drug-drug interactions, over or underutilisation, excessive or insufficient dosing or duplicate therapy (Academy of Managed Care Pharmacy, 2009:4).

The issues or criteria addressed by a concurrent DUR include (Shailaja, 2016:4):

- Drug-drug interactions.
- Drug dosage modifications.
- Drug-disease modifications.
- Duration of treatment.
- Over or underutilisation.
- Drug-patient precautions (such as age, allergies).
- Therapeutic interchange.

2.5.7.3 Retrospective

A retrospective DUR involves reviewing the pharmacotherapy after the drug has been administered to the patient. It usually occurs after the patient has been discharged and relies on previously recorded patient information. Although it is the easiest and least costly approach, there is no opportunity to modify therapy for the patients on whom the data were collected (Sachdeva & Patel, 2010:15).

This review aims at detecting patterns in the prescribing, dispensing and administration of drugs. Target interventions and prospective standards can be developed in order to prevent medication misuse or abuse. This can be done based on the analysis of the current medication use pattern. The outcomes of this review can assist prescribers on improving the healthcare of the patients, either individually or based on a specific population such as patients with BD (Academy of Managed Care Pharmacy, 2009:4).

The issues or criteria addressed by a retrospective drug utilisation review include (Shailaja, 2016:5):

- Appropriate generic use.
- Adverse drug reactions.
- Cost to patient.
- Clinical abuse/misuse.
- Drug-disease contraindications.
- Drug-drug interactions.
- Evaluation of indications.

- Inappropriate duration of treatment.

- Incorrect drug dosage.

- Use of formulary medications when appropriate.

- Over and underutilisation of drugs.

- Therapeutic appropriateness and/or duplication.

An integration of both a retrospective and prospective drug utilisation review will result in optimal prescribing practices in an 'ideal' world.

2.5.7.4 Cross-sectional

Cross-sectional data provides a brief overview of the use of a drug during a specific period of time such as over a year or month. Comparisons with similar data collected from a different country or hospital may then be conducted using cross-sectional studies. This type of study can be conducted before or after an intervention and is based on the drug, problems, indication, prescriber and patient. Drug use can be analysed using a defined set of criteria or guidelines in a cross-sectional study (Sachdeva & Patel, 2010:14; Shalini *et al.*, 2010:805).

2.5.7.5 Longitudinal

This type of data is a requirement for studying patterns in drug use and is often in the interest of public health authorities. A claims database can be used to generate total drug use as needed by drug-based longitudinal data. Longitudinal data can be based on statistically valid samples obtained from pharmacies or medical practices. Repeated cross-sectional surveys such as practice based data are used to obtain longitudinal data. The collection of data is done continuously even though the patients and practitioners constantly changes. As a result, the overall trend can be determined. However, the prescribing trends of individual practices or practitioners cannot be determined from such data (WHO, 2003c:17; Shalini *et al.*, 2010:805).

2.5.7.6 Continuous longitudinal studies

It is possible to acquire continuous longitudinal data at the specific patient or practitioner level. A distinctive identifier is often used by claim databases in order to follow individual patients. Information regarding the co-prescribing, course of therapy and concordance with therapy based on the period between prescriptions can be

gathered from this data. Electronic prescribing is becoming more common and databases that comprise of a full medical and prescribing report are being developed to provide continuous data at patient level. A wide ranges of issues such as change in therapy, adverse effects and health outcomes can be addressed by these databases (WHO, 2003c:17; Shalini *et al.*, 2010:805).

2.5.8 Types of drug use information

The problem being evaluated defines the type of information that is required. This information includes the overall use of drugs, drug classes, distinct generic compounds or specific products. The condition being treated, prescriber information and patient information are required. To ensure the economic and effective use of drugs, data based on the costs of drugs are essential. Drug use information is categorised as drug based information, patient based information, patient information and prescriber information. This information assists in the promotion of rational use of drugs (WHO, 2003c:13; Shalini *et al.*, 2010:805)

2.5.8.1 Drug based information

In order to respond to some clinically relevant questions that involve aggregation of drug use at different levels, detailed information is required. Data on current trends in total drug use, information on doses, information on indications and dosage regimens is vital in answering the clinically important questions (WHO, 2003c:13; Shalini *et al.*, 2010:805).

2.5.8.2 Problem based information

This type of drug use information involves addressing the question of how a particular condition is managed. Knowledge of the particular groups of drug used to treat a particular condition are not important. There are different types of information that may be required and this includes reason for the problem, drugs prescribed for the condition, severity of the condition being managed, other drugs prescribed, drug therapy *vs* non-drug therapy and how the drug was supplied (WHO, 2003c:15; Shalini *et al.*, 2010:805).

2.5.8.3 Patient information

Information on the patient and other demographic factors are important for the studies. In some instances, information regarding the beliefs, attitudes, perceptions and knowledge of the patient will be useful. Co-morbidities may be vital in the determination of drug therapy choice and adverse effects. The age, gender and ethnicity of a patient also provide useful information (WHO, 2003c:16; Shalini *et al.*, 2010:805).

2.5.8.4 Prescriber information

Determination of drug use involves the critical role of prescribers. There are claims that there is a significant difference in prescribing patterns of drugs between doctors. These prescribing patterns lack rational explanations. Understanding why and how drugs are prescribed is of primary importance in dissecting factors that influence prescribing. Prescriber information can be used to address questions such as (WHO, 2003c;16-17; Shalini *et al.*, 2010:805):

- Does the prescriber's medical education influence prescribing patterns?
- Is the prescribing profile dependent on the age and gender of patient?
- Which prescribers usually prescribe recently released drugs?
- Is there a difference in the prescribing patterns between specialists and general practitioners?
- Are there differences between prescribing patterns in rural and urban areas or between small or large practices?
- Can factors that determine and change prescribing patterns be identified?

2.5.9 Aims of a drug utilisation review

The goals of a DUR are to promote optimal medication therapy and ensure that drug therapy meets the standard of care. A DUR also aims to (WHO, 2018):

- Evaluate the effectiveness of drug therapy.
- Create guidelines for the appropriate use of drugs.
- Enhance responsibility in the medicine use process.
- Control medicine costs.

- Prevent medication related problems such as adverse effects, treatment use and over-use.

- Identify problems and key areas where further education of health care providers may be required.

Consequently, a DUR may improve the quality of care provided by healthcare providers and reduce the cost associated with treatment. The probability of obtaining favourable health outcomes is enhanced when the quality of care is improved (Academy of Managed Care Pharmacy, 2009:3).

2.5.10 Steps involved when conducting a drug utilisation review

The steps involved in a drug utilisation review are:

- **Step 1: Identification of drugs or areas of therapeutic practice to be evaluated.**

Not all drugs used in a hospital facility can be evaluated, therefore it is important to identify drugs whose evaluation will improve use. A criterion has to be well defined for comparison of optimal use and actual use of a drug. Relevant outcomes that are hoped to be achieved by the DUR must be specified in the criteria. Drugs that are usually chosen for a DUR include drugs that have a high volume, high frequency of adverse effects, high cost values, commonly prescribed, drugs associated with a potential of drug interactions, drugs used in high risk patients and drugs with a NTI such as lithium (Academy of Managed Care Pharmacy, 2009:5; Sachdeva & Patel, 2010:14).

- **Step 2: Designing the DUR study.**

It is important to identify the objectives of the DUR and the methods that will be used to conduct the DUR. Numerous methods can be used when conducting the DUR but observational methods are more common. Cross-sectional studies and examination of drug use prior and after interventions to improve prescribing are some of the common observational methods used. Concurrent, prospective and retrospective studies may be implemented in a DUR depending on the timing of the data collection. All these are contributing factors in the design of a DUR (WHO, 2003a:86; Sachdeva & Patel, 2010:14-15).

- **Step 3: Definition or establishment of standards and criteria.**

It is important to define or establish the criteria by which the DUR will be conducted. Criteria may be defined as statements that define correct drug use with regards to different components. Clinical or research literature should support the chosen criteria and must be scientific based. A hospital standard treatment guideline, relevant literature or other national drug use protocols may be used to establish the criteria for the DUR. Criteria must be valid, outcome oriented and easily measured. Standards can be defined as professionally established expressions of the acceptable range of deviation from the criteria. Thresholds can be defined once the criteria has been established and can be used to define expectations or goals for compliance with the criteria. It is important to limit the number of criteria reviewed by a DUR to anywhere between three and five as having many DUR criteria complicates the DUR study process. Table 2-31 shows the various components of drug use that are used in defining the criteria for a DUR (WHO, 2003b:87; Sachdeva & Patel, 2010:15).

Table 2-31. Various components of drug use that are used for drug utilisation research criteria (WHO, 2003b:87; Sachdeva & Patel, 2010:15).

Component	Criteria
Administration	- Dispensed quantity - Steps involved in the administration of a drug
Dosing	- Dosing interval - Duration of treatment - Dosing specific to the indication
Interactions	- Lack of drug interactions (drug-drug, drug-food or drug-disease interactions)
Monitoring	- Clinical monitoring - Laboratory monitoring
Outcomes	- Obtain desired outcome, e.g. reduce manic episodes in BD patients
Patient education	- Information given to patient regarding the drug - Information given to patients regarding their disease

Preparation	• Steps involved in the preparation of a drug for administration
Selection	• Drug is appropriate for clinical condition
Uses	• Lack of contraindications • Appropriate indication of drug

- **Step 4: Data collection.**

Data is gathered to determine the actual use of drugs either retrospectively from patient records or prospectively during dispensing and course of treatment. Retrospective data collection can be carried out away from patient areas and is quicker. Data should be collected from random samples of patient files in the health-care facility. The therapy of at least thirty patients or hundred patients for common clinical conditions should be reviewed (WHO, 2003a:87; Sachdeva & Patel, 2010:15).

Data collection tools should be designed to reflect endpoints that will be evaluated. It is important that the designed data collection tool is user friendly to promote completion by data collectors. Simple 'yes or no' questions can be used in a data collection tool. Data sources include patient files, dispensing records, laboratory reports and adverse drug reaction (ADR) reports among others. Some of the aspects of drug use that are normally part of a data collection tool include (WHO, 2003a:87-88; Sachdeva & Patel, 2010:15) :

- Patient demographics.
- Disease severity.
- Co-morbidities.
- Indications.
- Contraindications.
- Adverse or adverse effects.
- Dosing information.
- Drug interactions (drug-drug or drug-disease interactions).
- Monitoring drug treatment.

- **Step 5: Data analysis.**

Data is evaluated from the DUR programme and presented in a tabulated form according to the criteria on the DUR. Acceptable thresholds (patient numbers that meet the indicator) should be determined before the comparison. Data should be summarised into main groups and compared with previously recorded criteria and guidelines. This should be done to check for any deviations or discrepancies, whether positive or negative, and reasons for these deviations must be explained. Reasons for deviations must be evaluated and if necessary, the criteria may be redefined. Some of the reasons responsible for deviations in results include obsolete procedures, drug use for new indications and gaps in awareness or misinformation (WHO, 2003a:88; Academy of Managed Care Pharmacy, 2009:5; Sachdeva & Patel, 2010:15-16).

- **Step 6: Feedback of results.**

It is important to scientifically interpret the results and report the findings of a DUR to the appropriate team within an organisation (such as pharmacists) or individual prescribers. This is done to ensure the success of the study (WHO, 2003a:88; Sachdeva & Patel, 2010:16).

- **Step 7: Development and implementation of interventions.**

Problem resolving is the next step after identification of drug use problems. Interventions that will improve drug use should be developed and can either be educational or operational. Interventions may include alteration of the standard treatment guidelines and formulary manual, establishment of prescribing restrictions and drug order forms as well as the education of healthcare professionals through workshops, letters, circulation of protocols, etc. Operational interventions include modification of order forms and prescribing restrictions (WHO, 2003a:88; Academy of Managed Care Pharmacy, 2009:5; Sachdeva & Patel, 2010:66).

2.5.11 The need for drug utilisation reviews

A DUR plays an important role helping managed health care systems understand, interpret, evaluate and improve the prescribing, administration and use of medications. The use of DURs provides results that can be used to promote effective and efficient

use of healthcare resources that may be scarce (Academy of Managed Care Pharmacy, 2009:1).

DURs are required due to the fact that drugs are usually not used to their full potential or according to their generally accepted criteria. It is important to realise that inappropriate use of drugs presents a potential hazard to patients and increases the cost of expenses. All prescribing is not always done to meet the patient's needs and all patient needs are not necessarily met by drug therapy. This then raises concern of inappropriate and expensive prescribing as well as under prescribing of other drugs. As a result, this necessitates the use of drug utilisation reviews to review the drug utilisation patterns to ensure safe and effective treatment (Truter, 2008:91; Shalini *et al.*, 2010:803).

2.5.12 Applications of drug utilisation reviews

Drug utilisation reviews can be applied in the following ways (Lubbe, 2012:17; Truter, 2008:92-99):

- **Clinical:** DURs can be used to study the prescribing practices of drugs by medical practitioners and is part of a qualitative study.
- **Therapeutic:** The therapeutic profiles of drugs can be determined and their therapeutic effects and adverse effects monitored.
- **Quality assurance:** A DUR can be used to assess the quality of a drug and the health care provided by medical institutions.
- **Adverse effects:** Studies regarding the effects of a medicine such as adverse effects may be used to identify adverse effects and their severity and frequency.
- **Interventions:** A DUR may be utilised as a tool in interventions to alter the prescribing patterns of certain drugs.
- **Therapy appropriateness:** A DUR may be used to analyse the appropriateness of therapy that is prescribed by medical practitioners. This aids in the prevention of future prescribing mistakes.
- **Indicators:** DURs can be used to develop prescribing indicators that will help medical practitioners.

- **Patient compliance:** DURs can be used to study if prescribed drugs are administered to patients at optimal conditions and identify issues associated with compliance.

- **Economic:** Drug use can be expressed in terms of costs and a DUR can be used to analyse costs by patient, specific drug or provider, or can be a combination of the three characteristics. Containment of medical costs has become a topic of interest as there is tension between manufactures to retain profits and patients that require the best possible care without harming their own financial position.

- **Outcomes:** A DUR can be implemented to determine and assess the clinical outcomes of treatment.

- **Fraud and abuse:** It is possible to use a DUR to recognise and try to control fraud with regards to the quality care and cost of drugs.

- **Prescription volume:** DURs can be useful in evaluating the clinical use of drugs by determining their frequency.

- **Improvement of quality care:** A DUR focuses on enhanced quality of care for patients and can be used to assess the appropriateness, cost effectiveness and medical necessity of interventions.

2.5.13 Limitations of drug utilisation reviews

Drug utilisation studies have some limitations associated with them and these include (Lubbe, 2012:42-43) :

- Lack of a diagnoses or indication for a specific drug treatment, making it difficult for evaluation of the prescribed treatment by the medical practitioner.

- Medical records are not computerised, making it tedious to obtain data.

- Some diagnoses may not be entered, updated or available. Consequently, this compromises the effectiveness of a DUR.

- Inconsistencies in the classification of diagnosis and medications.

- DURs mostly focus on the weaknesses of treatments, often creating a negative perception of a DUR. It is seen as a limitation as it mainly points out the healthcare professionals' mistakes instead of educating and assisting them to execute their duties.

2.5.14 Published drug utilisation reviews on lithium

A retrospective drug utilisation study on the use (prescribing, dispensing and monitoring patterns) of lithium has not been conducted in South Africa. There is no data regarding its use either in the public or private sector. It is evident that there is limited data available on the use of lithium in South Africa. In general, there are limited drug utilisation reviews that have been published both internationally and nationally that describe the monitoring and usage of lithium.

In 2013, Thakkar *et al* conducted a drug utilisation study of psychotropic drugs prescribed in the psychiatry outpatient department of a tertiary care hospital. Psychiatric conditions are part of the top 10 conditions that contribute to Disability Adjusted Life Years (DALYs), therefore they saw the need to conduct such a study. The objectives of their study were to (Thakkar *et al.*, 2013:2759):

- Outline the various drugs that are used in psychiatric disorders.
- Find any differences between the recommended and actual prescribing patterns of psychotropic drugs.
- Analyse the drug utilisation patterns observed and the reason(s) for the deviation(s) observed.

The study was in the form of a retrospective cross-sectional DUR type and they used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines in their manuscript. The selection criteria for the study was patients of both genders, all ages who were suffering from a psychiatric illness and were being treated with a psychotropic drug. They analysed six hundred prescriptions according to the WHO guidelines of conducting drug utilisation studies. The data was collected from patients that attended the outpatient department from 1 January 2012 to 31 May 2012 (Thakkar *et al.*, 2013:2759-2760).

Out of the 600 prescriptions analysed, 1074 of the 1217 drugs contained in the prescriptions were psychotropic drugs and these were used for treating conditions such as schizophrenia, BD and anxiety disorders. The observed drug use pattern in mood disorders was that lithium was only used in 1.3% of the patients with BD. It was found that in general lithium was superior to valproate in treating BD. The low therapeutic index and frequent monitoring of the serum levels of lithium was found to

be crucial. The low use of lithium in their hospital was due to the fact that lithium has a NTI and that obtaining the drug serum levels of lithium proved to be difficult (Thakkar *et al.*, 2013:2760,2762).

However, another article by Piparva *et al.*, in Gujarat in 2011 showed that lithium was prescribed in 73% of the patients with BD. The NICE guidelines of 2006 consider the use of lithium in the long term management of BD (Piparva *et al.*, 2011:54). They concluded that lithium was the least commonly used drug to treat BD at their hospital with carbamazepine being the most commonly used drug (Piparva *et al.*, 2011:54).

Piparva *et al.*, in 2011 focused on a drug utilisation study of psychotropic drugs in outdoor patients in a teaching hospital in Jamnagar. They conducted this study due to the impact of psychotropic drugs in psychiatric practice and the need to continuously monitor their use, effectiveness and safety in clinical practice. They carried out a prospective drug utilisation study for 6 months and the selection criteria were patients of both genders and all ages. Their exclusion criteria were patients that were referred, in-patients or patients with epilepsy (Piparva *et al.*, 2011:54).

De Fazio *et al* in 2017 conducted a systematic review on the use of lithium in lifetime mania. They stated that BD had a greater impact and mortality in elderly patients than in younger patients with about 5% to 19% of the elderly presenting with BD in the psychiatric ward. Lithium remains the drug of choice in treating BD and has better efficacy than other mood stabilisers. However, there is lack of data or studies regarding its use in elderly patients (De Fazio *et al.*, 2017:756).

Articles based on the pharmacotherapy of BD in the elderly that were published 1970 and August 2016 were used in this study. Two of the authors of the article reviewed all the retrieved studies independently. The selection criteria were the elderly of both genders and greater than 50 years of age with BD. Seminal articles on the use of lithium in mixed-age groups were used. The inclusion criteria included a sample size of at least ten patients and studies comparing lithium monotherapy with other mood stabilisers or placebo. Evaluations of the tolerability of lithium measured as frequency of discontinuation of lithium were part of the inclusion criteria (De Fazio *et al.*, 2017:757).

The exclusion criteria for the study were articles that focused on the prescription of lithium in a psychiatric condition other than BD and lithium prescription in patients that had BD due to secondary general medical conditions. Other exclusion criteria were if lithium was used to augment other treatments, if lithium was used in the treatment of other episodes in addition to mania and if lithium was compared to other classes of drugs such as antidepressants, typical and atypical antipsychotics (De Fazio *et al.*, 2017:757).

The results from a retrospective study of 46 patients with BD on lithium for 12 weeks showed that lithium was less effective in treating the elderly when compared with younger patients at 28% and 17% non-responsiveness respectively. Subsequent studies showed that treatment of acute mania in elderly BD with lithium was effective (De Fazio *et al.*, 2017:759).

A recent retrospective, study of patients older than 75 years of age, provided evidence for the efficacy and safety of lithium and answered some outstanding questions from previous studies. A group of 25 patients on lithium therapy was compared with patients who received other therapies. The lithium group showed a bigger improvement in the Clinical Global Impression (CGI) score. Most recent research provides some accurate information about the efficacy of lithium in the elderly though lithium efficacy cannot be compared across heterogeneous samples of studies. (De Fazio *et al.*, 2017:763).

The study of De Fazio *et al.*, concluded that lithium is the first drug of choice in treating BD in geriatrics. Evidence from their studies showed that there was a great need of monitoring the lithium plasma levels closely and that lithium is well tolerated and effective in geriatrics at lower doses. Generally, there have been few controlled studies on the efficacy and use of lithium in the elderly, but its use has been decreasing due to its toxicity and risks of drug interactions (De Fazio *et al.*, 2017:763).

The results of the study showed that out of the 600 cases analysed, 12.33% had BD and the drugs used to treat it were lithium, sodium valproate and carbamazepine. It was seen that the mood stabilisers were only restricted to BD and that an alternative was prescribed if lithium was ineffective. This proved that lithium was the preferred drug for treating BD (Piparva *et al.*, 2011:56).

An article by Chakrabarti in 2017 analysed the medication non-adherence in BD by reviewing the rates, demographic and clinical predictors. He found that lithium was the main part of the studies that focused on mood stabilisers. In general, his study showed that the rate of non-adherence in treating BD when mood stabilisers were used was between 34% and 38%. Many of the studies on the non-adherence with lithium were done between 1970 and 1990. The non-adherence associated with the treatment of BD was linked to the adverse effects of medications. A positive association with the presence of adverse effects was reported in 35 studies of this review with more than a third involving lithium (Chakrabarti, 2017:114-116).

2.6 Chapter 2 summary

This chapter extensively reviewed lithium and its therapeutic uses, psychiatric disorders and drug utilisation reviews. The following chapter will describe the methodology that was employed in this research study

CHAPTER 3.
RESEARCH METHODOLOGY

3.1 Introduction

The research methods that were implemented when conducting this study are comprehensively described in this chapter. The subsections that comprise this chapter include study design, study setting, study sample, study source, data collection process and statistical analysis. In addition, the ethical considerations are discussed in detail. Finally, the limitations and weaknesses of the research method are mentioned.

The patient files that were reviewed in this study were for inpatients and outpatients that were being treated with lithium between the period of 1 January to 31 December 2017 at Fort England Hospital.

The general aim of the study was to analyse the use of lithium in treating psychiatric conditions such as bipolar disorder (BD). Investigating the prescribing and monitoring patterns of lithium in both inpatients and outpatients would determine if lithium was being prescribed correctly and patients being monitored according to the recommended guidelines.

The patient files containing clinical notes, prescription charts and results of laboratory tests were analysed. This facilitated the identification of inconsistencies that may be present in the current prescribing and monitoring patterns at Fort England Hospital.

3.2 Aim and research objectives of the empirical study

3.2.1 General research aim

The general aim of this study was to conduct a drug utilisation review (DUR) of lithium, through investigating its prescribing and monitoring patterns in inpatients and outpatients at a public sector psychiatric hospital in Grahamstown (Cacadu District Municipality, Makana Local Municipality, Eastern Cape Province, South Africa).

3.2.2 Specific research objectives

In order to achieve the aim of the current study, the research project consisted of a literature survey and an empirical investigation on lithium at the psychiatric hospital.

The objectives of the literature survey were discussed in Chapter 1 and the review presented in Chapter 2. This chapter focuses on the methodology for the empirical study.

The specific research objectives of the empirical investigation included the following:

- To determine the prescribing patterns of lithium at Fort England Hospital and compliance with the recommended treatment guidelines, which are the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) for South Africa: Hospital adult level and the National Institute for Health and Care Excellence (NICE) international guidelines. The South African Society of Psychiatrists (SASOP) Treatment Guidelines for Psychiatric Disorders was consulted. However, the current SASOP guidelines do not have specific guidelines regarding the prescribing and monitoring of lithium in patients. They were therefore not considered in the study as the main study component involved the prescribing and monitoring of lithium. The American Psychiatric Association guidelines of 2016 outline the recommended treatment recommendations to help psychiatrists develop plans for the care of adult patients with bipolar disorder. This practice guideline is based on available evidence and clinical consensus. However, it does not state the recommended doses of lithium and the monitoring parameters of patients on lithium therapy. As a result, The NICE guidelines were more useful than the APA guidelines.

- Pharmacovigilance: To identify medication problems (interactions and adverse effects) associated with the use of lithium, considering its narrow therapeutic index (NTI).

3.3 Research methodology

3.3.1 Study design

A descriptive, cross-sectional research approach was applied to analyse the retrospective data obtained from individual patient files and recorded using a structured data collection tool. The data collected was from patient files who were on treatment with lithium during the treatment period 1 January to 31 December 2017. The data was collected once for each patient.

A quantitative DUR involves multidisciplinary operations used to collect, organise, analyse and account for information on actual drug use. Indications for prescribing a drug and the prescribing data are linked in this type of review (Truter, 2008:92; Sachdeva & Patel, 2010:13). A qualitative DUR is explorative in nature and is aimed at gaining an in-depth understanding of the beliefs and perspectives. It utilises methods such as focus group discussions and in-depth interviews with small sample size (Elseviers, 2016:18).

Cross-sectional research can be descriptive in nature and is considered the most dependable with correlations among variables in a data set being detected. Periodic data can be analysed in a cross-sectional research approach (Neuman, 2014:38).

A retrospective DUR was utilised. According to the Academy of Managed Care Pharmacy, a retrospective DUR is a type of DUR that reviews drug therapy after the patient has received the medication (i.e. after the prescribing, dispensing and use of medicine) (Academy of Managed Care Pharmacy, 2009:1). The information already present in the patient files were used to collect the data retrospectively.

3.3.2 Study setting

The research and data collection was conducted at Fort England Hospital in Grahamstown. Fort England Hospital was established in 1875 as the first mental health facility in South Africa. It is a tertiary specialist psychiatric hospital with 313 beds and has various healthcare teams that care for both in- and outpatients.

Fort England Hospital has an outreach programme where they send specialised psychiatric medicines to 4 community psychiatric clinics in the Eastern Cape. The community clinics that benefit from these outreach programmes have patients that were discharged from Fort England Hospital.

The names of the outpatient clinics to which patients that were part of the study sample at Fort England Hospital were discharged to are outlined in Table 3-1:

Table 3-1. Outpatient clinics to which patients of the study sample being treated at Fort England Hospital were discharged to.

List of outreach hospitals to which patients were discharged		
	Town	**Hospital**
1	Adelaide and Bedford	Adelaide Hospital
2	Alice	Victoria Hospital
3	Fort Beaufort	Fort Beaufort Provincial Hospital
4	Peddie	Nompumelelo Hospital

3.3.3 Study sample

The study sample consisted of both male and female in- and outpatients of all ethnic groups who were older than 18 years and who were on lithium treatment between 1 January 2017-31 December 2017. Patients who had lithium therapy discontinued were also considered as it could point to adverse effects. Data was collected once for each patient and a 12-month period was chosen to ensure that there were sufficient participants for the study. A total of 40 patients were used as the study sample out of the 43 patients identified during the study period. Three patient files were excluded due to incomplete data.

The identification of patients that were eligible for the study occurred through the collection of patient discharge summaries and their patient files. The patient files and discharge summaries were obtained from the pharmacy department at Fort England Hospital. An all-inclusive sample was utilised since the study sample was limited and therefore every patient that was on lithium treatment for the period was included. The religion, employment status and diagnosis of the patient were not a basis for exclusion from the study.

3.4 Source of data

The first and second set of data collected was from patient files of inpatients that were initiated on lithium therapy and outpatients that were on lithium therapy at Fort England Hospital. The third set of data was from patient files of patients that were discharged from Fort England Hospital to the outreach hospitals who were on lithium therapy during the study period. Though patient files were a rich source of data, it was

important to regularly check the information for accuracy, completeness and consistency.

The researcher had access to the pharmacy department at Fort England hospital which is where the patient files were stored. The patient files were identified by going through all the patient files of patients at Fort England Hospital. Files of patients that were on lithium therapy were then set aside to be used in the study.

3.4.1 Inpatients at Fort England Hospital

The patient files were included in the study to allow for the determination of the prescribing, dispensing and monitoring patterns of lithium at Fort England Hospital.

The information that was analysed for the purposes of the study included all the prescriptions charts, doctor's notes, nurse's notes, laboratory test results and any other relevant information that was in the file. This gave a full description of the patient's consultation sessions and treatment history.

3.4.2 Outpatients at Fort England Hospital

The files of patients that were part of the outpatient clinic at Fort England Hospital were included in the study to aid in the determination of the prescribing, dispensing and monitoring patterns of lithium therapy at Fort England Hospital.

These patients came on a monthly basis to collect their medication, consult the psychiatrists and have any tests required done. All the information that was in their patient files including their prescription charts, doctor's notes, laboratory tests and any other relevant information in their files was assessed for purposes of the study. This allowed the researcher to obtain information on the consultation sessions and treatment history of each patient.

3.4.3 Patients discharged from Fort England Hospital to outreach hospitals

The patient files of patients that were discharged from Fort England Hospital to the four outreach hospital clinics listed above were included in the study. These were files of patients that were previously admitted at Fort England Hospital for treatment and then discharged to the outreach hospitals. These patients required long term care,

received specialist medicines such as lithium and were consulted by a specialist on a monthly basis. The patient files were readily accessible at Fort England hospital.

3.5 Research instrument

A data collection tool was designed to collect data for the study. The relevant information that was required from the patient files was recorded with the data collection tool.

3.5.1 Design of the data collection tool

The data collection tool was a structured data collection form containing information such as the patient demographics, social and medical history, current diagnosis, past medical history, current medication, drug interactions, adverse effects and baseline and follow-up monitoring of lithium therapy. The prescribed medication was checked as it could be useful in identifying, resolving and preventing potential and actual drug-related problems with regards to lithium.

Age is an important study variable with regards to lithium use because it has an impact on the pharmacology of lithium. There is a decrease in lithium tolerability as the age increases. Older patients require a dose that is 31% lower than that for patients that are less than 50 years of age (Arnaoudova, 2014:520).

Ethnic or cultural factors have been deemed significant determinants of a patient's response to psychotropic medication in clinical and cross-national studies. One study showed that there was a difference in lithium response among Hispanics, African Americans and non-Hispanic whites with bipolar disorder (Gonzalez *et al.*, 2015:224). It is therefore important to record the race to determine if there were any treatment responses that were dependent on the race.

A decrease in the prescription patterns of lithium has been noted due to the adverse effect and toxicity burden associated with its use. Some of the adverse effects of lithium include weight gain, nausea, tremor and hypothyroidism. Adverse effects are another important variable in both prescription patterns and adherence of lithium (Gitlin, 2016:1).

Lithium therapy may be combined with other pharmacological treatments to treat other co-existing conditions such as hypertension. Lithium can interact with many drugs, such as thiazide diuretics, leading to lithium toxicity (Katzung, 2012:516). It then becomes important to note the current medication to check for any possible drug interactions.

Lithium has been shown to produce a variety of adverse effects when used in people with cardiovascular diseases, pre-existing hypothyroidism, renal insufficiency and diabetes mellitus among others (Post, 2017:1175). It was then important that any existing medical conditions be noted in this study. Due to the toxicity potential associated with the use of lithium, it is essential to monitor and record parameters such as serum lithium levels, body weight, thyroid function and renal function.

Recent studies have shown that there is a link between psychiatric disorders and substance abuse. Based on this information, alcohol use and other substance abuse was an important variable in this study.

Printed copies of the data collection form were used to record the data for each patient. Data was coded and collated onto an electronic spreadsheet.

3.5.2 Testing the validity of the data collection tool

It was important to test if the data collection tool measured all the parameters that were required for the study. The initial data collection form was used to obtain information for 5 randomly selected patients (2 inpatient and 3 outpatient files) from the study sample in a pilot study. From this test, the initial data collection form (ANNEXURE A) was revised to create a final data collection form that was then used to obtain all the information required for the study (ANNEXURE B). However, only 2 of the patient files from the pilot study were included in the actual study conducted. The other 3 patient files were excluded in the study based on lack of information required for the study.

3.5.3 Structure of the data collection tool

The data collection tool was structured in a way that allowed for a complete investigation into the use, prescribing and monitoring patterns of lithium at Fort

England Hospital. The criteria that were necessary for this investigation are discussed below.

3.5.3.1 Patient demographics

3.5.3.1.1 Patient identification number

No patient identifiable information was recorded in this study to maintain patient anonymity. Instead, each patient file was assigned a unique number between 1 and 40 for the patient sample.

3.5.3.1.2 Age

The date of birth of the patient was recorded as it allowed the researcher to determine the age of the patient. This information was obtained from the patient's file. The calculated age of the patient was then recorded on the data collection form. In some cases, the age of the patient was already recorded in the file.

The age of the patients in the study sample ranged from to 21 to 84 years. This motivated the chosen age categorisation of the patients. It was decided not to divide the age categories into exact intervals of 10 years, e.g. 15 to 25 years, but rather to express the patient's age by referring to the age group within which the patient falls into. The four age categories are outlined in Table 3-2 below.

Table 3-2. Age categories.

Age categories		
1	> 18 and ≤ 30 years	Young adults
2	≥ 31 and ≤ 50 years	Middle aged adults
3	≥ 51 and ≤ 65 years	Mature adults
4	> 65 years	Geriatrics

3.5.3.1.3 Gender

The gender of the patients was obtained and recorded as outlined in Table 3-3.

Table 3-3. Gender categories.

Gender	
1	Male
2	Female

3.5.3.1.4 Race

The race of the study sample was obtained and recorded so that the researcher could determine the racial composition of the study sample. The racial categories are outlined in Table 3-4.

Table 3-3. Racial categories.

Race	
1	African
2	Coloured
3	Indian
4	Caucasian
5	Other

3.5.3.2 Height

The height of the patient was recorded from the patient file. This was important to record as it was vital in calculating the body mass index (BMI) of the patient.

3.5.3.3 Patient social history

3.5.3.3.1 Substance use

It was important to record any substance use on the data collection tool. It is known that there is a strong relationship between BD and the use of substances. A study by Lagerberg *et al.* showed that there is an increase in illicit substance use in patients with BD when compared to the general population. Impaired functioning has been noted in patients that have severe substance use and BD. This then affects the current treatment and requires more research into the psychopathological mechanisms involved (Lagerberg *et al.*, 2010:8).

Comorbidities such as substance abuse are very prevalent among patients with BD with 65% of BD patients being substance abusers. This may be a result of self-medication to alleviate the symptoms of BD or may be primary disorders. The commonly abused substances are alcohol, cannabis, cocaine, and stimulants. Substance use and dependence may result in alterations in mood and behaviour that is similar to mood disorders (Theodore *et al*., 2012:1).

A list of drugs that are subject to abuse was provided on the data collection tool. Any drug(s) used by the patient were recorded on the data collection. The categories of drugs of abuse included in the data collection tool are outlined in Table 3-4 below.

Table 3-5. Substance abuse categories.

Drug abuse	
1	None
2	Alcohol
3	Cannabis (dagga)
4	Methamphetamines
5	Other

3.5.3.3.2 Smoking status

It was important to note if the patient was a smoker or non-smoker. This information was obtained from the social history of the patient. The smoking status of the study sample is outlined in Table 3-6 below.

Table 3-6. Smoking status of study sample.

Smoking status	
1	Smoker
2	Non-smoker

Studies have shown that cigarette smoking is prevalent and has devastating effects in patients that suffer from BD. According to epidemiological data, there is a relatively high prevalence of smoking among BD patients when compared to other Axis I psychiatric conditions. One potential explanation for the high prevalence of smoking among BD patients is the monoamine oxidase (MAO)-inhibiting effects of the tobacco

smoke as well as the ability of nicotine to release neurotransmitters such as dopamine and serotonin that improve mood and induce self-pleasure (Heffner *et al.*, 2011:441). MAOs act on neurotransmitters such as serotonin and MAO inhibiters increase the levels of serotonin in the brain (Ramachandraih *et al.*, 2011:181). Smoking in BD potentially increases the antidepressant effects of psychotropic drugs.

Table 3-7 below outlines the prevalence of smoking among patients that have BD and other psychiatric conditions (Heffner *et al.*, 2011:440-441).

Table 3-7. Prevalence of smoking in psychiatric conditions (Heffner *et al.*, 2011:440-441).

Axis I Psychiatric condition	Prevalence of smoking
Alcohol abuse and dependence	44%
BD	69%
Drug abuse or dependence	49%
Generalized anxiety disorder	46%
Major depression	37%
Nonaffective psychosis	49%
Post-traumatic stress disorder (PTSD)	36-40%

3.5.3.3.3 Employment status

It was important to note the employment status of the patient in the study sample. Literature indicates that people with mental problems are often turned down from work or avoid looking for work because they anticipate discrimination (Thornicroft, 2010:414). The employment categories are outlined in Table 3-8 below.

Table 3-8. Employment status categories.

Employment status	
1	Employed
2	Unemployed
3	Other

3.5.3.3.4 Pregnancy status

It was important to establish the pregnancy status since studies have shown that there is an increased risk associated with the use of lithium in early pregnancy. The risk of developing Ebstein's anomaly (a right ventricular outflow tract obstruction defect) and general cardiac effects increase in infants with the use of lithium (Patorno *et al.*, 2017:2245).

Lithium exposure to the foetus during the late stages of pregnancy has resulted in neonatal adaptation syndrome (NAS) in some infants. The NAS is characterised by cardiac arrhythmias, feeding difficulties, lethargy, muscle twitching, poor suck and grasp. The condition usually resolves in 1 to 2 weeks but intensive neonatal monitoring and longer hospital stays may be required (Epstein *et al.*, 2015:20).

The pregnancy status of the patient was recorded as outlined in Table 3-9 below.

Table 3-9. Pregnancy status categories.

Pregnancy status	
1	Yes
2	No

3.5.3.3.5 Breastfeeding status

The breastfeeding status of the women in the study sample was established. This was important as one study reported that 10% to 17% of the maternal serum containing lithium was present in the infant. It has been suggested that women on lithium therapy can be supported to breastfeed their infants. However, the mothers should be educated to monitor their babies for changes such as signs of dehydration, lethargy and feeding problems (Bogen *et al.*, 2013:71).

The categories included for the breastfeeding status were recorded as outlined in Table 3-10 below.

Table 3-10. Breastfeeding status categories.

Breastfeeding status	
1	Yes
2	No

3.5.3.4 Patient medical history

3.5.3.4.1 Allergies

Allergic reactions form part of adverse drug reactions (ADRs) though they form only 6 to 10% of ADRs. Allergic or hypersensitivity reactions can be induced by drugs and these include drug intolerance which can be defined as "*an undesired drug effect produced by the drug at therapeutic or sub therapeutic dosages*" (Smith, 2013:12).

It was therefore important to record any allergy(s) in order to identify any potential hypersensitivity reactions that could occur from the patient's current treatment. The categories for the allergies are shown in Table 3-11 below.

Table 3-11. Allergies categories.

Allergies	
1	Yes
2	No

3.5.3.4.2 Family history of chronic diseases

The family history, if any, of chronic diseases of the patient was recorded. Studies have shown that the risk of developing schizoaffective disorder was strongly linked to BD and schizophrenia among first degree relatives. The risk of developing BD and schizophrenia was found to be high if there is a family member with BD and schizophrenia respectively (Brown *et al.*, 2011:1).

Metabolic adverse effects such as hypothyroidism, hyperparathyroidism, weight gain and nephrogenic diabetes insipidus (NDI) have been noted in patients that are treated with lithium. Family history of hypothyroidism or any other thyroid illness in a first degree relative is a risk factor for developing hypothyroidism during lithium treatment.

The use of lithium is associated with weight gain, one study showed that 62% of patients on lithium treatment reported significant weight gain. Obesity in the family is a major risk factor of gaining weight during lithium therapy (Livingstone & Rampes, 2009:347).

The categories for the family history are outlined in Table 3-12 below.

Table 3-12. Family history categories.

Family history	
1	Cardiac disease
2	Epilepsy
3	Diabetes Mellitus Type II
4	Hypertension
5	Psychiatric condition
6	None
7	Other

3.5.3.4.3 Co-morbid diseases

Any existing co-morbid diseases that the patient had were obtained from the medical history and the discharge summary in the patient file and recorded.

The categories of the co-morbid diseases are shown in Table 3-13 below.

Table 3-13. Co-morbid diseases or conditions categories.

Co-morbid diseases or conditions	
1	Cardiac disease
2	Epilepsy
3	Hypertension
4	Renal impairment
5	Hypothyroidism
6	Other
7	None

Lithium has a severe adverse effect profile due to its NTI with toxicity being common. It can cause life threatening conditions such as renal impairment, cardio toxic effects

such as arrhythmias, cardiomyopathy, simple ECG disorders and even acute myocardial infarction (AMI) at therapeutic and toxic levels especially in patients with underlying heart disease (Asim *et al.*, 2016:10).

Lithium has been shown to have effects on renal function such as a reduced estimated glomerular filtration rate (Bocchetta *et al.*, 2015:1). Other studies have shown that it takes about 10 to 20 years for a patient to develop lithium induced nephropathy. This nephropathy can then slowly progress to end stage renal disease (Judge & Winearls, 2015:1942). Therefore, any co-morbid diseases or conditions that may have been a result of the lithium therapy should be identified.

3.5.3.4.4 Past surgical procedures

Any surgical procedures that the patient had were recorded. The categories for the surgical history of the patient are outlined in Table 3-14 below.

Table 3-14. Surgical history categories.

Surgical history	
1	Yes
2	No

3.5.3.5 Suicide risk

Any risk of suicidal ideation was obtained from the doctor's notes and recorded. The categories for suicidal risk are outlined in Table 3-5 below.

Table 3-15. Suicide risk categories.

Suicide risk	
1	Yes
2	No

Long term treatment with lithium in patients with affective disorders has proven to have suicide preventing effects. Clinical reports have indicated that this effect may occur early at the beginning of lithium treatment (Lewitzka *et al.*, 2015:1).

This was useful in the study to determine if lithium therapy was effective in treating suicidal ideation in patients with affective disorders.

3.5.3.6 Number of admissions

The number of times the patient was admitted to Fort England Hospital between the period of January 2017 to December 2017 was recorded from the file and discharge summaries. Table 3-16 below outlines the categories for the number of previous admissions.

Table 3-16. Number of previous admissions categories.

Number of admissions	
1	No admission
2	One admission
3	Two admissions
4	Three admissions
5	More than three admissions

3.5.3.7 Date of initial episode of a mental illness

The medical history of the patient provided information of when the initial episode of a mental condition occurred. If available, the date was recorded. The categories for the date of initial episode are outlined in Table 3-17 below.

Table 3-17. Date of initial episode categories.

Date of initial episode	
1	Available
2	Not available

3.5.3.8 Diagnosis

The diagnosis of the patient was recorded. Lithium is indicated for use in the management of acute manic and hypomanic episodes, prophylaxis and treatment of bipolar disorder, management of treatment resistant depression and control of aggressive behaviour or intentional self-harm (Rossiter, 2016:484). Lithium has been used to treat the symptoms of schizophrenia, even though evidence of the beneficial effects in schizophrenia have not been established (Johnsen & Kroken, 2012:289).

Table 3-18 outlines the categories of the different diagnosis among the study sample.

Table 3-18. Diagnosis categories.

Diagnosis	
1	Bipolar disorder
2	Schizophrenia
3	Schizoaffective disorder
4	Other

3.5.3.9 Lithium use

3.5.3.9.1 Previous treatment with lithium

The past prescriptions and medical history provided information on whether the patient were on lithium therapy before 2017. The result was recorded and the categories to choose from are outlined in Table 3-19 below.

Table 3-19. Previous treatment with lithium categories.

Was the patient on lithium before 2017?	
1	Yes
2	No
3	No information

3.5.3.9.2 Date of initiation of lithium therapy

The date of initiation of lithium therapy was obtained from past prescriptions and the medical history available in the patient's file. If available, the date was then recorded under the categories shown in Table 3-20 below.

Table 3-20. Date of lithium initiation categories.

Date of initiation of lithium therapy	
1	Available
2	Not available

3.5.3.9.3 Period of lithium therapy

The number of years that the patient was on lithium therapy was obtained by calculating the time that passed from the date of the first initiation of lithium and recorded.

The categories for the number of years passed on lithium therapy are outlined in Table 3-21 below.

Table 3-21. Number of years on lithium therapy categories.

Number of years that the patient was on lithium therapy	
1	< 1 year
2	> 1 year and ≤ 5 years
3	> 5 years and ≤ 10 years
4	> 10 years
5	No information

3.5.3.10 Past medication history

The past medication history of all the psychiatric medication that the patient received was important to record as it would assist in justifying the use of lithium and its efficacy. Changes could also point to adverse effects experienced or lack of response to other psychiatric medication.

The following information was recorded on the data collection form:

- Name of the medication.
- Dosage form.
- Route of administration.
- Strength.
- Dosing frequency.
- Date of initiation of therapy.
- Date of therapy discontinuation.
- Reason for therapy discontinuation.

The reasons for therapy discontinuation were subsequently recorded. Table 3-22 shows the categories for therapy discontinuation.

Table 3-22. Categories for therapy discontinuation.

Reasons for therapy discontinuation	
1	Allergy
2	Adverse effects
3	Change in therapy
4	Change in diagnosis
5	Failed therapy
6	Non-adherence
7	Safety
8	Successful therapy

3.5.3.11 Current medication

The following information regarding the current drugs that each patient on was recorded:

- Name of medication.
- Dosage form.
- Route of administration.
- Strength of medication.
- Dosing frequency.
- Date of initiation of therapy.

Analysis of the current medication was important as results could potentially provide information regarding any drug and treatment problems.

3.5.3.12 Drug interactions

Lithium was found to be the most common psychiatric medication involved in ADRs in a retrospective study conducted in 2010. Lithium is not metabolised and interactions occur through other mechanisms. Drugs such as diuretics, ACE inhibitors, NSAIDs, xanthines and calcium channel blockers interact with lithium, causing different levels and effects (Hoeft, 2014:119).

3.5.3.12.1 Presence of drug interactions

The current medication recorded on the data collection form allowed for the identification of any possible drug interactions between lithium and other prescribed drugs.

The categories for drug interactions are outlined in Table 3-23.

Table 3-23. Drug interactions categories.

Presence of any drug interactions	
1	Yes
2	No

3.5.3.12.2 Information supplied if there were any drug interactions

Any drug interactions identified between lithium and other drugs were recorded on the data collection form. In the presence of drug interactions, the following information was recorded:

- Number of drug interactions present.
- Names of drugs that interact with lithium.

An example of a drug interaction that may occur is the co-administration of lithium and a calcium channel blocker such as amlodipine. This drug interaction results in decreased serum lithium levels as it enhances lithium excretion (Handler, 2009:740). Therefore, calcium channel blockers should be avoided in patients on lithium therapy.

3.5.3.13 Adverse effects

Lithium carries a 'black box' warning which implies its potential to cause lethal adverse effects. All systems of the body may exhibit adverse effects associated with the use of lithium. Adverse effect concerns do play a significant role in lithium non-adherence (Oruch *et al.*, 2014:468).

3.5.3.13.1 Presence of adverse effects

The doctor's notes in the patient file provided information regarding any adverse effects that the patient may have experienced as a result of lithium therapy. The information was recorded under the categories outlined in Table 3-24.

Table 3-24. Presence of adverse effects categories.

Adverse effects reported	
1	Yes
2	No

3.5.3.13.2 Types of adverse effects present

Lithium is known to cause a number of dose dependent adverse effects (Rossiter, 2016:485) . If the patient experienced any adverse effects, it was indicated on the data collection form under the relevant category. Based on the most common adverse effects of lithium, the following categories were included as shown in Table 3-6.

Table 3-25. Categories of types of adverse effects.

Types of adverse effects present	
1	Goitre
2	Hypothyroidism
3	Nausea
4	Polyuria
5	Tremor
6	Vomiting
7	Weight gain
8	Other

3.5.3.13.3 Treatment of adverse effects

The patient file provided information on any treatment for adverse effects the patient may have received. It was also determined how the adverse effects were treated. The categories to choose from are shown in Table 3-26 below.

Table 3-26. Categories of treatment of adverse effects.

	Were the adverse effects treated?
1	Yes
2	No

If "Yes" was chosen, the treatment details were recorded.

3.5.3.14 Monitoring requirements

The monitoring requirements recommended by the South African and NICE guidelines are outlined in Table 3-27 below.

Table 3-27. Recommended guidelines (Department of Health, 2015:15.1; National Institute of Health and Care Excellence, 2014).

Classification	South African guidelines	NICE guidelines
Renal function	Before initiation then every 6-12 months	Before initiation then every 6 months
Thyroid function	Before initiation then every 6-12 months	Before initiation then every 6 months
Metabolic function	None	Weight, BMI and fasting blood glucose annually. Blood pressure and pulse monthly
Serum lithium levels	After dose increment: every week, then after 1 month, then 3 months, then six-monthly during maintenance therapy	Every 3 months
Electrolytes, e.g. sodium and chloride	Regularly	Every 6 months
Calcium levels	Prior to initiation and annually	Every 6 months

3.5.3.15 Baseline monitoring

Lithium requires close monitoring due to its NTI. It interferes with kidney, thyroid and metabolic functions and therefore regular, specific laboratory tests have to be conducted. Baseline monitoring should be done prior to initiation of lithium therapy. If any actual baseline tests were conducted, they were compared to the recommended guidelines for the monitoring of thyroid function to determine the level of compliance. The compliance with the South African and NICE guidelines was reported separately.

3.5.3.15.1 Thyroid function

Lithium is known to inhibit thyroid function at various points in the thyroid axis. Studies have shown that between 0 and 47% of patients on long-term lithium treatment develop hypothyroidism. Subclinical hypothyroidism is common in female patients and patients with rapid mood cycling (Joffe, 2010:392).

The thyroid function monitoring was determined from the laboratory results obtained in the patient's file before initiation of lithium therapy. The date on which the tests were performed was recorded as well as the result. The following thyroid function markers were assessed and recorded:

- TSH levels.
- Free thyroxine (T_4).
- Tri-iodothyronine (T_3).

It is important to detect and treat hypothyroidism at an early age. The clinical biochemical findings in thyroid adverse effects of lithium are outlined in Table 3-28 below (Schneider *et al.*, 2018:1).

Table 3-28. Biochemical findings of thyroid conditions (Schneider *et al.*, 2018:1).

Condition	Biochemical findings
Hypothyroidism	• Increased TSH • Decreased FT$_4$ • Positive anti-thyroid peroxidase (TPO)
Subclinical hypothyroidism	• Increased TSH • Normal FT$_4$
Hyperthyroidism (rare)	• Decreased TSH • Increased FT$_4$

The NICE guidelines and the South African guidelines (STGs and SAMF) recommend the monitoring of thyroid function before and after the initiation of lithium therapy.

Table 3-29. Categories of compliance with recommended guidelines for baseline thyroid function.

Compliance with recommended guidelines for baseline thyroid function monitoring	
1	Compliant
2	Non-compliant

Compliant means that all the thyroid function tests were conducted before lithium initiation. Non-complaint means that none of the thyroid function tests were conducted before lithium initiation.

3.5.3.15.2 Renal function

Studies have shown that chronic tubule-interstitial nephropathy can be induced by long term lithium treatment and can progressively lead to renal failure. Lithium induced nephropathy can develop over several decades. It is therefore mandatory to monitor the estimated creatinine clearance in long term lithium treatment patients (Kumarguru *et al.*, 2013:374).

Information regarding the renal function tests was obtained from the laboratory tests in the patient's file. The results of all the renal function tests as well as the date on which they were performed was recorded on the data collection form:

- Creatinine clearance.
- Estimated glomerular filtration rate (eGFR).
- Urea.
- Electrolytes (sodium, potassium, and chloride).

The electrolyte panel is used to screen for imbalances in electrolytes and to monitor effects of a treatment that is known to cause an imbalance. Electrolyte tests include sodium, potassium and chloride and are used for diagnosing and managing renal function and other conditions. Potassium is the most convincing electrolyte that is a marker of renal failure with hyperkalaemia being the most clinically significant complication of renal failure (Gowda *et al.*, 2010:171).

Creatinine is commonly used as a measure of kidney function with serum creatinine concentration being used to calculate the glomerular filtration rate (GFR). The progression of renal disease is monitored by creatinine clearance (Gowda *et al.*, 2010:170).

Urea is a major nitrogenous waste product of protein and amino acid catabolism and filtered by the glomeruli. The estimated renal function depends on the concentration of urea in the serum. An increase in blood urea nitrogen (BUN) is associated with kidney disease or failure, while low levels indicate malnutrition, trauma and use of opioids (Gowda *et al.*, 2010:170).

Data obtained from baseline results was analysed and used to determine the level of compliance with the recommended guidelines with regards to renal function monitoring. Compliance with the NICE and South African guidelines (STGs and SAMF) was reported separately under the categories outlined in Table 3-30 below.

Table 3-30. Categories of compliance with recommended guidelines for baseline renal function.

Compliance with recommended guidelines for baseline renal function monitoring	
1	Compliant
2	Non-compliant

Compliant means that all the renal function tests were conducted before lithium initiation. Non-complaint means that none of the renal function tests were conducted before lithium initiation.

3.5.3.16 Metabolic monitoring

Information regarding the metabolic monitoring was obtained from each patient file. The results of all the metabolic tests as well as the date on which they were performed were recorded on the data collection form.

- Weight.
- Fasting blood glucose.
- Blood pressure.
- Pulse.

The NICE guidelines recommend metabolic monitoring prior and after the initiation of lithium therapy.

If any actual baseline tests for metabolic monitoring were conducted, they were compared to the NICE guidelines for metabolic monitoring to determine the level of compliance.

Table 3-31 shows the categories of compliance with recommended guidelines for baseline metabolic function.

Table 3-31. Categories of compliance with recommended guidelines for baseline metabolic function.

Compliance with recommended guidelines for baseline metabolic monitoring	
1	Compliant
2	Non-compliant
3	Partially compliant

Compliant means that all metabolic function tests (weight, blood pressure, pulse and fasting blood glucose levels) were conducted before lithium initiation. Non-compliant means that none of the metabolic function tests were conducted before lithium initiation. Partial compliance means that some of the metabolic function tests were conducted before lithium initiation.

If any actual follow-up tests for metabolic monitoring were conducted, they were compared to the NICE guidelines for the metabolic monitoring to determine the level of compliance.

Table 3-32 outlines the categories of compliance with recommended guidelines for follow-up metabolic function.

Table 3-32. Categories of compliance with recommended guidelines for follow-up metabolic function.

Compliance with recommended guidelines for follow-up metabolic monitoring	
1	Compliant
2	Non-compliant
3	Partially compliant

Compliant means that all metabolic function tests (weight, blood pressure, pulse and fasting blood glucose levels) were conducted after lithium initiation at the recommended times. Non-compliant means that none of the metabolic function tests were conducted after lithium initiation. Partial compliance means that some of the metabolic tests were conducted after lithium initiation.

3.5.3.16.1 Weight and body mass index

The NICE guidelines recommend that weight and BMI should be monitored on an annual basis (Kirkham *et al.*, 2013:261).

The patient's baseline weight and height were determined and the BMI calculated from the information extracted in the patient file. The findings as well as the date of assessment were recorded.

It was determined whether follow-up monitoring of weight and BMI was performed. The date of assessment as well as the result was recorded on the data collection tool.

3.5.3.16.2 Blood pressure and pulse

The NICE guidelines, the International Society for Bipolar Disorders guidelines and World Federation of Societies of Biological Psychiatry guidelines have recommended that blood pressure and pulse be monitored prior to initiation of therapy, then during the first 6 months and during maintenance treatment (Nederlof *et al.*, 2018:3).

The blood pressure and pulse readings of the patient were obtained from the medical history. The findings as well as the date of assessment were recorded.

It was also determined whether follow-up monitoring of blood pressure and pulse was performed. The results as well as the date of assessment were recorded.

3.5.3.16.3 Blood glucose

The fasting blood glucose level of the patient was obtained from the medical history available in the patient file. The results as well as the date of assessment were recorded on the data collection tool.

3.5.3.17 Follow-up monitoring

3.5.3.17.1 Thyroid function

According to the South African Medicines Formulary (SAMF), thyroid function should be monitored on a 6 to 12-month basis and more frequently in elderly patients (Rossiter, 2016:485). The NICE bipolar guidelines recommend 6 to 12-month monitoring of thyroid function (Kirkham *et al.*, 2013:261).

It was determined if follow-up thyroid function tests were conducted. This was done by reviewing the results of the thyroid function tests performed. The results of the tests as well as the date of assessment were recorded.

If any actual follow-up tests were conducted, results were compared to the recommended guidelines for the monitoring of thyroid function to determine the level of compliance. The compliance with the South African (STGs and SAMF) and NICE guidelines was reported separately.

The categories of compliance with recommended guidelines for follow-up metabolic function are shown in Table 3-33 below.

Table 3-33. Categories of compliance with recommended guidelines for follow-up metabolic function.

Compliance with recommended guidelines for follow-up thyroid function monitoring	
1	Compliant
2	Non-compliant
3	Partially compliant

Compliant means that all thyroid function tests were conducted after lithium initiation at the recommended times. Non-compliant means that none of the thyroid function tests were conducted after lithium initiation. Partial compliance means that some of the thyroid function tests were conducted after lithium initiation.

3.5.3.17.2 Renal function

The NICE BD guidelines and the STGs of South Africa recommend that patients on lithium therapy maintenance have their renal function monitored every 6. Renal function tests should be conducted more frequently if there is evidence of renal impairment (Kirkham *et al.*, 2013:261; Rossiter, 2016:485).

It was determined if follow-up renal function tests were conducted. This was done by reviewing the results of the renal function tests performed. The results of the tests as well as the date of assessment were recorded.

Data obtained from follow-up test results was analysed and used to determine the level of compliance with the recommended guidelines with regards to renal function monitoring. Compliance with the NICE and South African (STGs and SAMF) guidelines was reported separately.

Table 3-34 shows the categories of compliance with recommended guidelines for follow-up renal function.

Table 3-34. Categories of compliance with recommended guidelines for follow-up renal function.

Compliance with recommended guidelines for follow-up renal function monitoring	
1	Compliant
2	Non-compliant
3	Partially compliant

Compliant means that all renal function tests were conducted after lithium initiation at the recommended times. Non-compliant means that none of the renal function tests were conducted after lithium initiation. Partial compliance means that some of the renal function tests were conducted after lithium initiation.

3.5.3.17.3 Lithium serum levels

Lithium is a commonly prescribed drug with a narrow therapeutic index. Serum levels that are below 0.4 mmol/L are generally ineffective and those above 1.0 mmol/L are beneficial to few patients. Levels that are above this upper threshold are usually associated with lithium toxicity such as confusion and renal damage. Treatment guidelines therefore recommend that serum lithium levels be checked regularly throughout treatment to ensure that it remains within the therapeutic range (Collins *et al.*, 2010:1).

The SAMF recommends regular monitoring of lithium serum concentration at one week intervals after each dose increment, then at one month, three months and at 6 month intervals during maintenance therapy (Rossiter, 2016:485). The NICE guidelines recommend monitoring serum levels at 3 to 6 month intervals in people on a stable dose (Kirkham *et al.*, 2013:261).

The NICE and South African (STGs and SAMF) guidelines recommend the monitoring of lithium serum levels after the initiation of lithium therapy.

It was determined whether follow-up serum level tests on lithium were conducted. This was done by reviewing the results of the serum level tests performed. The results of the tests as well as the date of assessment were recorded.

Data obtained from follow-up test results was analysed and used to determine the level of compliance with the recommended guidelines with regards to lithium serum levels monitoring. Compliance with the South African and NICE guidelines was reported separately under the categories outlined in Table 3-35 below.

Table 3-7. Categories of compliance with recommended guidelines for follow-up lithium levels.

Compliance with recommended guidelines for follow-up lithium serum level monitoring	
1	Compliant
2	Non-compliant
3	Partially compliant

Compliant means that all follow-up lithium serum level monitoring was conducted after lithium initiation at the recommended times. Non-compliant means no follow-up lithium serum level monitoring was conducted after lithium initiation at the recommended times. Partial compliance means that some of the follow-up monitoring for lithium serum levels were conducted at the recommended times.

3.5.4 Study variables and measurements

The study variables and measurements utilised in the study are outlined in Table 3-8 below.

Table 3-36. Study variables and measurements.

Study variables	Study measurements
Age	Co-morbid diseases or conditions
Gender	Diagnosis
Race	Lithium doses
Family history	Drug interactions
Pregnancy	Adverse effects
Smoking history	Compliance with recommended guidelines
Drug abuse	
Surgical history	

3.5.5 Levels of measurement

The design of a study is important as it determines the types of data analysis that will be used in that study. The "levels of measurement" or scales of measure were proposed by a psychologist named Stanley Smith Stevens in 1946. Levels of measurement can be described as the amount of information present in a data element and the degree of detail present. Stevens claimed that all measurements in science were classified as interval, nominal (categorical), ordinal (continuous) and ratio (Thompson, 2009:57; Marateb *et al.*, 2014:47).

3.5.5.1 Interval measures

The distance that exists between data elements can be determined at the interval level of measurement. Interval scales are constant metric scales with equal distances between values and an arbitrary zero point. A reference point and a true zero does not exist. They are measured on a linear scale and can be positive or negative numbers (Thompson, 2009:57; Marateb *et al.*, 2014:48). However, in this study, the interval level measure was not used.

3.5.5.2 Nominal measures

Nominal variables are also called categorical variables and they are names of categories. Nominal data has no ordering between categories, no distance measure between variables and can be categorically listed in any order without the relationship between variables being affected. These variables reflect qualitative differences more

than quantitative ones. Some nominal variables, also known as dichotomous variables, have two possible values. Examples of nominal variables include gender, race and the presence or absence of adverse effects (Thompson, 2009:57; Marateb *et al.*, 2014:47). Nominal variables such as gender and race were applied in this study.

3.5.5.3 Ordinal measures

A discreet ordinal scale is a nominal variable that has an inherent order though the interval between scale points may be uneven. Continuous ordinal scales occur when the measurements are continuous. Ordinal scales have direction but arithmetic functions cannot be performed due to the lack of equal distance between variables. Examples of ordinal scales include BMI (severely underweight, underweight, normal, overweight, obese), severity of pain (1-10 scale) and the 4-item-rating scale (sometimes, never, always, often) (Thompson, 2009:57; Marateb *et al.*, 2014:48).

An example of an ordinal variable used in this study was the BMI ranking of the patients. The categories for the BMI included underweight, normal, overweight and obese.

3.5.5.4 Ratio measures

Data elements that have a true zero are measured at the ratio (continuous) level of measurement. Ratio scales are the most informative metric scales with a meaningful zero point and meaningful numerical relationships between values. Ratio level data can be transformed by addition, multiplication and division without altering their relative values. Common examples of ratio scales include weight, height and pulse rate (Thompson, 2009:57; Marateb *et al.*, 2014:48).

An example of a ratio variable in the study is the number of admissions. Because of the absolute zero, we know that a patient that has been admitted at Fort England Hospital 4 times has been admitted two times more than a patient that has been admitted twice. Therefore, the number of admissions is a ratio-level variable.

3.5.6 Reliability and validity of research instruments

Reliability and validity are used to demonstrate and communicate the rigour of research processes and the credibility of research findings.

3.5.6.1 Reliability

Reliability is described as whether an assessment instrument produces the same results each time it is used in the same setting with the same subjects. Reliability means that the instrument is consistent and dependable. Reproducibility (reliability) is a prerequisite for the validity of a test that consistently produces true measurements (Sullivan, 2011:119; Swanson, 2014:2).

Reliability can be estimated in various way depending on the type of assessment instrument. Reliability is sometimes referred to as internal validity or the internal structure of an assessment tool. A test used to measure internal consistency is the Cronbach alpha which calculates the correlation between all variables in every combination. A value that is close to 1 represents a high reliability estimate and a test/retest should produce the same results each time. The test/retest is a more conservative reliability test when compared to the Cronbach alpha. Analysis of variance (ANOVA) can also be used to generate a generalisability coefficient that can determine how much measurement error can be attributed to each factor (Sullivan, 2011:119). However, the test to measure internal consistency was not employed in this study.

A true score is the genuine value of the parameter being measured and reflects what the researcher already knows. An error score is regarded as the factors that prevent a certain measure from being perfectly reliable. These errors consequently reduce the accuracy and consistency of the instrument. The errors made can either be systematic or random (Sarmah & Bora Hazarika, 2012:509).

Systematic errors are the errors that are consistent across the uses of the measurement error. Random errors have inconsistent effects and have different sources. The sources of random errors include (Sarmah & Bora Hazarika, 2012:509):

- Researcher variations such as stress and fatigue.
- Variation of administration condition such as noise.
- Bias of measurement device.
- Bias of participants such as guessing or cheating.
- Bias of the test administrator such as scoring errors.

The reliability of the data obtained from the study was ensured by having a colleague cross checking all the entered data.

3.5.6.2 Validity

Validity is used to determine whether a research instrument measures what it is intended to measure. A measurement instrument should not only be reliable but must also be valid. If the performances measured by a test are accurate then the test is valid. Educational and statistical validity are included in validity. A measure can't be valid without being reliable, but can be reliable without being valid (Sarmah *et al.*, 2012:515).

Validity is the interpretation or specific purpose of the assessment tool with particular settings rather than being a property of the tool itself. Study results can only be credible if the assessment tool is reliable and valid. The use of an instrument with high reliability is not enough to produce credible results (Sullivan, 2011:119).

3.5.6.2.1 Estimating validity

A criterion variable is used to determine or estimate the validity of a test. A co-efficient of validity is used to express the extent of validity (Sarmah *et al.*, 2012:515).

3.5.6.2.2 Types of validity

There are different types of validity and different types of tests require different types of validity. There are two classes of validity depending on the methods used by the researcher for ascertaining validity of the test. The two classes of validity are (Sarmah *et al.*, 2012:516):

1. **Logical validity:**

This is a simple form of validity where a superficial and subjective assessment of whether your study or test measures what it is supposed to measure is applied (Bolarinwa, 2015:196).

2. **Criterion validity:**

Criterion related validity is used when one is interested in determining the relationship of scores on a test to a specific criterion. It is a measure of the extent to which the

findings of an instrument compare to another instrument or predictor (Bolarinwa, 2015:196).

Some criterion external to the study can be used to validate the results of certain research questions. Certain questions related to statistics such as gender or compliance with regards to the monitoring requirements of lithium therapy were compared to the 'gold standards' available in literature.

Logical and criterion validity are further divided into several categories outlined in Table 3-37 below (Mulia, 2014:91).

Table 3-37. Categories of logical and criterion validity (Mulia, 2014:91).

Categories of logical validity	Categories of criterion validity
Content validity	Concurrent validity
Face validity	Predictive validity
Construct validity	

3.5.6.2.2.1 Content validity

Content validity involves the extent to which an instrument fully assesses or measures the concept of interest. The validity of the content of a test is satisfactory when the sampling of items is wide and an adequate number of standard questions are utilised. Rational analysis of the instrument by experts familiar with the construct of interest or experts on the research subject is involved in the development of a content valid instrument (Bolarinwa, 2015:197).

Content validity was applied in this study since it measures the extent to which a test covers the field of study. This means that it will indicate the extent to which items on the data collection tool represent the parameters under investigation. The data collection tool should therefore include questions related to the matter being investigated.

The supervisor and two co-supervisors assessed the contents of the data collection tool. Content validity was employed in this study.

3.5.6.2.2.2 Face validity

Face validity occurs when an individual and/or researcher who is an expert on the research subject reviewing an instrument concludes that it measures the characteristic or trait of interest. It involves an expert that has reviewed the instrument and agreeing that the test is a valid measure of the concept which is being measured just on the face of it. This means that the expert examines whether each of the items on the instrument matches any given theoretical domain of the concept being investigated. Face validity is often considered casual and an inactive measure of validity yet it is the most commonly used (Bolarinwa, 2015:196).

Face validity was applied in the study and a number of people were consulted in the development phase to judge the face validity of the data collection tool. These included the supervisor and two co-supervisors.

3.5.6.2.3 Collecting and analysing data concurrently

The data was collected and analysed concurrently so that there was a mutual interaction between what the researcher knew and what the researcher had to know. This interaction between data collection and analysis ensured reliability and validity.

3.5.7 Implementation plan

The researcher first determined if the pharmacy department at Fort England Hospital kept a register for patients that were initiated and maintained on lithium therapy. There was actually no register that was kept at the hospital so other sources were used to identify patients that were on lithium therapy for the study period of 1 January to 31 December 2017. The sources used were:

- Ward scripts for inpatients that contained information about the medication they were receiving and the period in which they were on that medication.
- Files that contained all 2017 scripts for outpatients.

The researcher had access to the Fort England pharmacy which was the storage location of patient files. The researcher then went through all the patient files that were available in the pharmacy department and identified which patient files would be useful for the study.

The researcher then investigated if Fort England Hospital had set protocols with regards to the initiation and monitoring of lithium. The researcher learnt that there were no set protocols and no international guidelines that were officially implemented. Therefore, there was a need to investigate the monitoring practices of lithium therapy as a possibility of insufficient monitoring practice was identified.

The designed data collection tool was then used to collect the data required for the study.

3.5.8 Data collection

The data collection process took place from 29 August 2018 to 30 November 2018 and data was recorded on the data collection form. Patient files were obtained from Fort England Hospital and included all in- and outpatients that were on lithium therapy for the required study period. The data collection process was conducted by the primary researcher at Fort England Hospital.

3.5.9 Data capturing and editing

All data captured on the data collection form was coded and collated on an electronic spreadsheet using Microsoft® Excel 2016.

Every criterion that was investigated and recorded on the data collection form was assigned a column on the spreadsheet. Data recorded on the data collection form was then captured onto the corresponding column on the Excel spreadsheet.

The data capturing process occurred between 1 December 2018 up to 20 December 2018. The statistical programme Statistical Analysis System® (SAS Institute Inc.) was used for statistical analysis once the data from the Excel spreadsheet was exported to it.

3.5.10 Data management and storage

3.5.10.1 During data collection

Data privacy and confidentiality was managed at all times with captured and processed data being stored on password-protected computers in locked offices, further protected by firewalls and the latest antivirus software.

Patient files did not leave the pharmacy. Hard copies of the data collection form and the electronic spreadsheet were kept safe during the study period by the researcher.

3.5.10.2 After study completion

The supervisor would store the hard copies of the data collection forms in a secure cupboard for five years.

3.5.11 Statistical analysis

Collected data from the data collection form was arranged, analysed, summarised and presented (graphs and tables) with Microsoft® Excel 2016 and the Statistical Analysis System® (SAS Institute Inc.).

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

Variables included in the study were explained using descriptive statistics. These included frequencies (n), percentages (%), means, medians, standard deviations (SDV) and 95% confidence intervals (CI).

Comparisons were explained using inferential statistics. The chi-square test and Cramér's V value were used to determine whether an association existed between proportions of two categorical variables.

3.5.11.1 Descriptive statistics

Descriptive statistics were used to describe the data obtained with the data collection tool.

3.5.11.1.1 Variables

Statistical variables can be categorised as discrete or continuous (Mendenhall *et al*., 2013:10).

3.5.11.1.2 Discrete variables

Variables are considered discrete if the possible values that it can attain are distinguishable from each other. Discrete variables have no in-between values. An

example of a discrete variable is the gender of a patient which can be categorised as "0" for male and "1" for female (Mendenhall *et al*., 2013:10).

3.5.11.1.2.1 Continuous variables

Unlike discrete values, the different possible values of continuous variables are indistinguishable. Continuous variables can have additional in-between values. An example of a continuous variable in this study was the body weights of patients (Mendenhall *et al*., 2013:10).

3.5.11.1.3 Mode

The mode can be defined as the value that occurs the most in a data set. It is possible for a data set not to have a mode if each value occurs once. A data set that has two or more values of equal frequency which is greater than that of any other value has more than one mode (Manikandan, 2011:214).

Though the mode can be easily calculated and is the only measure of central tendency that can be used for data measured in a nominal scale, it is rarely used as a summary statistic (Manikandan, 2011:214).

3.5.11.1.4 Median

The median is the value that occupies the middle position when all observations are arranged in either ascending or descending order. The median is the value that divides the frequency distribution into two halves. 50% of the observations on a distribution have scores that are either below or at the median. The median is therefore also referred to as the 50th percentile or positional average. The median can be determined for ratio, interval, and ordinal (Manikandan, 2011:214).

3.5.11.1.5 Average or arithmetic mean

The average is one of the best-known and popular statistics and is calculated by the sum of all the observations in the data set, divided by the total number of measurements. The mean can be used in interval or ratio scale data sets. The average is calculated using the following formula (Rosner, 2011:8):

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

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

3.5.11.1.6 Frequency

Frequency (f) can be defined as the number of times that a specific value is obtained for a specific variable in the study population (Rosner, 2011:22). An example is how substance abuse can be categorised as discrete data with regards to alcohol, tobacco and drug abuse and the number of times these occur is then expressed as relative percentage frequencies. Cumulative frequencies are useful to answer questions on ordinal scales of data such as:

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

The relative frequency and relative frequency density can also be determined from the frequency by deciding on class intervals and the length of such intervals. A histogram can graphically represent the relative frequency density by plotting the relative frequency density on the left y-axis, the frequency on the right y-axis and the class ranges on the x-axis. A frequency polygon can also be constructed by plotting the relative frequency densities against class middle points. Plotting the relative accumulative frequency against the class ranges will result in a relative accumulative frequency polygon (Rhodes, 2017:11).

3.5.11.1.7 Standard deviation

The SDV is the measure of the spread of the data around the mean and is most commonly used. SDV is utilised when one wants to summarise the variability in data, whether it is sample characteristics or response patterns (Carter, 2013:15).

The SDV typically characterises the distance of an observation from the distribution centre or middle value. A greater variability results from greater dispersion of observations with a low SDV representing a lesser variability and a high SDV representing more spreading out of the data (Barde & Barde, 2012:114).

SDV is calculated using the following equation (Barde & Barde, 2012:114):

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

3.5.11.1.8 Confidence interval

The confidence interval (CI) is used to describe the level of uncertainty about the true value of a parameter in a population. The confidence interval is usually reported as 95% or 99% and is the degree of variation that the researcher wished to ensure. This means that 95% or 99% of the time the true population will fall into the interval (Foster, 2014:31). A confidence interval is more useful compared to the *p*-value used in hypothesis tests as it only reflects a level of statistical significance (Clarke, 2012:66).

3.5.11.2 Inferential statistics

3.5.11.2.1 The *p*-value

This is defined as the probability under the assumption of no effect or difference (null hypothesis), of obtaining a result equal to or more extreme than what was actually observed. The *p*-value measures the likelihood that any differences observed in a group are due to a chance (Dahiru, 2011:22).

A *p*-value less than 0.05 (5% significance) is a standard that is used to show that there is evidence against the tested hypothesis (null hypothesis). A result is therefore statistically significant if the *p*-values are $p < 0.05$ (Greenland *et al*., 2016:341). The conditions associated with hypothesis testing are outlined in Table 3-38 (Dahiru, 2011:22).

Table 3-38. Conditions of hypothesis testing (Dahiru, 2011:22).

	Condition of null hypothesis	
Results of experiment	True	False
Accept null hypothesis	Correct decision (1-α)	Type II error (β)
Reject null hypothesis	Type I error (α)	Correct decision (1-β)

3.5.11.2.2 Chi-square test

The chi-square test (χ^2) is a non-parametric test often used in clinical research when testing the hypothesis of nominal variables. It is used to analyse categorical data such as male or female patients and smokers or non-smokers. This test determines whether there is an association between proportions of two or more categorical variables. It also provides information on the significance of differences and which categories account for the differences (Mchugh, 2013:143).

The assumptions that underlie a chi-square test are (Singhal & Rana, 2015:69):

- Data should be randomly drawn from a sample.
- Sample size should be sufficiently large with a minimum of 20 to 50 as the sample size. If the chi-square test is done on a smaller sample, it could lead to type II errors (accepting the null hypothesis when it is actually false).
- Variables considered should be mutually exclusive.

3.5.11.2.3 Cramér's V

This is a popular measure of association used for nominal random variables. Cramér's V equals 0 when there is no relationship between the two variables being investigated. It generally has a maximum value of 1 regardless of the sample size. This makes it possible to use Cramér's V to compare the strength of association between any two variables (Gingrich, 2004:782).

Table 3-39 outlines the Cramér's V values and the interpretation thereof (Parker & Rea, 2005:255).

Table 3-39. Cramér's V values and its interpretation(Parker & Rea, 2005:255).

Value of φ or Cramér's V	Interpretation
0.0 - < 0.1	Negligible association
0.1 - < 0.2	Weak association
0.20 - < 0.4	Moderate association
0.4 - < 0.6	Relatively strong association
0.6 - < 0.8	Strong association
0.8 - 1.0	Very strong association

In this study where the chi-square test returned a $p < 0.05$ (statistical significance), the implication of that was further explored by calculating Cramér's V value to determine the relative strength of the relationship between the two parameters.

3.6 Ethical considerations

Approval for the research project proposal was granted by the Rhodes University Faculty of Pharmacy Higher Degrees Committee. The final letter of approval is appended in ANNEXURE C.

Before the data collection process could begin, applications for ethical approval were submitted to the:

- Rhodes University Faculty of Pharmacy Ethics Committee. The final letter of approval (PHARM-2018-06) is appended in ANNEXURE D.
- Fort England Hospital Research Committee. The final letter of approval (PHARM-2018-06) is appended in ANNEXURE E.
- Eastern Cape Department of Health Research Committee. The final letter of approval (EC_201808_008) is appended in ANNEXURE F.

The implementation of the research project and data collection process could only begin after permission was granted by the respective bodies.

Prescriber and patient confidentiality were the main ethical considerations for the study. It was important to maintain patient confidentiality at all times hence no patient name or file number was recorded. A unique identification number was assigned to each patient and numbers between 1 and 40 were used. There was no personal

interaction between the researcher and the patients. The only source of information used was the patient file. The data was only collected by the primary researcher who was a master's degree candidate at Rhodes University. No employees of the pharmacy department or other departments at Fort England Hospital assisted the primary researcher in the data collection process.

Informed patient consent was not obtained as there was no direct contact between the researcher and the patients. No feedback regarding the outcomes of the study was given to individual patients.

Prescribers were neither identified, nor interviewed during the course of the study.

3.7 Chapter 3 summary

This concludes a discussion of the research methodology, statistical aspects and ethical aspects that were employed in this study. The next chapter will describe the results and discussion.

CHAPTER 4.
RESULTS AND DISCUSSION

4.1 Introduction

This chapter reports and discusses the results of the research conducted. The results were obtained with the data collection tool from the files of 40 patients and analysed. Results displayed in tables as percentages were rounded off to two decimal places.

4.2 Demographics

4.2.1 Age

Age categories were used to simplify the interpretation of the results obtained. Table 4-1 outlines the results of the age distribution of the study sample.

Table 4-1. Age distribution of the study sample (n=40).

Age category	n	Percentage (%)
> 18 and ≤ 30 years	10	25.00
≥ 31 and ≤ 50 years	16	40.00
≥ 51 and ≤ 65 years	11	27.50
> 65 years	3	7.50
Total	40	100

The results show that the majority of the patients involved in the study sample were between the ages of 31 and 50 years (n=16; 40.00%). The mean age of the study sample obtained from the results was 43.88 ± 15.81 years.

The age of the youngest patient involved in the study was 21 years and the oldest being 84 years. The median age was 42 years and the mode was 60 years among the study sample.

Age has an impact on the pharmacology of lithium. There is a decrease in lithium tolerability as the age increases (Arnaoudova, 2014:520). Older patients require a dose that is 31.00% lower than that for patients that are less than 50 years of age (Arnaoudova, 2014:520). It was therefore important to note the age of the patients.

4.2.2 Gender

The results of the gender distribution of the patients involved in the study is outlined in Figure 4–1.

Gender distribution of the study sample

■ Female (n=18)   ■ Male (n=22)
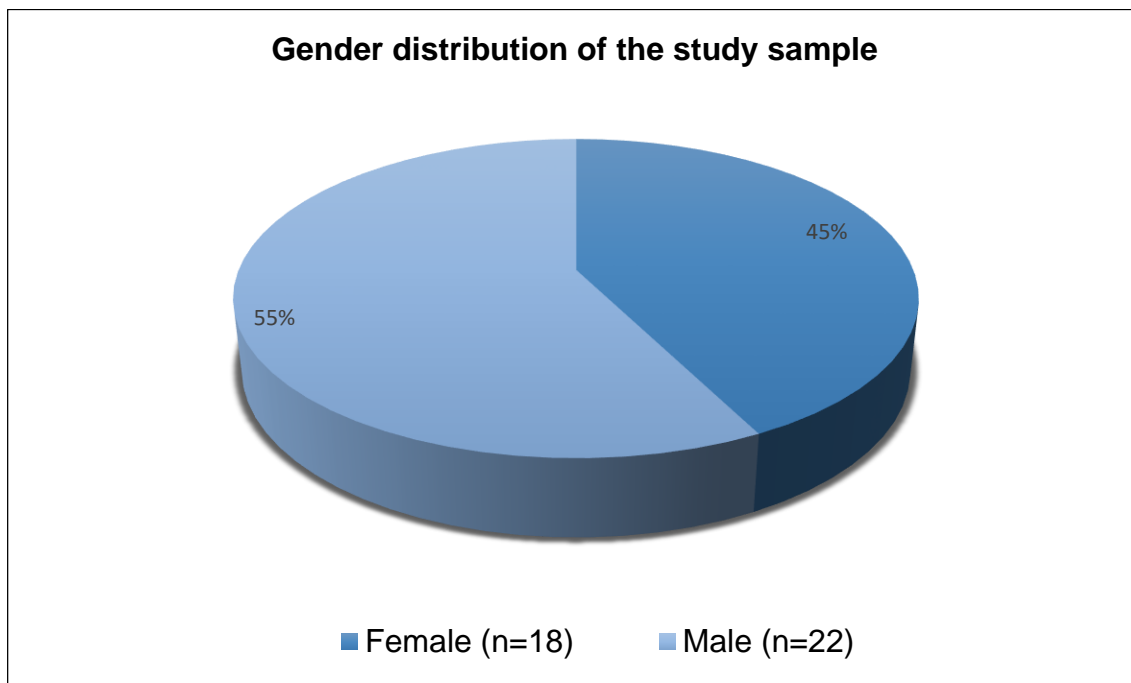
Figure 4–2: Gender distribution of the study sample (n=40).

The results show that most of the patients involved in the study were males (n=22; 55.00%).

Literature indicates that equal numbers of men and women are affected by psychiatric conditions (Depression and Bipolar Support Alliance, 2018).

4.2.3 Age by gender

The age by gender distribution of the study sample is outlined in Table 4-2 below.

Table 4-2. Age by gender (n=40).

Age categories	Gender		Total
	Male n (%)	Female n (%)	n (%)
> 18 and ≤ 30 years	4 (40.00%)	6 (60.00%)	10 (100.00%)
≥ 31 and ≤ 50 years	10 (62.50%)	6 (37.50%)	16 (100.00%)
≥ 51 and ≤ 65 years	7 (63.64%)	4 (36.36%)	11 (100.00%)
> 65 years	1 (33.33%)	2 (66.67%)	3 (100.00%)
Total	**22 (100.00%)**	**18 (100.00%)**	**40 (100.00%)**

The results show that most female patients involved in the study were in the age group of 18 to 30 years (n=6; 33.33%) and 31 to 50 years (n=6; 33.33%). Most males involved in the study were in the 31 to 50 years (n=10; 45.45%) age group.

The relationship between age and gender was further explored and explained below.

Results of the chi-square test show the association between age and gender was not statistically significant (*p*=0.400).

4.2.4 Race distribution

The results of the race distribution of the patients involved in the study is illustrated in Figure 4–3 below.

Race distribution of the study sample

3%

3%

42%

52%

- African (n=21)
- Caucasian (n=17)
- Indian (n=1)
- Colored (n=1)
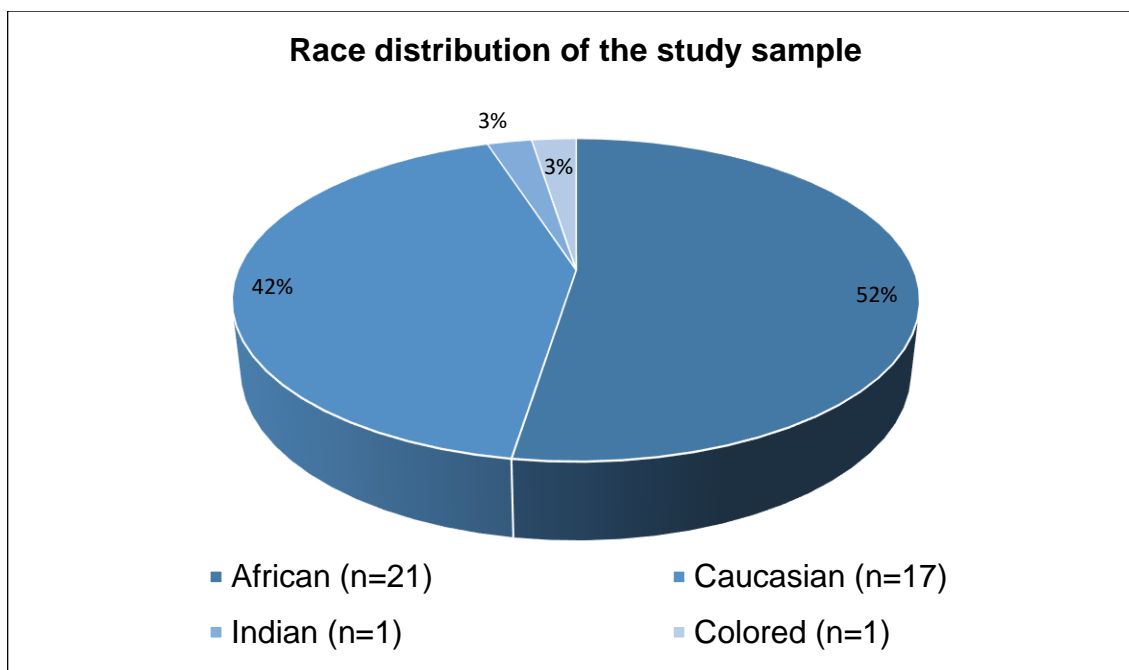
Figure 4–4. Racial distribution of study sample (n=40).

The results indicate that just over half of the patients involved in the study were of African descent (n=21; 52.00%). There was only one person of Indian descent (n=1; 3.00%) and one of coloured descent (n=1; 3.00%) in the study sample.

One study showed that there was a difference in lithium response among Hispanics, African Americans and non-Hispanic whites with bipolar disorder (Gonzalez *et al.*, 2015:224). It was therefore important to note the use of lithium among different racial groups. The results support this literature as there was different proportions of racial distribution among the study population.

4.2.5 Age by race

The results of the age by race distribution of the study sample is outlined in Table 4-3 below.

Table 4-3. Age by race (n=40).

Age categories	Race				Total
	African n (%)	Caucasian n (%)	Coloured n (%)	Indian n (%)	n (%)
> 18 and ≤ 30 years	6 (54.55%)	4 (36.36%)	0 (0.00%)	1 (9.10%)	11 (100.00%)
≥ 31 and ≤ 50 years	12 (80.00%)	2 (13.33%)	1 (6.67%)	0 (0.00%)	15 (100.00%)
≥ 51 and ≤ 65 years	3 (27.27%)	8 (72.73%)	0 (0.00%)	0 (0.00%)	11 (100.00%)
> 65 years	0 (0.00%)	3 (100.00%)	0 (0.00%)	0 (0.00%)	3 (100.00%)
Total	**21 (100.00%)**	**17 (100.00%)**	**1 (100.00%)**	**1 (100.00%)**	**40 (100.00%)**

The results show that most African patients were in the age group of 31 to 50 years (n=12; 57.14%) and most Caucasian patients (n=8; 47.06%) were between the ages of 51 and 65 years. The one Coloured patient was in the age group of 31 to 50 years and the one Indian patient was in the age group of 18 to 30 years.

The association between age and race was further explored and the results of the statistical comparison are explained below.

Results of the chi-square test show that the association between age and race was not statistically significant (p=0.520).

4.3 Social history

4.3.1 Substance use

Table 4-4 outlines the results obtained for patients with regards to substance use.

Table 4-4. Substance use distribution of study sample (n=40).

Substance use category	n	Percentage (%)
Users	26	65.00
Non-users	14	35.00
Total	40	100

The results show that most of the patients involved in the study used substances (n=26; 65.00%).

Comorbidities such as substance abuse are very prevalent among patients with BD with 65.00% of BD patients being substance abusers. This may be a result of self-medication to alleviate the symptoms of BD or may be primary disorders (Theodore *et al.*, 2012:1). The results are consistent with literature as 65.00% of the study sample abused substances.

4.3.2 Smoking status

The results of the smoking status of the study sample is outlined in Figure 4–5.
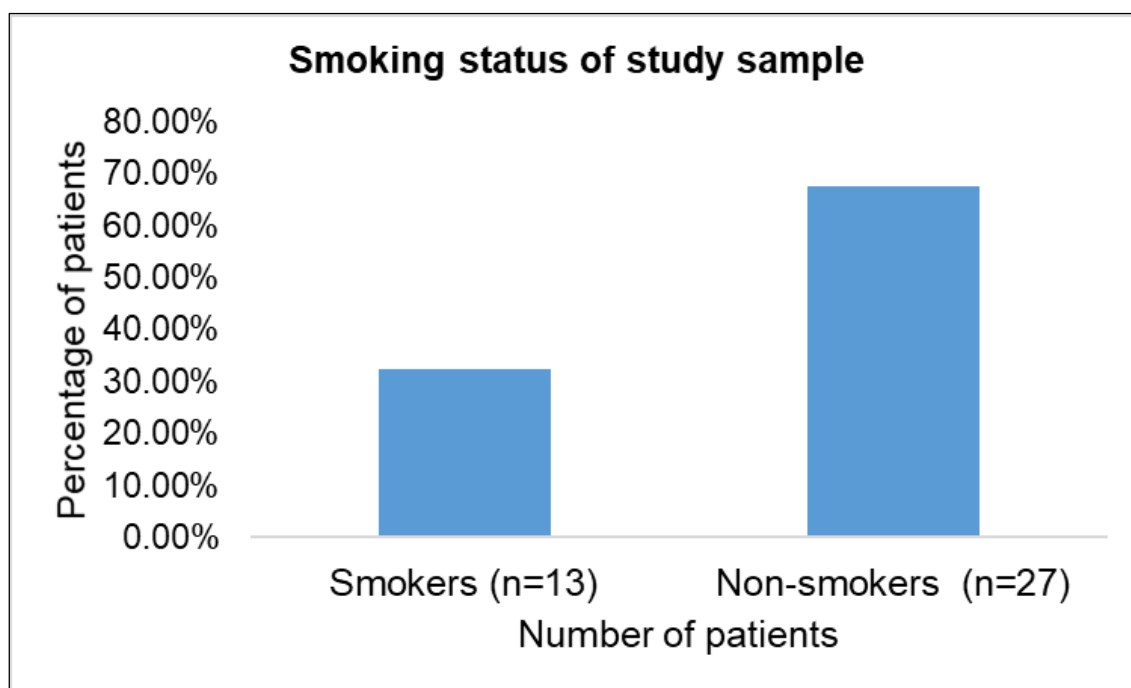
Figure 4–6. Smoking status of the study sample (n=40).

The results show that majority of the patients involved in the study did not smoke (n=27; 67.50%).

Epidemiological data has shown that there is a relatively high prevalence of smoking among BD patients when compared to other Axis I psychiatric conditions (Heffner *et al.*, 2011:441). The results were, however, inconsistent with this literature as majority of the study sample were non-smokers.

4.3.3 Alcohol use

Figure 4–7 outlines the results obtained with regards to alcohol use among the study sample.

Alcohol use among study sample

50%   50%

■ Users (n=20)   ■ Non-users (n=20)
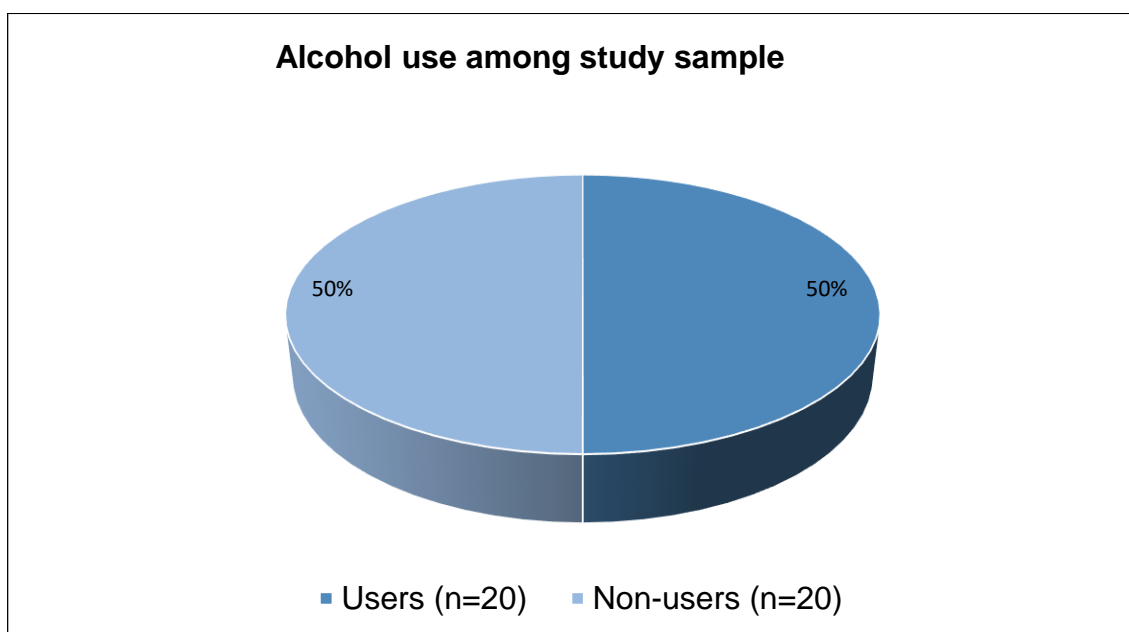
Figure 4–8. Alcohol use among the study sample (n=40).

The results show that half of the patients involved in the study abused alcohol (n=20, 50.00%).

The results are consistent with literature that suggests that the commonly abused substances are alcohol, cannabis, cocaine, and stimulants (Theodore *et al.*, 2012:1).

4.3.4 Cannabis use

The results obtained with regards to cannabis (dagga) use among the study sample are outlined in Table 4-5.

Table 4-5. Cannabis use in the study sample (n=40).

Cannabis use category	n	Percentage (%)
Users	13	32.00
Non-users	27	68.00
Total	40	100

The results show that most patients involved in the study did not abuse cannabis (n=27; 68.00%).

Though literature suggests that most patients with mental conditions abuse cannabis, the results indicated otherwise (Theodore *et al*., 2012:1).

4.3.5 Methamphetamine use

Figure 4–9 outlines the results obtained with regards to the use of methamphetamines among the study sample.
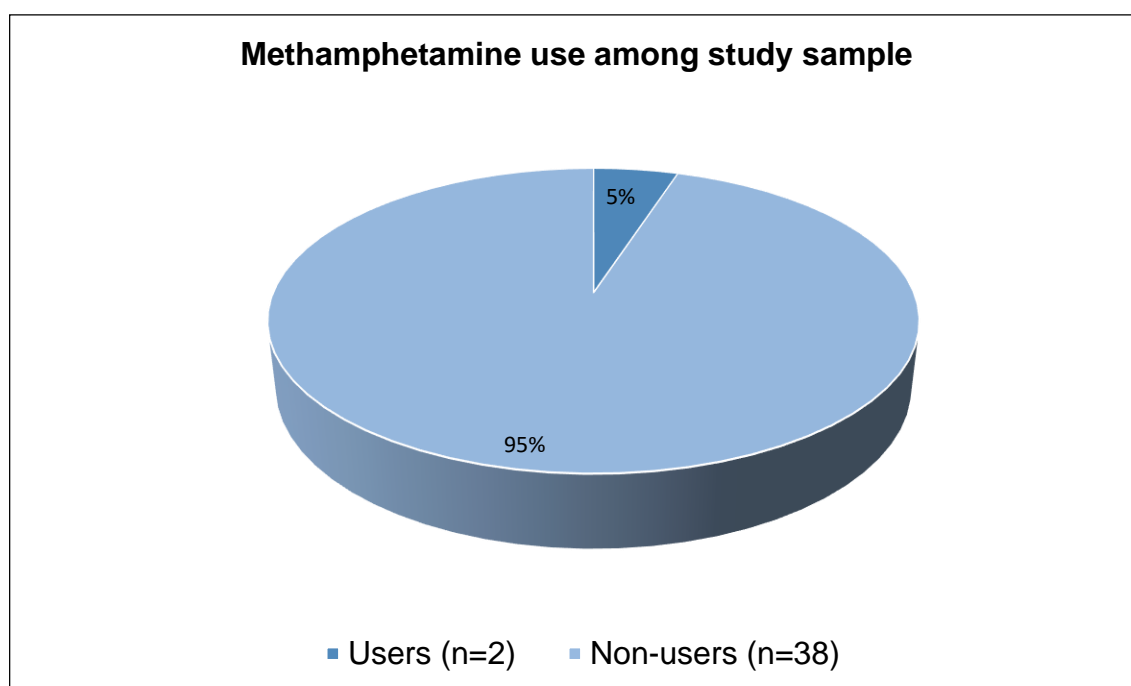
Figure 4–10. Methamphetamine use in the study sample (n=40).

The results show that most patients involved in the study did not abuse methamphetamines (n=38; 95.00%).

Methamphetamine is a stimulant that has been suggested to be prevalently used by people with mental conditions (Theodore *et al.*, 2012:1). However, the majority of this study sample did not use methamphetamines.

4.3.6 Other substances use

The results obtained for the abuse of other drugs (besides alcohol, cannabis and methamphetamines) are indicated in Table 4-6.

Table 4-6. Other drugs of abuse among the study sample (n=8)[6].

Drug of abuse	n	Percentage (%)
Benzodiazepines	3	37.50
Cocaine and Mandrax	2	25.00
Heroin	1	12.50
Heroin, Cocaine, Benzodiazepines and Mandrax	1	12.50
Mandrax	1	12.50
Total	8	100

The results indicate that the most abused substance other than alcohol, tobacco, cannabis and methamphetamines was benzodiazepines (n=3; 37.50%). Methaqualone, also known as Mandrax, and heroin were the least used drugs (n=1; 12.50%).

4.3.7 Employment status

The results obtained with regards to employment status of the study sample are indicated in Figure 4–11.

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[6] For the purposes of this study, 8 patients were included as 8 patients out of the study sample abused other substances other than alcohol, cannabis (dagga), tobacco and methamphetamines.
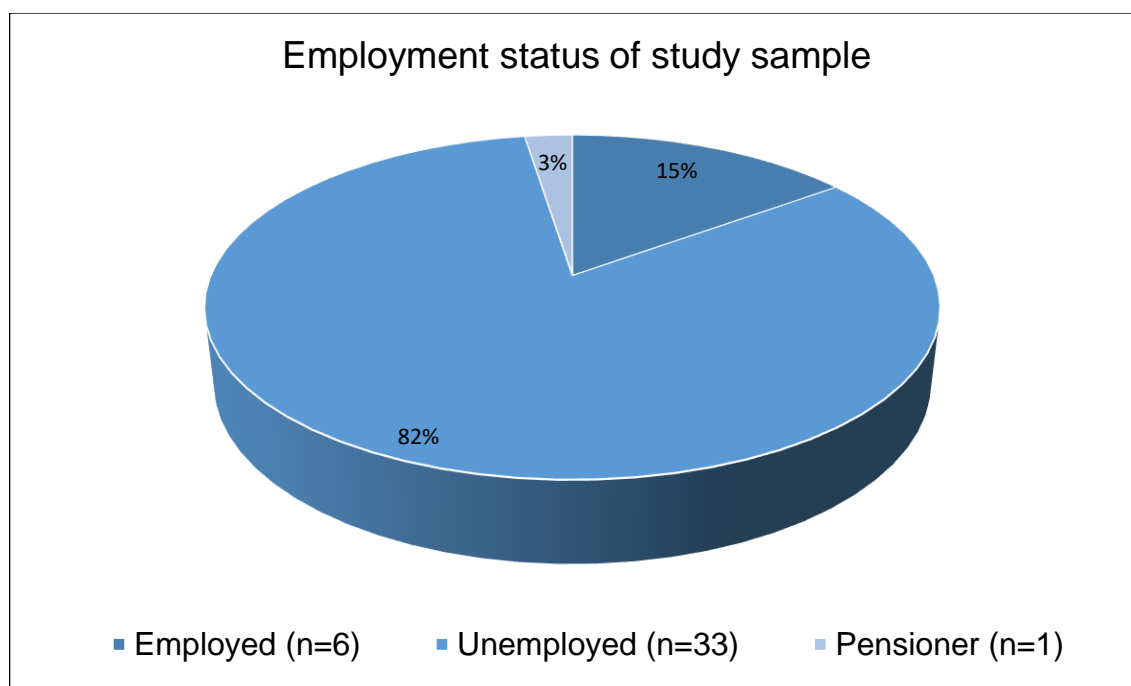
Figure 4–12. Employment status of the study sample (n=40).

The results indicate that most of the patients involved in the study were unemployed (n=33; 82.00%).

The relationship between employment status and diagnosis was further explored and the results of the statistical comparison are shown in the following table.

The results obtained for the statistical analysis of employment status and diagnosis are outlined in Table 4-7.

Table 4-7. Statistical analysis of employment by diagnosis.

Statistic	Value	Probability
Chi-square	44.72	< 0.0001
Cramér's V	0.61	

The statistical analysis performed through the chi-square test show that the association between employment and diagnosis was significant ($p < 0.0001$). A Cramér's V value of 0.61 show that there was a strong association between employment status and diagnosis in patients on lithium treatment.

This is consistent with literature that suggests that people with mental problems are often turned down from work or avoid looking for work because they anticipate

discrimination. Social exclusion, gossip, over-inferring of mistakes to illness and lack of opportunities for advancement are some of the discriminatory behaviours exhibited by managers and colleagues once one discloses their mental condition (Thornicroft, 2010:414). These contributing factors could explain why 82% of the study sample was unemployed.

The Mental Health Action Plan 2013-2020 report indicated that mental disorders have large economic consequences with a recent study estimating that between 2011 and 2030, US$16.3 million of economic output will be lost as a result of the global impact of mental disorders (WHO, 2013a:8). These results are consistent with the literature as 82.00% of the study sample was unemployed, yet the majority of them were of productive age.

However, it is possible that the reason for the high unemployment rate among the study sample is the existing high unemployment levels in South Africa which is a stark reality in the research setting.

4.3.8 Pregnancy and breastfeeding status

The results of the pregnancy and breastfeeding status of the female patients in the study sample is indicated in Table 4-8 below.

Table 4-8. Breastfeeding and pregnancy status of the female study sample (n=17).

Breastfeeding status	n	Percentage (%)	Pregnancy status	n	Percentage (%)
Breastfeeding	0	0.00	Pregnant	0	0.00
Not Breastfeeding	17	100.00	Not Pregnant	17	100.00
Total	17	100	Total	17	100

None of the female patients (n=17;100%) in the study sample were either pregnant or breastfeeding.

These results were important as lithium is a Category D drug that is not safe for use during pregnancy. Category D in pregnancy means that there is positive evidence of risk on the unborn human foetus. The use of category D drugs in pregnant women is

deemed acceptable when the potential benefits outweigh the potential risks (Wood, 2013:78).

Lithium is excreted in breast milk and breastfeeding is not recommended as levels can reach toxic levels in the infant. It was therefore important to establish if the female patients involved in the study breastfed their infants.

4.3.9 Baseline and follow-up body weight

The results of the availability of the body weights of the study sample before and after receiving lithium therapy are outlined in Table 4-9 below.

Table 4-9. Availability of the body weights of the study sample before and after lithium initiation (n=40).

Availability of weight before lithium therapy	n	Percentage (%)	Availability of weight after lithium initiation	n	Percentage (%)
Yes	33	82.50	Yes	29	72.50
No	7	17.50	No	11	27.50
Total	40	100	Total	40	100

The body weights of the patients before they were initiated on lithium therapy could be obtained for the majority of the patients (n=33; 82.50%) in the study sample.

The results of the body weights of the 33 patients that were weighed before lithium therapy are described: The mean body weight was 64.78 ± 36.45 kg; the minimum body weight was 53.90 kg; the maximum body weight was 156.90 kg; and the median body weight was 68.00 kg with a mode of 75.00 kg.

Other risk factors for weight gain include high baseline weight, young age, female gender and co-administration of antidepressants (Livingstone & Rampes, 2009:351). The baseline weight was therefore important.

The body weights of the patients after initiation with lithium therapy was available for most of the patients (n=29; 72.50%).

The results of the body weights of the 29 patients that were weighed after the initiation of lithium therapy showed that the mean body weight was 59.70 ± 43.21 kg; the minimum body weight was 52.60 kg; the maximum body weight was 151.00 kg; and the median body weight was 66.55 kg with no mode.

One study showed that 62.00% of patients on lithium treatment reported significant weight gain (Livingstone & Rampes, 2009:351). The results are inconsistent with this literature as many patients did not experience significant weight gain.

4.3.10 Body mass index

The body mass index (BMI) categories were used to simplify the interpretation of the results obtained. Figure 4–13 outlines the results of the BMI distribution of the study sample.

BMI of study sample

- Categories of BMI:
- <18.5 (n=3)
- 18.5-24.9 (n=6)
- 25-29.9 (n=6)
- ≥30 (n=5)
- Unavailable (n=20)
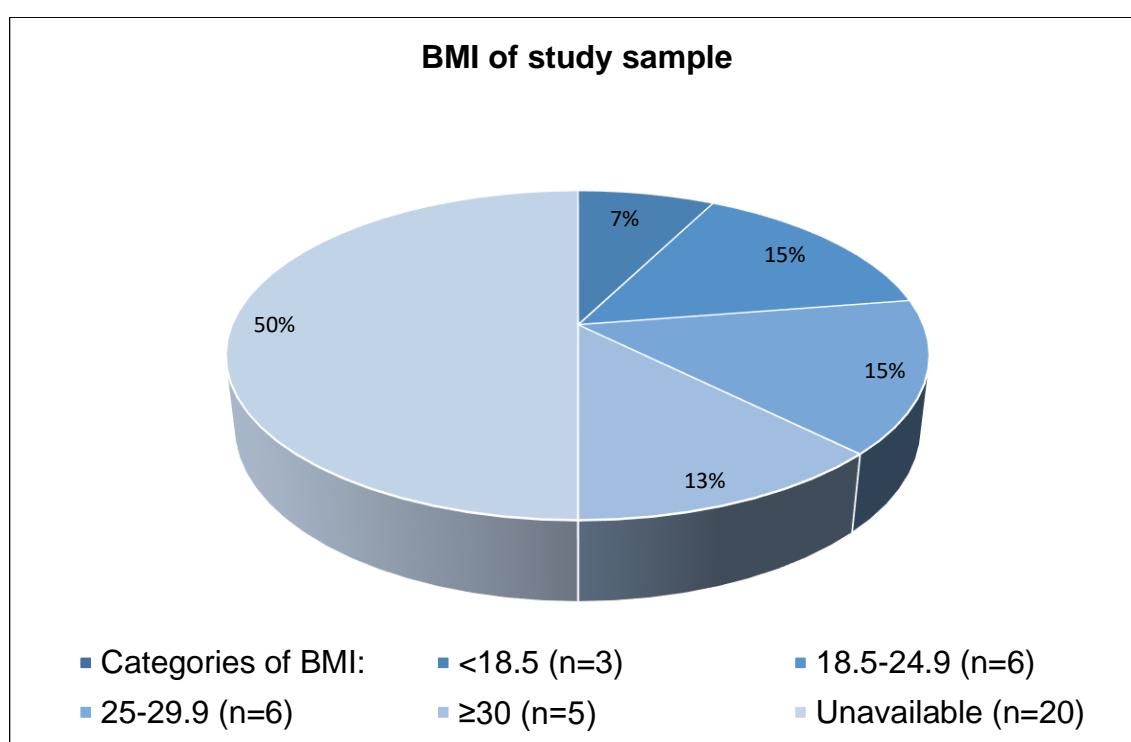
Figure 4–14. Body mass index distribution of the study sample (n=40).

The results show that the BMI could not be determined for most of the patients in the study sample (n=20; 50.00%). This was due to a lack of either their height or weight readings. In a few cases (n=3; 7.00%), the patients were in the underweight category. However, 13.00% (n=5) of the study sample had a BMI in the obese category and 15.00% (n=6) were in the overweight category.

Out of the 20 known BMIs, 11 (55.00%) of them were in the overweight and obese categories.

4.3.11 Baseline and follow-up blood pressure and pulse

The results of the availability of the baseline and follow-up blood pressure and pulse readings of the study sample are outlined in Table 4-10 below.

Table 4-10. Availability of blood pressure and pulse readings (n=40)

Availability of baseline blood pressure and pulse readings	n	Percentage (%)	Availability of follow-up blood pressure and pulse readings	n	Percentage (%)
Yes	32	80.00	Yes	38	95.00
No	8	20.00	No	2	5.00
Total	40	100	Total	40	100

The results show that the baseline blood pressure and pulse was measured in 80.00% (n=32) of the cases.

The results clearly showed that the blood pressure and pulse readings were taken for most patients (n=38; 95.00%) during the follow-up monitoring phase.

4.3.12 Baseline and follow-up blood glucose levels

The results of the availability of the baseline and follow-up blood glucose readings of the study sample are outlined in Table 4-11 below.

Table 4-11. Availability of follow-up blood glucose levels (n=40).

Availability of baseline blood glucose levels readings	n	Percentage (%)	Availability of follow-up blood glucose levels readings	n	Percentage (%)
Yes	31	77.50	Yes	14	35.00
No	9	22.50	No	26	65.00
Total	40	100	Total	40	100

The results clearly indicate that baseline blood glucose levels were taken for 77.50% (n=31) of the patients.

The results also indicate that most patients (n=26; 65.00%) did not have their follow-up blood glucose levels measured. Therefore, there is a great need to improve the monitoring of this parameter.

4.4 Medical history

4.4.1 Diagnosis

Table 4-12 indicates the results of the different diagnoses of the study sample.

Table 4-12. Diagnoses of the study sample (n=40).

Diagnosis	n	Percentage (%)
Bipolar disorder	33	82.50
Schizoaffective disorder	2	5.00
Schizophrenia	3	7.50
Major Depressive Disorder	2	5.00
Total	40	100

The results indicate that most patients had a diagnosis of bipolar disorder (n=33; 82.50%) followed by schizophrenia (n=3; 7.50%). Schizoaffective disorder (n=2; 5.00%) and major depressive disorder (n=2; 5.00%) were the least diagnosed mental disorders in the study sample.

4.4.2 Diagnosis by race distribution

The results of the diagnosis by race distribution of the study sample is outlined in Table 4-13 below.

Table 4-13. Diagnosis by race (n=40).

Diagnosis	Race				Total
	African n (%)	Caucasian n (%)	Coloured n (%)	Indian n (%)	n (%)
Bipolar disorder	18 (55.55%)	13 (39.39%)	1 (3.03%)	1 (3.03%)	33 (100.00%)
Schizoaffective disorder	1 (50.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	2 (100.00%)
Schizophrenia	2 (66.67%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	3 (100.00%)
Major Depressive disorder	0 (0.00%)	2 (100.00%0	0 (0.00%)	0 (0.00%)	2 (100.00%)
Total	21 (100.00%)	17 (100.00%)	1 (100.00%)	1 (100.00%)	40 (100.00%)

The results show that majority of the patients for all racial groups were diagnosed with BD. Of the African patients, 85.71% (n=18) were diagnosed with BD while 13 (76.47%) Caucasian patients had BD. One patient (n=1; 100.00%) of both Indian and Coloured descent had BD.

The results of the statistical analysis of diagnosis by race distribution are explained below.

The statistical analysis represented by a chi-square *p*-value of 0.960 shows that the association between diagnosis and race was non-significant.

4.4.3 Suicide risk

Figure 4–8 demonstrates the results of the suicide risk of the study sample.

Suicide risk among study population

- At risk (n=10) - Not at risk (n=30)
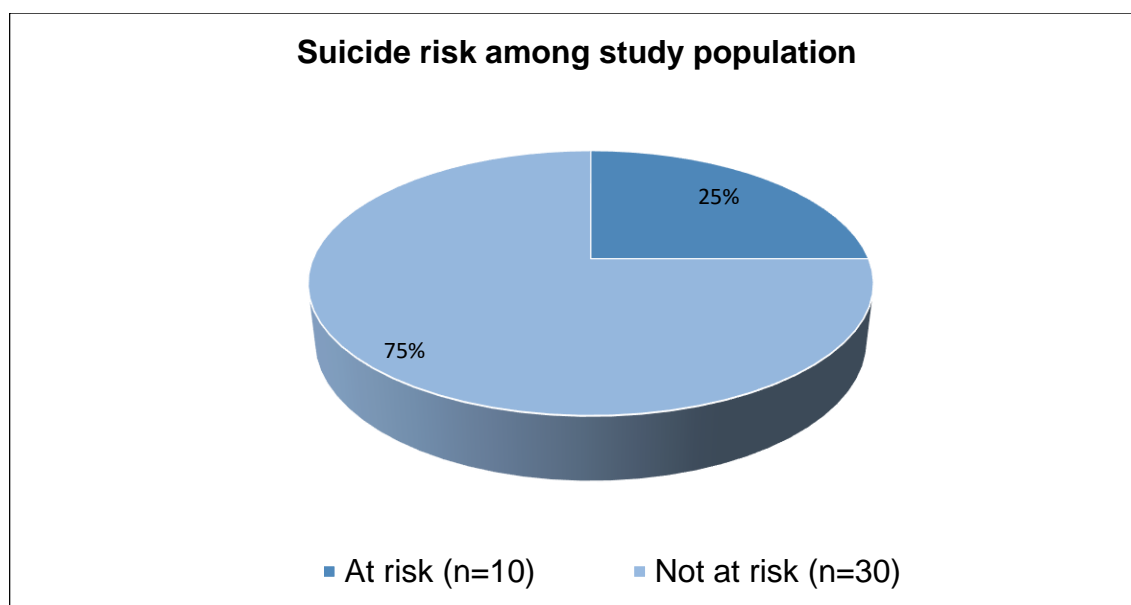
Figure 4–8. Suicide risk of the study sample (n=40).

The results indicate that most patients did not have suicidal ideation (n=30; 75.00%). The low number of suicidal risks could be due to the anti-suicidal effects that lithium possesses.

Long term treatment with lithium in patients with affective disorders has proven to have suicide preventing effects. Clinical reports have indicated that this effect may occur early at the beginning of lithium treatment (Lewitzka *et al.*, 2015:1). The results are therefore consistent with this literature.

4.4.4 Allergies

Table 4-14 indicates the results of the allergies of the study sample.

Table 4-14. Allergies of the study sample (n=40).

Allergies	n	Percentage (%)
Yes	1	2.50
No	39	97.50
Total	40	100

Only one of the patients (n=1; 2.50%) in the study sample was allergic to penicillin. Most of the study sample did not have any reported allergies.

Allergic reactions form part of adverse drug reactions (ADRs) though they form only 6 to 10% of ADRs. Allergic or hypersensitivity reactions can be induced by drugs and these include drug intolerance (Smith, 2013:12). It was then determined that all patients were not prescribed any medication that they were allergic to.

4.4.5 Co-morbid conditions

Figure 4–9 below summarises the results obtained for the co-morbid disease states that the patients suffered from.
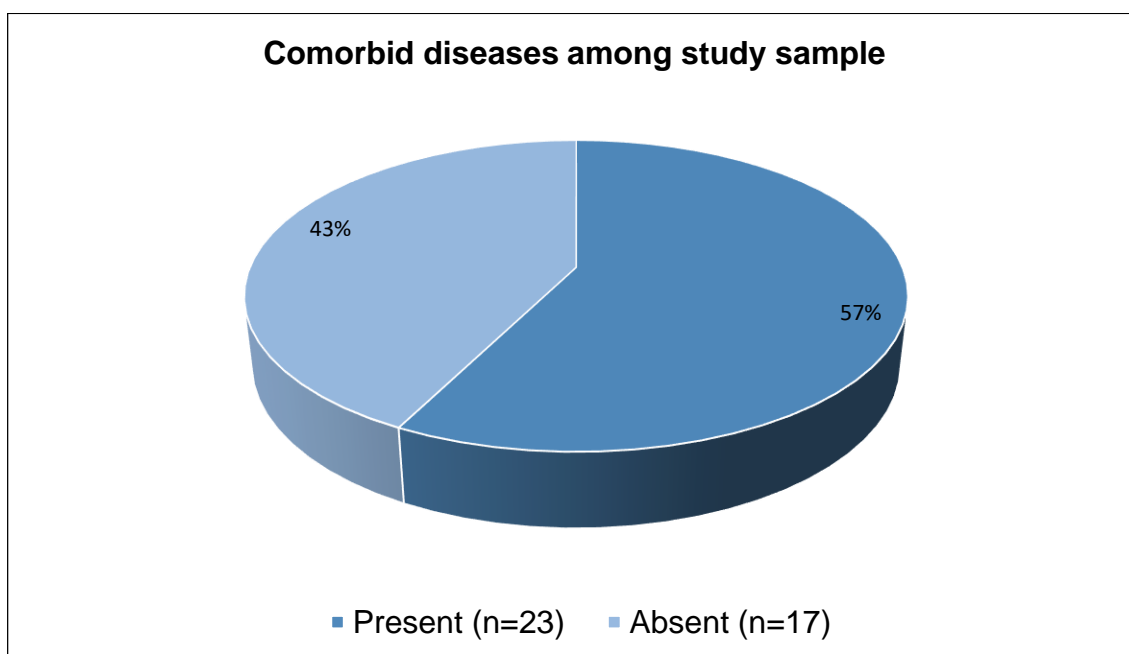
Figure 4–9. The prevalence of co-morbid diseases (n=40).

The results indicate that most patients had a primary diagnosis of a psychiatric condition with reported co-morbidities (n=23; 57.00%).

People with psychiatric disorders are at increased risk for chronic medical conditions. Depressive disorders commonly co-occur with conditions such as diabetes and cardiovascular disease. People with serious mental disorders and substance use disorders are at elevated risk for chronic medical conditions such as cardiovascular disease, diabetes and pulmonary disease (Cabassa *et al.*, 2013:541). The results are consistent with this literature as more than half of the patients had co-morbid diseases.

The co-morbid diseases that the study sample suffered from were further investigated and are summarised in Table 4-15 below.

Table 4-15. Co-morbid disease states (n=40).

Disease state	n	Percentage (%)
Asthma and Hypercholesterolemia	1	2.50
Antisocial Personality Disorder	1	2.50
Attention Deficit Hyperactivity Disorder	1	2.50
Attention Deficit Hyperactivity Disorder, Asthma and Anti-social Personality Disorder	1	2.50
Borderline Personality Disorder	1	2.50
Chronic Obstructive Pulmonary Disease, Hyperthyroidism and Traumatic Brain Injury	1	2.50
Dementia and Parkinson's Disease	1	2.50
Diabetes and HIV	1	2.50
Dyslipidaemia	1	2.50
Dyslipidaemia, HIV and Antisocial Personality Disorder	1	2.50
Galactorrhoea	1	2.50
Gastric Oesophageal Reflux Disease	1	2.50
HIV	2	5.00
HIV, Borderline Personality Disorder and Anti-social Personality Disorder	1	2.50
Hypercholesterolemia	4	10.00
Melanoma	1	2.50
Osteoarthritis and Hypercholesterolemia	1	2.50
Polysubstance Use Disorder	3	7.50
None[7]	17	42.50
Total	40	100

The results show that the most common co-morbid disease state was hypercholesterolemia (n=4; 10.00%).

4.4.6 Surgical history

The results of the surgical history of the study sample are outlined in Table 4-16.

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[7] The category "None" implies that that there was no co-morbid disease or condition.

Table 4-16. Surgical history of study sample (n=40).

Surgery performed	n	Percentage (%)
Yes	4	10.00
No	36	90.00
Total	40	100

The results indicated that most patients had not undergone any surgical procedure (n= 36; 90.00%). The 10.00% (n=4) of the patients that had undergone surgical procedures can be specified as follows:

- One female patient had a hysterectomy and cholecystectomy.
- One male patient had an appendectomy.
- One male patient had a thyroidectomy.
- One male patient had an incisional hernia.

4.4.7 Family history of conditions

Table 4-17 below summarises the results obtained for the family history of any diseases.

Table 4-17. Family history of diseases (n=40).

Disease state	n	Percentage (%)
None	25	62.50
Hypertension	1	2.50
Psychiatric condition	14	35.00
Total	40	100

The results indicate that more than half of the patients (n=25; 62.50%) in the study sample did not have any family history of any diseases. However, 35.00% (n=14) of the patients had a family history of a mental disorder. Due to the limited data available in the patients' files, it was not possible to distinguish between the various types of mental disorders.

Studies have shown that the risk of developing SD was strongly linked to BD and schizophrenia among first degree relatives. The risk of developing BD and schizophrenia was found to be high if there is a family member with BD and

schizophrenia respectively (Brown *et al.*, 2011:1). The results were consistent with this literature to some degree as 35.00% of the patients had a family history of a mental disorder.

4.5 Admission history

4.5.1 Number of previous admissions

Figure 4–10 represents the results for the number of previous admissions for the patients in the study sample.
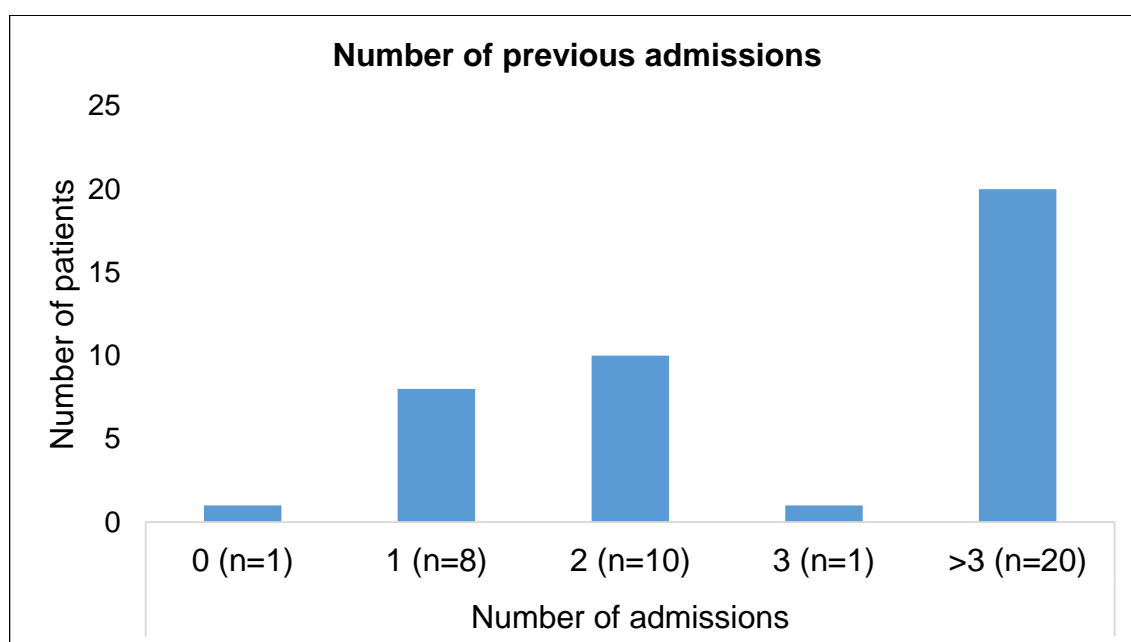
Figure 4–10. Number of previous admissions (n=40).

The results indicate that half the patients included in the study were admitted more than three times (n=20; 50.00%) to a psychiatric hospital. Only one person was not previously admitted.

4.5.2 Number of previous admissions by age

Table 4-18 summarises the number of previous admissions by age distribution for the patients included in the study sample.

Table 4-18. Number of previous admissions by age (n=40).

Age categories	Number of previous admissions					Total n (%)
	0 n (%)	1 n (%)	2 n (%)	3 n (%)	> 3 n (%)	
> 18 and ≤ 30 years	1 (100.00%)	3 (30.00%)	3 (30.00%)	0 (0.00%)	3 (30.00%0	10 (100.00%)
≥ 31 and ≤ 50 years	0 (0.00%)	3 (18.75%)	2 (12.50%)	0 (0.00%)	11 (68.75%)	16 (100.00%)
≥ 51 and ≤ 65 years	0 (0.00%)	1 (9.10%)	4 (36.36%)	1 (9.10%)	5 (45.44%)	11 (100.00%)
> 65 years	0 (0.00%)	1 (33.33%)	1 (33.33%)	0 (0.00%)	1 (33.33%)	3 (100.00%)
Total	1 (100.00%)	8 (100.00%)	10 (100.00%)	1 (100.00%)	20 (100.00%)	40 (100.00%)

The results indicate that most previous admissions were seen in the 31 to 50 years (n=16; 40.00%) age group. Patients older than 65 years of age were admitted the least number of times (n=3, 7.50%).

In addition, it was statistically explored whether a relationship existed between the number of previous admissions and age. The results are explained below.

The statistical analysis represented by a chi-square *p*-value of 0.320 indicated that the association between the number of previous admissions and age in the patient was non-significant.

4.6 Lithium use

4.6.1 Patients on lithium therapy prior to 2017

Table 4-19 indicates the results of the study sample with regards to patients who were on lithium therapy before 2017.

Table 4-19. Number of patients on lithium therapy before 2017 (n=40).

Were patients on lithium before 2017?	n	Percentage (%)
Yes	35	87.50
No	5	12.50
Total	40	100

From the results it is clear that most of the patients involved in the study sample were on lithium therapy before 2017 (n=35; 87.50%). In a few cases (n=5; 12.50%), lithium was initiated in 2017.

4.6.2 Availability of the initiation date of lithium

Figure 4–11 demonstrates the results obtained regarding the availability of the initiation date of lithium.
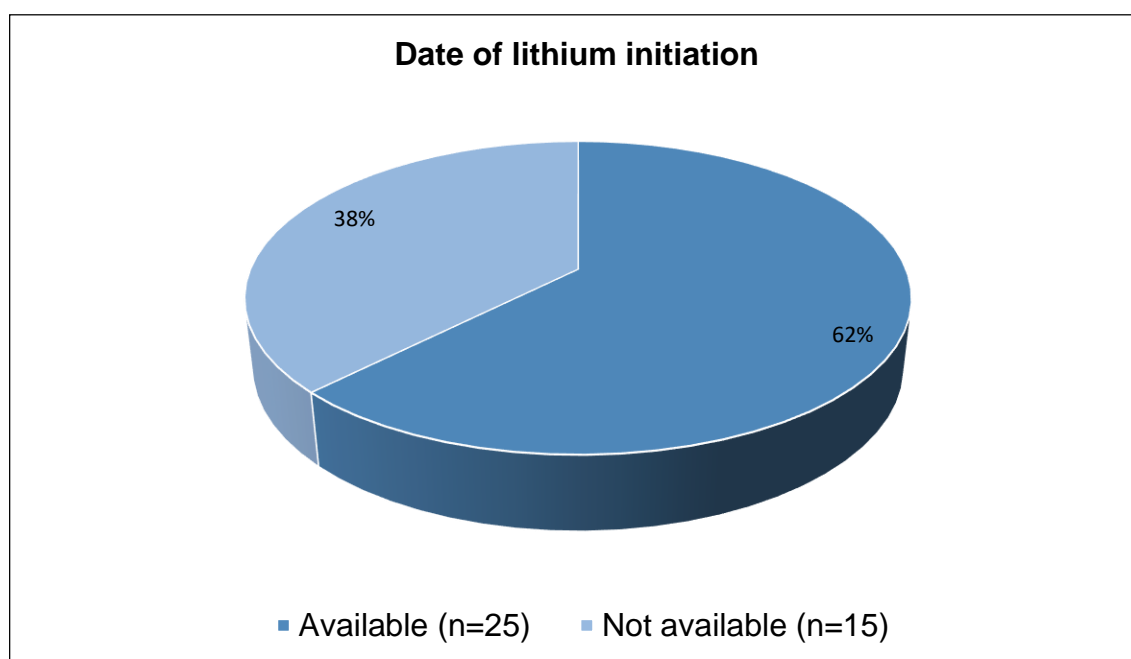
Figure 4–11. Availability of lithium initiation date (n=40).

The results indicate that the initiation date of lithium therapy was available for most patients (n=25; 62.00%).

4.6.3 Number of years passed since first initiation of lithium

Table 4-20 outlines the results for the number of years passed since the first initiation of lithium for the patients in the study sample.

Table 4-20. Number of years since lithium initiation (n=40).

Number of years on lithium therapy	n	Percentage (%)
< 1 year	5	12.50
≥ 1 and ≤ 5 years	13	32.50
> 5 and ≤ 10 years	2	5.00
> 10 years	5	12.50
Unknown	15	37.50
Total	40	100

In most cases (n=15; 37.50%), it was impossible to determine how long the patients in the study sample were on lithium therapy. In only a few cases (n=2; 5.00%) lithium therapy was initiated between 5 and 10 years ago. Equal numbers of patients (n=5; 12.50%) were on lithium therapy for less than a year and for more than 10 years. The data suggest that patients were using lithium as maintenance therapy.

4.6.4 Doses of lithium administered

The doses of lithium administered to the study sample is outlined in Table 4-21.

Table 4-21. Doses of lithium among study sample (n=40).

Strength of lithium	n	Percentage (%)
200 mg/day	1	2.50
250 mg/day	4	10.00
400 mg/day	1	2.50
500 mg/day	15	37.50
600 mg/day	1	2.50
750 mg/day	5	12.50
800 mg/day	3	7.50
1000 mg/day	8	20.00
1200 mg/day	1	2.50
1250 mg/day	1	2.50
Total	40	100

The results show that the most commonly prescribed maintenance daily dose of lithium among the patients in the study sample was 500 mg/day (n=15; 37.50%,) followed by 1000 mg/day (n=8; 20.00%).

Statistical results indicate that the mean dose of lithium was 657.50 ± 277.48 mg/day, the minimum dose was 200 mg/day and the maximum dose was 1250 mg/day. The median was 500 mg/day and the mode 500 mg/day.

The maintenance dose has a usual range of 750 mg-1000 mg/day (Rossiter, 2016:485). However, the results showed that most people were maintained on 500 mg/day and a few patients being maintained with over 1000 mg/day. This difference with the recommended maintenance dose could be due to the fact that lithium is dosed according to weight and age.

4.6.5 Doses by age

Table 4-22 shows the results obtained for doses of lithium by the age of patients in the study sample.

Table 4-22. Doses by age (n=40).

Doses of lithium	Age categories				Total n (%)
	> 18 and ≤ 30 years n (%)	≥ 31 and ≤ 50 years n (%)	≥ 51 and ≤ 65 years n (%)	> 65 years n (%)	
200 mg/day	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)	1 (100.00%)
250 mg/day	0 (0.00%)	2 (50.00%)	2 (50.00%)	0 (0.00%)	4 (100.00%)
400 mg/day	1 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)
500 mg/day	5 (33.33%)	5 (33.33%)	3 (20.00%)	2 (13.33%)	15 (100.00%)
600 mg/day	0 (0.00%)	0 (0.00%)	1 (100.00%)	0 (0.00%)	1 (100.00%)
750 mg/day	1 (20.00%)	3 (60.00%)	1 (20.00%)	0 (0.00%)	5 (100.00%)
800 mg/day	0 (33.33%)	2 (66.67%)	1 (33.33%)	0 (0.00%)	3 (100.00%)
1000 mg/day	1 (12.50%)	4 (50.00%)	3 (37.50%)	0 (0.00%)	8 (100.00%)
1200 mg/day	1 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)
1250 mg/day	1 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)
Total	**10 (100.00%)**	**16 (100.00%)**	**11 (100.00%)**	**3 (100.00%)**	**40 (100.00%)**

The results indicate that the most commonly prescribed dose of lithium was 500 mg/day among all age groups. Lithium 500 mg/day was prescribed in 5 patients (50.00%) between the ages of 18 and 30 years and in 5 (31.25%) patients between 31 and 50 years. Patients older than 65 years and those between 51 and 65 years

were prescribed 500 mg/day in 66.67% (n=2) and 27.27% (n=3) of the cases respectively.

It was further investigated whether a relationship existed between the lithium dose and patient age. The results of the statistical analysis summarised in Table 4-23.

Table 4-23. Statistical analysis of lithium doses by age (n=40).

Statistic	Value	Probability
Chi-square	14.41	0.02
Cramér's V	0.62	

The results show a strong relationship between lithium doses and age in the study sample as represented by a Cramér's V value of 0.62. The *p*-value of the chi-square test indicates that the association between lithium dose and age was significant.

The South African Medicine Formulary (SAMF) recommends that doses should be adjusted in elderly patients. Lower doses (0.4 to 0.7 mmol/L serum levels) of lithium should be administered to the elderly as they have decreased renal function and consequently decreased clearance of lithium (Rossiter, 2016:485). The results were consistent with this literature as geriatrics were maintained on doses as low as 200 mg/day and 500 mg/day.

4.6.6 Doses by race

Table 4-24 shows the results obtained for doses of lithium by race distribution.

Table 4-24. Doses by race (n=40).

Doses of lithium	Race categories				Total n (%)
	African n (%)	Caucasian n (%)	Coloured n (%)	Indian n (%)	
200 mg/day	0 (0.00%)	1 (100.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)
250 mg/day	1 (25.00%)	2 (50.00%)	1 (25.00%)	0 (0.00%)	4 (100.00%)
400 mg/day	0 (0.00%)	1 (100.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)
500 mg/day	8 (53.33%)	7 (47.67%)	0 (0.00%)	0 (0.00%)	15 (100.00%)
600 mg/day	0 (0.00%)	1 (100.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)
750 mg/day	4 (80.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	5 (100.00%)
800 mg/day	2 (66.67%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	3 (100.00%)
1000 mg/day	5 (62.50%)	3 (37.50%)	0 (0.00%)	0 (0.00%)	8 (100.00%)
1200 mg/day	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)	1 (100.00%)
1250 mg/day	1 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)
Total	**21 (100.00%)**	**17 (100.00%)**	**1 (100.00%)**	**1 (100.00%)**	**40 (100.00%)**

The results indicate that the most commonly prescribed dose of lithium among people of African (n=8; 38.10%) and Caucasian (n=7; 41.18%) descent was 500 mg/day. The dose was 250 mg/day in the Coloured patient and 1200 mg/day in the Indian patient.

It was further explored whether an association existed between the lithium doses by race and the results are summarised in Table 4-25.

Table 4-25. Statistical analysis of lithium doses by race (n=40).

Statistic	Value	Probability
Chi-square	56.23	0.01
Cramér's V	0.71	

Results suggest a strong association between lithium doses and race in the study sample as represented by the Cramér's V value (0.71). In addition, the results were found as significant as indicated by the small p-value ($p < 0.05$).

One study showed that there was a difference in lithium response among Hispanics, African Americans and non-Hispanic whites with bipolar disorder (Gonzalez *et al.*, 2015:224). The results are consistent with literature that suggests that there are differences in treatment responses as there were different doses used to maintain the different races.

4.6.7 Dosing frequency of lithium

The dosing frequency of lithium among the study sample is demonstrated in Figure 4–12 below.

Dosing frequency of Lithium

13%

87%

■ Frequency of dosage: Nocte (n=35)
■ Frequency of dosage: Twice a day(n=5)
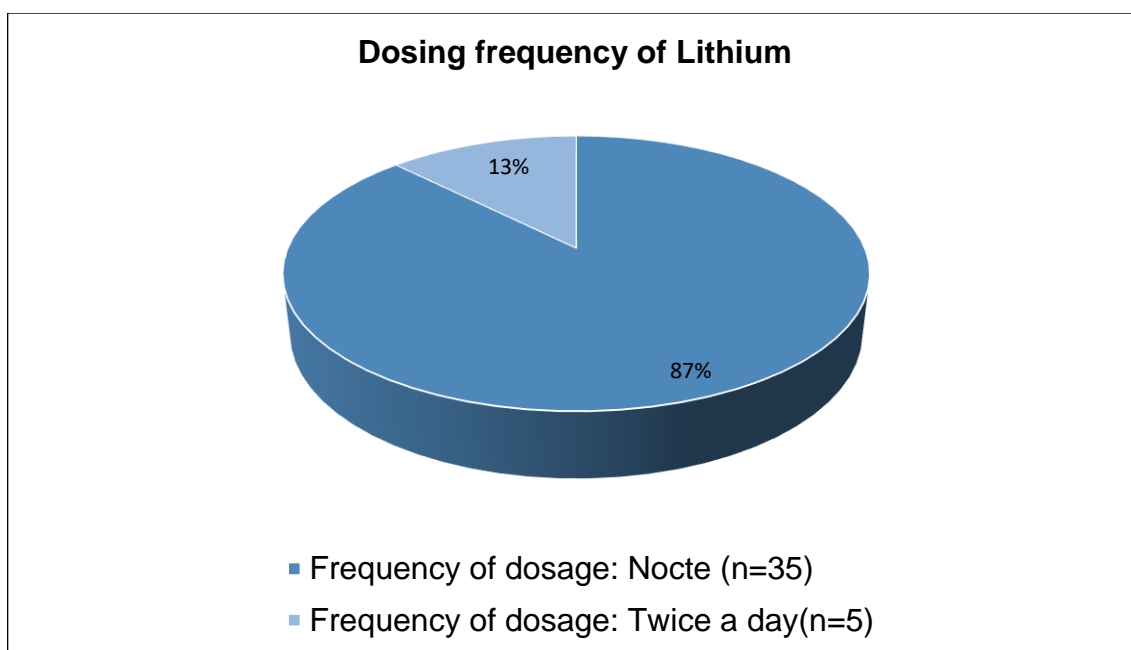
Figure 4–12. Dosing frequency of lithium (n=40).

From the results it is evident that the majority of the patients (n=35; 87.00%) in the study sample received their lithium therapy once a day at night, while only 13.00% (n=5) received it twice a day.

These results are consistent with literature that recommends the dosing of lithium at night or in two divided doses during the day (Rossiter, 2016:485).

4.6.8 Lithium serum levels

The results of the lithium serum levels in the study population are reported in Table 4-26 below.

Table 4-26. Lithium serum levels of study sample (n=40).

Parameter	Result (mmol/L)
Mean serum concentration	0.92
Standard deviation	0.28
Minimum concentration	0.40
Maximum concentration	1.40
Median concentration	0.90
Mode concentration	0.90

It was important to record these results to monitor for lithium toxicity. Thankfully, none of the patients in the study sample had toxic lithium serum levels.

An initial plasma level of 0.4-1.2 mmol/L is desired with the lower range (0.4 mmol/L) being the maintenance dose (Oruch *et al.*, 2014:468). Serum levels higher than 0.9 mmol/L have shown the best results, though patients can be maintained with serum concentrations as low as 0.6 mmol/L (Katzung, 2012:516). The results were consistent with the literature as the lowest and maximum concentrations of 0.4 and 1.4 mmol/L were used respectively.

4.7 Use of other drugs

4.7.1 Availability of names of other drugs previously used

Table 4-27 summarises the results regarding the availability of the names of drugs previously used to treat each patient's psychiatric condition.

Table 4-27. Availability of names of previously used antipsychotics (n=40).

Names of previously used antipsychotics available	n	Percentage (%)
Yes	40	100.00
No	0	0.00
Total	40	100

The results indicate that for all patients (n=40; 100.00%), the names of previously used drugs for the treatment of their psychiatric conditions were available.

4.7.2 Previous therapy received

Table 4-28 provides the names of other drugs that patients received prior to lithium therapy. These antipsychotics were taken by the patient since their first diagnosis with a mental condition.

Table 4-28. Previously used antipsychotics (n=40).

Drug	n	Percentage (%)
None	5	12.50
Bupropion, Sertraline, Clonazepam, Amitriptyline, Quetiapine and Venlafaxine	1	2.50

Drug	n	Percentage (%)
Risperidone, Diazepam, Citalopram, Sodium Valproate, Lamotrigine and Quetiapine	1	2.50
Venlafaxine, Lorazepam Quetiapine and Fluoxetine	1	2.50
Zuclopenthixol depot injection and Chlorpromazine	1	2.50
Sodium Valproate, Amitriptyline, Risperidone and Haloperidol	1	2.50
Sulpiride, Amitriptyline, Lorazepam, Fluoxetine and Lamotrigine	1	2.50
Risperidone, Lorazepam and Chlorpromazine	1	2.50
Clonazepam, Risperidone and Topiramate	1	2.50
Lorazepam, Sodium Valproate and Oxazepam	1	2.50
Amitriptyline and Quetiapine	1	2.50
Risperidone	1	2.50
Sulpiride, Haloperidol, Fluoxetine and Risperidone	1	2.50
Risperidone, Chlorpromazine, Haloperidol and Carbamazepine	1	2.50
Risperidone, Clonazepam and Sodium Valproate	1	2.50
Risperidone, Diazepam, Citalopram, Fluoxetine Olanzapine and Clonazepam	1	2.50
Risperidone, Sodium Valproate, Lorazepam, Venlafaxine and Clonazepam	1	2.50
Flupenthixol injection	1	2.50
Olanzapine	1	2.50
Fluphenazine injection, Haloperidol, Lorazepam and Clonazepam	1	2.50
Risperidone, Carbamazepine and Topiramate	1	2.50
Risperidone, Imipramine, Chlorpromazine and Zuclopenthixol depot injection	1	2.50
Carbamazepine	1	2.50
Clozapine and Sodium Valproate	1	2.50
Fluphenazine injection and Sodium Valproate	1	2.50
Zuclopenthixol depot injection	1	2.50

Drug	n	Percentage (%)
Lorazepam, Carbamazepine and Chlorpromazine	1	2.50
Risperidone, Amitriptyline and Diazepam	1	2.50
Risperidone, Clonazepam, Chlorpromazine and Haloperidol	1	2.50
Risperidone, Olanzapine, Oxazepam and Haloperidol	1	2.50
Risperidone, Olanzapine, Citalopram and Lorazepam	1	2.50
Risperidone, Clozapine, Fluoxetine and Haloperidol	1	2.50
Fluphenazine injection, Clozapine, Clonazepam, Lorazepam and Chlorpromazine	1	2.50
Fluphenazine injection, Lorazepam and Carbamazepine	1	2.50
Haloperidol	1	2.50
Lorazepam	1	2.50
Total	40	100

The results show that risperidone (n=17; 42.50%) was the most used antipsychotic prior to lithium initiation, followed by lorazepam (n=11; 27.50%). In a few instances, drugs such as imipramine, sertraline and fluphenazine were only previously used once (n=1; 2.50%). Only 5 of the patients in the study sample (12.50%) were not given any antipsychotic before lithium initiation.

4.7.3 Reasons for treatment discontinuation

Table 4-29 indicates the results obtained for treatment discontinuation of the antipsychotic drugs administered prior to initiation of lithium therapy.

Table 4-29. Reasons for discontinuing therapy (n=35)[8].

Reason	n	Percentage (%)
Allergy	0	0.00
Adverse effect	0	0.00
Change in therapy	0	0.00
Change in diagnosis	0	0.00
Failed therapy	35	100.00
Non-adherent	0	0.00
Safety	0	0.00
Successful Therapy	0	0.00
Total	35	100

Results show that in all cases, previously administered medication was stopped as a result of failed therapy. Lithium was then initiated to continue with the therapy.

4.7.4 Prescribers of lithium

Figure 4–13 indicates who prescribed lithium in the study sample.

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[8] For the purposes of this analysis, only 35 cases were included as 5 of the patients in the study sample were not given any antipsychotic before lithium initiation.

Who prescribed lithium?

40%   35%

25%

■ Medical Practitioner (n=14)   ■ Psychiatrist (n=10)
■ No information (n=16)
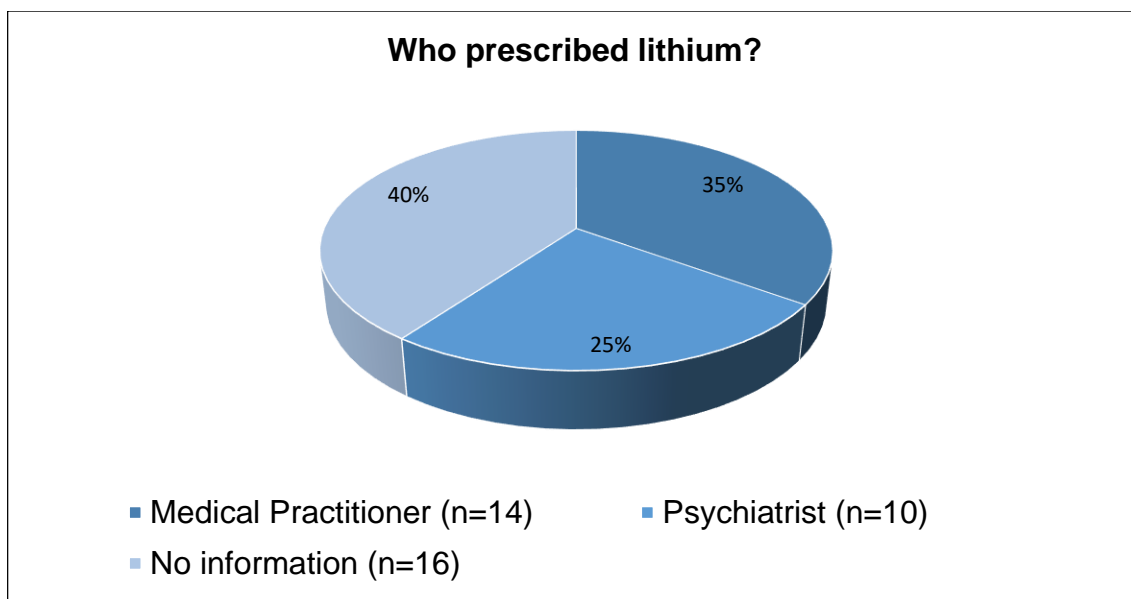
Figure 4–13. Prescriber of lithium (n=40).

From the results it is evident that only a quarter (n=10; 25.00%) of the patients in the study sample were prescribed lithium by a specialist psychiatrist.

4.8 Drug interactions

4.8.1 Presence of drug interactions

Any drug interactions that were identified between lithium and other drugs prescribed to the patients in the study sample are represented in Figure 4–14 below. The drug interactions were identified retrospectively from the patient file.
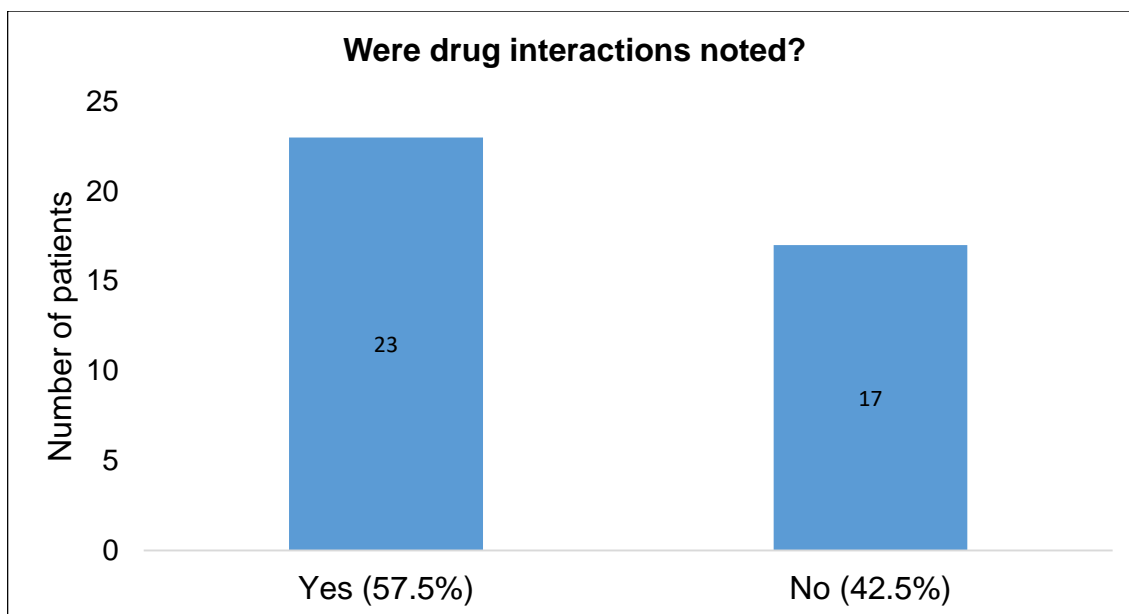
Figure 4–14. Presence of drug interactions (n=40).

The results show that most patients (n=23; 57.50%) in the study sample were on other drugs that interacted with lithium. It was important to note this as these drug interactions can either lead to lithium toxicity or decreased serum lithium levels of no therapeutic value.

Lithium was found to be the most common psychiatric medication involved in ADRs in a retrospective study conducted in 2010. Drugs such as diuretics, ACE inhibitors, NSAIDs, xanthines and calcium channel blockers interact with lithium, causing different levels and effects (Hoeft, 2014:119). The results were consistent with this literature as 57.50% of the patients had identified drug interactions.

4.8.2 Number of drug interactions noted

Table 4-30 outlines the number of drug interactions per patient identified between lithium and other drugs that patients in the study sample were taking.

Table 4-30. Number of drug interactions noted per patient (n=23)[9].

Number of drug interactions noted	n	Percentage (%)
One interaction	20	86.96
Two interactions	2	8.70
Three interactions	1	4.34
Total	23	100

The results show that one drug interaction was mostly observed (n=20; 86.96%) among the 23 patients of the study sample that had drug interactions identified.

The drug interactions noted between lithium and other drugs are outlined in Table 4-31.

Table 4-31. Drug interactions noted with lithium (n=23).

Drug interactions noted with lithium	n	Percentage (%)
Amitriptyline	1	4.35
Enalapril	3	13.04
Fluoxetine	1	4.35
Sodium Valproate	14	60.86
Theophylline	1	4.35
Enalapril and Hydrochlorothiazide	1	4.35
Sodium Valproate and Ritonavir	1	4.35
Sodium Valproate, Enalapril and Hydrochlorothiazide	1	4.35
Total	23	100

The results demonstrate that the most common drug interaction noted was between lithium and sodium valproate (n=14; 60.86%), followed by enalapril (n=3; 13.04%).

4.9 Adverse effects

The results of the adverse effects reported in the study sample are outlined in this section of the results.

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[9] For the purposes of this analysis, only 23 patients were used as drug interactions were only noted in these patients.

4.9.1 Adverse effects reported

Figure 4–15 displays the results for the reported adverse effects by patients on lithium therapy in the study sample. The adverse effects were reported during the period which the patient was on lithium therapy.

Were any adverse effects reported?

40%

60%

■ Yes (n=24)　　■ No (n=16)
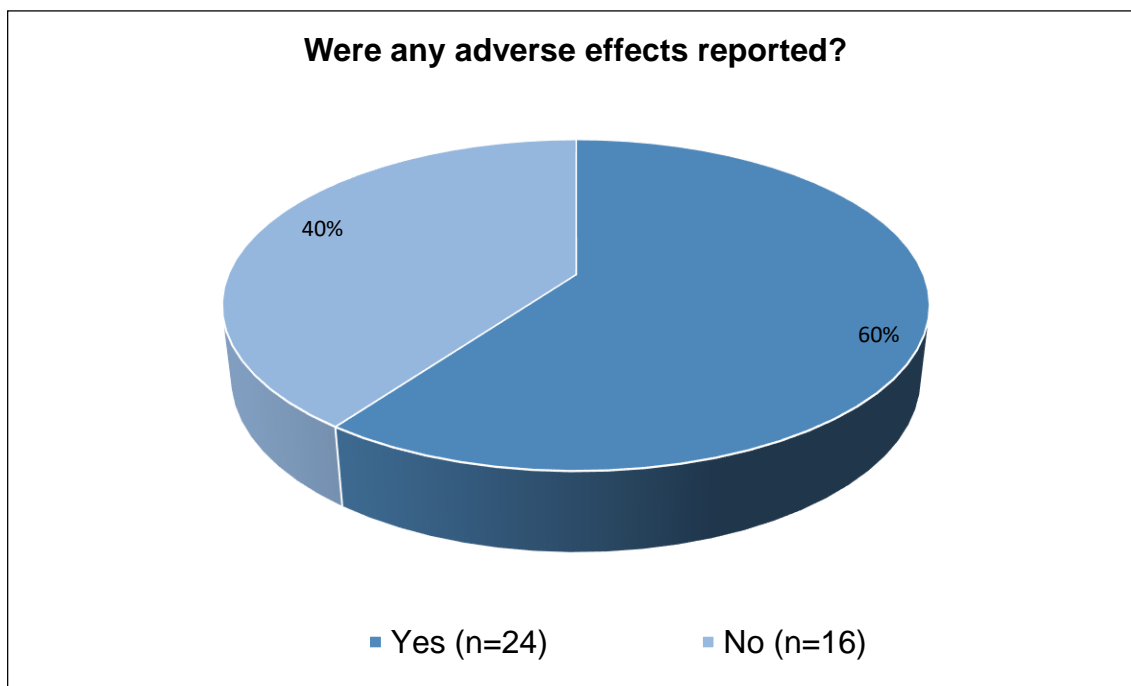
Figure 4–15. Number of patients that reported adverse effects (n=40).

The results show that just over half of the patients (n=24; 60.00%) reported experiencing adverse effects while on lithium therapy.

These results are consistent with literature that suggests that lithium carries a 'black box' warning which implies its potential to cause lethal adverse effects. All systems of the body may exhibit adverse effects associated with the use of lithium. Adverse effect concerns do play a significant role in lithium non-adherence (Oruch *et al.*, 2014:468).

4.9.2 Types of adverse effects reported

The results obtained for the adverse effects experienced by patients in the study sample are outlined in Table 4-32.

Table 4-32. Adverse effects reported (n=24)[10].

Adverse effect	n	Percentage (%)
Weight gain and hypothyroidism	2	8.33
Weight gain	7	29.17
Weight gain and tremor	1	4.17
Weight gain and blurred vision	1	4.17
Fatigue	1	4.17
Hypothyroidism	1	4.17
Hyperthyroidism	1	4.17
Tremor	8	33.31
Constipation	1	4.17
Diarrhoea	1	4.17
Total	24	100

The results demonstrate that tremor was the most common adverse effect associated with lithium use (n=8; 33.31%), followed by weight gain (n=7; 29.17%). One rare adverse effect experienced by a patient was hyperthyroidism.

One of the most common lithium induced adverse effects is tremor. This adverse effect occurs at therapeutic levels (Katzung, 2012:516). Metabolic adverse effects such as hypothyroidism and weight gain have been noted in patients that are treated with lithium. (Livingstone & Rampes, 2009:347). The common gastrointestinal (GIT) adverse effects associated with lithium use include nausea, vomiting, diarrhoea and constipation (Gitlin, 2016:3). The results were therefore consistent with literature.

4.9.3 Treatment of adverse effects

The results obtained for whether the reported adverse effects were treated or not are illustrated in Figure 4–16 below.

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[10] For purposes of this analysis, 24 cases were used as only 24 patients experienced adverse effects due to lithium therapy.

Were the adverse effects treated?

37%

63%

▪ Yes (n=9)   ▪ No (n=15)
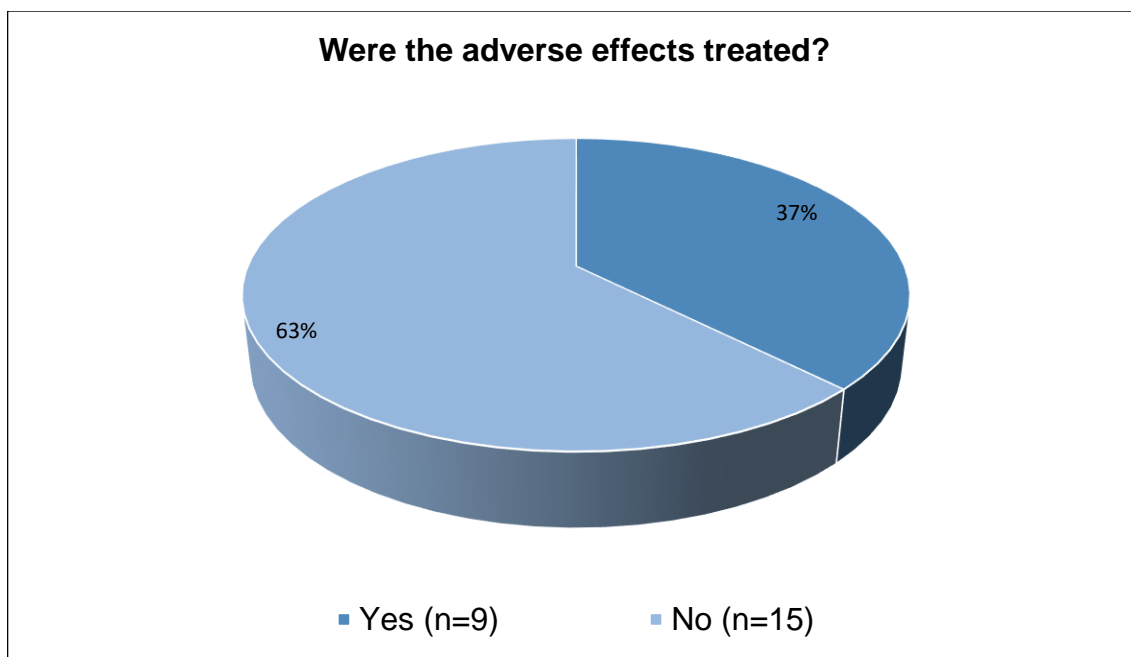
Figure 4–16. Treatment of adverse effects (n=24).

The results illustrate that out of the 24 patients that experienced adverse effects, only 9 patients received treatment for it (n=9; 37.00%). More than half (n=15; 63.00%) of the study sample was not treated for the experienced adverse effects.

4.10 Monitoring requirements

4.10.1 Extent of baseline monitoring compliance with the recommended guidelines

4.10.1.1 Baseline renal function monitoring

Table 4-33 displays the results obtained for baseline renal function monitoring performed according to the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) for South Africa: Hospital Level Adults (Department of Health, 2015:15.3) and NICE guidelines (National Institute of Health and Care Excellence, 2014).

Table 4-33. Compliance of baseline renal function monitoring according to South African guidelines (n=40).

Baseline renal function monitoring (South African guidelines)			Baseline renal function monitoring (NICE guidelines)		
Level of compliance	n	Percentage (%)	Level of compliance	n	Percentage (%)
Compliant	14	35.00	Compliant	14	35.00
Non-compliant	26	65.00	Non-compliant	26	65.00
Total	40	100	Total	40	100

From the results it is clear that in most cases, there was no compliance with the recommended South African guidelines for baseline renal function monitoring (n=26; 65.00%).

The results show there was no compliance with the recommended NICE guidelines for baseline renal function monitoring in half of the study sample (n=26; 65.00%).

The results indicate that patients are not being monitored correctly and there is room for improvement. Failure to monitor baseline renal function means that it will be hard to identify any renal impairment that may exist which is contraindicated in lithium use.

4.10.1.2 Baseline thyroid function monitoring

Table 4-34 displays the results obtained for baseline thyroid function monitoring performed according to the STGs (Department of Health, 2015:15.3) and NICE guidelines (National Institute of Health and Care Excellence, 2014).

Table 4-34. Compliance of baseline thyroid function monitoring according to the South African guidelines (n=40).

Baseline thyroid function monitoring (South African guidelines)			Baseline thyroid function monitoring (NICE guidelines)		
Level of compliance	n	Percentage (%)	Level of compliance	n	Percentage (%)
Compliant	12	30.00	Compliant	12	30.00
Non-compliant	28	70.00	Non-compliant	28	70.00
Total	40	100	Total	40	100

The results show that there was no compliance with the recommended South African or NICE guidelines for baseline thyroid function monitoring in both cases (n=28; 70.00%).

The results indicate that most patients are not being monitored for thyroid function prior to lithium initiation. Checking thyroid function prior to lithium therapy helps in identifying any existing problems with thyroid function. Lithium has shown to decrease thyroid function in most patients (Katzung, 2012:516).

Lithium causes hypothyroidism (Rossiter, 2016:485) and checking thyroid function prior to lithium therapy helps in identifying any existing thyroid problems. There is a need for clinical improvement in this aspect.

4.10.1.3 Baseline metabolic monitoring (NICE guidelines)

Table 4-35 displays the results obtained for baseline metabolic monitoring performed according to the NICE guidelines (National Institute of Health and Care Excellence, 2014).

Table 4-35. Compliance of baseline metabolic monitoring according to the NICE guidelines (n=40).

Level of compliance	n	Percentage (%)
Compliant	32	80.00
Partially compliant	4	10.00
Non-compliant	4	10.00
Total	40	100

The results show that in most cases, there was compliance with the NICE guidelines for baseline metabolic monitoring (n=32; 80.00%).

Lithium causes significant weight gain and NDI in patients. Lithium can also affect blood pressure and pulse as it can negatively impact cardiac function. This is because the lithium ion depresses the pace making activity of the sinus node, causing sinus arrhythmias, syncope episodes and heart block. Lithium causes this by interacting with pacemaker channels and/or the sodium-calcium exchanger (Oudit *et al.*, 2007:230).

The results indicate that there was little improvement required with regards to the metabolic monitoring. There was compliance in most cases which makes it easy to monitor for any changes in metabolic function.

4.10.2 Extent of follow-up monitoring compliance with the recommended guidelines

4.10.2.1 Follow-up renal function monitoring

The results obtained for follow-up renal function monitoring performed according to the STGs (Department of Health, 2015:15.3) and NICE guidelines (National Institute of Health and Care Excellence, 2014) are shown in Table 4-36 below.

Table 4-36. Compliance of follow-up renal function monitoring according to South African and NICE guidelines (n=40).

Follow-up renal function monitoring (South African guidelines)			Follow-up renal function monitoring (NICE guidelines)		
Level of compliance	n	Percentage (%)	Level of compliance	n	Percentage (%)
Compliant	5	12.50	Compliant	5	12.50
Partially compliant	16	40.00	Partially compliant	16	40.00
Non-compliant	19	47.50	Non-compliant	19	47.50
Total	40	100	Total	40	100

The results show that in most cases, there was no compliance regarding the recommended South African guidelines for follow-up renal function monitoring (n=19; 47.50%). The results also illustrate that there was no compliance with the recommended NICE guidelines for follow-up renal function monitoring in most cases (n=19; 47.50%).

Lithium is associated with an increased diagnostic incidence of renal impairment. About 20% of patients on long term lithium therapy develop chronic kidney disease (CKD) (Kerckhoffs *et al.*, 2018:1).

The risk of developing end stage renal disease (ESRD) for patients on lithium is six times greater than that of the general population. Lithium also causes lithium-induced nephropathy and it is becoming a common adverse effect (Gupta & Khastgir, 2012:217).

There is therefore a need to improve the follow-up monitoring of renal function. Renal function is greatly affected by lithium use and the incorrect monitoring of patients will result in unidentified renal problems that can negatively impact the patient's health.

4.10.2.2 Follow-up lithium serum level monitoring

Table 4-37 displays the results obtained for follow-up lithium serum levels monitoring performed in accordance with the STGs (Department of Health, 2015:15.3) and the NICE guidelines (National Institute of Health and Care Excellence, 2014).

Table 4-37. Compliance with follow-up lithium serum level guidelines according to South African and NICE guidelines (n=40).

Follow-up serum level monitoring (South African guidelines)			Follow-up serum level monitoring (NICE guidelines)		
Level of compliance	n	Percentage (%)	Level of compliance	n	Percentage (%)
Compliant	7	17.50	Compliant	7	17.50
Partially compliant	15	37.50	Partially compliant	15	37.50
Non-compliant	18	45.00	Non-compliant	18	45.00
Total	40	100	Total	40	100

The results show that in most cases, there was no compliance with the recommended South African guidelines for follow-up lithium serum levels monitoring (n=18; 45.00%). The results also illustrate that in most cases, there was no compliance with the recommended NICE guidelines for follow-up lithium serum levels monitoring (n=18, 45.00%).

This test measures the lithium levels in the blood to determine if they are in the therapeutic range. Lithium requires close monitoring of serum levels to avoid toxicity. It may also be done in order to assist with dose adjustment and to determine if additional drug therapy has an effect on lithium levels (Reddy & Reddy, 2014:346).

Lithium has a narrow therapeutic index (NTI) and toxicity usually results from accumulative high levels during on-going therapy. Lithium toxicity occurs when the plasma levels are above 1.5 mmol/L (Haussmann *et al.*, 2015:24). Lithium toxicity can possibly result death or neuronal damage and is common in the elderly as they have decreased renal function (Flood & Bodenham, 2010:78).

The results indicate that there is a need to clinically improve the monitoring of lithium serum levels. Inadequate monitoring of the patients will result in lithium toxic levels not being detected. It also becomes difficult to monitor therapeutic effectiveness (if lithium concentrations are within the therapeutic range) if lithium levels are not monitored as recommended.

4.10.2.3 Follow-up thyroid function monitoring

Table 4-38 displays the results for follow-up thyroid function monitoring performed in accordance with the STGs (Department of Health, 2015:15.3) and the NICE guidelines (National Institute of Health and Care Excellence, 2014).

Table 4-38. Compliance of follow-up thyroid function monitoring according to South African and NICE guidelines (n=40).

Follow-up thyroid function monitoring (South African guidelines)			Follow-up thyroid function monitoring (NICE guidelines)		
Level of compliance	n	Percentage (%)	Level of compliance	n	Percentage (%)
Compliant	0	0.00	Compliant	0	0.00
Partially compliant	39	97.50	Partially compliant	39	97.50
Non-compliant	1	2.50	Non-compliant	1	2.50
Total	40	100	Total	40	100

The results show that in most cases there was only partial compliance with the recommended South African and NICE guidelines for follow-up thyroid function monitoring (n=39; 97.50%). This means that some of the tests were conducted at the recommended times.

Lithium results in the inhibition of thyroid hormone secretion and coupling of iodotyrosines. Alteration of the thyroglobulin structure is also caused by lithium use. If the thyroid hormone secretion is inhibited, hypothyroidism and goitre result (Lazarus, 2009:910).

The results indicate that there is need to improve the follow-up monitoring of thyroid function. There is a risk of not identifying changes in thyroid function if thyroid function is not adequately monitored.

4.10.2.4 Follow-up metabolic monitoring (international guidelines)

Table 4-39 displays the results obtained for follow-up metabolic monitoring performed according to the NICE guidelines (National Institute of Health and Care Excellence, 2014).

Table 4-39. Compliance of follow-up metabolic monitoring according to international guidelines (n=40).

Level of compliance	n	Percentage (%)
Compliant	27	67.50
Partially Compliant	9	22.50
Non-Compliant	4	10.00
Total	40	100

The results show that in most cases, there was compliance with the NICE guidelines for follow-up metabolic monitoring (n=27; 67.50%). This means that the relevant metabolic tests were conducted as recommended.

This lithium-induced weight gain contributes to non-adherence in patients (Dent *et al.*, 2012:1). One study demonstrated that lithium causes weight gain in patients compared to patients taking other antipsychotics such as olanzapine (Adida *et al.*, 2012:721). Nephrogenic diabetic insipidus (NDI) can be caused by lithium use (Alsady *et al.*, 2016:1588).

The results indicate that there was little improvement required with regards to the metabolic monitoring. There was compliance in most cases which makes it easy to monitor for any changes in metabolic function.

4.10.3 Chapter 4 summary

The results of the empirical study were reported in this chapter. Results were reported based on the analyses of the data collected with the data collection tool. The

conclusions drawn from the results will be discussed along with the recommendations in the following chapter.

CHAPTER 5.
CONCLUSIONS AND
RECOMMENDATIONS

5.1 Introduction

The conclusions, limitations and suggested recommendations are stated in this chapter.

5.2 Conclusions

The specific research objectives of the study will be used to discuss the conclusions of the research.

The aim of the study was to analyse the prescribing and monitoring patterns of lithium at Fort England Hospital (a public sector psychiatric hospital) in the Makana District of the Eastern Cape Province in South Africa. Determination of compliance with the recommended guidelines with regards to the initiation and monitoring of lithium was done through an extensive drug utilisation review. The research showed that there is a need for clinical improvement in the current initiation and monitoring practices of lithium at Fort England Hospital.

It was determined if lithium was being rationally used at Fort England Hospital. Lithium is a drug that is indicated in bipolar disorder (BD) and other psychotic disorders such as schizoaffective disorder (SD). The participants involved in the study suffered from one of these conditions: BD, SD, schizophrenia or major depressive disorder (MDD). The study showed that lithium was correctly indicated in all 40 patients involved in the study. However, results showed that there is a need to improve the current practices to ensure better clinical outcomes.

5.2.1 Literature review

The conclusions drawn from the literature review conducted in Chapter 2 will be discussed below for each objective stated.

The first objective was to obtain information from the literature regarding the description of psychiatric disorders in general and their prevalence in South Africa:

- The psychiatric disorders that were identified were BD, SD, schizophrenia and MDD.

- There were no statistics found in the South African context regarding the prevalence of these disorders.

- Globally it was found that about 60 million people suffer from BD and 23 million people suffer from schizophrenia and psychosis (WHO, 2017).

- It was found that depression has accounted for 4.3% of the global burden of diseases with over 300 million people suffering from it and is one of the leading causes of disability (WHO, 2017a:5).

- BD is a mood disorder characterised by episodes of mania, hypomania and depression. It is classified as bipolar I, bipolar II and cyclothymic BD (Jann, 2014:489).

- SD is a chronic mental disorder characterised by symptoms of schizophrenia such as hallucinations and delusions and significant mood symptoms (Abrams *et al.*, 2008:1089).

- Schizophrenia is a mental disorder characterised by negative, positive and cognitive symptoms. Psychosis is one of the clinical features used to diagnose schizophrenia (Aleman, 2014:1).

- MDD is a mood disorder that presents with symptoms such as depressed mood, recurrent suicidal ideation and feelings of worthlessness (Villanueva, 2013:1).

The second objective was to discuss the pathophysiology of affective disorders in general and specifically bipolar disorder based on available literature:

- It was found that the exact aetiology of BD is not known but a combination of factors has been suggested.

- BD is thought to be caused by genetic, perinatal, neuroanatomic, neurochemical and environmental factors. The genetic aspects have shown that BD is 7 times likely to develop in people that have a first degree relative with BD (Ayano, 2016:2).

- Other studies have suggested that perinatal factors such as foetal hypoxia can lead to the development of BD. Increased glutamate levels is a neurochemical factor that causes BD (Ayano, 2016:2).

- Environmental factors that have been linked with BD include the recurrence of stressful events in one's life (Ayano, 2016:2).

- The exact aetiology of SD is unclear but a combination of factors has been proposed.

- Factors such as gender, genes, stress, brain structure and drug abuse are some of the factors that contribute to the development of SD (Abrams *et al.*, 2008:1091).

- Women have been seen to be more prone to SD due to clinically significant disturbances in emotions. People with first degree relatives have been seen to be more likely to develop SD (Yogeswary, 2014:1100).

- Stressful events and use of drugs such as LSD contribute to the development of SD. Affective symptoms have been linked to neuropeptides such as substance P (Paparelli *et al.*, 2011:1).

- Schizophrenia is caused by increased levels of dopamine in the brain and the hypofunction of N-Methyl-D-aspartate (NMDA) receptors (Brisch *et al.*, 2014:3).

- Abuse of drugs like phencyclidine (PCP) and genetic factors contribute to the development pf schizophrenia. Environmental factors such as prenatal exposure to viruses cause schizophrenia (Ham *et al.*, 2017:16).

- MDD is caused by numerous factors such as a decrease in serotonin and noradrenaline neurotransmission in the brain. Genetic studies have shown a greater susceptibility to developing depression if first degree relatives had depression (Villanueva, 2013:1).

The third objective was to determine the medicine treatment guidelines for psychiatric disorders and specifically bipolar affective disorders based on literature:

- It was found that the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) for South Africa: Hospital Level Adults had the treatment guidelines for psychiatric disorders.

- The first line treatment for BD was lithium and can be used in combination with other drugs such as lamotrigine to treat BD (Rossiter, 2016:484).

- International guidelines such as the National Institute for Health and Care Excellence (NICE) and Irish Medication Safety Network (IMSN) guidelines had treatment guidelines for BD and monitoring requirements for lithium therapy.

- The guidelines recommend that schizophrenia should be treated with a typical antipsychotic like haloperidol before combination treatment is used (Patel *et al.*, 2014:641).

- There were no treatment guidelines that were found to be specific to SD and treatment suggestions for SD include antidepressants, mood stabilisers and antipsychotics (Abrams *et al.*, 2008:1103).

- The STGs recommend the use of selective serotonin reuptake inhibitors (SSRIs) as first line treatment for MDD and there is no combination therapy of antidepressants for treating MDD (Department of Health, 2015:15.3).

The fourth objective was to find literature on the history of the development of lithium:

- Lithium was first discovered in 1817 by Johan August Arfwedson and It was initially used to dissolve urate crystals as it was thought that mania and depression were caused by urate crystals It was used in 1871 and 1886 to treat mania and depression respectively (Johnson, 1984:5).

- John Cade injected lithium into guinea pigs which then became placid and tranquilised. He then started using lithium to treat mania in 1948 (Johnson, 1984:5).

- In 1954 Schou concluded that lithium is a useful alternative to electrocardiogram (ECT) (Schou *et al.*, 1954:255-257).

- The food and drug administration (FDA) approved the use of lithium to treat mania in 1970 (Johnson, 1984:2).

The fifth objective was to obtain literature that would bring insight into the pharmacological properties of lithium (pharmacokinetics and pharmacodynamics) and compare it to other psycholeptics:

- Lithium has anti-manic properties and is a mood stabiliser (Oruch *et al.,* 2014:466).

- Lithium requires therapeutic drug monitoring (TDM) and has a narrow therapeutic index (NTI) and possesses a great risk of developing lithium toxicity (Blix *et al.*, 2010:52) .

- Lithium reduces suicidal ideation in patients with BD, SD and schizophrenia Lewitzka *et al.*, 2015:14).
- Lithium is administered orally and is rapidly absorbed by the gastrointestinal tract (GIT) (Rossiter, 2016:484).
- Lithium has a bioavailability between 80% and 100% and peaks in the plasma in 2 to 4 hours (Girardi *et al.*, 2016:295).
- Lithium has a volume of distribution of 0.5-0.7 L/kg and a half-life of 24 hours (Katzung, 2012:514).
- Lithium is not metabolised in the liver with 95% of it being passed in urine unchanged (Giusti *et al.*, 2012:154).
- Lithium clearance is 20 to 30% of the glomerular filtration rate (GFR) and it differs for everyone (Chiu *et al.*, 2007:270).
- The target plasma concentration for lithium is between 0.6 and 1.4 mmol/L. Toxicity occurs when serum lithium levels are above 1.5 mmol/L (Katzung, 2012:514).
- Lithium is more effective in mood stabilisation and ideation compared to antipsychotics. Lithium is more effective than carbamazepine and carbamazepine is rarely used because of its adverse effect profile. Lithium is more effective than lamotrigine in treating BD. Lamotrigine is associated with minimal adverse effects when compared to lithium (Grunze, 2010:127).
- Valproate is more effective than lithium in the treatment of mania associated with depressive symptoms or mixed mania. The combination of lithium and valproate has been seen to produce better clinical outcomes (Khoo, 2012:165).

The sixth objective was to discuss the toxicological properties of lithium (adverse effects, interactions, safety in pregnancy and lactation, use in specific patient populations) based on the available literature:

- Lithium is known to cause toxicity even at therapeutic ranges as a result of its NTI. Lithium has a severe adverse effect profile (Oruch *et al.*, 2014:468)
- Lithium affects cardiac, renal, thyroid, parathyroid and GIT function.
- The most common adverse effects are weight gain and tremor.

- Lithium toxicity is a medical emergency that can result in death and neuronal damage. The signs and symptoms associated with lithium toxicity are seizures, coma and impaired consciousness (Flood & Bodenham, 2010:78).

- Adverse effects of lithium negatively affect compliance to treatment (Gitlin, 2016:2).

- Antipsychotics, lamotrigine, carbamazepine and lamotrigine cause adverse effects that are not as severe as those caused by lithium.

- It was found that lithium interacts with a number of drugs including thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs) and antidepressants. Most of the drug interactions increase lithium levels resulting in lithium toxicity (Rossiter, 2016:484).

- Lithium is a Category D drug and its use in pregnancy is not recommended. When used in pregnancy, lithium causes foetal abnormalities such as the Ebstein anomaly (Healy *et al.*, 2015:368).

- Lithium is excreted into breast milk therefore breastfeeding is not encouraged. Lithium therapeutic levels can be reached in the infant causing adverse effects such as poor suckling (Lugt *et al.*, 2012:375).

- It was found that lithium doses are often decreased in geriatric patients as a result of their altered pharmacokinetics (Rossiter, 2016:485).

- Lithium is contraindicated in patients that have renal insufficiency as it causes lithium induced nephropathy in healthy patients (Gupta & Khastgir, 2012:217). Its use in patients that have pre-existing renal insufficiency is not recommended.

- Lithium flattens the T wave at therapeutic levels and use in the "sick sinus" syndrome is completely contraindicated Lithium use in patients with cardiovascular problems leads to lithium toxicity (Katzung, 2012:517).

- It was found that the use of lithium in severely dehydrated patients leads to toxicity (Portes, 2012:156).

- Lithium use in urinary retention results in lithium toxicity (Verhamme *et al.*, 2008:376).

- Literature showed that lithium use in paediatric BD has not been established (Rossiter, 2016:485).

- Lithium has been approved for use in patients between the age of 12 and 17 to treat mania (Rosen, 2010:3).

The seventh objective was to use literature to determine what constitutes a drug utilisation review and discuss the components thereof:

- Drug utilisation reviews (DURs) involve marketing, distribution, prescription and use of medicines in a society A DUR focuses on the medical, economic and social consequences of drug use It was found that they promote the rational use of drugs (Sachdeva & Patel, 2010:11).

- The three categories of DURs are retrospective, prospective and concurrent. DURs can either be qualitative or quantitative in nature (Navarro 2008:215).

- The goals of a DUR are to promote optimal medication therapy and ensure that drug therapy meets the standard of care. A DUR aims to control medicine costs and evaluate the effectiveness of therapy (WHO, 2018).

- It was found that there are 7 steps involved in conducting a DUR and these include data analysis, feedback, designing a DUR study and identifying problem areas that require evaluation (Sachdeva & Patel, 2010:14).

- DURs are needed identify adverse effects, monitor prescribing patterns and monitor clinical outcomes. A DUR can be applied in therapy appropriateness to help determine if the therapy being administered is appropriate (Lubbe, 2012:17; Truter, 2008:92-99).

- There are limitations associated with the use of DURs such as the fact that medical records are not computerised making the data collection process tedious (Lubbe, 2012:42-43).

The eighth objective was to use literature to discuss drug utilisation reviews on psycholeptics in general and specifically on lithium in the public and private sectors, locally and internationally:

- There were no DURs on lithium use in South Africa that could be found either in the private or public sector.
- DURs on lithium could be found at international level.

- Previously done DURs showed that lithium is the first choice in treating BD. Another article by Piparva *et al.*, in Gujarat in 2011 showed that lithium was prescribed in 73% of the patients with BD. This DUR also concluded that lithium was the least used drug in treating BD with carbamazepine being the most used drug (Piparva et al., 2011:51).

- De Fazio *et al.* in 2017 conducted a systematic review on the use of lithium in lifetime mania. They concluded lithium remains the drug of choice in treating BD (De Fazio *et al.*, 2017:756).

- Thakkar *et al.* conducted a drug utilisation (DU) study of psychotropic drugs in 2013 prescribed in the psychiatry outpatient department of a tertiary care hospital. 600 prescriptions were analysed and 1074 of the 1217 drugs contained in the prescriptions were psychotropic drugs used to treat schizophrenia, BD and anxiety disorders (Thakkar *et al.*, 2013:2760,2762).

- Lithium was only used in less than two percent of the patients with BD. It was found that lithium was generally superior to valproate in treating BD. The low use of lithium in their hospital was due to the fact that lithium has a NTI and that obtaining the drug serum levels of lithium proved to be difficult (Thakkar *et al.*, 2013:2760,2763).

The ninth objective was to use literature that will conceptualise the most appropriate parameters to conduct a drug utilisation review on lithium by investigating patient files:

- Lithium has a NTI and requires TDM. Lithium toxicity was found to be common in patients and serum levels need to be monitored.

- The STGs for South Africa and NICE guidelines have recommendations for lithium serum level monitoring.

- The STGs recommend monitoring lithium levels every week after dose increments then once a month and then once every 3 months when on maintenance therapy (Department of Health, 2015:15.3).

- It was found that NICE guidelines recommend monitoring lithium serum levels every 3 months (National Institute of Health and Care Excellence, 2014).

- The compliance of the current monitoring patterns of lithium serum levels at Fort England Hospital was an important parameter of investigation.

- The STGs and NICE guidelines have recommendations for renal function monitoring.
- Renal function tests such as GFR and creatinine clearance are used to determine renal function (Michels *et al.*, 2010:1003).
- It was found that that renal function should be monitored before lithium initiation and every 3 months according to the SAMF (Rossiter, 2016:485).
- NICE guidelines recommend that renal function should be monitored every 3 months after lithium initiation and prior to lithium therapy (National Institute of Health and Care Excellence, 2014).
- The renal function tests conducted at Fort England Hospital and the frequency in which they were conducted was then investigated.
- Compliance of the current renal function monitoring at Fort England Hospital with the recommended guidelines was then a parameter of interest.
- The STGs and NICE guidelines have recommendations for thyroid function monitoring.
- Thyroid function tests such thyroid stimulating hormone (TSH) and thyroxine (T_4) are used to determine thyroid function.
- It was found that thyroid function should be monitored prior to lithium initiation and after every 6 to 12 months after lithium administration according to the STGs (Department of Health, 2015:15.3).
- The NICE guidelines recommend monitoring thyroid function every 6 months (National Institute of Health and Care Excellence, 2014).
- The thyroid function tests conducted at Fort England Hospital and the frequency in which they were conducted was then investigated.
- The compliance of the current thyroid function monitoring at Fort England Hospital with the recommended guidelines became a parameter for investigation.
- The NICE guidelines recommend the monitoring of metabolic parameters such as weight, blood pressure and fasting blood glucose.
- The metabolic parameters need to be monitored before lithium initiation and during lithium therapy.
  The compliance of the current metabolic function monitoring at Fort England Hospital with the recommended guidelines became a parameter for investigation.

The tenth objective was to gain knowledge from the available literature on statistical terminologies that were used to analyse the data obtained from the empirical study:

- It was found that levels of measurement are classified as nominal, ordinal, ratio and interval (Thompson, 2009:57).

- Interval scales are constant metric scales with equal distances between values and an arbitrary zero point. Nominal variables are also called categorical variables and examples include gender and race (Thompson, 2009:57; Marateb *et al.*, 2014:47).

- A discreet ordinal scale is a nominal variable that has an inherent order though the interval between scale points may be uneven. It was found that continuous ordinal scales occur when the measurements are continuous and examples include the 4-item-rating scale (sometimes, never, always, often) (Thompson, 2009:57; Marateb *et al.*, 2014:47).

- Data elements that have a true zero are measured at the ratio (continuous) level of measurement. Examples include weight and height (Mendenhall *et al*., 2013:10).

- Descriptive statistics used in the study included mean, mode, median and standard deviation.

- Variables are considered discrete if the possible values that it can attain are distinguishable from each other. Discrete variables have no in-between values (Mendenhall *et al*., 2013:10).

- It was found that the different possible values of continuous variables are indistinguishable and can have additional in-between values (Mendenhall *et al*., 2013:10).

- The mode can be defined as the value that occurs the most in a data set. The median is the value that occupies the middle position when all observations are arranged in either ascending or descending order. The median was found to divide the frequency distribution into two halves (Manikandan, 2011:214).

- The mean is a popular statistic calculated by the sum of all the observations in the data set, divided by the total number of measurements. It was found that the mean can be used in interval or ratio scale data sets (Rosner, 2011:8).

- Frequency (f) is the number of times that a specific value is obtained for a specific variable in the study population (Rosner, 2011:22).

- The standard deviation (SDV) is the measure of the spread of the data about the mean and is most commonly used. SDV is used when one wants to summarise the variability in data whether it is sample characteristics or response patterns (Carter, 2013:15).

- The confidence interval (CI) is used to describe the level of uncertainty about the true value of a parameter in a population (Clarke, 2012:66).

- The inferential statistics used in the study include *p* value, chi squared test and Cramér's V.

- It was found that the ***p*** value is the probability under the assumption of no effect or difference (null hypothesis), of obtaining a result equal to or more extreme than what was actually observed (Dahiru, 2011:22)

- The chi squared test determines whether there is an association between proportions of two or more categorical variables (Mchugh, 2013:143).

- Cramér's V is a popular measure of association used for nominal random variables with a maximum value of 1. A value of 0 for Cramér's V shows that there is no association between the two variables being investigated (Gingrich, 2004:782).

5.2.2 Empirical study

The conclusions drawn for the empirical study are based on the results obtained in Chapter 4. An extensive DUR was used to achieve the specific research objectives, using the patient files of the study sample (n=40). Each specific objective of the empirical study will be discussed in this section.

The first objective of the empirical study was to determine the prescribing patterns of lithium at Fort England Hospital:

- The demographics of the study sample showed that most of the patients were male.

- Males constituted 55.00% (n=22) of the study sample while the remaining 45% (n=18) was females. Literature indicates that equal numbers of men are affected by BD. Results showed that there was a small difference between the number of men and women involved in the study.

- The results showed that majority of the patients involved in the study sample were between the ages of 31 and 50 years (n=15; 40.00%). These results show that most of the people in the study sample were of productive age in terms of work.

- Most female were between the ages of 18 to 30 years (n=6; 33.33%) and 31 to 50 years (n=6; 33.33%).

- Most males were between 31 to 50 years of age (n=10; 45.45%).

- The results indicated that 82.50% (n=33) involved in the study were unemployed.

- The chi-square test showed that the relationship between employment and diagnosis was in fact clinically significant ($p < 0.0001$).

- Cramér's V value of 0.61 showed a strong relationship between employment status and diagnosis in patients on lithium treatment.

- These results are consistent with literature that suggests that people with mental problems are often turned down from work or avoid looking for work because they anticipate discrimination (Thornicroft, 2010:414).

- The Mental Health Action Plan 2013-2020 report indicated that mental disorders have large economic consequences with a recent study estimating that between 2011 and 2030, US$16.3 million of economic output will be lost as a result of the global impact of mental disorders (WHO, 2013a). These results are consistent with the literature as 82.50% of the study sample was unemployed yet majority of them were of productive age.

- The demographics showed that only 7.50% (n=3) was comprised of patients that were older than 65 years.

- This was important as lithium pharmacokinetics are altered in geriatrics with geriatrics having a high risk of developing lithium toxicity. Doses often require adjustments in geriatrics.

- Most of the patients were of African descent (n=21; 52.00%). There was one person of Indian descent (n=1; 3.00%), one of coloured descent (n=1; 3.00%) and 42.00% (n=17) were Caucasian. One study showed that there was a difference in lithium response among Hispanics, African Americans and non-Hispanic whites with BD (Gonzalez *et al.*, 2015:224).

- Most African patients were between the ages of 31 to 50 years (n=12; 57.14%) and most Caucasian patients (n=8; 47.06%) were between the ages of 51 and 65 years. The coloured patient was between 31 and 50 years (n=1; 100.00%) while the Indian patient was in the 18 to 30 years age group.

- The results indicated that 82.50% (n=33) had a diagnosis of BD while 7.50% had a diagnosis of schizophrenia (n=3). Only 5.00% were diagnosed with SD (n=2) and 2 patients had MDD (5.00%).

- The results indicated that most patients of all racial categories were diagnosed with BD. Of the African patients, 85.71% (n=18) were diagnosed with BD while 13 (76.47%) Caucasian patients had BD. One patient (n=1; 100.00%) of both Indian and coloured descent had BD.

- Lithium is indicated for use in BD, MDD, SD and schizophrenia. The results therefore show that lithium was correctly indicated in all of the patients (n=40; 100%).

- All the women in the study (n=17; 100.00%) were not pregnant. Lithium is a known category D drug that should only be used in pregnancy if the benefits outweigh the risks. The results show that there was no risk of foetal abnormalities associated with lithium use as the female patients were not pregnant.

- In 100.00% of the cases (n=17) women did not breastfeed. Lithium is excreted in breast milk and cause lithium toxicity in the nursing infant. Breastfeeding is therefore not recommended and the results support this literature as none of the female patients were breastfeeding.

- Half (n=20; 50.00%) of patients included in the study had been admitted in a psychiatric hospital more than thrice. Only one person (n=1; 2.50%) had not been previously admitted.

- Most previous admissions were seen in patients between the ages of 31 and 50 years (n=16; 41.03%). Patient older than 65 years of age had been admitted the least number of times (n=3; 7.69%).

- Most of the patients were on lithium therapy before 2017 (n=35; 87.50%) with 32.50% (n=13) of the patients being on lithium therapy for a period between 1 and 5 years.

- There number of years that patients had been on lithium therapy could not be determined for 37.50% (n=15) of the patients.

- A quarter (n=10; 25.00%) of the study sample had suicidal ideation. BD results in a reduction in life expectancy by 9.2 years and one in five patients with BD completes suicide (Depression and Bipolar Support Alliance, 2018). Lithium is used to treat suicidal ideation and the results support literature that indicates that lithium is used to treat suicidal ideation in BD.

- Risperidone (n=17; 42.50%) was the most used antipsychotic prior to lithium initiation followed by lorazepam (n=11; 27.50%). Only 5 patients (12.50%) had received lithium as their first medication of choice.

- These results support literature that indicates that lithium is the first choice in BD and is more efficacious when compared to other antipsychotics, anticonvulsants and antidepressants. The fact that lithium was not used as the first line treatment could have contributed to the high number of admissions.

- The maximum, minimum and mean maintenance doses for lithium were determined.

- Most patients received a maintenance dose of 500 mg/day (n=15; 37.50%) and 20.00% (n=8) were maintained on 1000 mg/day. These results support literature that indicates that the usual maintenance dose for lithium is between 750 mg/day and 1000 mg/day though dosing is dependent on weight.

- The mean dosage was 657.50 ± 277.48 mg/day and the minimum dosage was 200 mg/day while the maximum dosage was 1250 mg/day.

- The results indicated that the most prescribed maintenance dose of lithium was 500 mg/day among all age groups.

- A *p* value of 0.620 for Cramer's V indicates a strong association between lithium doses and age in patients on lithium therapy.

- The results indicated that the most prescribed maintenance dose of lithium among people of African (n=8; 38.10%) and Caucasian (n=7; 41.18%) descent was 500 mg/day.

- All patients (n=1; 100.00%) of Indian descent were prescribed a maintenance dose of 1200 mg/day lithium.

- Patients of Indian descent were maintained on 250mg/day lithium in all cases (n=1, 100.00%).

- The chi square probability <0.05 showed that there is a clinical significance between lithium doses and age of patients.

- Most patients received their lithium therapy at night (n=35; 87.00%) while 13.00% (n=5) received lithium twice a day. These results are supported by literature that indicates that lithium should be given at night or in two divided doses.

- The mean lithium serum concentration was 0.9 ± 0.28 mmol/L. The lowest concentration was 0.4 mmol/L with a maximum concentration of 1.4 mmol/L.

- The target concentration of lithium is between 0.6 and 1.4 mmol/L and the results showed that the serum concentrations of the study sample were within the recommended range.

- Lithium serum levels greater than 1.5 mmol/L result in lithium toxicity and the results show that none of the patients had toxic lithium serum levels.

- Lithium was prescribed by a medical practitioner 35.00% (n=14) of the times. In 40.00% (n=16) of the cases the prescriber could not be determined due to lack of data.

- The results indicated that in most cases (n=26; 65.00%) there was non-compliance with both the recommended South African and NICE guidelines for baseline renal function monitoring. Compliance was only seen in 14 cases (35.00%) for both guidelines.

- The results are not consistent with literature that indicates that renal function should be assessed prior to lithium therapy initiation.

- The results indicated that in most cases (n=28, 70.00%) there was non-compliance with the recommended South African guidelines for baseline thyroid function monitoring. Compliance was only seen in 12 cases (30.00%).

- Compliance with the NICE guidelines regarding baseline thyroid function monitoring was seen in 12 cases (30.00%). There was non-compliance in most cases (n=28; 70.00%).

- The results are not consistent with literature that indicates that thyroid function should be assessed prior to lithium therapy initiation.

- Compliance with the NICE guidelines for baseline metabolic monitoring was seen in 80.00% (n=32) of the cases.

- There was no compliance with the recommended South African guidelines for follow-up renal function monitoring in 19 cases (48.00%). Compliance was only seen in 12.00% of the cases (n=5).

- The results are not consistent with literature that indicates that renal function should be assessed every 6-12 months.

- In 12.00% (n=5) of the cases there was compliance while 48.00% (n=19) of the cases were not compliant with the recommended NICE guidelines for follow-up renal function monitoring.

- The results are not consistent with literature that indicates that renal function should be assessed every 6 months.

- Compliance with the NICE guidelines for follow-up metabolic monitoring was seen in 67.50% (n=27) of the cases.

- In most cases there was no compliance with the recommended South African guidelines for follow-up lithium serum levels monitoring (n=18; 45.00%). There was compliance in only 17.50% (n=7) of the cases.

- There was no compliance with the recommended NICE guidelines for follow-up lithium serum levels monitoring in 18 cases (45.00%). Only 17.00% (n=7) of the cases were complaint with the guidelines.

- Literature indicates that lithium levels should be monitored every 3 months and the results are not consistent with this recommendation.

- In most cases there was partial compliance with the recommended NICE guidelines for follow-up thyroid function monitoring (n=39; 97.50%). There was non-compliance in none of the cases.

- There was no compliance in any of the cases (n=0). In 97.50% (n=39) of the cases there was partial compliance with the recommended STGs for follow-up thyroid function monitoring.

- The results clearly show that there is a need to improve the current practices of monitoring lithium therapy at Fort England Hospital. More emphasis on the importance of adhering with the recommended guidelines for monitoring lithium treatment is required.

The second objective of the empirical study was to identify medication problems (interactions and adverse effects) associated with the use of lithium, considering its narrow therapeutic index:

- The results indicated that 24 patients (60.00%) experienced adverse effects while on lithium therapy.
- The most common adverse effect was weight gain (n=11; 45.83%) followed by tremor (n=8; 33.33%).
- Only 4 patients (16.67%) experienced two adverse effects while the remaining 83.33% (n=20) experienced one adverse effect.
- Out of the 24 patients that experienced adverse effects, only 9 received treatment for the adverse effects experienced (n=9; 37.50%).
- Adverse effects of lithium are linked to the high rate of non-compliance with the treatment. The results showed that in most cases the reported adverse effects were not treated which can lead to non-compliance. Therefore, there is a significant need to pay attention to the detection and treatment of adverse effects among patients.
- Drug interactions were identified in most cases (n=23; 57.00%).
- Out of 23 patients that had identified drug interactions, 20 (86.96%) had one identified drug interaction with lithium.
- Two drug interactions were noted between lithium and other drugs in 2 patients (8.70%).
- Three drug interactions were noted in one patient (4.34%).
- A total of 27 drug interactions were identified in the study sample.
- According to the results, the most common drug interaction noted was between lithium and sodium valproate (n=14; 60.86%). There is conflicting literature regarding the lithium and valproate combination. Some literature suggests that the combination leads to lithium toxicity, while other literature suggests that the combination is safe. Therefore, this combination may be a cause of concern and patients should be carefully monitored.

- The combination of valproate and lithium has been well tolerated and is recommended for patients that do not respond to the first line treatment. However, some studies have shown that concomitant use of lithium and valproate leads to increased valproate concentrations and unchanged lithium concentrations. Any adverse effects reported from the combination are thought to be a result of cumulative toxicities of either drug, rather than potential interactions (Finley, 2016:935).

- Less common drug interactions were identified between lithium and amitriptyline (n=1; 4.35%), theophylline (n=1; 4.35%) and fluoxetine (n=1; 4.35%).

- More than half of the patients had identified drug interactions. This is worrying as these drug interactions can result in lithium toxicity or decreased lithium levels. It is therefore important to check for any potential drug interactions that may occur when lithium is concomitantly prescribed with other drugs such as thiazide diuretics.

5.3 Recommendations

This drug utilisation review on the use of lithium has produced useful results that can be used to make recommendations.

- The healthcare professionals should be educated on the recommended national and international monitoring guidelines to promote rational use of lithium.

- The importance of conducting renal and thyroid function tests before lithium therapy need to be re-emphasised as these tests help determine any deterioration in the functioning of these organs. Any abnormalities will affect the doses given to the patients. Health care professionals need to be educated on the implications of not doing these tests prior to lithium initiation.

- Pharmacists should be more involved in the TDM of lithium as literature has shown that TDM is more effective when pharmacists are fully involved.

- Educating health care professionals on the appropriate withdrawal of lithium. Lithium should never be abruptly stopped unless patients present with symptoms of lithium toxicity. Doses of lithium should be gradually decreased to minimise risks of manic and depressive episodes.

- Educating health care professionals on how to identify signs and symptoms of lithium toxicity. Health care professionals should also be educated on the appropriate methods of treating lithium toxicity.

- Educating patients on the signs and symptoms associated with lithium toxicity and to encourage them to report any adverse effects immediately to their clinician. The pharmacist can have an active role in this aspect of informing patients about the adverse effects associated with lithium toxicity.

- Leaflets on the use of lithium inclusive of doses, adverse effects, drug interactions and monitoring requirements can be designed and distributed to healthcare professionals.

- **Lithium leaflets were prepared by the primary researcher and distributed to the various healthcare professionals (doctors, nurses, psychologists, psychiatrists and pharmacists) and patients at Fort England Hospital.**

- A multi-disciplinary approach that improves communication between pharmacists, doctors and nurses regarding the monitoring requirements for lithium so as to improve the clinical outcomes of a patient's therapy.

- The primary researcher can organise a presentation at Fort England Hospital and invite doctors, pharmacists and nurses and educate them on the correct prescribing and monitoring requirements of lithium.

- **A presentation was prepared by the primary researcher on lithium use and was presented to the various healthcare professionals. The presentation included the indications for lithium, mechanisms of action, adverse effects, drug interactions and monitoring requirements.**

- Educating the families of the patients on their condition and treatment will improve the patient's adherence to therapy. The family can be informed of the possible adverse effects and monitoring requirements associated with lithium therapy. The pharmacist can play an active role of educating the family.

- Educating female patients of reproductive age on the risks that are associated with lithium use. Female patients can be encouraged to use contraceptives. Encouraging female patients to speak to their medical practitioner or pharmacist before they get pregnant so that safer options can be discussed. This will ensure that they give birth to healthy babies.

- Develop a system or tool that will assist in the identification of drug interactions and have guidelines on how to resolve them.

- Revise the Standard Treatment Guidelines and Medicines List for South Africa: Hospital Level Adults (2015) and incorporate the NICE guidelines for metabolic monitoring to ensure that patients are correctly monitored on lithium therapy.

- Emphasising the importance of incorporating the monitoring of calcium levels into the clinical monitoring of lithium as lithium affects the parathyroid gland. No tests were conducted to check for parathyroid gland function.

- Implementing an ongoing DUR at Fort England Hospital on lithium monitoring that will promote rational use of lithium.

- When inpatients are discharged, the date of lithium initiation and the latest results for thyroid and renal function and lithium serum levels need to be recorded on the discharge summary. The medical practitioner or psychiatrist should clearly write on the discharge summary when and how lithium monitoring should be conducted at the outpatient clinic e.g. every 3 months.

- Educate health care professionals on the necessary markers for renal and thyroid function.

- The use of lithium as a treatment option should be the first choice especially in patients with BD. The results showed that most patients had been given other psycholeptic therapy before lithium and were switched to lithium due to failed therapy. This proves that lithium should be used as a first line treatment.

5.4 Recommendations for future studies

- Conduct drug utilisation reviews on the use of lithium in other provinces in both public and private sector hospitals in South Africa. This will help determine the national trends associated with lithium use.

- Future studies can determine the prevalence of lithium toxicity in the South African population at large.

- Future studies that can determine the prevalence of tremor and weight gain in patients on lithium treatment among the South African population can be conducted.

- Future studies can investigate the roles of pharmacists in the TDM of lithium.

- Studies can be done to determine the need for lithium monitoring guidelines specific to South Africa.
- A future study of this nature can be expanded to include patient questionnaires or patient interviews on any concerns they may have on lithium therapy.

5.5 Limitations of the study

- Some patient files were incomplete making it difficult to obtain information that was relevant for the study.
- The results obtained were in the context of Fort England Hospital and therefore cannot be used as a reflection of lithium use in all hospitals in South Africa.
- The study was conducted in a public sector hospital in Eastern Cape and therefore results may not be a representation of lithium use in private sector hospitals in the Eastern Cape.
- There were no South African guidelines available for the monitoring of metabolic parameters during lithium therapy.
- There were no DURs found on the use of lithium either in the public or private sector in South Africa.
- Due to time constraints the monetary costs associated with lithium therapy could not be investigated. However, the aim was to investigate the prescribing and monitoring patterns of lithium.

5.6 Chapter 5 summary

The conclusions, recommendations and limitations of the study were discussed in this chapter. This DUR study is a valuable addition to the limited literature available relating to the prescribing and monitoring patterns of lithium, especially in the public sector in South Africa. It is hereby concluded that all the objectives of the study were achieved.

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ANNEXURE A.
INITIAL DATA COLLECTION FORM

Demographics					
Patient number:					
Date of birth:			Age:		
Race:	African	Coloured	Indian	Caucasian	Other
Height(m):		Weight(kg):		BMI:	
Social history					
Tobacco use:	Yes		No	No information	
Alcohol use:	Yes		No	No information	
Substance use:	Cannabis:		Methamphetamine:	Other:	
Pregnancy and lactation					
Pregnancy status:	Yes		No		
Breastfeeding:	Yes		No		
Allergies					
Allergies:	Yes		No		
Medical history					
Co-morbid diseases:	Cardiac disease	Renal impairment	Hypertension	Epilepsy	Other:
Family history	Cardiac disease	Hypertension	Diabetes mellitus type II	Obesity	Other:
Past medical conditions:					
Surgical history:	Yes		No	Details of surgery:	
Suicide risk:	Yes		No		
Admission history					
Date of admission:					
Diagnosis:	Bipolar disorder	Mania	Depression	Other:	
Date of discharge:					
Number of admissions:	0	1	2	3	<3
Date of initial episode:	Available		Not available	Details	
Lithium usage					
Date of first initiation of lithium:	Available		Not available	Details:	
Was patient on lithium before?	Yes		No	No information	
Number of years that patient has been on lithium therapy:					
Date of lithium therapy initiation upon admission:					
Number of days spent in hospital after initiation of lithium:					

Past medication						
Drug	**Dosage form**	**Route**	**Dose**	**Frequency**	**Initiation date**	**Discontinuation date**

Current medication						
Drug	**Dosage form**	**Route**	**Dose**	**Frequency**	**Initiation date**	**Discontinuation date**

Drug interactions			
Are there any drug interactions observed? :	Yes	No	No information
If yes provide details:			

Prescriber details			
Who prescribed lithium?	Psychiatrist	Medical practitioner	Other
Was a psychiatrist consulted by a medical practitioner before prescribing?	Yes	No	No information

Adverse effects				
Were any adverse effects reported?	Yes	No		No information
If yes, which adverse effects were reported?	Nausea	Vomiting	Diarrhoea	Polyuria
	Hypothyroidism	Goitre	Weight gain	Tremor
Other adverse effects:				

Were the adverse effects treated?	Yes	No		No information
If yes, how was the adverse effect treated?				

Baseline Monitoring				
Parameter	Assessed	Not assessed	Date assessed	Result
Thyroid function				
Thyroid stimulating hormone (mIU/l)				
Free thyroxine (ng/dl)				
Renal function				
Blood urea nitrogen (BUN) (mmol/L)				
Estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2)				
Creatinine clearance (ml/min)				
Lithium levels				
Lithium serum levels (mmol/L)				
Metabolic monitoring				
Weight (kg)				
Height (m)				
BMI (kg/m^2)				
Blood pressure (mmHg)				
Blood glucose (mmol/L)				

Follow up monitoring				
Parameter	**Date assessed**		**Result**	
Thyroid function				
Thyroid stimulating hormone (mIU/l)	6 months:		12 months:	
Free thyroxine (ng/dl)	6 months:		12 months:	
Renal function				
Blood urea nitrogen (BUN) (mmol/L)	6 months:		12 months:	
Estimated glomerular filtration rate(eGFR) (ml/min/1.73m^2)	6 months:		12 months:	
Creatinine clearance (ml/min)	6 months:		12 months:	

Lithium levels					
Lithium serum concentration (mmol/L)	1 week:	1 month:	3 months:	6 months:	1 year:

Metabolic monitoring		
Weight(kg)		
Height(m)		
BMI(kg/m^2)		
Blood pressure (mmHg)		
Blood glucose (mmol/L)		

Compliance with regards to thyroid function monitoring			
Compliance with recommended baseline monitoring	Compliant	Non-compliant	No information
Compliance with recommended follow up monitoring	Compliant	Non-compliant	No information

Compliance with regards to renal function monitoring			
Compliance with recommended baseline monitoring	Compliant	Non-compliant	No information
Compliance with recommended follow up monitoring	Compliant	Non-compliant	No information

Compliance with regards to metabolic monitoring			
Compliance with recommended baseline monitoring	Compliant	Non-compliant	No information
Compliance with recommended follow up monitoring	Compliant	Non-compliant	No information

ANNEXURE B.
REVISED DATA COLLECTION FORM

Demographics					
Patient identification number					
Date of birth			**Age**		
Gender	**Male**		**Female**		
Race	**African**	**Caucasian**	**Coloured**	**Indian**	**Other**
Weight (kg)		**Height (m)**		**BMI (kg/m²)**	

Social history			
Employment status	Employed	Unemployed	Other
Substance use			
Alcohol use	Yes	No	
Smoking status	Smoker	Non-smoker	
Cannabis	**Methamphetamines**	**Other**	
Pregnancy and lactation			
Pregnancy status	Yes	No	
Breastfeeding	Yes	No	

Medical history					
Allergies		Yes		No	
Co-morbid diseases	Cardiac disease	Renal impairment	Hypertension	Epilepsy	Other:
Family history	Cardiac disease	Hypertension	Diabetes mellitus type II	Psychiatric condition	Other:
Past medical conditions					
Surgical history	Yes	No		Details of surgery:	
Suicide risk		Yes		No	

Admission history					
Diagnosis	Bipolar Disorder	Schizoaffective disorder	schizophrenia	Major Depressive Disorder	Other:
Number of admissions	0	1	2	3	>3
Lithium use					
Was patient on lithium before 2017?	Yes	No		No information	
Date of first lithium initiation	Available	Not available		Details	
Number of years that patient has been on lithium therapy					
Past medication (excluding lithium)					

Drug	Dosage form	Route	Dose	Frequency	Initiation date	Discontinuation date & Reason

Codes for reasons of stopping therapy: **ST: successful therapy; FT: failed therapy; AE: adverse effects; AL: allergy; S: Safety; NA: non adherent; CIT: change in therapy**.

Current medication (including lithium)					
Drug	**Dosage form**	**Route**	**Dose**	**Frequency**	**Initiation date**

Drug interactions		
Were any drug interactions identified?	Yes	No
If yes, give details		

Adverse effects				
Were any adverse effects reported?	Yes		No	
If yes, which adverse effects were reported?	Tremor	Weight gain	Hypothyroidism	Goitre
	Polyuria	Nausea	Vomiting	Other
Were the adverse effects treated?	Yes		No	
If yes, how was the adverse effect treated?				

Baseline monitoring				
Thyroid function				
Parameter	Assessed	Not assessed	Date assessed	Result
Thyroid stimulating hormone (TSH) (mIU/L)				
Free thyroxine (T$_4$) (pmol/l)				
Triiodothyronine (T$_3$) (pmol/l)				

Baseline monitoring				
Renal function				
Parameter	Assessed	Not assessed	Date assessed	Result
Estimated glomerular filtration rate (eGFR) (mL/min/1.73m^2)				
Creatinine clearance (mL/min)				
Urea (mmol/l)				
Sodium (mmol/l)				
Potassium (mmol/l)				
Chloride (mmol/l)				
Metabolic monitoring parameters				
Weight (kg)				
Fasting Blood Glucose (mmol/l)				
Blood pressure (mmHg)				
Pulse (bpm)				

Follow-up monitoring			
Thyroid function			
Thyroid stimulating hormone (TSH) (mIU/L)	6 months:	12 months:	Other
Free Thyroxine (T$_4$) (pmol/l)	6 months:	12 months:	Other
Triiodothyronine (T$_3$) (pmol/l)	6 months:	12 months:	Other

Follow-up monitoring				
Renal function				
Parameter	**Monitoring timeline**			
	3 months	**6 months**	**12 months**	**Other**
Estimated glomerular filtration rate (eGFR) (mL/min/1.73m^2)				
Creatinine clearance (mL/min)				
Urea (mmol/l)				
Sodium (mmol/l)				
Potassium (mmol/l)				
Chloride (mmol/l)				

Follow up monitoring					
Lithium serum levels					
Parameter	**Monitoring timeline**				
	1 week	**1 month**	**3 months**	**6 months**	**Other**
Lithium serum concentrations (mmol/l)					

Follow-up monitoring (metabolic monitoring)					
Parameter	**Result 1**	**Result 2**	**Result 3**	**Result 4**	**Result 5**
Weight (kg)					
Fasting blood glucose (mmol/l)					
Blood pressure (mmHg)					
Pulse (bpm)					

Compliance with recommended guidelines for thyroid function monitoring		
Compliance with recommended STGs baseline monitoring	Compliant	Non-compliant
Compliance with recommended NICE baseline monitoring	Compliant	Non-compliant

Follow-up monitoring			
Compliance with recommended STGs follow-up monitoring	Compliant	Partially compliant	Non-compliant
Compliance with recommended STGs follow-up monitoring	Compliant	Partially compliant	Non-compliant
Compliance with recommended guidelines for renal function monitoring			
Compliance with recommended STGs baseline monitoring	Compliant	Non-compliant	
Compliance with recommended NICE baseline monitoring	Compliant	Non-compliant	
Follow-up monitoring			
Compliance with recommended STGs follow-up monitoring	Compliant	Partially compliant	Non-compliant
Compliance with recommended NICE follow-up monitoring	Compliant	Partially compliant	Non-compliant

Compliance with recommended guidelines for metabolic monitoring		
Compliance with recommended STGs baseline monitoring	Compliant	Partially compliant	Non-compliant
Compliance with recommended NICE baseline monitoring	Compliant	Partially compliant	Non-compliant
Follow-up monitoring		
Compliance with recommended STGs follow-up monitoring	Compliant	Partially compliant	Non-compliant
Compliance with recommended NICE follow-up monitoring	Compliant	Partially compliant	Non-compliant
Compliance with recommended guidelines for lithium serum level monitoring		
Compliance with recommended STGs follow-up monitoring	Compliant	Partially compliant	Non-compliant
Compliance with recommended NICE follow-up monitoring	Compliant	Partially compliant	Non-compliant

ANNEXURE C.
LETTER OF APPROVAL FOR STUDY FROM RHODES UNIVERSITY FACULTY OF PHARMACY HIGHER DEGREES COMMITTEE

RHODES UNIVERSITY
Where leaders learn

19 July 2018

Professor J. Bodenstein
Faculty of Pharmacy
Pharmacology Division
Rhodes University
Grahamstown
6139

Dear Professor Bodenstein

    HDC APPROVAL: **MS CHARLOTTE MAPFUMO (STUDENT NUMBER 613M5468)**

The Faculty of Pharmacy Higher Degrees Committee has approved the project proposal of Ms Charlotte Mapfumo, entitled "A drug utilisation review of Lithium at a public sector Psychiatric Hospital".
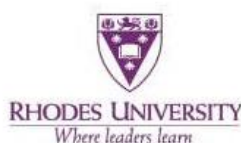
Thank you.

Yours sincerely

PROFESSOR S. DAYA
HEAD AND DEAN: FACULTY OF PHARMACY

FACULTY OF PHARMACY
RHODES UNIVERSITY
GRAHAMSTOWN 6139
SOUTH AFRICA

ANNEXURE D.
LETTER OF ETHICAL APPROVAL FOR STUDY FROM RHODES UNIVERSITY FACULTY OF PHARMACY RESEARCH ETHICS COMMITTEE

Faculty of Pharmacy
Artillery Road, Grahamstown, 6139, South Africa
PO Box 94, Grahamstown, 6140, South Africa
t: +27 (0) 46 603 8381
f: +27 (0) 46 603 7506
e: dean.pharmacy@ru.ac.za

www.ru.ac.za

RHODES UNIVERSITY
Where leaders learn

Grahamstown 19th August 2018

From:
Associate Professor Roman Tandlich, PhD
Chairperson of the Faculty of Pharmacy Ethics Committee
Faculty of Pharmacy
Rhodes University
P.O. Box 94
Grahamstown 6140
South Africa
e-mail: r.tandlich@ru.ac.za

To:
Professor Johannes Bodenstein, PhD and collaborators

Re: Feedback Letter on Ethics Committee Application PHARM-2018-06.

Dear Professor Johannes Bodenstein, Mrs. Mari-san Bodenstein, Professor Martie S. Lubbe and Ms. Charlotte Mapfumo,

Thank for your application for ethical approval entitled: "A drug utilisation review of lithium at a public sector psychiatric hospital". This application was considered by the Faculty of Pharmacy Ethics Committee under the tracking number: PHARM-2018-06. After reviewing the application and after the receipt of the necessary gatekeeper approval, you have submitted to the Faculty of Pharmacy Ethics Committee I am happy to inform you the Faculty of Pharmacy Ethics Committee grants final approval for your study.

You can proceed with making any necessary arrangements for your project. Please ensure that the Faculty of Pharmacy Ethics Committee is notified should any substantive changes(s) be made, for whatever reason, during the research process.

Yours sincerely,

Roman Tandlich, PhD

CHAIRPERSON: FACULTY OF PHARMACY ETHICS COMMITTEE

ANNEXURE E.
LETTER OF APPROVAL FOR STUDY FROM FORT ENGLAND HOSPITAL RESEARCH COMMITTEE

FORT ENGLAND HOSPITAL

Private Bag X1002, Grahamstown, 6140. Tel: +27 (0)46 622 7003. Fax: +27 (0)46 622 7630. clinicalsecfeh@gmail.com

RESEARCH PROPOSAL APPROVAL

Date: 02-August-2018

Dear Ms. C. Mapfumo

Thank you for your application to conduct research at Fort England Hospital. We are pleased to inform you that your research proposal has been approved by the Academic and Research Committee of Fort England Hospital (as indicated below). A copy of our Research Policy is included herewith, for your information. Please do not hesitate to contact me should you require any further information or assistance.

Yours sincerely,

Mo Nagdee
Chair: Academic and Research Committee

Primary Investigator	Name	Ms. C. Mapfumo		
	Position	M. Pharm. (Pharmacology Student)		
	Student or staff number	G13M5468		
	Address	Artillery Road, Grahamstown, 6139		
	Telephone	046-603 8381		
	Email	Johannes.Bodenstein@ru.ac.za		
Research project	Title	A drug utilisation review of Lithium at a Public Sector Psychiatric Hospital		
	Supervising University / Institution	Rhodes University		
	Supervisor	Prof. J. Bodenstein		
	Ethics Approval from Supervising University / Institution	~~No~~	**Yes** (insert ethics clearance reference no.) PHARM-2018-06	
Fort England Hospital Approval	Academic and Research Committee Chair / Clinical Head (M. Nagdee)	~~No~~	**Yes** (insert date) 02-August-2018	**Signature**
	Head: Psychology (I. Reid)	~~No~~	**Yes** (insert date) 02-August-2018	**Signature**
	Acting CEO (Mr. M. Dyalvane)	~~No~~	**Yes** (insert date) 02-August-2018	**Signature**
	Co-Opt Member Head: Pharmacy (S. Willows)	~~No~~	**Yes** (insert date) 02-August-2018	**Signature**
Additional comments				

ANNEXURE F.
LETTER OF APPROVAL FOR STUDY FROM EASTERN CAPE DEPARTMENT OF HEALTH RESEARCH COMMITTEE

Province of the
EASTERN CAPE
HEALTH

Enquiries:	Zonwabele Merile	Tel no: 083 378 1202
Email:	zonwabele.merile@echealth.gov.za	Fax no: 043 642 1409
Date:	28 August 2018	

RE: A DRUG UTILISATION REVIEW OF LITHIUM AT A PUBLIC SECTOR PSYCHIATRIC HOSPITAL. (EC_201808_008).

Dear Prof J. Bodenstein

The department would like to inform you that your application for the abovementioned research topic has been approved based on the following conditions:

1. During your study, you will follow the submitted amended protocol with ethical approval and can only deviate from it after having a written approval from the Department of Health in writing.

2. You are advised to ensure, observe and respect the rights and culture of your research participants and maintain confidentiality of their identities and shall remove or not collect any information which can be used to link the participants.

3. The Department of Health expects you to provide a progress update on your study every 3 months (from date you received this letter) in writing.

4. At the end of your study, you will be expected to send a full written report with your findings and implementable recommendations to the Eastern Cape Health Research Committee secretariat. You may also be invited to the department to come and present your research findings with your implementable recommendations.

5. Your results on the Eastern Cape will not be presented anywhere unless you have shared them with the Department of Health as indicated above.

Your compliance in this regard will be highly appreciated.

SECRETARIAT: EASTERN CAPE HEALTH RESEARCH COMMITTEE

ANNEXURE G.
PATIENT INFORMATION LEAFLET

When should you stop taking lithium?

You must continue taking your medicine even if you feel well.

Lithium and other medicines

Some medicines don't work well with lithium. It is important to

tell your doctor what other medicines you are taking.

Lithium and Alcohol

Alcohol intake while on lithium will make you more drowsy. Use

is not advised.

Operating heavy machinery and smoking

Smoking and operating heavy machinery while taking lithium is strongly discouraged.

References

Gitlin, M. (2016) 'Lithium side effects and toxicity: prevalence and management strategies', *International Journal of Bipolar Disorders*. Springer Berlin Heidelberg, 4(27), pp. 1–10.

Rossiter, D. (2016) *South African Medicine Formulary*. 12th edn. Edited by M. Blockman

Complied by Charlotte Mapfumo (B.Pharm).

LITHIUM

What is lithium?

Lithium is a psychiatric medication that is used as a mood stabiliser.

What is it used for?

Lithium is used to treat the following disorders:

- Mania
- Bipolar disorder
- Resistant or recurrent depression
- Schizoaffective disorder
- Other behavioural disorders such as self mutilation
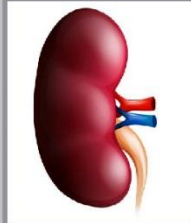
What are the effects of lithium ?

Lithium makes your mood better. It may take up to three weeks before you start experiencing the full benefits of lithium.

What should you do before you start taking lithium?

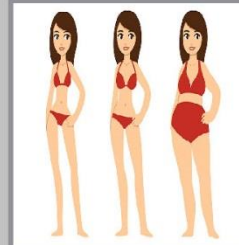Your kidney and thyroid function should be checked before you start taking lithium.

Possible side effects

It is important to know that you may experience all, some or none of the side effects. Some of the side effects you may experience include:

Tremors

Weight gain

Nausea

Thirst

Drowsiness

Goitre

What should you do if you experience adverse effects?

You should contact your doctor, nurse or pharmacist if you experience any of the side effects

Pregnancy and lactation

Lithium should not be used if you are pregnant or breast feeding.

Monitoring requirements

It is important to monitor lithium serum levels, kidney, thyroid and metabolic function while on lithium therapy. All appointments with your doctor should be kept while taking lithium