Bipolar disorder in the South African private health sector: Longitudinal analysis of prevalence, comorbidities and prescribing patterns

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PREFACE

This dissertation was written in an article format. Chapter 3 contains the results of the empirical investigation, written in the form of two manuscripts. The two manuscripts are prepared for submission to the following journals for publication:

- International journal of methods in psychiatry research
- Bipolar disorder

Both of the manuscripts and their references were written in accordance to the author guidelines specified by the respective journals (Annexures G and H). However, the complete reference list of the dissertation is listed according to the referencing style of the North-West University.

The dissertation is divided into four chapters. Chapter 1 provides an overview of the study and problem statement, research aims and objectives, as well as a description of the method followed to conduct the empirical investigation. Chapter 2 is a comprehensive literature review to fulfil the literature objectives stated in Chapter 1. Chapter 3 contains the manuscripts. The final chapter concludes this study, providing future recommendations, study limitations and strengths. References and annexures are provided at the end of the dissertation.

The contributions of each author for both manuscripts are subsequently outlined.

AUTHORS' CONTRIBUTIONS TO MANUSCRIPT 1

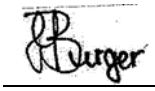
The contributions of each author for manuscript 1, "Trends in the incidence and prevalence of bipolar disorder and its coexisting chronic disease list conditions in the private healthcare sector of South Africa, 2010-2015", were as follow:

Author	Role in study
Mr AP Akinrogunde	Planning and designing of the study Implementation Data interpretation Writing of the manuscript and dissertation
Prof MS Lubbe (Supervisor)	Supervision of study and manuscript concept Data and statistical analysis Guidance and interpretation of the results Revising and approval of the final manuscript and dissertation
Prof JR Burger (Co-supervisor)	Co-supervision of study and manuscript concept Guidance and interpretation of the results Revising and approval of the final manuscript and dissertation
Mrs M Cockeran (Statistician)	Data and statistical analysis Verifying the results from the statistical analysis Revising and approval of the research proposal and final manuscripts.

With the following statement the co-authors confirm their role in the study and give their permission that the manuscript may form part of this dissertation.

I declare that I have approved the above mentioned manuscript and that my role in this study, as indicated above, is representative of my actual contributions and I hereby give my consent that it may be published as part of the MPharm study of AP Akinrogunde.

Prof MS Lubbe



Prof JR Burger

Mrs M Cockeran

AUTHORS' CONTRIBUTIONS TO MANUSCRIPT 2

The contributions of each author for manuscript 2, "Trends in the psychopharmacological prescribing patterns among bipolar disorder patients in the South African private health sector", were as follow:

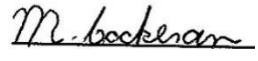
Author	Role in study
Mr AP Akinrogunde	Planning and designing of the study Implementation Data interpretation Writing of the manuscript and dissertation
Prof MS Lubbe (Supervisor)	Supervision of study and manuscript concept Data and statistical analysis Guidance and interpretation of the results Revising and approval of the final manuscript and dissertation
Prof JR Burger (Co-supervisor)	Co-supervision of study and manuscript concept Guidance and interpretation of the results Revising and approval of the final manuscript and dissertation
Mrs M Cockeran (Statistician)	Data and statistical analysis Verifying the results from the statistical analysis Revising and approval of the research proposal and final manuscripts.

With the following statement the co-authors confirm their role in the study and give their permission that the manuscript may form part of this dissertation.

I declare that I have approved the above mentioned manuscript and that my role in this study, as indicated above, is representative of my actual contributions and I hereby give my consent that it may be published as part of the MPharm study of AP Akinrogunde.

Prof MS Lubbe

Prof JR Burger



Mrs M Cockeran

ABSTRACT

Title: **Bipolar disorder in the South African private health sector: Longitudinal analysis of prevalence, comorbidities and prescribing patterns**

Bipolar disorder (BD) is a chronic affective disorder characterised by mood changes, fluctuating between depressive symptoms and manic symptoms. It is one of the psychiatric illnesses that have contributed to the chronic disease burden in South Africa.

The overall goal of this study was to assess possible changes, over a six-year period (2010-2015), in the prevalence and incidence of BD, and its coexisting chronic disease list (CDL) conditions as well as changes in the medicine prescribing patterns in the private health sector in South Africa by using medicine claims data.

Manuscript 1 conveyed on the findings of the investigation into the trends over a six-year period in the prevalence and incidence of BD and the prevalence of coexisting CDL conditions in patients with BD. The study followed a retrospective cohort study, analysing medicine claims data for the period 1 January 2010 to 31 December 2015. An open cohort design was used to determine trends in the incidence and prevalence rate of BD (ICD-10 code F31) over a six-year study period, whereas a closed (N = 1 228) cohort design was used to investigate the prevalence of coexisting CDL conditions in BD patients. The incidence rate per 1 000 beneficiaries was determined using 2010 as index year.

Bipolar disorder patients represented 0.6% (N = 968 131) and 0.8% (N = 843 792) of the total patient population on the database in 2010 and 2015, respectively. The majority of BD patients were females, representing 0.8% (2010) (N = 521 387) to 1.0% (2015) (N = 445 626) of the total number of female patients on the database. The mean age of the BD patients was 43.6 (15.8) years (95% CI 43.2-44.0), with the majority (96.4%, n = 5 471) older than 18.2 years in the index year (2010). Prevalence rate of BD increased from 5.9 (2010) to 7.9 (2015) per 1 000 beneficiaries, whereas incidence rate per 1 000 beneficiaries was 2.3 in 2011 vs. 2.1 in 2015. Female BD patients have higher incidence rates (2.9 in 2011 *vs*. 2.6 in 2015) than males (1.7 in 2011 *vs*. 1.6 in 2015).

The number of BD patients in the closed cohort (N = 1 228) with one or more coexisting CDL condition increased by 20.5% from 2010 (n = 594) to 2015 (n = 716); however, the increase in the mean number of coexisting CDL conditions per BD patient was practically insignificant ($P > .01$; Cohen's *d*-value < .8). BD patients newly registered with hypertension ($P < .0001$), hypothyroidism ($P < .0001$), hyperlipidaemia ($P < .0001$), type 2 diabetes mellitus ($P < .0001$),

epilepsy (*P* = .0065) and rheumatoid arthritis (*P* = .0253) increased. Hypertension, hyperlipidaemia and hypothyroidism combined was the most prevalent three chronic conditions-combination in BD patients.

Manuscript 2 reported the findings of the investigation into the possible changes, over a 6-year period, in the medicine prescribing patterns for patients with only BD. The study followed a longitudinal open cohort design to analyse retrospective data of patients identified with the diagnosis code ICD-10, F31, for bipolar disorder, on reimbursed medicine claims, from 1 Jan. 2010 to 31 Dec. 2015. These patients did not have any of the other coexisting CDL conditions that are covered through the prescribed minimum benefits as indicated in the South Africa Medical Scheme Act (131 of 1998). Change in medicine prescribing patterns was assessed by measuring the following: i) different types of active pharmaceutical ingredients; ii) frequency of monotherapy (include only one active pharmaceutical ingredient) or combination therapy (include more than one active pharmaceutical ingredients, based on the last month's prescription(s) of a patient in 2010 and 2015; iii) average number of medicine items per prescription per patient per year; and iii) average number of prescriptions per patient.

The study population consisted of 3627 patients in the index year (2010) and increased to 4332 in 2015. The study population was predominantly female, with a male: female ratio of 1:2.3 in 2010 and 1:1.88 in 2015. Major changes took place in the psychopharmacological prescribing during the study period. The average number of medicine items per prescription stayed constant at 2 medicine items per prescription per patient throughout the study years. The number of prescriptions per patient increased observably from 7.08(5.63) [6.94-7.23] in 2010 to 7.50(5.59) [7.37-7.63] (*P* = .00001, Cohen's *d*-value = .4) in 2015. The proportion of patients on combination therapy increased from 44.6% (2010) to 48.7% (2015). The most prevalent combination therapy in 2010 and 2015 was lamotrigine in combination with quetiapine or with a selective serotonin re-uptake inhibitor, or with bupropion or with valproate. The proportion of patients receiving anticonvulsants (35.4% *vs.* 34.7%), antidepressants (31.9% *vs*. 36.1%) and atypical antipsychotics (16.2% *vs.* 23.2%) as monotherapy increased significantly (*P* = .0001) from 2010 to 2015; the proportion of patients receiving lithium decreased marginally (4.9% *vs.* 4.2%) (*P* = .302). The increase in combination therapy and the constant high use of antidepressant as monotherapy should be further investigated in the private-insured BD population in South Africa.

KEYWORDS

Bipolar disorder, incidence, prevalence, coexisting chronic disease list conditions, psychopharmacological prescribing patterns, private sector, South Africa

LIST OF ABBREVIATIONS

5HT	5-Hydroxyltryptamine
AP	Antipsychotics
AA	Atypical antipsychotics
AC	Anticonvulsants
AD	Antidepressants
ACE	Angiotensin converting enzyme
ADHD	Attention deficit hyperactivety disorder
AIDS	Acquired immunodeficiency syndrome
BD	Bipolar disorder
BDA	Bipolar disorder algorithm
BD-I	Bipolar I disorder
BD-II	Bipolar II disorder
CANMAT	Canadian Network for Mood and Anxiety Treatment
CANMAT & ISBD	Canadian Network for Mood and Anxiety Treatment and International Society for Bipolar Disorders
CBT	Cognitive behavioural therapy
CDL	Chronic disease list
DBSA	Depression and Bipolar Support Alliance
DSM-V	Diagnostic Statistical Manual of Mental Disorders 5th Edition
ECT	Electroconvulsive therapy
FFT	Family focused therapy

LIST OF ABBREVIATIONS (CONTINUED)

GABA	Gamma-amino-butyric acid
GAD	Generalised anxiety disorder
GEE	Generalised estimating equation
GLM	Generalised linear models
HDL	High-density lipoproteins
HIV	Human Immunodeficiency Virus
HPCSA	Health Professions Council of South Africa
HREC	Health Research Ethics Committee
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
IPSRT	Interpersonal social rhythm therapy
ISBD	International Society for Bipolar Disorder
LDL	Low-density lipoproteins
LFBF	Low frequency blood oxygen level dependent fluctuation
L	Lithium
MAOIs	Mono-amine oxidase inhibitors
MBCT	Mindfulness-based cognitive therapy
MIMS	Monthly Index of Medical Specialties
MUSA	Medicine Usage in South Africa
NAPPI	National Pharmaceutical Product Index
NDRI	Noradrenaline (and dopamine) re-uptake inhibitors
NIMH	National Institute of Mental Health

LIST OF ABBREVIATIONS (CONTINUED)

NSAIDs	Non-steroidal anti-inflammatory drugs
NWU	North-West University
OCD	Obsessive compulsive disorder
PBM	Pharmaceutical Benefit Management
PD	Panic disorder
PDD	Prescribed daily dose
PRIME	Programme for improving mental health care
PTSD	Post-traumatic stress disorder
SA	South Africa
SADAG	South African Depression and Anxiety Group
SAPC	South African Pharmacy Council
SAS®	Statistical Analysis System®, SAS 9.4® (SAS Institute Inc., 2002-2012)
SERT	Serotonin transporter
SNRI	Serotine and noradrenaline re-uptake inhibitors
SP	Social phobia
SSRIs	Selective serotonin reuptake inhibitors
T	Tetracyclic antidepressants
TCAs	Tricyclic antidepressants
USA	United States of America
WHO	World Health Organization
WMH	World mental health

LIST OF DEFINITIONS

Bipolar disorder (BD):	Bipolar disorder is a serious mood disorder characterised with mania, major depression and hypomania (Goodwin, 2016:661; Goodwin *et al.*, 2016:508; NIMH, 2016).
Bipolar I disorder:	Bipolar I disorder (BD-I) refers to mood fluctuation from manic to depressive episode; mood is extremely abnormal with high activity or energy and presence or absence of psychotic symptoms (hallucination and delusion), or a history of at least one manic or mixed episode and at least one major depressive episode (WHO, 2016a).
Bipolar II disorder:	Bipolar II disorder (BD-II) implies mood change from hypomanic to depressive episode; there is low mood, reduced energy and decreased activity with or without psychotic symptoms (hallucination and delusion) (WHO, 2016a).
Burden of disease:	Burden of disease is the sum of life lost due to undue mortality and years-of-life lost due to being unhealthy (WHO, 2016c).
Chronic Disease List (CDL)	The chronic disease list consists of 26 specified chronic conditions for which treatment and medication are covered according to the prescribed minimum benefits (Council for Medical Schemes, 2010a).
Comorbidity:	Within the context of this study, comorbidity is the coexistence of one or more chronic diseases in BD patients (Krishnan, 2005:1; Sin *et al.*, 2006:1245; Surendran & Chakrabarti, 2016:1). In this study, the terms 'comorbidities', 'co-existing CDL conditions' and 'co-occurring CDL conditions' will be use as synonyms.
Cyclothymic disorder:	Cyclothymic disorder is also called cyclothymia. It means many episodes of hypomanic symptoms and many episodes of depressive symptoms in a patient, even though the patient never had full criteria for manic or major depressive episode (NIMH, 2016).

LIST OF DEFINITIONS (CONTINUED)

International Statistical Classification of Diseases and Related Health Problem, 11th Revision (ICD-11)	The International Classification of Diseases is the basis for the international standard for reporting diseases and health conditions. It is generally used for the identification of health trends and statistics regarding diseases, disorders, injuries and other related health condition. (WHO, 2018).
Non-pharmacological treatment:	Non-pharmacological treatment refers to psychosocial interventions in patients with bipolar disorder (Miklowitz *et al.,* 2008:77).
Other specified and unspecified bipolar disorders:	Bipolar disorder that does not match BD-I, BD-II and cyclothymic disorder (NIMH, 2016).
Pharmacological treatment:	Use of pharmacological agents for the treatment of specific disease, for example BD (Colin, 2013:165; Goodwin, 2009:351,353,354; Grunze *et al.,* 2009:91,94,101; Moreno *et al.*, 2007:1033).
Prescribed minimum benefits (PMBs):	The prescribed minimum benefits are a set of defined benefits to ensure that all medical scheme members have access to certain minimum health services, regardless of the benefit option they have selected (Council for Medical Schemes, 2010b).
Rapid cycling:	Rapid cycling refers to a situation whereby a patient has at least four manic, depressive, hypomanic or mixed episodes within a year period (Goodwin *et al.,* 2016:511).

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CHAPTER 1: FOUNDATION

1.1 Introduction

The main focus of the study is on possible changes in the medicine prescribing patterns for bipolar disorders (BD) and the prevalence of comorbidities in BD patients in the private sector of South Africa.

Chapter 1 will focus on the background, problem statement, study objectives, research methodology and ethical aspects applicable in this study.

1.2 Background and problem statement

Bipolar disorder (BD) is a chronic mental disease associated with functional and cognitive impairment in memory, attention and executive activities as a result of fluctuations in mood, energy and activity levels, as well as neuropsychosocial deficit (Best *et al.,* 2017:406; Cardoso *et al*., 2016:225; Goodwin *et al.,* 2016:495; NIMH, 2016; Samame *et al*., 2017:17). Bipolar disorder could be classified into bipolar I disorder (BD-I), bipolar II disorder (BD-II), cyclothymic disorder and rapid cycling (Goodwin *et al*., 2016: 508,511; NIMH, 2016). Bipolar I disorder is characterised by a manic episode or symptoms for at least seven days and usually requires hospitalisation due to its severity, while BD-II disorder is associated with depressive and hypomanic episodes (NIMH, 2016). The level of cognitive impairment differentiates BD-I disorder (high mood) from BD-II disorder (low mood) (Simonsen *et al.,* 2008:245). Cyclothymic disorder describes several periods of hypomanic and depressive symptoms for at least two years, while rapid cycling is associated with at least four manic, depression, hypomanic or mixed episodes in a year (Goodwin *et al.,* 2016:211; NIMH, 2016).

The International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), describes BD as an illness characterised with mood fluctuations between manic and depressive episodes. This change is often associated with a change in total levels of activity (WHO, 2016a). The ICD-10 Classification System ordered BD under mental and behavioural disorders, ranging from bipolar affective disorder (F31), bipolar affective disorder, current episode hypomanic (F31.0), bipolar affective disorder, current episode manic without psychotic symptoms (F31.1), bipolar affective disorder, current episode manic with psychotic symptoms (F31.2), bipolar affective disorder, current episode mild or moderate depression (F31.3), bipolar affective disorder, current episode severe depression without psychotic symptoms (F31.4), bipolar affective disorder, current episode severe depression with psychotic symptoms (F31.5), bipolar affective disorder, current episode mixed (F31.6), bipolar affective disorder, currently in remission

(F31.7), other bipolar affective disorders (F31.8), and bipolar affective disorder, unspecified (F31.9) (WHO, 2016a). Most of these disorders are usually recurrent and the beginning of an individual episode can always be traced to stressful situations and events (WHO, 2016a).

The 2015 Global Burden of Disease (GBD) study accentuated that BD affects approximately 44 million (CI, 38.2-50.9 million) people worldwide (Global Burden of Disease 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016:1568). The result of the World Health Organization (WHO) World Mental Health Survey Initiative, under a pooled sample of 11 countries, indicated that the lifetime prevalence rates of BD-I, BD-II, and sub-threshold BD were 0.6%, 0.4%, and 1.4%, respectively (Merikangas *et al.,* 2011:244). In the same study, the 12-month prevalence of BD-I, BD-II, and sub-threshold BD were 0.4%, 0.3%, and 0.8%, respectively.

Merikangas *et al*. (2007:545) found 18.2 years of age as the average age for initial occurrence of BD I disorder, and 1% prevalence in one's lifetime, while that of BD II disorder is 20.3 years of age and 1.1%, respectively. Higher rates are often found in women, although economic, social and ethnic factors are also likely to exert an influence (Grant *et al.,* 2005:1205, 1209; Kennedy *et al.*, 2005:257; Pratt, 2007:424; WebMD, 2016b). In addition, the pattern of one's life, coupled with genetic factors, among others, is also capable of predisposing an individual to BD (Pratt, 2007:425).

The 12-month prevalence of mood disorders in South Africa (SA) (Herman *et al*., 2009:343) was comparable with other countries involved in the World Mental Health (WMH) survey (Merikangas *et al.,* 2011:245). The prevalence of mental disorders was very high in the Western Cape of SA and very low in the Eastern Cape (Herman *et al*., 2009:343). In a systematic review of all Diagnostic and Statistical Manual IV (DSM IV) disorders from 1985 to 2002 in the Western Cape, it was found that the prevalence of mental disorders was 25% in adults, and 17% in children and adolescents.

Mental disorders are one of the health burdens in SA that require utmost attention (Kleintjes *et al*., 2006:157). Bipolar disorder was identified as one of the top 10 ranked chronic disease list (CDL) conditions (including HIV/AIDS) treated in the medical scheme environment in SA during 2016 (Research and Monitoring Unit of the Council for Medical Schemes, 2018:5). The Research and Monitoring Unit of the Council for Medical Schemes (2015:28) determined an annual increase in the prevalence rate of BD from 1.91 to 3.97 per 1 000 beneficiaries from 2010 to 2015 at an average growth of 15.8% (Research and Monitoring Unit of the Council for Medical Schemes, 2017:8,35). It was found that rate of increase in the prevalence of BD has reduced significantly between 2015 and 2016, with the rate only increasing by 0.31% (Research and Monitoring Unit of the Council for Medical Scheme, 2018:8).

In the private health sector of SA, females constantly had higher BD prevalence rates as opposed to males (Research and Monitoring Unit of the Council for Medical Schemes, 2017:35). Also, in 2013, 3.7 female and 2.06 male patients per 1 000 BD patients were diagnosed and treated in the private health sector of SA.

People in urban areas are more prone to mental disorders than people in rural areas as a result of high levels of urbanisation (Herman *et al*., 2009:343). Poverty also predisposes people to mental disorders, considering the following poverty indicators: low educational levels, lack of employment, lack of material possession, low income and housing difficulties (Patel & Kleinman, 2003:610). A study revealed that South Africans are more prone to mental disorders considering their historical background and current social conditions (Williams *et al*., 2008:211). The unmet need for care and treatment for mental disorders is increasing daily, particularly among the moderate and severe disorders (Williams *et al.,* 2008:211).

Stepwise diagnosis is inevitable in BD, due to the pattern of its presentations (Colin, 2013:164). The recommendations made by the International Society for Bipolar Disorder (ISBPD) for International Classification of Diseases 11th Revision (ICD-11), and DSM-V for BD are as follows: for BD-I, the DSM-V must remain the same, but for bipolar disorder II, the criteria should consider a probability approach, recognising the presence of positive family history of BD, psychomotor disturbance, atypical depressive symptoms and psychotic features for bipolar depression (Ghaemi *et al.,* 2008:119; Nuckols, 2013).

Comorbidity is the presence of one or more additional diseases co-existing with the primary disease of interest or coexistence of multiple chronic diseases (Marengoni *et al.,* 2011:430; Sin *et al*., 2006:1246). It is also referred to as the existing medical conditions at the time of diagnosis of the primary disease (Ording & Sorensen, 2013:200). Evidence from the study by Kilbourne *et al.* (2004:368) showed that the burden of medical comorbidities and their adverse outcomes are specifically severe in BD patients. Substance-use disorders and anxiety disorders are the most common disease conditions associated with BD (Colin, 2013:164). The high prevalence of cardiovascular diseases and its risk factors, such as dyslipidaemia, obesity, diabetes mellitus, smoking and hypertension, have also been confirmed in patients with BD (Birkenaes *et al*., 2007:917; Fagiolini *et al*., 2005:424; Fiedorowicz *et al.,* 2008:135; Kilbourne *et al*., 2004:370). Poor diet and exercise habits are also common in patients with mental illnesses (Strassnig *et al.*, 2005:426).

Bipolar disorder presents a special challenge that is different from other chronic mental illness such as schizophrenia, due to its cyclical presentation (alternating manic and depressive symptoms) (Kilbourne, 2005:473). This could cause patients to have little or no contact with

friends or care providers over a long period of time, predisposing BD patients to a high risk of medical comorbidity, poor adherence to care plan and social instability (Kilbourne, 2005:473).

Even with the availability of pharmacotherapy for BD that is efficacious, treatment outcomes remains suboptimal (Blanco *et al*., 2002:1005). The success of treatment of bipolar I disorder is a function of early detection, most suitable pharmacologic and psychosocial management and in-depth knowledge of long-term cyclic, current and relapsing patterns of the disease (Lim *et al*., 2001:166). A series of practice protocols and treatment guidelines has been developed for psychiatrists and other health professionals who are involved in mental health to serve as a framework for most appropriate treatments for BD (Lim *et al*., 2001:166).

Psychotropic drugs are a group of drugs that have the capacity to modify normal higher brain functions (Schulz & Steimer, 2000:181). Psychotropic medicines for the treatment of BD are categorised into five major groups: antidepressants, antipsychotic drugs, mood stabilisers and anticonvulsants, benzodiazepines and stimulants (Moreno *et al*., 2007:1035) (refer to Table 4.1, Annexure B). Many treatment guidelines recommended lithium and second-generation antipsychotic medications as first line treatment of BD (Nivoli *et al*., 2011:14; Nivoli *et al*., 2012:127).

Based on a study in the United States of America, risperidone and olanzapine were the most commonly used second-generation antipsychotics for the treatment of BD between 1998 and 2001, while quetiapine and aripiprazole were the most commonly used in 2009 (Pillarella *et al*., 2012:84). Quetiapine has been shown to be superior to paroxetine in terms of effectiveness in treating acute depressive episodes in BD-I and BD-II disorders (McElroy *et al.,* 2010:163). Karanti *et al*. (2016:50) indicated that the use of lithium has consistently decreased in both subtypes of BD in Sweden between 2007 and 2013, whereas the use of quetiapine and lamotrigine has increased. Olanzapine use in women has decreased. Valproate use in the treatment of BD-II disorder has decreased, while the use of antidepressants stayed constant. Antidepressant use in BD-I disorder has increased (Karanti *et al*., 2016:50).

According to Colin (2013:164), most prescriptions for the treatment of BD in SA are not likely to have a place in evidence-based practice. The South African Society of Psychiatrists accepted the bipolar disorder algorithm (BDA), as shown in Figure 4.1 in Annexure A, as the treatment guidelines for BD in SA (Colin, 2013:170; South Africa, 2009b:4). According to this treatment algorithm, lithium, valproate, lamotrigine, antidepressants, and mood stabilisers are used for the treatment of depressive episodes, whereas atypical antipsychotics, lithium, valproate and benzodiazepine are used for manic episodes (Colin, 2013:170; Malhi *et al*., 2009:33,34; South

Africa, 2009b:4; Yatham *et al.,* 2009:228). Drugs used in these episodes could be used as monotherapy or in combination.

This study aims to determine trends, over a six-year study period, in the incidence and prevalence of BD and its co-existing 26 chronic disease list (CDL) conditions by using retrospective medicine claims data. Diagnosis of chronic diseases was reported in 2015 to be on the increase amongst medical schemes beneficiaries (Research and Monitoring Unit of the Council for Medical Schemes, 2017:6). This upward trend in the diagnosis and treatment of many conditions on the CDL continued in 2016 (Research and Monitoring Unit of the Council for Medical Schemes, 2018:5).

Chronic diseases in BD patients have not been given an in-depth consideration in South Africa. Chronic diseases, also referred to as non-communicable diseases (NCDs), are not spread from person to person (WHO, 2016b). Multimorbidity is defined as the coexistence of multiple chronic diseases (Marengoni *et al.,* 2011:430). Comorbidity is then defined as an already existing disease in a person at the point of diagnosis of the disease of interest in a time period (Ording & Sorensen, 2013:200; Surendran & Charkrabarti, 2016:1). Chronic diseases are the largest cause of death in the world through cardiovascular diseases, ranging mainly from ischemic heart disease and stroke (17 million deaths in 2002), diabetes mellitus (1 million), cancer (7 million) and chronic lung disease (4 million) (Yach *et al*., 2004:2616). The 2015 Global Burden of Disease (GBD) study reported that BD affected approximately 44 million (95% CI, 38.2-50.9 million) people in the world (Global Burden of Disease 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016:1568). Furthermore, the more comorbidities one has, the higher the influence it has on treatment and medical costs, mortality predisposition and disability (Michaud & Wolfe, 2007:886). This make it necessary to identify comorbidities as early as possible. (Kilbourne *et al*., 2004:368; Kilbourne, 2005:471; Michaud & Wolfe, 2007:886). This present study will attempt to raise awareness of inappropriate prescribing and deviation from standard treatment guidelines or algorithms, so as to further improve the treatment outcomes in BD diagnosed patients in the South African private health sector.

The following are the research questions formulated for this study:

- What is the current burden of BD in South Africa and internationally?
- What are the current treatment guidelines for BD internationally and in South Africa?
- What is the prevalence of coexisting chronic disease with respect to CDL conditions in patients with BD?

- What are the current medicine prescribing patterns for BD in the South African private health sector?

1.3 Research aims and objectives

1.3.1 Research aims

The general research aim of this study was to assess possible changes, over a six-year period (2010-2015), in the prevalence and incidence of BD, and its coexisting CDL conditions as well as changes in the medicine prescribing patterns for BD in the private health sector in South Africa by using medicine claims data.

1.3.2 Specific research objectives

The specific research objectives included the following:

1.3.2.1 Specific research objectives: Literature review

The specific research objectives of the literature review, from published literature, included the following:

- To conceptualise the prevalence and incidence of BD and its comorbidities, nationally and internationally.
- To identify current treatment guidelines of BD by focusing on both national and international published consensus treatment guidelines from the literature.

1.3.2.2 Specific research objectives: Empirical investigation

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

- To determine trends, over a six-year period, in the prevalence and incidence of BD.
- To determine possible changes, over a six-year period, in the prevalence of coexisting CDL conditions in patients with BD.

- To investigate possible changes, over a six-year period, in the medicine prescribing patterns[1] for patients with only BD.

Table 1.1: Research objectives outlined from the empirical investigation and article in which they are addressed

Empirical objectives	Article	Reference
To determine trends, over a six-year period, in the prevalence and incidence of BD.	"Trends in the incidence and prevalence of bipolar disorder and its coexisting chronic disease list conditions in the private health sector of South Africa, 2010-2015."	Prepared for submission in the International Journal of Methods in Psychiatry Research
To determine possible changes, over a six-year period, in the prevalence of coexisting CDL conditions in patients with BD	"Trends in the incidence and prevalence of bipolar disorder and its coexisting chronic disease list conditions in the private health sector of South Africa, 2010-2015."	Prepared for submission in the International Journal of Methods in Psychiatry Research
To investigate possible changes, over a six-year period, in the medicine prescribing patterns for patients with only BD.	"Trends in the psychopharmacological prescribing patterns among bipolar disorder patients in the South African private health sector"	Prepared for submission in the journal Bipolar disorder

1.4 Research methodology

The research consisted of a literature review and an empirical study.

1.4.1 Literature review

Literature and research articles that were included in the literature review were selected as follows:

- An internet search was conducted using appropriate databases such as Google Scholar™, PubMed®, Scopus®, EBSCOHost®, ScienceDirect® and SA ePublications®.

- The following keywords were used in singular entities and in combination, in conducting the literature review: 'bipolar disorder', 'prescribing patterns in bipolar disorder', 'treatment

[1] Within the context of the study, medicine prescribing patterns included the following: i) different types of active pharmaceutical ingredients according to pharmacological groups; ii) frequency of monotherapy (includes only one active pharmaceutical ingredient per prescription) or combination therapy (includes more than one active pharmaceutical ingredients in therapy, based on the last month's prescription(s) of a patient in 2010 and 2015); iii) average number of medicine items per prescription per patient per year; and iii) average number of prescriptions per patient per year, stratified per age and gender group.

patterns in bipolar disorder', 'comorbidities in bipolar disorder', 'prevalence of bipolar disorder', 'incidence of bipolar disorder' and 'South Africa'.

- The most appropriate literature was chosen from the results to answer the research objectives.

1.4.2 Empirical investigation

The empirical investigation discussion covered the research design, data source, data fields, target and study population, study variables and validity, and reliability of the database.

1.4.2.1 Research design

A descriptive, observational research design was implemented using retrospective medicine claims data from a national representative pharmaceutical benefit management (PBM) company, for the study period 2010 to 2015. Descriptive studies attempt to find and describe the occurrence of a medical condition or problem (Waning & Montagne, 2001:46). It provides "insight data about the patterns of diseases or drug use problems in a population or group" (Waning & Montagne, 2001:46).

Observational research, within the context of pharmacoepidemiology, provides evidence about disease patterns and drug use problems through various characteristics of persons, place and time periods (Waning & Montagne, 2001:46). In observational research, the researcher makes no attempt to intervene (Hartung & Touchette, 2009:399).

Different variations of the abovementioned research design were implemented to achieve the different specific research objectives (refer to paragraph 1.3.2.2 and Figure 1-1):

- In the first objective, trends in the prevalence and incidence rate of BD, from 2010 to 2015, were determined. The analysis followed a longitudinal open cohort design, using retrospective data. A longitudinal design is an investigation where participant outcomes and possible treatments are collected at multiple follow-up times. The way in which variables change over time is examined (Brink *et al.*, 2012:114). Cohort studies are characterised by the following of groups, or cohorts of subjects, through time (Hartung & Touchette, 2009:402). Group allocation is defined by exposure (e.g. patients taking a specific drug or have a specific condition) or extent of exposure (e.g. drug dosing). In a closed cohort design, subjects or participants are not allowed to enter or leave the cohort according to defined events (International Society of Pharmacoepidemiology Midyear Meeting, 2013). In retrospective cohort studies, existing data such as administrative claims datasets or medical records are

used to analyse what happened following cohort assignment (Hartung & Touchette, 2009:402).

- In the second objective, changes in the prevalence of co-existing chronic disease list (CDL) conditions in patients with BD, over the entire six-year period, were determined. A longitudinal closed cohort design, using retrospective data, was used to achieve the objective. In a closed cohort design, subjects or participants enter into the study at one specific time, and stay in the study until the end of the study.

- In the third objective, possible changes in medicine prescribing patterns for BD patients with no other CDL condition, were investigated over a six-year period; a longitudinal open cohort design was used.

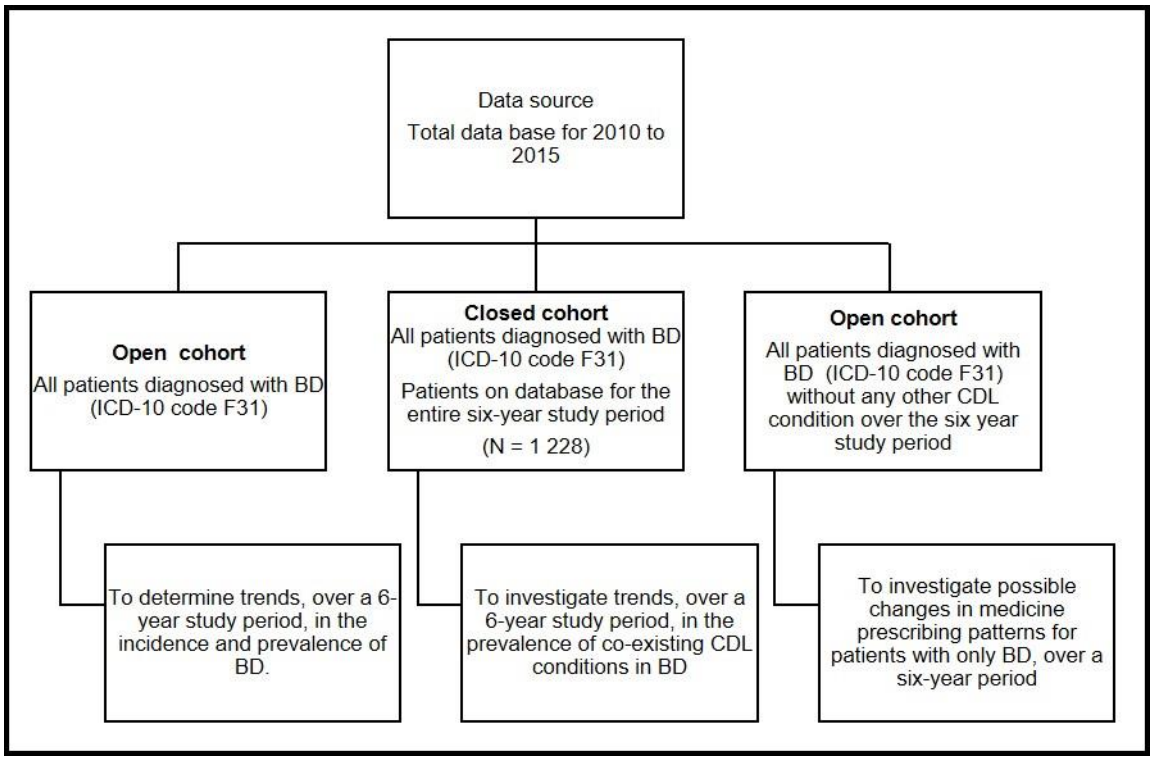

Figure 1.1: Organogram of study designs used

1.4.2.2 Data source

Retrospective data were obtained from the medicine claims database of a PBM company. The database is an electronic pharmaceutical claims processing system used for the management of medicine benefits, thereby acting as an interphase between the medical insurers, pharmacies and physicians. At the time of the study, the PBM was linked to most South African pharmacies and almost all the dispensing doctors in the country.

The medicine claims database of the PBM Company is an example of an administrative claims database. Administrative claims data can be used for drug utilisation research, epidemiological analysis, adherence studies and health policy analyses (Martin, 2010:204).

1.4.2.2.1 Validity and reliability of the data source

Data for the six years came from the same database, and therefore provided ground for results that were generalised to the concerned population. Data were treated with extra caution, cleaned by checking for duplication and incomplete patient information, and finally subjected to a random data check. The PBM has removed all information that could identify service providers and prescribers, medical scheme, health plans and members or beneficiaries before releasing the data for analysis. This was done to uphold confidentiality.

The integrity, validity and reliability of the data were confirmed by various validation procedures performed by the PBM, such as data integrity validation, eligibility management, medicine utilisation and clinical management; fully integrated pre-authorisation services, including exception management, management of medicines for the CDL, prescribed minimum benefits (PMB) and other conditions; medicine management in capitation environments and on-line medicine expenditure reporting; and supplementary services, which included network management, development and implementation of reference price lists, formulary management, and price and product file management.

1.4.2.2.2 Data fields

This study made use of the following data fields in the PBM database:

- Diagnosis information on the ICD-10 code;
- Diagnosis code provided by the PBM;
- Encrypted patient member number;

- Encrypted dependant code;
- Gender;
- Date of birth (to calculate the age of the patient);
- Date of treatment/prescription; and
- Drug information including the:
  - ✓ National Approved Product Pricing Index code of the active ingredient,
  - ✓ Name of active ingredient and trade name of the drug product,
  - ✓ Number of drugs dispensed, and
  - ✓ Number of prescriptions.

1.4.2.3 Target population

The target population for this study included all patients on a medical scheme, diagnosed with BD, with the same beneficiary profile within the South African private health sector for the period 2010 to 2015.

1.4.2.4 Study population

The total patient populations on the medicine claims database of the PBM for the respective years were: 968 131 (2010), 864 962 (2011), 815 792 (2012), 809 838 (2013), 838 618 (2014) and 843 792 (2015).

The study population included all patients on the medicine claims database of the PBM for the study period 2010 to 2015, who comply with the inclusion criteria.

1.4.2.4.1 Inclusion criteria

The inclusion criteria included all patients with the diagnosis code ICD-10 F31 for BD, on a reimbursed medicine claims, for at least once per annum, during the study period 1 January, 2010 to 31 December, 2015.

1.4.2.4.2 Exclusion criteria

Patients (n = 2) with incomplete information, e.g. date of birth or gender, were excluded from the study.

1.4.2.5 Study variables

A variable is a feature of a population for which more than one value is possible for that population (Pagano, 2013:6).

The following study variables were used in the study:

1.4.2.5.1 Age

The Statistical Analysis System, SAS 9.4 (SAS Institute Inc., 2002-2012), was used to determine the age of every patient at time of first dispensing in the index year (2010) and divided into two groups: ≤18.2 years and >18.2 years, based on the results of a national comorbidity survey in the USA (Merikangas *et al.*, 2007:545) showing that BD initially occurred at an average age of 18.2 years.

1.4.2.5.2 Gender

Sex and gender were considered synonyms and also used to denote whether a prescription was prescribed for a female or a male.

1.4.2.5.3 Time/study period

The database was divided annually: 2010, 2011, 2012, 2013, 2014 and 2015, although certain analyses were done continuously across the six-year period.

1.4.2.5.4 Chronic disease list (CDL) conditions

The CDL conditions, as determined by the Medical Scheme Act (131 of 1998) (South Africa, 2003; South Africa, 2009a; South Africa, 2009b), were included in this study (Council for Medical Schemes, 2012:22-39; South Africa, 2003; South Africa, 2009a; South Africa, 2009b) (refer to Table 1.2). The International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD10-codes) was used to identify the CDL conditions (WHO, 2016a) as well as a diagnosis code provided by the PBM. Individual patients' chronic conditions influence the choice of treatment algorithm.

Table 1.2: Chronic disease list (CDL) conditions of South Africa

Chronic disease list condition	ICD-10 code
Addison's disease	E27.1
Asthma	J45, J46
Bronchiectasis	J47,Q33.4
Bipolar disorder	F31
Cardiac failure	I27.9, I50.0, I50.1
Cardiomyopathy	I42.0, I42.1, I42.2
Chronic obstructive pulmonary disease	J43.0, J44.0
Chronic renal failure	N03.0, N04.0, N05.0
Coronary artery disease	I20.0, I25.0
Crohn's disease	K50.0, K50.8
Diabetes insipidus	E23.2
Diabetes mellitus 1	E10.0, E12.0, O24.0
Diabetes mellitus 2	E10.0, E11.9, E12.0
Dysrhythmias	I47.2, I48
Epilepsy	G40.0, G41.0
Glaucoma	H40.0,Q15.0
Haemophilia A and B	D66, D67
Hypertension	I10, I12.0, I13.0, I15.0, O11
Hyperlipidaemia	G45.0, I20.0, I21.0, I22.0, I24.0, I25.0, I63.O, I65.0, I66.0, I70.0
Hypothyroidism	E01.8, E02, E03.0
Ulcerative colitis	K51.0, K51.9
Multiple sclerosis	G35
Parkinson's disease	G20, G21.0
Rheumatoid arthritis	M05.00, M06.00, M08.00
Schizophrenia	F20.0
Systemic lupus erythematosus	M32.0, L93.0, L93.2

1.4.2.5.5 Active ingredient of a drug

In the MIMS, medicine products are listed with respect to active ingredients as well as trade names (Snyman, 2015). Each medicine product could also be identified by using the National Approved Product Pricing Index (NAPPI) code as indicated on the database (Snyman, 2015).

The active ingredient of the medication prescribed to BD patients were classified according to the following pharmacological groups as indicated in the Monthly Index of Medical Specialities (MIMS®)(Snyman, 2015):

- Central nervous system stimulants;
- Sedative hypnotics;
- Anxiolytics (benzodiazepines, other);
- Antidepressants (tricyclic, non-tricyclic, mono-amine oxidase inhibitors [selective and non-selective], selective serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, noradrenaline [and dopamine] re-uptake, tetracyclic, melatonergic specific, lithium, others);
- Antipsychotics;
- Anti-epileptics;
- Antiparkinson agents;
- Antivertigo and anti-emetic agents;
- Antimigraine agents;
- Alzheimer's disease.

1.4.2.5.6 Incidence and prevalence rate

Both BD incidence and prevalence rate were calculated per 1 000 medical scheme beneficiaries for that specific year.

In this study, the prevalence rate of treated BD was calculated per 1 000 medical scheme beneficiaries per year as follows (CDC, 2018a):

Prevalence rate = $= \frac{\text{Allnewandpre-exitingcasesduringagiventimeperiod}}{\text{Populationduringthesametimeperiod}} (X\ 10^{n})$

$n = 3$

The incidence rate was calculated as follows (CDC, 2018b):

Incidence rate: $= \frac{Number\ of\ \ new\ cases\ of\ disease\ in\ a\ specified\ period}{Size\ of\ population\ at\ start\ of\ the\ specified\ period}\ (X\ 10^n)$

$n = 3$

The population in the equations includes the total population or the population of the specific gender or age group on the database who claimed medication during the study period.

Incidence was used to determine the proportion of patients who were newly treated for BD per year in the population covered by medical schemes during the study period (2010-2015) without taking into account when participants were diagnosed (CDC, 2018a). Each participant was followed from the first time that he/she was identified on the PMB central database. Participants who cancelled their membership with a medical scheme administered by the PBM during the study period did not contribute to the year's denominator whereas new members of medical schemes contributed to the denominator.

1.5 Statistical analysis

The Statistical Analysis System®, SAS 9.4® software (SAS Institute Inc., 2002-2012) and Statistical Package for the Social Sciences (IBM SPSS® 22) was used to analyse the data for the empirical investigation.

A *P*-value of 0.05 or less was considered statistically significant at a two-sided α-level. The practical significance of results was computed when the *P*-value was statistically significant.

1.5.1 Descriptive statistics

Variables were expressed using descriptive statistics, which include number (n) and proportions presented as percentages (%), arithmetic means, standard deviations (SD) and 95% confidence intervals (CI).

1.5.2 Inferential statistics

- The chi-square (χ^2) test was used to establish whether an association existed between proportions of two or more groups, e.g. BD patients who claimed CNS medication or not and gender groups. The Cramér's V statistic was used to test the practical significance of association (practical significance was interpreted as follows: effect size of .1 was small; .3 effect size was medium and an effect size of .5 was large) (Steyn, 1999; Swanepoel *et al.*, 2010:262).

- One-way analysis of variance (ANOVA) was used to test for significant differences between: i) average number of prescriptions (a prescription consisted of one or more medicine items claimed on the same day at the same pharmacy) claim per patient for the different years; and ii) average number of medicine items per prescription per patient per year for the different years. If a difference was detected, post-hoc tests were used to determine where the differences lie (Lillian & Charles, 2008: 158-170)..

- A two-sample t-test was used to compare the number of prescriptions per patient per year between the different gender and age groups. Cohen's d-value was considered for practical significance; the magnitude of the d-values was interpreted as follows: .2 a small effect, with no significant difference, > .2 and ≤.8 a medium effect with an observable significance, > .8 a large effect and a significant difference (Steyn, 1999).

- A generalised linear model with log-link (Poisson distribution) (Heiman, 2011:161) was applied to determine trends in the mean number of CDL conditions per BD patient in the closed cohort over a six-year study period. A possible gender influence on trends in the mean number of CDL conditions per BD patient was also assessed. Cohen's d-value was considered for practical significance, with a d-value of > 0.8 as a large effect and of practical significance.

- McNemar's test (Adedokun & Burgess, 2012:25) was used to determine whether there was a statistically significant change in the proportions of BD patients with a specific CDL condition or combination of CDL conditions in 2015 compared to 2010. This test was also used to determine whether there was a statistically significant change in the different types of active ingredients, according to pharmacological group and sub-pharmacologcial groups prescribed to BD patients in 2010 vs. 2015.

1.6 Ethical considerations

This study was approved by the Health Research Ethics Committee of North-West University (Ethics approval number: NWU-00179-14-A1-01) (Refer to Annexure F) and goodwill permission to perform the study was obtained from the board of directors of the PBM Company. The researcher, study leaders and statistician signed a confidentiality agreement.

The study was considered to be of low risk, since retrospective medicine claims data were used.

1.7 Chapter summary

This chapter consists of the background and problem statement of the project, study aims and objectives, the literature review and empirical research methodology followed in the study and empirical considerations. The empirical research methodology includes the research design, data source, validity and reliability of the data source, data fields, target and study populations, inclusion and exclusion criteria and study variables.

The literature review will be presented in Chapter 2.

CHAPTER 2: LITERATURE REVIEW

The following will be discussed in this chapter: definition, classification, diagnosis, burden and treatment of bipolar disorder (BD).

2.1 Definition and classification of bipolar disorder

Bipolar disorder is a serious recurrent and chronic mental illness that manifests as mania, major depression and hypomania, and is characterised by functional and cognitive impairment in memory, attention and executive functions because of fluctuations in mood, energy, activity levels and neuro-psychosocial deficit (Bauer *et al.,* 2001:231; Best *et al*., 2017:406; Cardoso *et al.,* 2016:225; Goodwin, 2016:661; Goodwin *et al.*, 2016:508; Kilbourne, 2005:471; Malhi *et al.,* 2007:114; NIMH, 2016; Samame *et al*., 2017:17).

Bipolar disorder is associated with mood fluctuations (high and low) in sleep, energy, thinking and behaviour, as shown in Table 2.1 (WHO, 2016c).

Table 2.1: Mood fluctuation in BD

High mood fluctuations	Low mood fluctuations
Excessive happiness	Sadness
Hopefulness	Loss of energy
Excitement	Feeling hopeless and worthless
Sudden change from state of happiness to anger	Lack of interest in activities
Restlessness	Unexplained crying
Rapid talk and poor concentration	Trouble making decisions
Unexplained high sexual urge	Lack of sleep
Poor judgement	Suicidal tendency
Drug and alcohol abuse	Fluctuations in appetite that result in loss of weight or weight gain

Bipolar disorder is classified into bipolar I disorder (BD-I), bipolar II disorder (BD-II), cyclothymic disorder and other specified and unspecified bipolar and related disorders (NIMH, 2016).

Bipolar I disorder involves the following: mood fluctuation from manic to depressive episode, i.e. mood is extremely abnormal, with high activity, and the presence or absence of psychotic symptoms (hallucination and delusion) or a history of at least one manic or mixed episode and at least one major depressive episode (WHO, 2016c). In BD-II, the mood changes from hypomanic to depressive episodes, i.e. there is low mood, reduced energy and decreased activity with or without psychotic symptoms (hallucination and delusion) (WHO, 2016c). The main difference

between BD-I and BD-II is the level of impairment relating to loss of reality and impulsivity; BD-I is characterised by significant cognitive impairment or dysfunction, whereas BD-II is characterised by less significant cognitive impairment or dysfunction (Rihmer & Pestality, 1999:667; Simonsen *et al*., 2008:245).

Cyclothymic disorder (cyclothymia) refers to many episodes of hypomanic symptoms and many episodes of depressive symptoms experienced by a patient; however, the patient never has full criteria for a manic or major depressive episode (NIMH, 2016; WHO, 2016c). Rapid cycling is a situation whereby a patient has at least four manic, depression, hypomanic or mixed episodes within a year period (Goodwin *et al.,* 2016:511).

Other specified and unspecified bipolar and related disorders are BD symptoms that do not match BD-I, BD-II or cyclothymic disorder (NIMH, 2016).

2.2 Diagnosis of bipolar disorder

Appropriate diagnosis and intervention are important in ensuring that BD patients are healthy and productive (NIMH, 2016). It is important to ascertain whether the BD is perhaps as a result of other causes, for example low thyroid or mood symptoms due to drug/alcohol abuse, level of severity, period lasted for and the frequency of happening (WebMD, 2016a).

The ICD-10 diagnosis codes of BD range from F31.0 to F31.9, as indicated:

- Patients with F31.11 to F31.13 are similar, but differ in severity of illness;
- Patients with F31.31 to F31.4 are similar, but differ in severity of illness;
- Patients with F31.73 to F31.76 are similar, but differ in having either mania, hypomania or depressed with partial or full remission of conditions; and
- Patients with F31.9 are similar, but differ by either having mania or hypomania, depression or unspecified bipolar and related disorders (American Psychiatric Association, 2013; WHO, 2016c).

Table 2.2 shows the diagnosis of BD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) (American Psychiatric Association, 2013; WHO, 2016a).

Table 2.2: Diagnosis of BD diseases according to ICD-10 codes

ICD-10 code	Description
F31.0 (Bipolar I disorder (BD-I), current or most recent episode hypomania	This diagnosis implies an ongoing situation whereby a patient is highly functioning with elevated mood and energy levels.
F31.11 (BD-I, current or most recent episode manic, mild)	An ongoing situation whereby a patient is having mood or behaviour fluctuations, lengthened loss of sense of reality, highly prone to harming himself as a result of impulsiveness and risky behaviour and destroying crucial relationships. The level of the condition (F31.0) is mild.
F31.12 (BD-I, current or most recent episode, moderate)	In this case, the patient has the same characteristics as in F31.11, but at a moderate level.
F31.13 (BD-I, current or most recent episode, severe)	The same characteristics as for patients with F31.11 will be applicable, but in a severe state.
F31.2 (BD-I, current or most recent episode manic with psychotic features)	This diagnosis indicates an ongoing situation whereby a patient is having mood or behaviour fluctuations, psychotic symptoms (hallucination and delusion), lengthened loss of sense of reality, highly prone to harming himself as a result of impulsiveness, and risky behaviour and destroying crucial relationships.
F31.31 (BD-I, current or most recent episode depressed, mild)	Characteristics similar to the typical major depressive conditions by a patient in addition to fluctuations in sleep, appetite, concentration, energy, loss of interest in things initially admired, hopelessness, worthlessness and suicidal tendency although in mild state.
F31.31 (BD-I, current or most recent episode depressed, moderate)	The same signs and symptoms as for patients with F31.31, but at a moderate level.
F31.4 (BD-I, current or most recent episode depressed, severe)	This diagnosis indicates the same characteristics as for patients with a diagnosis of F31.31, but in a severe state.
F31.5 (BD-I, current or most recent episode depressed with psychotic features)	This diagnosis relates to an ongoing expression of characteristics similar to the typical major depressive conditions in a patient in addition to fluctuations in sleep, appetite, concentration, energy, loss of interest in things initially admired, hopelessness, worthlessness, suicidal tendency and psychotic symptoms (hallucination and delusion).
F31.73 (BD-I, current or most recent episode hypomanic in partial remission)	Indicates a situation whereby a patient is highly functioning with elevated mood and energy levels, damaging important relationships, though partially resolving/recovering towards normal.
F31.73 (BD-I, current or most recent episode manic in partial remission)	Characteristics whereby a patient is having mood or behaviour fluctuations, lengthened loss of sense of reality, highly prone to harming himself as a result of impulsiveness and risky behaviour and destroying crucial relationships, though partially recovering towards normal.

ICD-10 code	Description
F31.74 (BD-I, current or most recent episode hypomanic in full remission)	The same signs and symptoms in F31.73, but the patient has fully recovered from the conditions.
F31.74 (BD-I, current or most recent episode manic in full remission)	A situation whereby a patient is having mood/behaviour fluctuations, lengthened loss of sense of reality, highly prone to harming himself as a result of impulsiveness and risky behaviour and destroying crucial relationships; but the patient has fully recovered from F31.73 conditions.
F31.75 (BD-I, current or most recent episode depressed in partial remission)	An expression of characteristics similar to the typical major depressive conditions by a patient in addition with fluctuations in sleep, appetite, concentration, energy, loss of interest in things initially admired, hopelessness, worthlessness and suicidal tendency, although the patient is partially recovered from F31.73 conditions.
F31.76 (BD-I, current or most recent episode depressed in full remission)	The same signs and symptoms as in F31.75, but the patient has fully recovered from the conditions.
F31.81(BD-II)	The patient's mood changes from hypomanic episodes to depressive episodes. The mood of the patient is also high and irritable, but there are no psychotic symptoms (hallucination and delusion).
F31.89 (Other specified bipolar and related disorder)	A patient exhibiting other specified types of BD, for example cyclothymic disorder, mixed disorder and rapid cycling.
F31.9 (BD-I, current or most recent episode depressed unspecified)	Unspecified ongoing expression of characteristics similar to the typical major depressive conditions by a patient, in addition to fluctuations in sleep, appetite, concentration, energy, loss of interest in things initially admired, hopelessness, worthlessness and suicidal tendency.
F31.9 (BD-I, current or most recent episode hypomania unspecified)	Unspecified situation whereby a patient is highly functioning with elevated mood and energy levels and also damaging important relationships.
F31.9 (BD-I, current or most recent episode manic unspecified)	An unspecified condition whereby a patient is having mood/behaviour fluctuations, lengthened loss of sense of reality, highly prone to harming himself as a result of impulsiveness and risky behaviour and destroying crucial relationships.
F31.9 (BD-I, current or most recent episode unspecified)	Patients having BD-I with ongoing or recently unspecified episode.
F31.9 (Unspecified bipolar and related disorder)	Patients have other or unspecified types of BD.

2.3 The burden of bipolar disorder

The burden of disease is defined as the sum of life lost resulting from undue mortality and years-of-life lost being unhealthy (WHO, 2016c). Burden of disease could also be said to be the sum of impacts or cost of disease and disability on a person and society considering health, environmental, social, political and economic factors (Centers for Disease Control and Prevention, 2013:5). Persons living with BD are very prone to suffer from general medical conditions, low quality-of-life, stigmatisation, high cost of treatment, disability, suicidal intention and causes inconvenience for caregivers and family members (Dell'Osso *et al.,* 2016:57; Esan *et al*., 2016:130; Kilbourne *et al.,* 2004:368; Woods, 2000:38).

2.3.1 Prevalence of bipolar disorder

The lifetime population prevalence between BD-I and BD-II varies (Dell'Osso *et al.,* 2015:257). The lifetime prevalence of BD-I in the United States of America has been shown to range from 0.7% in the 1990s to 1.0% in the 2000s compared to BD-II, whereas lifetime prevalence has reduced between 2.0% and 3.0% in the 1990s to 1.1% in the 2000s (Merikangas *et al.,* 2007:543, Pini *et al.,* 2005:430). More recently, Blanco *et al*. (2017:310) reported a lifetime prevalence of 2.1% for BD-I. A much higher lifetime prevalence of all sub-types of BD has been reported in the USA (Fovet *et al.,* 2015:345).

The 12-month prevalence of BD-I in the USA has been shown to range from 0.4% and 1.5%, while that of BD-II has been 3% (Blanco *et al.,* 2017:310; Merikangas *et al.,* 2011:241).

Europe has a lifetime prevalence of 0.6% for mania, 0.4% for depression and a 12-month prevalence of 0.4% for BD-I and 0.3% for BD-II, respectively (Merikangas *et al*., 2011:241). A systematic review of BD studies in Belgium (Brussels region), Czech Republic, Germany national, former Western Germany, Munich region, Hungary national, Iceland national, Northern Ireland district of Derry region, Republic of Ireland country of Monaghan region, Italy Florence area, the Netherlands national, Spain Reus region, Spain Cantabria region and Switzerland showed a 12-month prevalence of both BD-I and BD-II to be approximately 1% (Pini *et al*., 2005:430,431,432).

In Asia, the lifetime prevalence of mania and depression is 0.6% and 0.4%, respectively, whereas the 12-month prevalence for BD-I and BD-II is 0.4% and 0.3%, respectively (Merikangas *et al*., 2011:241). A study in China showed that the prevalence of BD is lower in China compared to Western countries, with a 12-month and lifetime prevalence for BD-I to be 0.06% and 0.09%, respectively, whereas both the 12-month and lifetime prevalence for BD-II were 0.04% (Zhang *et al.,* 2016:413). The lifetime prevalence of BD among adults in South Korea is 4.3% (95% CI, 2.6-6.9) (Kim *et al.,* 2016:248). In contrast to the World Mental Health (WMH) survey report by

Merikangas *et al*. (2011), a study done in Singapore (Subramaniam *et al*., 2013:194) showed that the lifetime and 12-month prevalence of BD-I were 1.1% and 0.5%, respectively, which is higher than that found by Merikangas and colleagues. In Singapore, the lifetime and 12-month prevalence for BD-II were 0.06% and 0.04%, respectively (Subramaniam *et al*., 2013:194).

The lifetime and 12-month prevalence of BD-I and BD-II in Nigeria was 0.0% (Gureje *et al.*, 2006:468). Lifetime prevalence of BD-I for males and females in the Butajira district in Ethiopia was shown to be 0.6% and 0.3%, respectively (Negash *et al.,* 2005:193). Esan and Esan (2015:28) found the lifetime prevalence of BD in Nigeria and Ethiopia to be 0.1% to 0.6%. Bipolar II disorder is the most prevalent in the northern part of Nigeria (Aiyeloro *et al*., 2011:94).

In 2009, in South Africa, the lifetime prevalence of any mental disorder was 30.3% (Herman *et al*., 2009:339,340). The Western Cape has the highest lifetime prevalence, while the Northern Cape has the lowest lifetime and 12-month prevalence rate of mental disorders (Herman *et al*., 2009:339). South Africa has a relatively high 12-month prevalence of mental disorders (Herman *et al.,* 2009:343). The report from the South African Stress and Health (SASH) study showed that the 12-month prevalence of mental disorders in SA is 16.5%, which is similar to what is obtainable in some international communities (Demyttenaere *et al.,* 2004:2585; Williams *et al.*, 2008:211).

A systematic review conducted in the Western Cape, South Africa, showed that the prevalence of mental disorders for adolescents, including children and adults, was 17.0% and 25%, respectively, and the annual prevalence for adjusted and non-adjusted values for comorbidity of BD was 1.0% and 1.0%, respectively (Kleintjes *et al.,* 2006:157,159). The Council for Medical Schemes (2018:5) reported that BD was one of the top 10 ranked CDL conditions (including HIV/AIDS) treated in the medical scheme environment in South Africa during 2016. The Research and Monitoring Unit of the Council for Medical Schemes (2018:8) indicated that the rate of increase in the prevalence of treated BD had reduced significantly between 2015 and 2016, with an increase of only 0.31%. This is in total contrast to the over 11% increase observed on average between 2011 and 2016 in the medical scheme environment in South Africa (Council for Medical Schemes, 2018:8).

The SASH study showed that the following factors, among others, were responsible for the high prevalence of mental disorders (Williams *et al*., 2008:211,212,215,217):

- Policies centred on racism/racial oppression,
- Political and non-political violence and victimisation,
- Gender inequality,

- Crime,
- Lack of adequate number of psychiatrists, psychiatric nurses and social workers,
- Unequal distribution of mental health services.

2.3.1.1 Factors that influence the prevalence of bipolar disorder

The following factors influence the prevalence of BD:

2.3.1.1.1 Gender

The prevalence of BD-II was higher in women than in men, with BD-I more prevalent in males irrespective of the country where studies were conducted on BD (Aiyeloro *et al.,* 2011:94; Asaad *et al.,* 2014:347; Grant *et al*., 2005:1205; Merikangas *et al.*, 2011:244; Kennedy *et al*., 2005:2572; Kwajaffa *et al.,* 2016:19; Sit, 2004:91; WebMD, 2016b). Men are highly susceptible to develop unipolar mania and even earlier onset due to non-social behaviour in childhood (Kennedy *et al*., 2005:257). Women are more predisposed to mixed episodes and depression due to female hormones and reproductive factors (Grant *et al.,* 2005:1205, 1209; Kennedy *et al.*, 2005:257; WebMD, 2016b).

2.3.1.1.2 Age distribution and age of onset

The World Health Organization (WHO) and World Mental Health (WMH) (WHO WMH) surveys conducted in Belgium, Colombia, France, Germany, Israel, Italy, Japan, Lebanon, Mexico, Netherlands, New Zealand, Nigeria, People's Republic of China, South Africa, Spain, Ukraine and USA showed that the onset age of mood disorders ranges between the late 20s and early 40s (Kessler *et al.,* 2007:171). Pini *et al.* (2005:431) indicated that the mean age of onset of BD in European countries is between 20 and 30 years. The age of onset for BD in USA is either 18 or 19 years and BD-I is more common in older persons than the younger ones (Blanco *et al.,* 2017:310; NIMH, 2016; Post *et al*., 2008:151). Research in the USA has shown that BD can affect patients from all groups (DBSA, 2016). The incidence of BD in England is high in women above 25 years of age (Kennedy *et al*., 2005:257).

The mean age of people living with BD and the mean age of onset for BD in the south-eastern part of Nigeria were 33.17 years and 22.9 years, respectively (Onyeama *et al*., 2010:154,155). The mean age of BD patients in the northern part of Nigeria was 28.3 years (Aiyeloro *et al.*, 2011:94). The highest number of patients diagnosed with BD in the north-eastern part of Nigeria was between 25 and 34 years, followed by 15 to 24 years of age (Kwajaffa *et al.*, 2016:19). A study in the Butajira district of Ethiopia showed that the mean age of onset of mania and BD is 22

and 23.4 years, respectively (Negash *et al*., 2005:193). Most patients with BD in Cairo, Egypt, were between 18 and 55 years of age (Asaad *et al.,* 2014:347).

Herman *et al.* (2009:342) found that mental disorders are common among South Africans between the ages of 35 and 49 years; however, it is much earlier in female patients (18 to 34 years of age). The development of BD among South Africans starts between the ages of 20 and 30 years (South African Bipolar Site, 2016).

2.3.1.1.3 Socio-economic status and family history

Individuals with lower socio-economic status (income, employment etc.) are more prone to suffer from mental disorders or BD (Schoeyen *et al.,* 2011:68; WHO, 2000:422). Grant *et al*. (2005:120) found from the national epidemiologic survey on alcohol and related conditions, 2001 to 2002 database, that Americans with lower economic income usually have higher odds of BD-I compared to Asians and Hispanics. Blanco *et al.* (2017:310) found from the national epidemiologic survey on alcohol and related conditions, during 2012 to 2013, that Americans with lower income have a lower possibility of developing BD-I compared to others with higher income. Bipolar disorder affects an equal number of men and women in all social status levels in the USA (DBSA, 2016).

People with a family history of BD and certain genes tend to be more prone to suffer from BD, even at an earlier age than persons who never had either a family history or the genes; nevertheless, this is not always the case (Goodwin, 2016:661; NIMH, 2016; Post *et al.*, 2016:63). It has also been shown that people with BD have a different brain structure, functioning differently from healthy individuals or persons suffering from other types of mental disorders (NIMH, 2016).

Most BD patients in the north-eastern part of Nigeria were employed (Kwajaffa *et al*., 2016:20). A study in the Butajira district of Ethiopia showed that most of the patients diagnosed with BD-I were illiterate and from rural areas (Negash *et al*., 2005:193). Employment, educational and social status may not necessarily make an individual susceptible to BD.

South Africans with high incomes are more susceptible to mental disorders than those with low to average incomes (Herman *et al.*, 2009:342). However, according to South African Depression and Anxiety Group (SADAG), the following socio-economic factors predispose South Africans to BD: poverty, social deprivation, social conflict, unemployment, inadequate housing and exposure to crime and violence (SADAG, 2016a). Perhaps, future studies may ascertain these reasons.

2.3.1.1.4 Marital status

Research has shown that married persons in South Africa (Herman *et al.,* 2009:342), similar to studies conducted in other countries, are less susceptible to mood disorder or BD-I than unmarried individuals (Blanco *et al.,* 2017:310; Grant *et al.,* 2005:1205; Kwajaffa *et al.,* 2016:19; WHO, 2000:422).

2.3.1.1.5 Race

Research has shown that the incidence of BD is higher among blacks than Caucasians in the UK (Lloyd *et al*., 2005:126). Bipolar disorder affects an equal number of men and women across different races (Depression and Bipolar Support Alliance, 2016). Bipolar I disorder is higher among white Americans than black Americans, Hispanics and Asians/Pacific Islanders (Blanco *et al.*, 2017:310). This shows that race may be a predisposing factor for BD.

2.3.1.1.6 Educational status

Study done in Norway showed similarity in the level of education of BD patients and the general population (Schoeyen *et al*., 2011:68). Americans with higher educational status were more prone to BD-I than those with lower educational status (Blanco *et al.,* 2017:310). Most of the patients diagnosed with BD in the northern part of Nigeria had secondary and post-secondary education (Aiyeloro *et al*., 2011:94). A research project done in the north-eastern part of Nigeria showed that most BD patients had no secondary or post-secondary education (Kwajaffa *et al.,* 2016:24). Most of the patients diagnosed with mood disorder in SA had elementary and secondary education (Herman *et al*., 2009:342).

2.4 Comorbidities in bipolar disorder patients

Comorbidity is defined as the coexistence of one or more additional diseases or specific disease together with the disease of interest in an individual in a particular period of time (Krishnan, 2005:1; Sin *et al*., 2006:1245; Surendran & Chakrabarti, 2016:1). It is also referred to as an already established syndrome at the point of diagnosis of the disease of interest (Ording & Sorensen, 2013:200). It is unknown whether a syndrome is really comorbid or a treatment outcome or both among BD patients (Krishnan, 2005:1).

A study by Yasseen *et al*. (2010:30) showed that most BD patients do not have comorbidities with only a few having one to two comorbidities. Beyer *et al.* (2005:401,402), however, identified that the number of comorbidities increases with age in BD patients. This implies that the older a BD patient becomes, the higher the likelihood of comorbidities.

According to Hawke *et al.* (2013:3) anxiety disorder (GAD), panic disorder, obsessive compulsive disorder (OCD) and post-traumatic stress disorder are common comorbidities with BD. The presence of comorbidities in BD patients could result in poor treatment prognosis (Goodwin *et al*., 2016:511). Studies in New Mexico, the USA, Australia and Brazil have shown that better understanding of comorbidities could only be achieved by thorough investigation into the differences and similarities or relationships between diseases, as this will provide ground for achieving desirable treatment outcomes (Bogenschutz & Nurnberg, 2000:23; Meghani *et al.,* 2013:1). Effective and efficient treatment of comorbidities could be achieved better with individual patient-centred treatment than a disease-oriented approach or strategy (Weel & Schellevis, 2006:550).

The following lifetime and current comorbidities were identified in patients diagnosed with BD: substance use disorders (for example stimulants, sedatives, cocaine, opiates, marijuana and hallucinogens), anxiety disorders (panic disorder with agoraphobia, panic disorder without agoraphobia, social phobia, specific phobia, OCD, GAD and post-traumatic stress disorder (PTSD), personality disorders (dependent, avoidant, paranoid, schizoid, histrionic, antisocial, and conduct disorder), attention deficit hyperactivity disorders (ADHD), shoplifting, overspending, gambling, conduct disorders, eating disorders (bulimia nervosa and anorexia nervosa), alcohol abuse and dependence (Blanco *et al.,* 2008:911; Bolyan *et al*., 2004:1106; Fovet *et al*., 2015:351; Goodwin *et al*., 2016:512; Grant *et al*., 2005:1205,1207,1210; Jones *et al.,* 2015:328; Klassen *et al.,* 2010:1; McElroy *et al.,* 2001:420,423; Nabavi *et al*., 2015:1405; Subramaniam *et al.,* 2013:191; Surendran & Chakrabarti, 2016:1). These disorders are discussed in subsequent paragraphs.

2.4.1 Anxiety disorders

Various studies revealed a relationship between BD and anxiety disorders (Goodwin, 2016:661; Krishman, 2005:1; Nabavi *et al.,* 2015:1405; O'Garro-Moore *et al.,* 2015:180; Stratford *et al.,* 2015:19). Generalised anxiety disorder, OCD, PD, social phobia and PTSD are examples of anxiety disorders (Bolyan *et al*., 2004:1106; Nabavi *et al.,* 2015:1405, 1416). Generalised anxiety disorder (GAD) (18.1%), OCD (25.9%) and PD are the most common anxiety disorders (Bolyan *et al.,* 2004:1106; Subramaniam *et al*., 2013:191). Generalised anxiety disorder and phobia disorder are the types of anxiety disorders with the most pronounced negative impacts on BD patients' outcomes (Bolyan *et al.,* 2004:1106).

A study done in Sao Paulo, Brazil, showed that anxiety disorders (OCD, PD, social phobia (SP) and PTSD) are the most common comorbidities with BD (Issler *et al*., 2004:32,33). Anxiety disorders prolong the duration and severity of BD and prolong the time to reach euthymia (Bolyan

et al., 2004:1106; O'Garro-Moore *et al.,* 2015:180). Bipolar disorder patients with GAD are prone to suffer from increased impairment, disability, poor quality of life and productivity, and have a tendency to commit suicide (Simon, 2009:13).

2.4.2 Substance use disorders

A systematic review and meta-analysis conducted between 1990 and 2015 in Austria showed that substance use disorders (alcohol and illicit drug use disorder) are common among BD patients (Hunt *et al.,* 2016:321,324). Adolescent BD patients who are highly predisposed to substance use often suffer from comorbid psychiatric disorders, trauma, sexual and physical abuse, all of which worsen BD illness as was shown in South Carolina, USA (Deas, 2006:18). Alcohol, cocaine, marijuana/cannabis, opiates and inhalants are examples of substance use. However, alcohol is the most common abused substance, while marijuana is the most abused drug (Deas, 2006:19, 21; Hunt *et al.,* 2016:324; McElroy *et al.,* 2001:423). Depression, anxiety disorder, conduct disorder and ADHD are common psychiatric comorbidities associated with substance use disorders (Blanco *et al.,* 2008:911; Deas, 2006:21). Suicidal tendency is common in depressed patients using substances, especially alcohol (Carra *et al.,* 2014:125; Deas, 2006:21).

There is a marked relationship between BD-I and substance use and personality disorders, but the relationship does not extend to alcohol abuse (Grant *et al.,* 2005:1205). The relationship between patients with BD and alcohol use disorder is likely to be traced to some underlying genetic factors (serotonergic and dopaminergic pathways) (Yasseen *et al*., 2010:30).

In SA, the two major comorbidities associated with BD are substance-use and anxiety disorders (Colin, 2013:164,165). Substance-use disorders are often associated with men and persons with higher levels of education (Herman *et al.,* 2009:342).

2.4.3 Eating disorders

A study done in Pennsylvania, USA, showed that BD patients usually suffer from eating disorders, which could be the basis for obesity seen among these patients (Wildes *et al.,* 2008:51). Binge eating behaviour is very common among BD patients (Martins *et al.,* 2016:88; McElroy *et al.,* 2016:216; Woldeyohannes *et al.,* 2015:531). However, McElroy *et al.* (2001:420,424) indicated that eating disorders are the least common among the comorbidities associated with BD. It has been shown, however, that binge eating behaviour in particular is rather common among BD patients (Martins *et al.,* 2016:88; McElroy *et al.,* 2016:216; Wildes *et al*., 2008:51; Woldeyohannes *et al.,* 2015:531). Lifetime binge eating causes obesity/severe obesity, similar to lifetime bulimia

nervosa (McElroy *et al.,* 2011:191), the latter which often co-exist with anxiety disorder among BD patients (McElroy *et al.,* 2011:191).

2.4.4 Other types of comorbidities

Medical comorbidities that are common in BD patients includes: cardiovascular diseases (i.e., hypertension and congestive heart failure), endocrine-related diseases (i.e., diabetes, hyperlipidaemia), liver diseases such as hepatitis C, chronic obstructive pulmonary disease (COPD), blood-related diseases, musculoskeletal diseases, tuberculosis, HIV/AIDS, malaria, headache, hypothyroidism, allergic rhino-conjunctivitis, obesity, chronic constipation, irritable bowel syndrome, metabolic syndrome, hiatus hernia, dysmenorrhea, urticaria, atopic dermatitis, psoriasis, seborrheic dermatitis, bronchial asthma, biliary lithiasis and injuries (Beyer *et al.,* 2005:401; Kilbourne, 2005:473; Perugi *et al.,* 2015:95; Prince *et al*., 2007:862,863,864,866; Rej *et al*., 2015:528). Of these, the most common in BD patients are: hypertension (25%), hyperlipidaemia (23%), type 2 diabetes mellitus (17%), obesity (12%), infectious diseases, e.g. HIV (6%), hepatitis C (1.9%), diseases of the circulatory system (13.0%), diseases of nervous system and sensory organs (10.7%) (Beyer *et al*., 2005:401; Kilbourne, 2005:471).

Kwajaffa *et al*. (2016:20) showed that in the north-eastern part of Nigeria, substance use (15%), personality (10%), anxiety (7%) and others (attention deficit hyperactivity, sleep, conduct and persistent delusion) disorders were the most common psychiatric comorbid disorders. Chronic infections (HIV/AIDS and tuberculosis) (6%), hypertension (5.9%), migraine (4%), cerebrovascular disease (3%), diabetes mellitus (2%), epilepsy (2%) and others (recurrent malaria, chronic kidney disease, chronic liver disease, chronic osteoarthritis, sickle cell disease, congenital deafness, otitis media and lymphoma) (3%) were the medical comorbidities with BD patients (Kwajaffa *et al.,* 2016:21,22). Schizophrenia, psychosomatic disorder, anxiety disorder, malaria and hypertension are the major comorbidities with BD patients in the northern part of Nigeria (Aiyeloro *et al.,* 2011:94).

2.4.5 Complications of bipolar disorder

The major complications with BD are suicide, homicide, addictions, reduced quality of life, low or non-compliance with treatment, and cognitive or functional impairment (Abood *et al*., 2002:243; Bakare *et al.*, 2011:388; Bauer *et al*., 2017:207; Fovet *et al.,* 2015:348; Fuentes *et al.,* 2016:215; Pini *et al*., 2005:430; Soreff, 2016; Torrent *et al.,* 2006:254).

The following are complications of BD and other conditions that are threatened by BD:

- Bipolar disorder in pregnancy and childbirth

Pregnant BD patients are highly susceptible to gestational hypertension, antepartum haemorrhage, high risk of mood disorders after delivery, and high rate of induction of labour as shown by a systematic review in Sweden (Rusner *et al.,* 2016:331).

- Low quality of life

Poor psychosocial functioning is common in bipolar depression (Torrent *et al.*, 2006:254). Studies have shown that BD patients do suffer from longer duration of illness, higher levels of disability, as well as lower functioning and higher frequency of hospitalisation compared to patients with other mental disorders (Abood *et al*., 2002:243; Pini *et al*., 2005:430).

- Disability adjusted life years

Bipolar disorder is a public health problem and the seventh most common cause of disability-adjusted life years (early death) (Fovet *et al.,* 2015:348). The disability-adjusted life year for BD was 1.1% in the USA (McKenna *et al*., 2005:418). Patients diagnosed with BD in European countries are highly prone to suffer from other mental disorders concurrently, i.e. physical illness, high levels of impairments and disabilities (Pini *et al*., 2005:425). Data on disabilities associated with BD in these countries, however, are limited because BD-I and BD-II are rare mental disorders (Pini *et al.,* 2005:430).

- Low or non-compliance with treatment

Fluctuations between manic and depressive episodes result in non-compliance with care plans, lack of willingness to seek treatment and also an increased likelihood of contracting infections perhaps due to free-care attitude or behaviour (Fuentes *et al.,* 2016:215; Kilbourne, 2005:474).

- Cognitive/functional impairment

Patients with BD often suffer from cognitive or functional impairment (Bakare *et al.*, 2011:388; Bauer *et al.,* 2017:207; Cullen *et al.,* 2016:165; Fuentes *et al.,* 2016:215). Persistent cognitive impairment is a common complication of BD, though, occurring more often in episodes of mania (Torrent *et al.*, 2006:254).

- Suicidal tendency

A systematic review of studies on suicide in BD patients showed that the risk of committing suicide among BD patients is 20 to 30 times greater than in the general population (Pompili *et al.,* 2013:457). Suicide attempts are also higher in persons with BD compared to those with other psychiatric disorders or illnesses (Carra *et al.,* 2014:125; Goldstein *et al.*, 2005:525; Oquendo *et al*., 2000:107). Studies on BD and suicidal tendency have shown the following factors as the cause of an increase in the level of craving for committing suicide among BD patients: gender (no difference between male and female), age of disease onset (younger age), duration of illness (especially in the first year), severity of illness, religious affiliation, personality characteristics, family history of suicide, exposure to trauma in early life, psychosocial precipitants and presence of comorbidities (substance use and panic disorders) (Goldstein *et al*., 2005:529,531,532; Schaffer *et al.,* 2015:1). Suicidal tendency in BD-II patients, in particular, are often coupled with having depression or mixed depression (Balazs *et al.,* 2006:133; Goodwin *et al.,* 2016:534; Tondo & Baldessarini, 2016:88).

Suicide and reluctance to seek healthcare are the major complications associated with BD-I patients in Ethiopia (Negash *et al*., 2005:193). The South Africa Stress and Health Study showed that BD is one of the specific health challenges in SA (Williams *et al*., 2008:211). Bipolar disorder has a negative impact on South Africans' social lives, school, work and family (SADAG, 2016a).

2.5 Cost of treatment of bipolar disorder

A study showed the cost of treatment of BD in California, USA to be $45 billion (Li *et al*. 2002:131). A systematic review of studies on the cost of treating BD in the USA in 1990 was estimated to be between $30.4 and $43.7 billion (Kleinman *et al.*, 2003:601).

Studies on the cost of treating BD are very insignificant in Europe, because it is underestimated, however, in France, it was estimated that the cost for treating mania in 1999 was 3 billion euro (De Zelicourt *et al.*, 2003:1081). The number of studies on the cost of treating BD in major European countries is very limited, nevertheless, the estimated cost (direct and indirect) of treating BD in the United Kingdom (UK) was £2 billion between 1999 and 2000 and £4.59 billion in 2009 (DaGupta & Guest, 2002:227; Fajutrao *et al.*, 2009:1,4). The annual estimated costs of treating 100 000 hospitalised adult BD patients in France and Spain were €226 500 and €232 000, respectively (Gonzalez-Pinto *et al.,* 2010:152). This will of course have a negative impact on the welfare of the public.

A study in Cape Town showed that it costs South Africans in both the public and private sectors $3.6 billion (R51 732 000 000) out of their income to treat BD (PRIME, 2012). According to South African Depression and Anxiety Group, the costs of treatment (drugs and other services) for depression in the private health sector, between 2008 and 2012, have risen from R96.7 million to R494 million (SADAG, 2016b). Treatment of BD may be more costly than that of other mental illnesses.

2.6 Treatment of bipolar disorder

Bipolar I disorder is characterised by periods of severe mood episode fluctuations, ranging from mania to depression, whereas BD-II is a milder type of mood elevation characterised by alternation between hypomania episodes and severe depression (WebMD, 2016a). Bipolar I disorder is associated with abnormal, consistently elevated irritable mood with persistent high activity/energy throughout the day for at least a period of one week, whereas BD-II is associated with at least one episode of major depression with a hypomanic episode lasting for at least two to four days (American Psychiatric Association, 2013; Yatham *et al.,* 2009:242).

Treatment of BD is complex as it involves pharmacological (drug use) and non-pharmacological (psychosocial or psychotherapy) treatments, choice of healthy diets, physical exercise, and chronorhythms therapy which should be dynamic and of fluctuating nature (Chen *et al.,* 2010:512-521; Jann, 2014:498; McIntyre, 2015; Miklowitz *et al.,* 2008:77). Treatment outcomes have also not been encouraging, even with available efficacious treatment options, due to side effects, other unmet needs and susceptibility to other medical comorbidities that could negatively impact the productive life activities of BD patients (Fountoulakis *et al.,* 2012:S1,S2; Kilbourne, 2005:471). Researches have shown that the side effects of drugs used in the treatment of BD have a negative impact on vital organs and systems of the body (Atasoy *et al.,* 2007:1225; Kilbourne, 2005:473). A consensus statement by the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists and North American Association for the Study of Obesity showed that atypical antipsychotics cause weight gain, and cardiovascular risk factors amongst other side effects (American Diabetes Association *et al.,* 2004:596; Goodwin *et al.,* 2016:534; Howes, 2007:361; Pacchiarotti *et al.,* 2015:1045).

Extrapyramidal side effects (dystonia, akathisia, tardive dyskinesia and tremor at rest) are common with the typical antipsychotics and these have resulted in stigmatisation, patients' distress, reduced functioning/productivity and non-adherence to treatment plan) among BD patients (American Diabetes Association *et al.,* 2004:596). Refer to Table 2.2 for other common side effects of drugs used in the treatment of BD.

Other factors that may also affect treatment outcomes include the delay in treatment seeking behaviour among patients, and non-compliance. For example, Seedat *et al.* (2002:483,484) highlighted the following as the causes of delay in seeking treatment among BD patients in SA: early age of symptoms onset (median of 26 years), patients did not know where to go, wanted to handle the situation on their own, inaccurate diagnosis and thoughts of embarrassment. Non-compliance to treatment plans is common among BD patients (Bates *et al.,* 2010:e1; Barraco *et al*., 2012:110; Fuentes *et al.,* 2016:215). A study in Turkey also showed high rates of dropout from treatment plans by BD patients (Oflaz *et al.,* 2015:68).

The success of treatment of BD patients is furthermore dependent on the following: i) an increased awareness of mental diseases; ii) effective communication between prescribers and BD patients; iii) prescribing of appropriate doses of indicated drugs; and iv) ongoing monitoring for positive and negative effects of drugs (Goodwin, 2009:348; Seedat *et al*., 2002:483; Wang *et al.,* 2000:926). In addition, the early identification and treatment of BD are necessary towards preventing its severity (Kessler *et al*., 2007:168).

According to Colin (2013:165,166,167), the South African Society of Psychiatrists' guidelines for the treatment of BD advocate both pharmacological and non-pharmacological treatment guidelines of other countries.

2.6.1 Pharmacological treatment of bipolar disorder

The pharmacological agents (psychotropic drugs) used in bipolar disorder are categorised based on medication groups (i.e., mood stabilisers including anticonvulsants, antidepressant, antipsychotics, benzodiazepines and stimulants) or therapeutic actions (e.g. antimanic agents, antidepressant agents and maintenance agents) (Colin, 2013:165; Goodwin, 2009:351,353,354; Grunze *et al.,* 2009:91,94,101; Moreno *et al.*, 2007:1033). Treatment of BD could further be divided into acute treatment of mania, maintenance treatment, acute treatment of depression, partial or no treatment, bipolar II disorder, treatment of complex bipolar manifestations (mixed states) and treatment of the two major comorbidities (anxiety disorders and substance-use disorders) of BD (Colin, 2013:165; McIntyre, 2015).

A study done at Tara Hospital in SA showed that multiple prescriptions (antipsychotics, anticonvulsants, antidepressants, mood stabilisers and benzodiazepines) are necessary for the optimal treatment of BD patients (Holzapfel, 2016). Some of these pharmacological agents are effective in all phases of BD treatments.

2.6.1.1 Mood stabilisers

Mood stabilisers are drugs mainly used in the treatment of BD as well as for mood swings that are common in other psychiatric illnesses (NIH, 2016). Conventional examples of mood stabilisers are lithium and anticonvulsants (e.g. carbamazepine, valproic acid and lamotrigine) (NIH, 2016).

2.6.1.1.1 Lithium

Lithium is a safe and effective mood stabiliser used in the treatment of BD (Martindale, 2002:296; Pratt, 2007:432). An in-depth understanding of the strategic management of plasma levels of lithium is necessary in order to broaden the scope of usage and improve the desirable treatment outcomes of lithium in BD patients (Malhi *et al*., 2012:192). Lithium is used in the treatment of manic and depressive episodes as well as in the maintenance phase of BD (Goodwin, 2009:351,354; Malhi *et al*., 2012:196). It is also used for preventing relapse and suicide in BD patients (Goodwin *et al.,* 2016:528; Tondo & Baldessarini, 2016:88). Lithium has better efficacy than valproate in clinical practice (Kessing *et al*., 2011:57).

- Mechanism of action

The underlying mechanism of action of lithium when used for the treatment of BD is yet to be understood (Malhi *et al.,* 2012:196), however, it was suggested that the mechanism of action related to the antidepressant activity be due to increased concentration of excitatory neurotransmitter (glutamate) in the post-synaptic neuron through N-methyl-d-aspartate receptor stimulation caused by the acute use of lithium and the prevention of its reuptake through glutamate transporters (Malhi *et al.,* 2012:196).

The mechanism of antimanic activity of lithium may be ascribed to the regulation of both the synthesis and release of dopamine in the presynaptic terminal, blocking of the post-synaptic transmission of dopamine by attenuating the G-proteins' functions and prevention of adenyl-cyclase and cyclic adenosine monophosphate pathways in the brain (Malhi *et al.,* 2012:196). The antimanic action of lithium in the treatment of BD has also been traced to the reduction of excitatory neurotransmitters (glutamate and dopamine) and an increase in the neurotransmission and concentration of gamma-aminobutyric acid (GABA) (inhibitory neurotransmitter) in the brain, resulting in reduced neural over-excitation (Malhi *et al.,* 2012:196; Malhi *et al.,* 2013). The monotherapeutic use of lithium as a maintenance therapy prevents symptom recurrence, maintain treatment and reducing untoward effects in BD patients (Malhi *et al*., 2012:197). It is, therefore, a reliable prophylactic treatment option to prevent mania and depression (Malhi *et al.,* 2012:202).

- Dosage

The dose of lithium is a function of the chosen preparation as different lithium salts have varied bioavailability (Martindale, 2002:296). Lithium is used for treating BD at an initial dose of 450 mg to 675 mg twice daily, with 225 mg twice daily in elderly and at initial dose of 450 mg twice daily for prophylaxis (Martindale, 2002:296). Lithium is given for five to seven days with an initial dose of 2 mg/kg/day in the manic or depressive phase of BD (750-1500 mg/kg); however, the dose could be adjusted to ascertain the desired plasma concentration (Goodwin *et al.,* 2016:523; Rossiter, 2014:483,484).

- Contraindications

The use of lithium is contraindicated in BD patients with the following: renal insufficiency, cardiovascular impairment, thyroid dysfunction, tremor, pregnancy, central nervous system diseases and oedema (DeBattista, 2012a:505,506; Martindale, 2002:292,293,294; Pratt, 2007:432; Rossiter, 2014:483). Except in patients with thyroid insufficiency, lithium could be used in renal and cardiovascular impairment, but with caution and under specialist supervision (Pratt, 2007:432).

- Side effects

The common adverse effects associated with the use of lithium are as follows: neurologic and psychiatric side effects, e.g. tremor, reduction of thyroid function, polydipsia, polyuria, glomerulopathy and nephrotic syndrome, oedema of the eyes, face, lips, tongue, throat, feet, hands, ankles and lower legs, nausea and vomiting, slurred speech, loss of coordination, change of vision, hallucination, bradycardia-tachycardia syndrome, sexual dysfunction, teratogenesis and leucocytosis (DeBattista, 2012a:505,506; Goodwin *et al*., 2016:506; Martindale, 2002:292; NIH, 2016).

- Drug-drug interactions

Lithium interacts with thiazides and loop diuretics, selective serotonin reuptake inhibitors (SSRIs), nonsteroidal anti-inflammatory drugs (NSAIDs), thyroid drugs, neuroleptic drugs, angiotensin converting enzyme (ACE) inhibitors, xanthines, muscle relaxants, methyldopa and angiotensin receptor blockers (ARBs) (DeBattista, 2012a:508; Martindale, 2002:294,295; Pratt, 2007:434; Rossiter, 2014:483).

2.6.1.1.2 Anticonvulsant agents

Examples of anticonvulsants that are used as mood stabilisers in the treatment of BD are valproate or valproic acid, carbamazepine and lamotrigine (DeBattista, 2012a:507; Johannessen, 2000:108; Martindale, 2002:346,352,368).

- Indications

Anticonvulsant agents are indicated for the treatment of BD (DeBattista, 2012a:507; Johannessen, 2000:108; Martindale, 2002:346,352,368).

- Mechanism of action

The mechanism of action of valproic acid, carbamazepine and lamotrigine in the treatment of BD are unknown (DeBattista, 2012a:507,508). Studies have shown that Divalproex® (valproic acid and valproate) exerts its pharmacological actions in the brain of BD patients through one or a combination of the following: blockade of voltage activated sodium channels, influencing excitatory neurotransmitter and different actions on inhibitory neurotransmitter (gamma-amino butyric acid) (Johannessen, 2000:103,108; Pratt, 2007:432).

- Dosage

Valproate is given 600 to 900 mg/day up to 1 500 mg/day. Lamotrigine is given 25 mg/day until the patient stabilised. The dosage can be increased to a maximum dose of 100 to 400 mg/day or 50 to 200 mg daily (Martindale, 2002:346,352; Rossiter, 2014:460,462). Carbamazepine is given as a dosage of 400 to 600 mg/day in divided doses to a maximum of 1.6 mg daily (Martindale, 2002:369; Rossiter, 2014:464).

- Contraindications

Use of carbamazepine or valproic acid is contraindicated in patients already having cutaneous reactions, hepatic/pancreatic insufficiency, polycystic ovarian syndrome, heart disease, haematological reaction, hypersensitivity reaction, alopecia and bruising/coagulation abnormalities (Martindale, 2002:342,343,367; NIH, 2016; Pratt, 2007:432; Tennis & Stern, 1997:542). Lamotrigine should not be used during pregnancy, or in patients suffering from liver and kidney insufficiency (Martindale, 2002:351,352; Rossiter, 2014:463).

- Side effects

Common side effects with the use of the three anticonvulsants are as follows: tremors, hepatic dysfunction, increased weight, nausea, gastrointestinal disturbances, thrombocytopenia (valproate), rash, dizziness, headache, diplopia, teratogenesis (lamotrigine), blood dyscrasia, photosensitivity reaction, drowsiness, dizziness, generalised erythematous rashes, and Stevens-Johnson syndrome (carbamazepine) (DeBattista, 2012a:506,507,508; Goodwin *et al.,* 2016:506; Martindale, 2002:342,351,366; Porter & Meldrum, 2012:419).

- Drug-drug interactions

Anticonvulsants indicated in the treatment of BD illness are prone to particularly pharmacokinetic interactions either by induction or inhibition of metabolizing enzymes that will result in a decrease or increase in the serum concentration of these anticonvulsants and also other drugs (Johannessen & Landmark, 2010:254). The following are the drug interactions profile of the three (lamotrigine, valproic acid and carbamazepine) anticonvulsants: valproate interacts with phenobarbital, carbamazepine, warfarin, aspirin, phenytoin, lamotrigine, rifampicin, felbamate, ethosuximide, and primidone (Martindale, 2002:344). Carbamazepine interacts with phenytoin, valproate, verapamil, fluoxetine, macrolides antibiotics, anticoagulants, danazol, phenobarbital, propoxyphene, fluoxetine and primidone; and lamotrigine interacts with valproate, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, sertraline, succinimides and topiramate (Johannessen & Landmark, 2010:254; Martindale, 2002:344,352,368; Porter & Meldrum, 2012:418,419).

2.6.1.2 Antidepressants

Selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), tetracyclic antidepressants, noradrenergic and specific serotonin antagonists, serotonin non selective antagonist and re-uptake inhibitors, serotonin and noradrenalin re-uptake inhibitors, noradrenalin and dopamine re-uptake inhibitors and selective noradrenalin re-uptake inhibitors may be used for treating BD (Martindale, 2002:271; Pratt, 2007:430-431; Rossiter, 2014:495).

- Indications

All the antidepressant groups can be used in the treatment of bipolar disorder (Martindale, 2002:271; Rossiter, 2014:495).

Selective serotonin re-uptake inhibitors (SSRIs), (e.g. sertraline, paroxetine) and noradrenalin and dopamine re-uptake inhibitors (e.g. bupropion) are the most common antidepressants used in the treatment of depressive episodes in BD patients, because they are more safe (reduced rates of manic switch) (Anand *et al.*, 2005:1334; Pacchiarotti *et al.*, 2013:1249).

- Mechanism of action

There is no clear or understandable mechanism of action; however, studies have shown that the mechanism of antidepressant action of SSRIs is by blockade of serotonin transporter (SERT) or enhancement of corticolimbic low frequency blood oxygen level-dependent fluctuation (LFBF) correlations/connectivity (Anand *et al*., 2005:1334,1341; DeBattista, 2012b:528).

- Dosage

Fluoxetine is given 20 mg/day to a maximum dose of 60 mg/day, paroxetine is given 20 mg/day to a maximum dose of 50 mg/day and sertraline is given 50 to 100 mg/day at bed time to a maximum dose of 200 mg to 300 mg/day depending on severity of the case (Martindale, 2002:278,288,302; Rossiter, 2014:500,501).

- Contraindications

The use of SSRIs is contraindicated in heart disease, bleeding disorder, diabetes, nursing mothers, kidney disease and pregnancy (Martindale, 2002:286; Rossiter, 2014:499; Sanz *et al.,* 2005:482). Treatment of pregnant BD patients with SSRIs, particularly paroxetine, could cause neonatal convulsion and neonatal withdrawal syndrome because of activity on cholinergic receptors (Sanz *et al.,* 2005:482,484,485).

- Side effects

The common adverse effects with the use of SSRIs are erectile dysfunction, fatigue, dry mouth, rash, drowsiness, headache, and agitation, while the rare side effects are serotonin syndrome, hallucination, sexual dysfunction, extrapyramidal effects, hyponatremia in elderly, teratogenesis and suicidal tendency (DeBattista, 2012b:528; Goodwin *et al.,* 2016:506; Martindale, 2002:284; NHS choices, 2015).

- Drug-drug interactions

Common drug-drug interactions with SSRIs are pharmacokinetic in nature (concurrent use with any tricyclic antidepressants (TCAs) or fluvoxamine results in TCA toxicity or bradycardia/hypotension) (Debattista, 2012b:526). Pharmacodynamic interactions result in serotonin syndrome when SSRIs are used concurrently with monoamine oxidase inhibitors (Debattista, 2012b:526). Other interacting drugs are anticoagulants, anti-malaria drugs, NSAIDs, antiretrovirals (protease inhibitors), beta-blockers, opioid analgesics and lithium (Martindale, 2002:287; Pratt, 2007:433).

2.6.1.3 Antipsychotics

Antipsychotic agents used in treating BD are categorised into typical (chlorpromazine, fluphenazine, haloperidol, and perphenazine) and atypical antipsychotics (quetiapine, clozapine, olanzapine, risperidone, ziprasidone, lusaridone [not available in South Africa] and aripiprazole) (DeBattista, 2012a:507; Martindale, 2002:649; NIH, 2016).

- Indications

Antipsychotics are indicated in the manic, depressive and maintenance phases of BD, ADHD, eating disorders, PTSD, OCD and GAD (DeBattista, 2012a:507; Martindale, 2002:649,650,685; NIH, 2016).

- Mechanism of action

The mechanism of action is by blocking dopamine (D_1, D_2, D_3, D_4, and D5) postsynaptic receptors, 5-HT_2a, and histaminergic (H_1) receptors blockade (DeBattista, 2012a:507; Martindale, 2002:673,704; Pratt, 2007:432; Yatham *et al.,* 2005:40).

- Dosage

Table 2.3 shows the dosages of the antipsychotics (Martindale, 2002:673, 685, 687, 696, 703, 704; Rossiter, 2014:480, 481, 485, 486, 487, 488):

Table 2.3: Dosages of the antipsychotics

Drug	Dosage
Fluphenazine	Initial dose is 12.5 mg, although could be increased to maximum of 50 mg or 100 mg based on a patient's response.
Haloperidol	0.5-5 mg every 8 hours daily up to a maximum dose of 20 mg or 100 mg/day
Chlorpromazine	25 mg every 8 hours daily to a maximum dose of 800 mg/day
Aripiprazole	15-30 mg/day
Clozapine	12.5-25 mg/day to a maximum of 900 mg daily
Olanzapine	5-15 mg/day to a maximum dose of 20 mg/day
Quetiapine	Start with 100 mg/day to a maximum dose of 800 mg/day or 25 mg on day 1, 50 mg on day 2, 100 mg on day 3, 150 mg on day 4. Dosage adjustment can be made to 300 mg to 450 mg daily in divided doses to 750 mg daily.
Risperidone	2-3 mg/day to a maximum of 6 mg/day
Ziprasidone	40 mg every 12 hours to a maximum of 160 mg/day in two divided doses

- Contraindications

The use of antipsychotics is contraindicated in agitated patients, central nervous system depression and patients with endocrine dysfunction and cardiovascular dysfunction, liver disease, skin disease and epileptic patients (DeBattista, 2012a:497; Martindale, 200:704,686,684; Rossiter, 2014:480,481).

- Side effects

The adverse effects associated with the atypical antipsychotics are agranulocytosis, diabetes, hypercholesterolemia, hyperprolactinemia, blurred vision, dry mouth, drowsiness, QT interval prolongation, and increase in weight, while tardive dyskinesia, akathisia, dystonia and hyperprolactinemia are the side effects of typical antipsychotics (DeBattista, 2012a:507; Martindale, 2002:660,662,684,686).

- Drug-drug interactions

Interactions occur when antipsychotics are used concomitantly with other drugs that inhibit cytochrome P450 enzymes such as anticonvulsants, antacids, antibacterial, antihypertensive, antihistamine drugs, antimalarial, antimigraine drugs, antiarrhythmic agents, anaesthetic agents, nicotine and NSAIDs (DeBattista, 2012a:495; Martindale, 2002:664,665,677,678; Pratt, 2007:434).

2.6.1.4 Stimulants

Stimulants are classified in two categories: traditional stimulants called amphetamine-based compounds (lisdexamfetamine, dexmethylphenidate and dextroamphetamine) and the psychostimulant, and modafinil (Gonzalez & Suppes, 2008:33).

- Indications

Stimulants are used for the treatment of residual depression and drug-induced sedation in BD patients and for ADHD (Carlson *et al*., 2004:416; Luscher, 2012:563; Martindale, 2002:1505).

- Mechanism of action

Amphetamines (stimulant) influence the release of dopamine and express its antidepressant activity in BD patients by blockade of the serotonin transporter (SERT), and therefore increasing the extracellular concentration of serotonin in the brain (Luscher, 2012:563,564).

- Dosage

Obesity in adults: Amphetamine could be used at an initial dose of 5 mg orally 30 to 60 minutes before food and at maximum dose of 30 mg daily (Drugs.com, 2016).

Narcolepsy (6-11 years): Amphetamine is used at an initial oral dose of 5 mg daily, increased with 5 mg increments daily until the desirable response is reached. In 12 years and older, it is given at initial oral dose of 10 mg daily and increased with 10 mg increments daily until desirable response is reached (Drugs.com, 2016; Martindale, 2002:1508). Adult dose ranges from 5 mg to maximum of 60 mg daily (Martindale, 2002:1508).

Hyperactivity in children: The use of amphetamine is not allowed in children who are less than five years old (Martindale, 2002:1508). Children of six years old and older could be given a starting dose of 5 mg once or twice daily of amphetamine. The daily dose may be increased by 5 mg

weekly if necessary to a maximum dose of 20 mg daily; however, older children could be given 40 mg daily (Barkley *et al.,* 2003:97; Martindale, 2002:1508).

- Contraindications

The use of amphetamine is contraindicated in patients with mania, kidney disease, drug or alcohol abuse, cardiovascular dysfunction, stroke as well as pregnant women and breastfeeding mothers (Colin, 2013:165; Luscher, 2012:563; Martindale, 2002:1508).

- Side effects

The following are the common adverse effects with the use of amphetamines: agitation, confusion, gastrointestinal disturbances, dry mouth, impaired libido, impotence, anorexia, teeth grinding, skin flushing, tachycardia, dysrhythmias, increased blood pressure and stroke (Martindale, 2002:1507). The use of amphetamine indirectly increases the possibility of HIV and hepatitis infection in the society (Luscher, 2012:563).

- Drug-drug interactions

Amphetamine interacts with the following drugs: omeprazole, lithium, antidepressants, warfarin, antiseizure agents, antacids, alcohol, MAOIs, beta-blockers, TCAs and vitamin C (Drugs.com, 2016a; Martindale, 2002:1508).

2.6.1.5 Benzodiazepines

Examples of benzodiazepines used in the treatment of BD are diazepam, lorazepam, clonazepam and alprazolam (Chouinard, 2004:7).

- Indications

Benzodiazepines are indicated in the treatment of mania in BD patients (Ashton, 2007:412; Chouinard, 2004:7).

- Mechanism of action

The mechanism of action of benzodiazepines is through positive modulation or enhancement of activity of GABA receptors in the brain, and therefore improve GABAergic synaptic transmission and sedation (Ashton, 2007:412; Luscher, 2012:565; Martindale, 2002:680; Porter & Meldrum, 2012:418).

- Dosage

The dosage of benzodiazepine is as follow: Diazepam (2 mg 1-3 times daily up to a maximum dose of 30 mg/day in divided doses though, with the highest dose at bed time or 5 mg to 15 mg in adults at bed time or 1 mg to 5 mg in children at bed time). Lorazepam should be administered in doses of 1 mg every 8-12 hours daily to a maximum dose of 6 mg/day or 1 mg to 4 mg given at bed time (Ashton, 2007:416; Martindale, 2002:680,698; Rossiter, 2014:491).

- Contraindications

Benzodiazepines should not be used during pregnancy, breastfeeding, depressed central nervous system, depressed respiratory function, and glaucoma (Ashton, 2007:414; Martindale, 2002:676).

- Side effects

The major side effects with the use of benzodiazepines include tolerance and dependence, rebound insomnia, over-sedation, hangover, liver damage, hypersensitivity, impaired sexual functions and carcinogenicity (Ashton, 2007:413,414; Martindale, 2002:675,676).

- Drug-drug interactions

The major interaction (increase the depressing activity of drugs on the central nervous system) of benzodiazepines occurs when used concurrently with alcohol, other hypnotics, antihistamines or opioids, and sedative tricyclic antidepressants (Ashton, 2007:413,414; Porter & Meldrum, 2012:418). Other drugs that benzodiazepines interact with are analgesics, antibacterial, anti-arrhythmic, anticoagulants and anti-epileptic agents (Martindale, 2002: 677,678).

2.6.2 Treatment of mania in bipolar disorder patients

According to the Consensus Group of the British Association for Psychopharmacology concerning treatment of mania episodes, prescribers are advised to consider the following for individual patients (Goodwin, 2009:351):

- Diagnosis of mania;
- Assessment of safety;
- Patient and family preferences;
- Consider need for admission;

- Communicate/explain treatment plan including need for medications;
- Severity of mania, whether a patient is on an antidepressant;
- Whether the patient is already on long-term treatment;
- Presence of lack of sleep; and
- Review of patient's response to treatment.

As recommended by the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders' (ISBD) collaborative update of CANMAT guidelines for the management of patients with BD, the following steps could be exercised by prescribers to achieve desirable treatment outcomes in the treatment of acute mania in individual BD patients (Yatham *et al*., 2009:228):

- Assess safety/functioning;
- Implement treatment setting;
- Discontinue antidepressants;
- Rule out medical causes;
- Discontinue illicit substances, alcohol and caffeine;
- Establish behavioural strategies and psychoeducation (general principles);
- Assess medicine status;
- Start/optimise medication(s) and assess compliance;
- Add another drug or switch treatment in case patient is not responding; and
- Add another medicine to evidence based drugs.

Mood stabilisers, e.g. lithium, anticonvulsants (valproate disodium, carbamazepine etc.), antipsychotics (olanzapine, risperidone, quetiapine, aripiprazole, paliperidone, ziprasidone) and benzodiazepines are the medications used for the treatment of mania in BD (DeBattista, 2012a:503; Collins, 2014:19; Goodwin *et al.,* 2016:506; Pratt, 2007:432). Lithium, antipsychotics, valproate, carbamazepine and benzodiazepine are the common drugs for mania/mixed episode treatment of BD; however, injectable antipsychotics or benzodiazepines should be used in severe

mania/mixed episodes (refer to Figure 4-2 in Annexure C) (Goodwin, 2009:351). Goodwin (2016:661,662) advised that oral dopamine receptor antagonists/partial agonist or valproate could be considered in treating severe mania in BD patients.

Mood stabilisers (lithium, valproate or valproic acid and carbamazepine), as well as typical and atypical antipsychotics are the first-line drugs for the treatment of mania or acute mania in BD patients; however, evidence that atypical antipsychotics have superior efficacy as mood stabilisers are limited (DeBattista, 2012a:506; Fountoulakis *et al.,* 2012:S1; Yatham *et al.*, 2009:225; Yildiz *et al*., 2011:386).

Despite the fact that lithium has advantages of preventing recurrence or relapse of mania, most clinicians do not prefer/use it as first-line drug in the treatment of acute mania because of its associated delay in response, fluctuations in physical exertion and fluid intake (Pratt, 2007:432). The use of either valproate or antipsychotics alone or concurrently with benzodiazepines should be the first line of treatment for acute or severe manic episodes (Goodwin, 2009:351; Pratt, 2007:432). Valproate should not be used in BD patients who are of child bearing age in order to avoid fatal teratogenesis and impaired mental growth (Goodwin *et al.,* 2016:502).

Carbamazepine is a reliable substitute to lithium; however, only to be used when the latter is not efficacious (DeBattista, 2012a:507). A study has shown that mania in children should be treated with aripiprazole (Goodwin *et al,* 2016:506). Planning and initiation of long-term treatment of a BD patient are a function of successful initial phase treatment (Goodwin *et al.,* 2016:502).

The South African Society of Psychiatrists (SASOP) treatment guidelines for psychiatric disorder advises that a prescriber should start treatment of mania in BD patients with an antimanic drug that is tolerable and efficacious as well as having potential for, or possibility of an acute treatment continuation into the maintenance phase (Colin, 2013:166,170).

Mood stabilisers, e.g. lithium and anticonvulsants (valproate disodium, carbamazepine etc.), antipsychotics (olanzapine, quetiapine, aripiprazole, paliperidone, risperidone, ziprasidone) and benzodiazepines are the medications used for the treatment of BD in SA (Colin, 2013:166). These drugs could be used as a single drug or as a combination treatment. The treatment guidelines of the SASOP indicates that the outcomes is better when either valproate or lithium is used together with a short-term administration of an atypical antipsychotic agent (Colin, 2013:166,170). Acute mania should not be treated with phenytoin, topiramate, gabapentin, lamotrigine and oxcarbamazepine (Colin, 2013:166). Carbamazepine as an anticonvulsant should be used only to a lesser extent, and haloperidol as an antipsychotic drug should only be used when other alternatives have failed, because it is not efficacious in maintenance treatment (Colin, 2013:166).

According to the SASOP's guidelines, prescribers could consider combining two mood stabilisers, e.g. lithium and valproate, lithium and carbamazepine or combining an atypical antipsychotic with a mood stabiliser (olanzapine and lithium or olanzapine and valproate) for BD patients not responding to mania treatments (Colin, 2013:170; Conus *et al.,* 2015:975). If there is partial or no response to treatment in BD patients with severe manic episodes or high suicide risk, prescribers can consider the substitution of antimanic agents and/or the use of electroconvulsive therapy (ECT) (Colin, 2013:169).

The SASOP's treatment algorithm (Colin, 2013:166,169,170) for mania is similar to international treatment guidelines regarding the treatment procedures for BD-I (Collins, 2014:19; Conus *et al.,* 2015:975; DeBattista, 2012a:503,506,507; Goodwin, 2009:351; Goodwin *et al*., 2016:502,506; Pratt, 2007:432; Yatham *et al.*, 2009:228; Yildiz *et al.,* 2011:386).

2.6.2.1 Treatment of depression in bipolar disorder patients

The Consensus Group of the British Association for Psychopharmacology recommends that the treatment of depressive episodes in BD should give preference to the following procedures (Goodwin, 2009:353):

- Diagnosis of bipolar depression;
- Assessment of suicide risk;
- Patient and family preferences;
- Treatment setting;
- Communicate/explain severity of risks;
- Treatment options;
- Eliminate stressors;
- Consider severity of depression;
- Whether patient is on maintenance treatment;
- Whether there is presence of BD-I;

- Whether evidence-based psychotherapy is available, e.g. cognitive behavioural therapy, family focused therapy and interpersonal social rhythms therapy (refer to Figure 4-3, Annexure D).

The Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBPD) collaborative update of CANMAT guidelines for the management of patients with BD advised prescribers to consider the under-listed steps in treating bipolar depression (Yatham *et al.,* 2009:231):

- Review the general principles;
- Examine medicine status;
- Start/optimise medication(s);
- Assess compliance;
- Add to medication or switch therapy (use electroconvulsive therapy, third-line agents and evidence-based options) in case a patient is not responding to treatment.

Antidepressants are classified based on their pharmacological actions (e.g. monoamine oxidase inhibitors and selective serotonin reuptake inhibitors), or chemical structure (e.g. tricyclic) and are also different with regard to the adverse effects and toxicity profile in the case of overdose (Pratt, 2007:428). Prescribers could exercise individualisation in their choice of antidepressants as males may perhaps tolerate imipramine better than females will, and selective serotonin reuptake inhibitors (SSRIs) are more tolerated with less toxicity even in overdose, compare to tricyclic antidepressants (Pratt, 2007:428).

The older antidepressants have marked toxicity profiles and adverse effects, unlike the recently introduced antidepressants (Ferguson, 2001:22). The tolerability factor and a patient's previous response to treatment with a particular type of antidepressant should not be over-emphasised by prescribers when making a choice of which antidepressants to use (Ferguson, 2001:22). Quetiapine, lamotrigine, selective serotonin re-uptake inhibitors or other antidepressants, but not tricyclic antidepressants, are indicated for the treatment of depressive episodes in BD patients (Goodwin, 2009:353). Antimanic agents could be added to antidepressants if mania is present in BD patients (Goodwin, 2009:353; DeBattista, 2012a:507). Atypical antipsychotics share pharmacological activities (through serotonin $5HT_2$ receptor antagonist and $5HT_{1A}$ and dopamine receptor partial agonist action) that are common in antidepressant actions, and therefore is the basis for their concurrent use in the treatment of depression (Blier & Szabo, 2005:30; DeBattista

& Hawkins, 2009:369,370; Jarema, 2007:23; McIntyre *et al.,* 2014:1). Lithium, lamotrigine and quetiapine could be used mono-therapeutically. Quetiapine, olanzapine, lithium and selective serotonin re-uptake inhibitors (SSRIs) as the first-line treatment for bipolar depression (DeBattista & Hawkins, 2009:371; DeBattista, 2012a:503; Fountoulakis *et al.,* 2012:S1; Yatham *et al.,* 2009:225). Mild depression in BD patients should not be treated with antidepressants, but with non-drug strategies or lithium (Goodwin *et al*., 2016:503; Pratt, 2007:427,431). Quetiapine, olanzapine, aripiprazole and lamotrigine are efficacious in short-term treatment of depression (Goodwin, 2016:661; Goodwin *et al.,* 2016:525,526).

Another treatment option for depression in BD patients is ECT, which is only considered when a patient has been referred to a psychiatrist. Electroconvulsive therapy has a faster onset of action, but the effect does not last longer; however, antidepressants are required to prevent relapse (Pratt, 2007:431).

In SA, the first-line antidepressant used as a monotherapy for depressive episodes in BD patients includes quetiapine, olanzapine, valproate, lithium and lamotrigine (Colin, 2013:167). The second-line antidepressant agents that could be used as combination therapy are: risperidone, olanzapine and fluoxetine combination, lithium and antidepressant combination, lithium and valproate, and the use of lamotrigine as an add-on to lithium (Colin, 2013:167). Antidepressant and antimanic maintenance agents could be given simultaneously to reduce the incidence of switching; however, the antidepressant should, thereafter, be gradually reduced after two or three months of sustainable recovery (Colin, 2013:170). Prescribers could switch to another antidepressant or combine psychotherapy with an antidepressant in case a depressive patient fails to respond to treatment (Colin, 2013:170). The use of psychotherapy (cognitive behavioural therapy (CBT), family focused therapy (FFT) and interpersonal social rhythm therapy (IPSRT)) as adjuncts with antidepressants has a marked benefit in the treatment of depressive episodes (Colin, 2013:166,170).

The SASOP's treatment algorithm (Colin, 2013:166,167,170) for bipolar depression is similar to international treatment guidelines in terms of treatment procedures for BD (Blier & Szabo, 2005:30; DeBattista, 2012a:503,507; Goodwin, 2009:353; Goodwin *et al.,* 2016:503,525,526; Jarema, 2007:23; Mclntyre *et al.,* 2014:1; Pratt, 2007:427,428,431; Yatham *et al*., 2009:225,231).

2.6.2.2 Maintenance therapy in bipolar disorder patients

The Consensus Group of the British Association for Psychopharmacology advised prescribers to follow these steps for maintenance therapy in BD (refer Annexure E) (Goodwin, 2009:354):

- Diagnosis of euthymic;
- Educate and encourage adherence to care plan;
- Consider maintenance therapy (protect against manic pole if mania predominates and protect against depressive pole if depression predominates);
- Consider combination therapy in case there is a failure of protection against manic pole and protection against depressive pole; and
- Establish psychoeducation, outpatient supervision by specialist clinician and strategies for preventing relapse.

In maintenance therapy, mood stabilisers are necessary for long-term treatment in order to prevent relapse to either pole of BD (Goodwin, 2009:354). Lithium, olanzapine, valproate and lamotrigine remain the first-line drugs for maintenance therapy in BD (DeBattista, 2012a:507; Yatham *et al*., 2009:225).

The presence of acute stressors, insomnia or anxiety should be treated with antipsychotics or benzodiazepines in the short term (Goodwin, 2009:354). Maintenance treatment is centred on averting recurrence of mood episodes, while ensuring optimal functioning and treatment of inter-episode sub-syndrome symptoms (Malhi *et al*., 2009:33). The success in lifetime treatment or management of BD is a function of maintenance treatment (Malhi *et al*., 2009:33).

In SA, the maintenance treatment for BD, as indicated by the SASOP's treatment guidelines for psychiatric disorders, suggested that prescribers should consider either or all of the following factors before initiation of treatment:

- Two previous mood episodes over a time period, one mood episode in the last five years;
- Severe acute episodes associated with suicide risk/psychotic features and;
- Continuous functional disability (Colin, 2013:167,170).

Consideration for maintenance therapy is crucial for every diagnosis of BD (Colin, 2013:167). The following drugs are commonly used clinically for maintenance treatment: tricyclic antidepressants

(imipramine, amitriptyline, clomipramine, doxepin, nortriptyline and trimipramine), monoamine oxidase inhibitors (tranylcypromine, phenelzine, and moclobemide), selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram), atypical antipsychotics (quetiapine, risperidone and olanzapine), anticonvulsants (valproate and lamotrigine), and lithium (Colin, 2013:167).

Consideration should be given to the efficacy and tolerability profile, individual patient preference, safety, re-evaluation of treatment plans and other factors that may predispose patients with BD to comorbid conditions and psychosocial stressors (Colin, 2013:167). Maintenance treatment is necessary:

- If acute episodes are severe with psychotic characteristics or existing functional disability;
- If mood episodes have been experienced in the past five years; and
- If there is a record of two recent mood episodes over a time period (Colin, 2013:170).

Olanzapine, valproate, lithium, lamotrigine, aripiprazole and quetiapine could be used as an adjunct to valproate or lithium (Colin, 2013:167).

The SASOP's treatment algorithm (Colin, 2013:167,170) for maintenance therapy of BD is similar to international treatment guidelines (DeBattista, 2012a:507; Goodwin, 2009:354; Malhi *et al*., 2009:33; Yatham *et al.,* 2009:225).

2.6.3 Treatment of mixed-state bipolar disorder patients

A mixed state is defined as the simultaneous presence/diagnosis of manic and depressive episodes in a BD patient (Goodwin, 2009:366). Achieving desirable treatment outcomes, in the short term, is guaranteed with the use of antipsychotics, mood stabilisers and ECT. (Goodwin, 2009:366).

Mixed state in BD patients in SA is treated with either valproate or atypical antipsychotics mono-therapeutically or concurrently with fluoxetine (Colin, 2013:169). The SASOP's treatment algorithm (Colin, 2013:169) for mixed state BD is similar to international treatment guidelines (Goodwin, 2009:366).

Table 2.4 shows the summary of drug classes, mechanism of action, adverse effects, contraindications, interactions and usual therapeutic dosages of medications used in the treatment of BD.

Table 2.4: Summary of drugs used in pharmacological treatment of BD

Pharmacological group	Mechanism of action	Adverse effects	Contra-indications	Interactions	Usual therapeutic dosage
Antidepressants **Selective serotonin reuptake inhibitors (SSRIs)** Fluoxetine, Paroxetine, Sertraline	Marked selective serotonin transporter (SERT) blockade	Sexual dysfunction	Pregnancy, kidney disease	Some CYP inhibition (fluoxetine 2D6 and 3A4; fluvoxamine 1A2; paroxetine 2D6), MAOIs, TCAs.	Fluoxetine (20 mg/day, maximum of 60 mg/day), Paroxetine (20 mg/day, maximum of 50 mg/day) Sertraline (50-100 mg/day, maximum of 200 mg/day).
Antipsychotics **Atypical antipsychotics** Aripiprazole, Clozapine, Olanzapine, Quetiapine, Risperidone, Ziprasidone	5-HT2A and D2 receptors blockade.	Agranulocytosis, diabetes, hypercholesterolemia, hyperprolactinemia, QT prolongation, and increase in weight.	Agitated patients, endocrine dysfunction and cardiovascular dysfunction.	Drugs that inhibit cytochrome P450 enzymes, e.g. ketoconazole.	Aripiprazole (15-30 mg/day), Clozapine (12.5-25 mg/day, maximum of 900 mg/day), Olanzapine (5-10 mg/day, maximum of 20 mg/day), Quetiapine (start with 100 mg/day, maximum of 800 mg/day), Risperidone (2-3 mg/day, maximum of 6 mg/day) Ziprasidone (40 mg every 12 hours, maximum of 80 mg every 12 hours).

Pharmacological group	Mechanism of action	Adverse effects	Contra-indications	Interactions	Usual therapeutic dosage
Typical antipsychotics Haloperidol, Chlorpromazine, Fluphenazine	5-HT2A and D2 receptors blockade.	Tardive dyskinesia, akathisia, dystonia, parkinsonism symptoms and hyperprolactinemia	Agitated patients, endocrine dysfunction and cardiovascular dysfunction.	Drugs that inhibit cytochrome P450 enzymes, e.g. ketoconazole	Fluphenazine (12.5 mg to maximum of 50 mg based on patient response). Haloperidol (0.5-5 mg every 8 hours daily, maximum of 20 mg/day). Chlorpromazine (25 mg every 8 hours daily, maximum of 800 mg/day).
Mood stabilizers Lithium	Not clear. Reduce inositol signalling and inhibition of glycogen synthase kinase-3 (GSK-3).	Tremor etc. reduction of thyroid functions, polydipsia, polyuria, glomerulopathy and nephrotic syndrome, oedema, bradycardia-tachycardia syndrome and leucocytosis	Renal insufficiency, cardiovascular impairment, thyroid dysfunction, tremor, pregnancy and oedema	Thiazides, NSAIDs	2 mg/kg/day, maximum of 750-1500 mg/day of lithium.

Pharmacological group	Mechanism of action	Adverse effects	Contra-indications	Interactions	Usual therapeutic dosage
Anticonvulsants Carbamazepine Lamotrigine Valproate	Not known.	Tremor, hepatic dysfunction, increased weight, nausea (valproate), rash, dizziness, headache, diplopia (lamotrigine), and blood dyscrasia (carbamazepine)	Cutaneous reactions, hepatic insufficiency and bruising/coagulation abnormalities (valproate and carbamazepine). Myoclonic epilepsy (lamotrigine).	Phenobarbital, carbamazepine, phenytoin, lamotrigine, rifampicin, felbamate, ethosuximide, and primidone (valproate), phenytoin, valproate, verapamil, fluoxetine, macrolides antibiotics, danazol, phenobarbital, propoxyphene, fluoxetine and primidone (carbamazepine), and valproate, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, sertraline, succinimides and topiramate (lamotrigine).	Valproate (600-900 mg/day, maximum of 1500 mg/day) Lamotrigine (25 mg/day, maximum of 400 mg/day). Carbamazepine (400-600 mg/day).
Benzodiazepines e.g. diazepam, lorazepam	Positive modulation of GABA4 receptors in the brain (GABA	Over-sedation and hangover, rebound insomnia, tolerance and dependence	Pregnancy and lactation.	Alcohol, sedative antidepressant, antihistamines, opioids and other hypnotics.	Diazepam (2-5 mg every 8 hours, maximum of 30 mg/day). Lorazepam (1mg every 8-12 hours, maximum of 6 mg/day).

Pharmacological group	Mechanism of action	Adverse effects	Contra-indications	Interactions	Usual therapeutic dosage
Stimulants e.g. amphetamine	Blockade of serotonin transporter (SERT)	Agitation, confusion, tooth grinding, skin flushing, tachycardia, dysrhythmias, increased blood pressure and strokes	Mania, cardiovascular insufficiency and stroke.	Omeprazole, lithium, antidepressants, antiseizure agents, warfarin and MAOIs.	Obesity: 5 mg to 30 mg (max) daily. Narcolepsy: 5 mg daily in 6 to 11 years old, 10 mg daily in 12 years old and above and 5 mg to 60 mg (max) in adults.

The following references were used for the compilation of Table 2.4: Anand *et al*., 2005; Ashton, 2007; Barkley *et al*., 2003; Carlson *et al*., 2004; Chouinard, 2004; Drugs.com, 2016; DeBattista, 2012; Geddes *et al.,* 2004; Gonzalez & Suppes, 2008; Goodwin, 2009; Goodwin *et al*., 2016; Johannessen, 2000; Johannessen & Landmark, 2010; Kessing *et al.,* 2011; Malhi *et al.,* 2012; Malhi *et al.,* 2013; Martindale, 2002; NHS choices, 2015; NIH, 2016; Pacchiarotti *et al.,* 2013; Porter & Meldrum, 2012; Pratt, 2007; Rossiter, 2014; Sanz *et al.,* 2005; Tennis & Stern, 1997; Tondo & Baldessarini, 2016.

2.6.4 Non-pharmacological treatment of bipolar disorder patients

A survey report in the United Kingdom has shown that BD could be treated psychosocially and outlined the following as the most essential psychotherapies for treating BD (Miklowitz *et al.,* 2008:77):

- Monitoring of moods and early warning signs;
- Recognising and managing factors that trigger stress and interpersonal conflicts;
- Stabilising sleep/wake rhythms and daily responsibilities;
- Developing relapse prevention plans;
- Reducing self-stigmatisation;
- Encouraging adherence to medication taking; and
- Reducing drug use and alcohol (including caffeine in sensitive person).

Electroconvulsive therapy (psychotherapy) has been shown to be beneficial in treating BD patients with severe mania, treatment resistant mania, mixed state, high suicidal risk, depression, resistant depression and severe depression in pregnancy (Goodwin *et al*., 2016:503,504,528; Pina *et al.,* 2016:23; Valenti *et al.,* 2008:54,55). Recommendation from the British Association for Psychopharmacology for the treatment of BD showed that ECT could be used to treat severe mania in pregnant women and severe bipolar depression (Goodwin, 2009:366,368). The use of psychosocial interventions (cognitive behavioural therapy (CBT), family/caregiver interventions, psycho-education and interpersonal and social rhythm therapy (IPSRT) as adjuncts to drug treatments in BD patients has been beneficial (Miklowitz *et al.*, 2008:511; Yatham *et al.,* 2009:227). Reduction in mood fluctuations, need for drugs, hospitalisation and rate of relapse, as well as increased compliance with medication and functioning are the advantages of psychosocial interventions in BD patients (Frank *et al.,* 2005:996; Miklowitz *et al.,* 2008:77; Reinares *et al.,* 2008:511; Scott, 2001:s164; Yatham *et al.,* 2009:227).

In South Africa, electroconvulsive therapy, CBT, family focused therapy (FFT) and IPSRT are the indicated psychotherapies used as adjuncts to antidepressants to improve functioning and prevent treatment relapse in BD patients with depressive episodes (Colin, 2013:170). A study

done in the Western Cape has shown that mindfulness-based cognitive therapy (MBCT) impacts positively on mindfulness and emotion as well as alleviates anxiety in BD patients (Ives-Deliperi *et al*., 2013:1152).

The South African Society of Psychiatrists' guidelines (Colin, 2013:170) for non-pharmacological treatment of BD is similar to international treatment guidelines (Frank *et al.,* 2005:996; Goodwin, 2009:366,367; Goodwin *et al*., 2016:503,504,528; Miklowitz *et al.,* 2008:77; Pina *et al.,* 2016:23; Reinares *et al.,* 2008:511; Scott, 2001:s164; Valenti *et al.,* 2008:54,55; Yatham *et al*., 2009:226).

2.7 Chapter summary

This chapter consists of the following: definition, classification, diagnosis, complications, prevalence, comorbidities, burden and treatments of BD.

Chapter 3 with consists of the results in the form of two manuscripts.

CHAPTER 3: RESULTS AND DISCUSSION

3.1 Introduction

This chapter contains two manuscripts that present the results and discussions of this study's empirical investigation presented in article format. Each manuscript conformed to the guidelines for authors per requirement for each journal.

3.2 Manuscript 1

Objectives one and two from the empirical investigation are addressed in manuscript 1:

- To determine trends, over a six-year period, in the prevalence and incidence of BD.
- To determine possible changes, over a six-year period, in the prevalence of coexisting CDL conditions in patients with BD.

Manuscript 1 is prepared and will be submitted to the journal *International journal of methods in psychiatric research.* Refer to Annexure G for the specific author guidelines of the journal.

Trends in the incidence and prevalence of bipolar disorder and its coexisting chronic disease list conditions in the private health sector of South Africa, 2010-2015

Short running title: Bipolar disorder and coexisting conditions

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Abstract

Objectives: To determine trends in the incidence and prevalence rate of bipolar disorder (BD) and its coexisting chronic disease list (CDL) conditions over a six-year period.

Methods: We conducted a retrospective, cohort study, analysing medicine claims data from 2010 to 2015. The incidence and prevalence rate of BD (ICD-10 code F31), and the number and type of CDL conditions coexisting in individual BD patients were determined. The incidence rate per 1 000 beneficiaries was determined using 2010 as index year.

Results: Prevalence rate of BD increased from 5.9 (2010) to 7.9 (2015) per 1 000 beneficiaries, whereas the incidence rate per 1 000 beneficiaries was 2.3 in 2011 vs. 2.1 in 2015. The proportion of BD patients with one or more coexisting CDL condition increased by 20.5% over the six-year period. BD patients newly registered with hypertension ($p < 0.0001$), hypothyroidism ($p < 0.0001$), hyperlipidaemia ($p < 0.0001$), type 2 diabetes mellitus ($p< 0.0001$), epilepsy ($p = 0.0065$) and rheumatoid arthritis ($p = 0.0253$) increased.

Conclusion: Incidence of BD remained nearly the same, however, the prevalence, as well as the proportion of BD patients newly registered with hypertension, hypothyroidism, hyperlipidaemia, type 2 diabetes mellitus, epilepsy and rheumatoid arthritis increased significantly.

KEYWORDS

Bipolar disorder (BD), incidence, prevalence, coexisting chronic disease list conditions, South Africa

INTRODUCTION

Bipolar disorder (BD) is a chronic mental disease associated with functional and cognitive impairment in memory, attention and executive functions because of a neuro-psychosocial deficit and fluctuations in mood, energy and activity levels (Goodwin *et al.*,, 2016; National Institute of Mental Health [NIMH], 2016; Samame, Szmulewicz, Valerio, Martino, & Strejilevich, 2017). The cyclical nature of BD, with alternating manic and depressive symptoms or mixed states, predisposes patients to increased susceptibility for high-risk medical conditions, poor compliance to care plans, social instability and isolation from friends and caregivers (Jann, 2014; Kilbourne, 2005; Kilbourne *et al.*,, 2004). Bipolar disorder can be classified into bipolar I disorder (BD-I), bipolar II disorder (BD-II), cyclothymic disorder and rapid cycling (Goodwin *et al.*, 2016; NIMH, 2016).

Various factors may influence the prevalence of BD, e.g. gender, socio-economic status, family status, age, marital status, educational background and race (Blanco *et al.*, 2017; Kwajaffa *et al.*, 2016; Schoeyen *et al.*, 2011). The 2015 Global Burden of Disease (GBD) study accentuated that BD affects approximately 44 million (CI 38.2-50.9 million) people worldwide (Global Burden of Disease 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). The lifetime prevalence between BD-I disorder and BD-II disorder varies (Dell'Osso *et al.*, 2015). The result of the World Health Organization (WHO) World Mental Health Survey Initiative, under a pooled sample of 11 countries, indicated that the lifetime prevalence rates of BD-I, BD-II, and sub-threshold BD were 0.6%, 0.4% and 1.4%, respectively (Merikangas *et al.*, 2011). In the same study, the 12-month prevalence of BD-I, BD-II and sub-threshold BD was 0.4%, 0.3% and 0.8%, respectively. The USA had the highest lifetime and 12-month prevalence of BD (4.4% and 2.8%, respectively), while India had the lowest (both 0.1%). In Europe and Asia, the lifetime and 12-month prevalence of BD-I disorder were 0.6% and 0.4% and, for BD-II disorder, it was 0.4% and 0.3%, whereas in Africa (Nigeria and Ethiopia), the lifetime prevalence of BD was found to be between 0.1% and 0.6% (Esan & Esan, 2015; Merikangas *et al.*, 2011).

In a more recent study in the USA, the lifetime and 12-month prevalence of BD-I were found to be 1.5% and 2.1%, and this did not differ between male (1.6% and 2.2%) and female patients (1.5% and 2.0%) (Blanco *et al.*, 2017). However, the World Mental Health Survey Initiative in 2011 found that the lifetime prevalence of BD-I and sub-threshold BD was greater in males than in females, whereas females had higher rates of BD-II than their male counterparts did (Merikangas *et al.*, 2011).

In 2009, BD was included as one of 26 chronic/non-communicable conditions included in the chronic disease list (CDL) of South Africa under the prescribed minimum benefits (PMB) (South Africa, 2003; South Africa, 2009). The PMBs that include the CDL is a feature of the South African Medical Schemes Act (Act 131 of 1998). Through the PMB and the CDL, the Medical Schemes Act (Act 131 of 1998) ensures that all medical scheme beneficiaries with any CDL conditions are continuously provided with certain minimum health services, irrespective of their selected benefit option. By way of a therapeutic algorithm for the 26 CDL conditions, all costs relating to the diagnosis, medication, doctors' consultations and tests must be covered by medical schemes.

In 2015, BD was listed in the 10th position as the most prevalent CDL condition in the medical scheme environment in South Africa (Research and Monitoring Unit of the Council for Medical Schemes, 2017). The Research and Monitoring Unit of the Council for Medical Schemes. (2017) reported an annual increase in the prevalence of BD from 1.91 to 3.97 per 1 000 beneficiaries between 2010 and 2015 at an average growth of 15.8%. In 2015, BD was more prevalent in females (5.01 per 1 000 female beneficiaries) as opposed to males (2.80 per 1 000 male beneficiaries). Only a few beneficiaries with BD were under the age of 14 years in 2015.

Individuals with BD possess a substantial burden of coexisting non-communicable diseases, suggesting the need for earlier detection and treatment of these conditions in patients with BD (Kilbourne *et al.*, 2004; Kilbourne, 2005). Anxiety disorder, substance use disorder and eating disorders are the major comorbidities associated with BD; however, the coexistence of non-communicable diseases such as cardiovascular, endocrine, and blood-related diseases, among others, is also implicated as BD comorbidities (Prince *et al.*, 2007; Wildes, Marcus & Fagiolini, 2008).

Treatment outcomes of BD may also be influenced by coexisting non-communicable diseases (Kilbourne *et al.*, 2004; Kilbourne, 2005). Recent evidence suggests that antipsychotics, antidepressants and mood stabilisers used in treating BD may be associated with an increased risk of metabolic syndrome, e.g. impaired glycaemic control and weight gain (Palmiere, Augsburger & Varlet, 2016; Masand & Gupta, 2002). Therefore, the coexistence of non-communicable diseases in BD patients may be a threat to patients and third party payers since more resources will be needed to treat these coexisting chronic conditions (Guo, Keck, Li, Jang & Kelton, 2008; Kilbourne *et al.,* 2005; Peele, Xu & Kupfer, 2003).

The Research and Monitoring Unit of the Council for Medical Schemes identified an upward trend in the number of medical scheme beneficiaries with multiple CDL conditions from 2010 to 2015 (Research and Monitoring Unit of the Council for Medical Schemes, 2017). The prevalence of coexisting CDL conditions or non-communicable diseases in BD patients has not been reliably delineated in the private health sector of South Africa. Therefore, the aims of this study were to determine trends, over a six-year study period, in the incidence and prevalence rate of BD and its coexisting CDL conditions by using retrospective medicine claims data.

METHOD

Study design

We conducted a retrospective cohort study, analysing medicine claims data for the period 1 January 2010 to 31 December 2015. An open cohort design was used to determine trends in the incidence and prevalence of BD over a six-year study period, whereas a closed cohort design was used to investigate the prevalence of coexisting CDL conditions in BD patients (Figure 1).

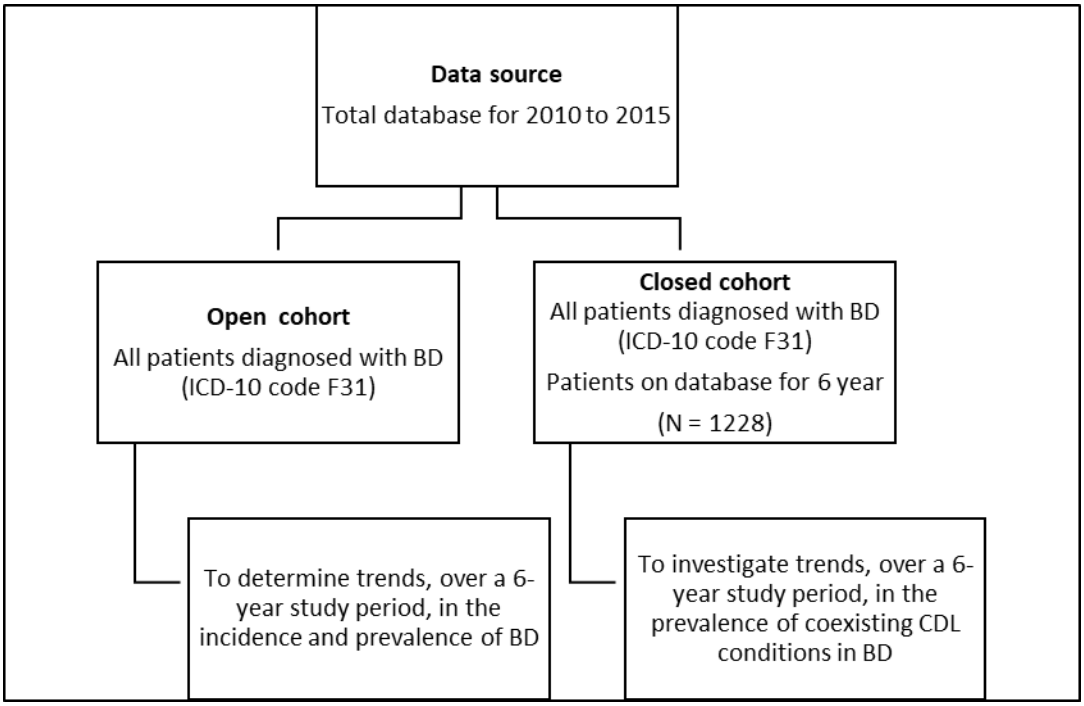

Figure 1: Study design

Data source

Medicine claims data were obtained from a nationally representative pharmaceutical benefit management company (PBM). This PBM Company currently manages the medicine benefits of 1.8 million beneficiaries on behalf of more than 40 medical schemes. All of South Africa's pharmacies and 98% of all dispensing doctors are represented on this service provider's database. Several automated validation processes were applied by the PBM to ensure the quality of data. There were no missing data fields in the datasets used for the study.

Data fields used in this study include the gender, date of birth, date of treatment, encrypted patient's medical scheme member number and dependent code and diagnosis information (ICD-10 code, diagnose code) (World Health Organization [WHO], 2016).

Study population

The total patient population in the database for the respective years were: 968 131 (2010), 864 962 (2011), 815 792 (2012), 809 838 (2013), 838 618 (2014) and 843 792 (2015). The study population for the open cohort included all patients, as presented in Table 2, with an International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) diagnosis-code for BD (ICD-10 code F31) (WHO, 2016). The study population for the closed cohort consisted of 1228 BD patients (ICD-10 code F31).

Study variables

The independent variables included the age and gender of patients. The incidence rate of BD, the prevalence of BD, the mean number of CDL conditions per patient and type of CDL conditions co-occurring with BD were the dependent variables.

Patient age was determined at time of first dispensing in the index year (2010) and divided into two groups: ≤18.2 years and >18.2 years, based on the results of a national comorbidity survey in the USA (Merikangas *et al.,* 2007) showing that BD initially occurred at an average age of 18.2 years.

The following equation was used to calculate the prevalence rate of BD patients per 1 000 medical schemes beneficiaries per year (Centers for Disease Control and Prevention [CDC], 2018a):

$$\text{Prevalence rate} = = \frac{\text{All new and pre-existing cases during a given time period}}{\text{Population during the same time period}} (X\ 10^{n})$$

$$n = 3$$

The population in the equation includes the total population or the population of the specific gender or age group on the database who claimed medication during the study period.

The BD incidence rate was calculated as per 1 000 medical schemes beneficiaries for that specific year. The incidence rate was calculated as follows (CDC, 2018b):

Incidence rate: $= \frac{Number\ of\ \ new\ cases\ of\ a\ disease\ in\ a\ specified\ period}{Size\ of\ population\ at\ start\ of\ the\ specified\ period}\ (X\ 10^n)$

$n = 3$

The population in the equation includes the total population or the population of the specific gender or age group on the database who claimed medication during the study period.

The incidence was used to determine the proportion of the study populations who have newly registered their BD status with their medical schemes during the study period (2010-2015) without taking into account when the disease was developed. Each participant was followed from the time he/she was registered as a BD patient with the PMB central database. Patients who cancelled their membership with a specific medical scheme did not contribute to the year's denominator whereas new members contributed to the denominator.

The CDL conditions of South Africa were used to categorise the coexisting non-communicable diseases (South Africa, 2003; South Africa, 2009). The CDL conditions, as indicated in Table 1, were identified by using the different ICD-10 codes (Council for Medical Schemes, 2012; South Africa, 2003; South Africa, 2009) in conjunction with the PMB CDL code provided by the PMB for registered CDL claims.

Table 1: Chronic Disease List (CDL) of South Africa

Chronic disease	ICD-10 code
Addison's disease	E27.1
Asthma	J45, J46
Bipolar disorder	F31
Bronchiectasis	J47, Q33.4
Cardiac failure	I27.9, I50.0, I50.1
Cardiomyopathy	I42.0, I42.1, I42.2
Chronic obstructive pulmonary disease	J43.0, J44.0
Chronic renal failure	N03.0, N04.0, N05.0
Crohn's disease	K50.0, K50.8
Diabetes insipidus	E23.2
Diabetes mellitus 1	E10.0, E12.0, O24.0
Diabetes mellitus 2	E10.0, E11.9, E12.0
Dysrhythmias	I47.2, I48
Epilepsy	G40.0, G41.0
Glaucoma	H40.0,Q15.0
Haemophilia A and B	D66, D67
Hypertension	I10, I12.0, I13.0, I15.0, O11
Hyperlipidaemia	G45.0, I20.0, I21.0, I22.0, I24.0, I25.0, I63.O, I65.0, I66.0, I70.0
Ulcerative colitis	K51.0, K51.9
Coronary artery disease	I20.0, I25.0
Multiple sclerosis	G35
Parkinson's disease	G20, G21.0
Rheumatoid arthritis	M05.00, M06.00, M08.00
Schizophrenia	F20.0
Systemic lupus erythematosus	M32.0, L93.0, L93.2

Statistical analysis

The Statistical Analysis System®, SAS 9.4 program and Statistical Package for the Social Sciences (IBM SPSS® 22) were used to analyse the data. Variables were expressed using descriptive statistics, which include frequencies (*n*) presented as percentages (%), arithmetic means, standard deviations (SD) and 95% confidence intervals (CI). A *P-value* of .05 or less was considered statistically significant at a two-sided α-level.

A generalised linear model with log-link (Poisson distribution) was applied to determine trends in the mean number of CDL conditions per BD patient in the closed cohort over a six-year study period. A possible gender influence on trends in the mean number of CDL conditions per BD patient was also assessed. Cohen's *d*-value was considered for practical significance, with a *d*-value of > .8 as a large effect and of practical significance.

McNemar's test was used to determine whether there was a statistically significant change in the proportions of BD patients with a specific CDL condition (Table 4) or combination of CDL conditions (Table 5) in 2015 compared to 2010.

Ethical considerations

This study was approved by the Health Research Ethics Committee of North-West University (NWU-00179-14-A1-01) and goodwill permission to perform the study was obtained from the board of directors of the PBM Company.

RESULTS

The general characteristics of the total database and open cohort study population are presented in Table 2. Bipolar disorder patients represented 0.6% (2010) to 0.8% (2015) of the total patient population on the database. The majority of BD patients were females, representing 0.8% (2010) to 1.0% (2015) of the total number of female patients on the database. The mean age of the BD patients was 43.6 (15.8) years (CI 43.2-44.0 years), with the majority (96.4%, n = 5 471) older than 18.2 years in the index year (2010). The percentage of BD patients older than 18.2 years decreased from 96.4% to 91.4% over the study period.

Table 2: General characteristics of the total patient population and open cohort study population (BD patients) on the database

	Study years					
Total database:	2010	2011	2012	2013	2014	2015
Total number of patients (N)	968 131	864 962	815 792	809 838	838 618	843 792
Gender						
Male, n (%)	446 744 (46.1)	402 488 (46.5)	384 159 (47.1)	379 756 (46.9)	392 235 (46.8)	398 166 (47.2)
Female, n (%)	521 387 (53.9)	462 470 (53.5)	431 630 (52.9)	430 077 (53.1)	446 382 (53.2)	445 626 (52.8)
Age groups (years)						
≤18.2, n (%)	210 604 (21.8)	185 657 (21.5)	170 839 (20.9)	179 331 (22.1)	192 244 (22.9)	205 841 (24.4)
>18.2, n (%)	757 527 (78.2)	679 305 (78.5)	644 953 (79.1)	630 507 (77.8)	646 374 (77.1)	637 951 (75.6)
Study population						
Number of BD patients, N **(%)**	5670 (0.6)	5910 (0.7)	6140 (0.8)	6614 (0.8)	6876 (0.8)	6642 (0.8)
Gender						
Male, n (%)†	1665 (29.4)	1788 (30.3)	1960 (31.9)	2113 (31.9)	2174 (31.6)	2154 (32.4)
Female, n (%)†	4005 (70.6)	4122 (69.7)	4180 (68.1)	4501 (68.1)	4702 (68.4)	4488 (67.6)
Age groups (years)						
≤18.2, n (%) §	199 (3.5)	281 (4.8)	326 (5.3)	443 (6.7)	510 (7.4)	571 (8.6)
>18.2, n (%) §	5471 (96.5)	5629 (95.2)	5814 (94.7)	6171 (93.3)	6366 (92.6)	6071 (91.4)

† Total number of males or females/total number of patients in the study population ×100

§ Total number of patients' ≤18.2 years or > 18.2 years/total number of patients in the study population×100

Figure 2 shows that the number of BD patients per 1 000 beneficiaries increased by 34.30% from 5.86 in 2010 to 7.87 in 2015. The same trend was observed in male and female BD patients with increases of 45.04% and 31.12%, respectively.

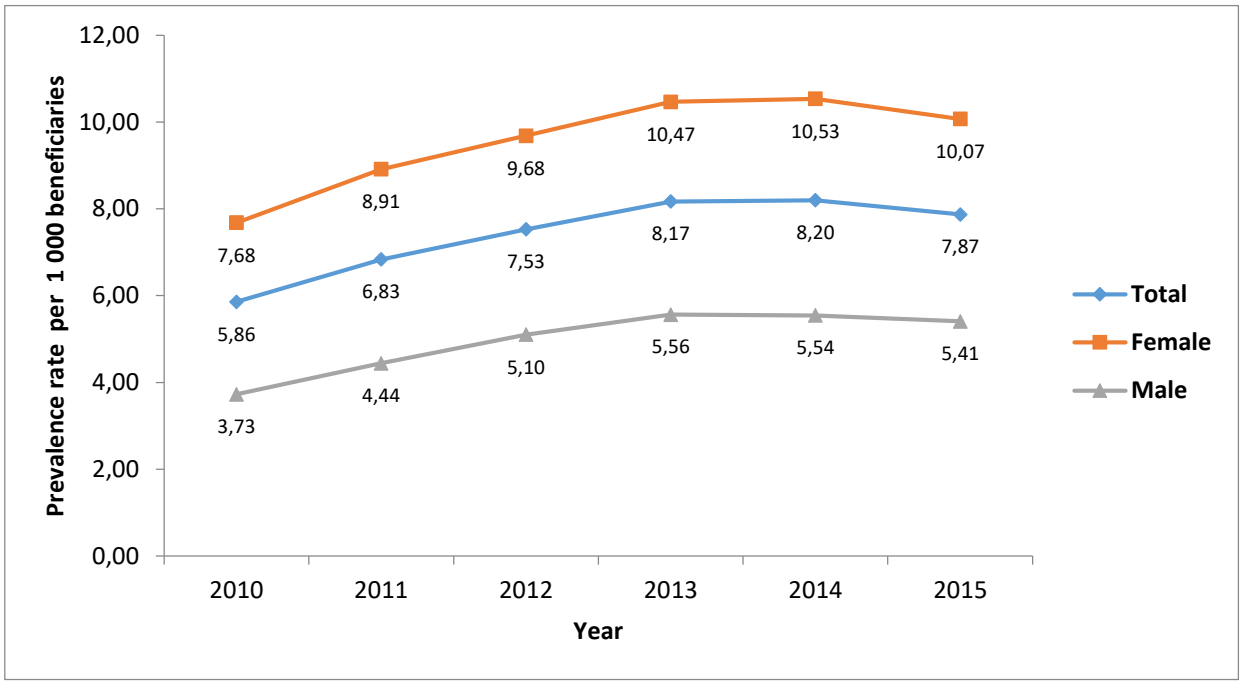

Figure 2: Prevalence rate of BD patients per 1 000 beneficiaries per year stratified by gender

The incidence rate of BD patients per 1 000 beneficiaries stayed nearly the same during the study period; 2.33 in 2011 vs. 2.11 in 2015. Higher incidence rates (2.92 in 2011 vs. 2.60 in 2015) were found for females than for males (1.65 in 2011 vs. 1.57 in 2015) (Figure 3).

The majority of BD patients (N = 1 228) in the closed cohort were female (72.6%). The mean age of BD patients was 47.7 (14.0) years (CI 46.9-48.5 years), with the majority of the patients (98.4%, n = 1 208) older than 18.2 years in the index year (2010).

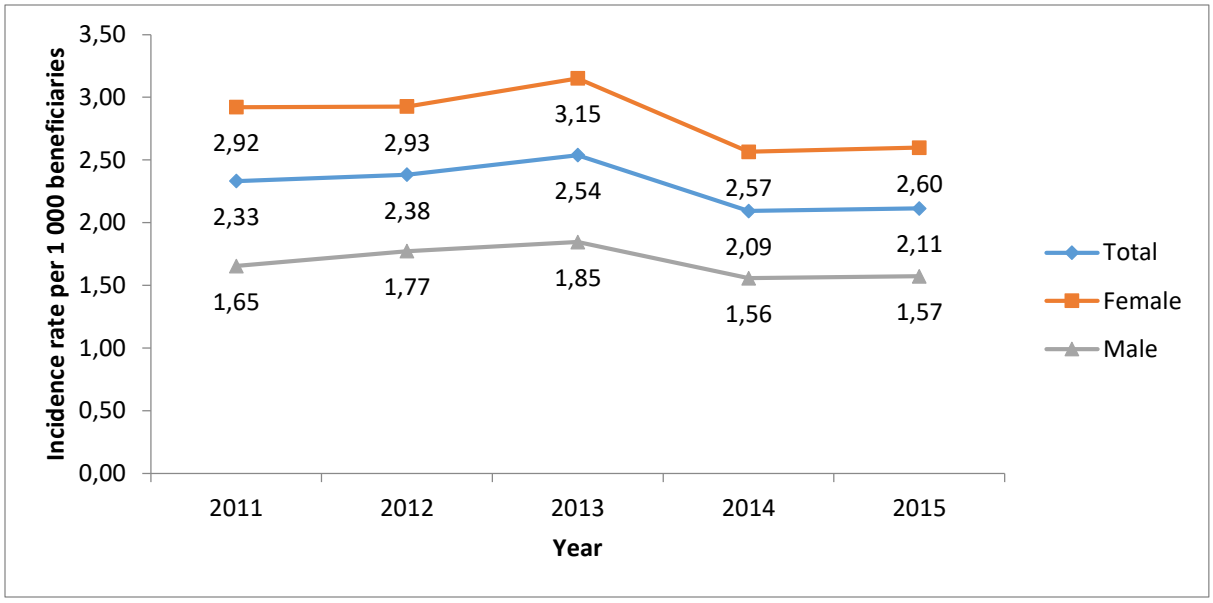

Figure 3: Incidence rate of BD patients per 1 000 beneficiaries stratified by gender

In the index year (2010), 51.6% (n = 634) of the BD patients had no coexisting CDL condition. Over the six-year study period, the total number of BD patients with one or more coexisting CDL condition increased by 20.5% (n=122) (Table 3). The majority of these patients had either one (25.9% vs. 28.4%) or two (12.6% vs. 16.9%) other CDL conditions coexisting with BD respectively for 2010 and 2015. However, the increase in the mean number of coexisting CDL conditions per BD patient, from 2010 {0.85 (0.03) (CI 0.79 -0.91)} to 2015 {1.07 (0.03) (CI 1.01 – 1.14)} was practically insignificant ($P < .0001$; $d < .8$). There was no difference in the mean number of coexisting CDL conditions per patient ($P > .05$) between BD men and women (Table 3).

Table 3: Number of coexisting CDL conditions in BD patients in the closed cohort (N = 1 228)

Number of coexisting chronic conditions	**2010 n (%)**	**2011 n (%)**	**2012 n (%)**	**2013 n (%)**	**2014 n (%)**	**2015 n (%)**	***P-value***
0	634 (51.6)	585 (47.6)	570 (46.4)	546 (44.5)	533 (43.4)	512 (41.7)	
1	318 (25.9)	336 (27.4)	337 (27.4)	345 (28.1)	339 (27.6)	349 (28.4)	
2	155 (12.6)	185 (15.1)	179 (14.6)	182 (14.8)	188 (15.3)	207 (16.9)	
3	84 (6.8)	83 (6.8)	92 (7.5)	101 (8.2)	115 (9.4)	100 (8.1)	
4	26 (2.1)	29 (2.4)	33 (2.7)	41 (3.3)	41 (3.3)	46 (3.7)	
5	8 (0.7)	8 (0.7)	16 (1.3)	11 (0.9)	11 (0.9)	13 (1.1)	
6	3 (0.2)	1 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)	1 (0.1)	
7		1 (0.1)					
Number of CDL conditions per BD patient Mean (SD) [95% CI]	0.85 (0.03) [CI 0.79-0.91]	0.92 (0.03) [CI 0.85-0.98]	0.97 (0.03) [CI 0.90-1.04]	1.01 (0.03) [CI 0.95-1.08]	1.05 (0.03) [CI 0.98-1.12]	1.07 (0.03) [CI 1.01-1.14]	< .0001

The most prevalent coexisting CDL conditions in BD patients over the six-year study period were hypertension, hypothyroidism, hyperlipidaemia, type 2 diabetes mellitus, asthma and epilepsy (Table 4). There was a statistically significant increase in the proportion of BD patients, between 2010 and 2015 with the following CDL conditions: hypertension (22.8% vs. 30.9%; $P < .0001$), hypothyroidism (18.4% vs. 24.0%; $P < .0001$), hyperlipidaemia (17.0% vs. 21.5%; $P < .0001$), type 2 diabetes mellitus (7.2% vs. 9.2%; $P < .0001$), epilepsy (4.6% vs. 6.3%; $p = .0065$) and rheumatoid arthritis (1.1% vs. 1.9%; $P = .0253$). The number of BD patients with schizophrenia decreased statistically significantly from 2010 to 2015 (1.4% vs 0.6%; $P = .0184$).

Table 4: Type of coexisting CDL conditions in BD patients in the closed cohort (N = 1 228)

Coexisting CDL condition	2010 n (%)	2015 n (%)	*P-value*†
Addison's disease	1 (0.1)	1 (0.1)	
Asthma	77 (6.3)	83 (6.7)	.4386
Bronchiectasis	0 (0)	0 (0)	
Cardiac failure	14 (1.1)	16 (1.3)	.5271
Cardiomyopathy	3 (0.2)	0 (0)	
Chronic obstructive pulmonary disease	3 (0.2)	8 (0.6)	.0588
Chronic renal disease	0 (0)	0 (0)	
Coronary artery disease	11 (0.9)	0 (0)	
Crohn's disease	2 (0.2)	2 (0.2)	
Diabetes insipidus	0 (0)	0 (0)	
Type I diabetes mellitus	4 (0.3)	3 (0.2)	.6547
Type 2 diabetes mellitus	88 (7.2)	113 (9.2)	<.0001
Dysrhythmias	8 (0.6)	12 (0.9)	.2059
Epilepsy	57 (4.6)	77 (6.3)	.0065
Glaucoma	14 (1.1)	20 (1.6)	.0833
Haemophilia A & B	0 (0)	0 (0)	
Hyperlipidaemia	209 (17.0)	264 (21.5)	<.0001
Hypertension	280 (22.8)	380 (30.9)	<.0001
Hypothyroidism	226 (18.4)	295 (24.0)	<.0001
Multiple sclerosis	4 (0.3)	0 (0)	
Parkinson's disease	8 (0.6)	10 (0.8)	.5271
Rheumatoid arthritis	14 (1.1)	24 (1.9)	.0253
Schizophrenia	17 (1.4)	7 (0.6)	.0184
Systemic lupus erythematosus	1 (0.1)	2 (0.2)	.3173
Ulcerative colitis	1 (0.1)	1 (0.1)	

†McNemar test

Table 5: Top 10 coexisting CDL conditions, alone or in combination, in BD patients in the closed cohort (N = 1 228)

CDL condition combinations	2010 n (%)	2015 n (%)	*P-value*†
BD only	634 (51.6)	512 (41.7)	
BD/hypothyroidism	104 (8.5)	103 (8.4)	.9042
BD/hypertension	90 (7.3)	112 (9.1)	.0218
BD/hyperlipidaemia	51 (4.2)	50 (4.1)	.8981
BD/hyperlipidaemia/hypertension	35 (2.9)	46 (3.7)	.0782
BD/asthma	25 (2.0)	21 (1.7)	.3711
BD/hypertension/hypothyroidism	23 (1.9)	49 (4.0)	<.0001
BD/epilepsy	22(1.8)	34 (2.8)	.0285
BD/hyperlipidaemia/hypothyroidism	20 (1.6)	25 (2.0)	.2971
BD/hyperlipidaemia/hypertension/hypothyroidism	10 (0.8)	22 (1.8)	.0186
BD/type 2 diabetes mellitus	10 (0.8)	11 (0.9)	.7389

†McNemar test

Table 5 indicates the ten most prevalent combinations of CDL conditions that co-occurred with BD. The BD-hypothyroidism combination was the most prevalent combination during 2010 (8.5%) vs. 2015 (8.4%), followed by BD-hypertension (7.3% vs. 9.1%), and BD-hyperlipidaemia (4.2% vs. 4.1%). The hypertension-hypothyroidism combination was the most prevalent chronic condition-combination with BD during 2010 (2.9%) vs. 2015 (3.7%). There was a statistically significant increase in the number of BD patients who were newly registered with the following combination of CDL conditions: BD with hypertension (P = .0218); BD with hypertension and hypothyroidism (P < .0001); BD with epilepsy (P = .0285); and BD with hyperlipidaemia, hypertension and hypothyroidism (P = .0186).

DISCUSSION

Although the total number of BD patients with one or more coexisting CDL conditions in the closed cohort increased with 20.5% from 2010 to 2015, there was no significant increase in the mean number of coexisting CDL conditions per BD patient over the study period (Table 3).

The prevalence of BD (5.9 in 2010 to 7.9 in 2015 per 1 000 beneficiaries) (Figure 2) found in this study is almost the same as what a South African pharmaceutical benefit management company, Mediscor, reported in 2015 (6.9 per 1 000 beneficiaries) (Bester, Badenhorst, Greeff, & De Jager, 2015). It is, however, higher than the estimated BD prevalence in the medical scheme environment of South Africa (1.9 to 3.9 per 1 000 beneficiaries) as reported by the Research and Monitoring Unit of the Council for Medical Schemes (2017) for the same study period. This may

be due to the uniqueness of medical schemes (open or closed) and characteristics of medical scheme members on the different databases used.

Also in this study, the prevalence of BD (0.6% to 0.8%) (Table 2) over the study period is less than the 12-month prevalence rates of BD in the United States of America (2.1%), higher than that of Europe and Asia for BD-I (0.4%) and for BD-II (0.3%) and similar to that reported for South African males and females (0.6% and 0.8%) (Blanco *et al.,* 2017; Ferrari *et al.*, 2016; Merikangas *et al.*, 2011).

Gender and age are among the factors that influence the prevalence of BD (Kwajaffa *et al.*, 2016; Schoeyen *et al.*, 2011). The majority (70%) (Table 2) of BD patients in this study were females, with higher incidence rates (2.9 in 2011 *vs*. 2.6 in 2015) than males (1.7 in 2011 *vs*. 1.6 in 2015) (Figure 2)**.** Females, in general, have a higher susceptibility to BD as a result of female hormones and reproductive factors (Kennedy *et al.,* 2005).

The majority (over 90%) (Table 2) of BD patients in the study were above 18 years of age. This is comparable to the studies conducted in the United States of America (26 years), the north-eastern part of Nigeria (25 to 34 years) and Cairo, Egypt (18 to 55 years) (Asaad *et al.*, 2014; Blanco *et al.*, 2017; Kwajaffa *et al.,* 2016). The mean age of BD patients in this study was 43 years, which is higher than what was reported in the northern (28 years) and south-eastern (33 years) parts of Nigeria (Aiyelero *et al.*, 2011; Onyeama, Agomoh, & Jombo, 2010). Bipolar disorder often develops in a person's late teens or early adult years. At least half of all cases start before the age of 25 years. Bipolar disorder in later life is a complex and confounding neuropsychiatric syndrome with diagnostic and therapeutic challenges (Kennedy *et al.,* 2005).

Various factors predispose BD patients to additional chronic conditions, *inter alia*, medication side effects, unhealthy lifestyles, deprived access to healthcare services, socioeconomic status and biological predisposition (Evans-Lacko, Zeber, Gonzalez, & Olvera, 2009). Although the total number of BD patients with one or more coexisting CDL condition increased from 48.4% in 2010 to 58.3% in 2015, the increase in the mean number of coexisting CDL conditions per BD patient was practically insignificant ($P < .01$; $d < .8$). The high level of coexisting chronic conditions observed in this study may have been due to the majority of BD patients in the closed cohort being adults (mean age of 43 years). This may be supportive to what was reported in the USA (Beyer, Kuchibhatla, Gersing, & Krishnan, 2005) that the number of coexisting chronic conditions increases with age in BD patients. This increase was independent of gender.

Sub-optimal psychosocial activities in BD patients and antipsychotic medications have the potential to cause significant increases in weight gain, and negatively influence insulin sensitivity and lipid metabolism, thereby predisposing BD patients to hypertension, type 2 diabetes mellitus and hyperlipidaemia (Hajek *et al.*, 2015; Yumru *et al.*, 2007).

Hypothyroidism is the most common thyroid dysfunction in BD patients (Kilbourne *et al.*, 2004; Martino & Strejilevich, 2015). Hypothyroidism, to a larger extent, may be as a result of the side-effect of lithium, as reported in China (Zhang *et al.,* 2006). Asthma, as another chronic condition coexisting with BD, may be linked to a particular subtype of BD that has mood reactivity and temperamental mood instability features (Perugi *et al.*, 2015). Epilepsy is one of the neurological medical conditions that co-exist with BD; however, the reason is yet unknown (Knott, Forty, Craddock, & Thomas, 2015). Bipolar disorder patients may also be susceptible to auto-immune diseases such as rheumatoid arthritis (SayuriYamagata, Brietzke, Rosenblat, Kakar, & McIntyre, 2017). It was therefore no surprise that hypertension, hypothyroidism, hyperlipidaemia, type 2 diabetes mellitus and asthma (Table 4) were the most prevalent coexisting chronic conditions in our study population over the six-year period. There was also a statistically significant increase in the proportion of BD patients from 2010 to 2015 who were newly registered with hypertension ($P < .0001$), hypothyroidism ($P < .0001$), hyperlipidaemia ($P < .0001$) and type 2 diabetes mellitus ($P < .0001$), but there was no statistically significant increase in epilepsy ($p = .0065$) and rheumatoid arthritis ($P = .0253$).

The most prevalent three chronic conditions-combinations coexisting with bipolar disorder patients in our study were also hypertension, hyperlipidaemia and hypothyroidism (Table 5). This is similar to studies conducted in northern Taiwan, Canada and Poland (Chen *et al.*, 2017; Hajek *et al.*, 2015; Wysokiński, Strzelecki, & Kłoszewska, 2015).

LIMITATION OF THIS STUDY

The total population counted in the database, reflects the claiming portion of the population. The portion of the population that did not claim any medication during the study period was excluded, thus the prevalence and incidence of BD were overestimated.

We could not differentiate between the different classes of BD, which makes comparison with international epidemiological studies difficult.

We could not definitely determine whether the increase in prevalence of coexisting CDL conditions in BD patients occurred as a result of improved documentation and management of health information of CDL conditions by medical schemes and healthcare providers in South

Africa. We could also not determine whether it was the result of the uniqueness of the medical scheme members or the benefit design of medical schemes managed by the PBM.

A lack of clinical data on the BD patients made it difficult to determine whether medications used to treat BD resulted in the development of coexisting CDL conditions.

CONCLUSION AND RECOMMENDATIONS

This study established base-line information on the incidence and prevalence and coexisting chronic disease list conditions of BD patients in the private health sector of South Africa. The incidence of BD remained nearly the same through the study years; however, the medical scheme environment in South Africa should be concerned about an increased trend in the prevalence thereof.

The number of BD patients with one or more additional CDL conditions increased over the study period. Hypertension, hyporthyroidism, hyperlipidaemia, type 2 diabetes mellitus, rheumatoid arthritis and epilepsy were the most prevalent comorbidities with BD patients.

This study advises healthcare practitioners on the need to give utmost attention to hypertension, hyperlipidaemia, and type 2 diabetes mellitus among other comorbidities common in BD patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest with regard to the research, authorship and/or publication of this manuscript.

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3.3 Manuscript 2

Objective 3 from the empirical investigation is addressed in manuscript 2:

- To investigate possible changes, over a six-year period, in the medicine prescribing patterns for patients with only BD.

Manuscript 2 was prepared and will be submitted to the journal *Bipolar disorder.* The specific guidelines of the *Bipolar Disorder* Journal were given in Annexure H.

Trends in the psychopharmacological prescribing patterns among bipolar disorder patients in the South African private health sector

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Short running title: Prescribing in bipolar disorder patients

Abstract

Objectives: To investigate, over a six-year period, the possible changes in the psychopharmacological prescribing patterns among privately-insured South African patients diagnosed with bipolar disorder.

Method: The study followed a longitudinal open cohort design to analyse retrospective medicine claims data of patients identified with the diagnosis code ICD-10, F31, for bipolar disorder, on reimbursed medicine claims, from 1 Jan. 2010 to 31 Dec. 2015. Measurements included: i) different types of active pharmaceutical ingredients; ii) monotherapy *vs.* combination therapy; iii) number of medicine items per prescription; and iii) number of prescriptions per patient.

Results: The number of prescriptions per patient per year increased observably from 7.08(5.63) [6.94-7.23] to 7.50(5.59) [7.37-7.63] (P = .00001, Cohen's d-value = .4). The proportion of patients on combination therapy increased from 44.6% (2010) to 48.7% (2015). The most prevalent combination therapy in 2010 and 2015 was lamotrigine in combination with quetiapine or with a selective serotonin re-uptake inhibitor, or with bupropion or with valproate. The proportion of patients receiving anticonvulsants (35.4% *vs.* 34.7%), antidepressants (31.9% *vs*. 36.1%) and atypical antipsychotics (16.2% *vs.* 23.2%) as monotherapy increased significantly (P = .0001) from 2010 to 2015; the proportion of patients receiving lithium decreased marginally (4.9% *vs.* 4.2%) (P = .302).

Conclusions:

Major changes took place in the psychopharmacological prescribing patterns during the study period. The increase in combination therapy and the constant high use of antidepressant as monotherapy should be further investigated in the private-insured bipolar disorder population in South Africa.

KEYWORDS

Bipolar disorder, psychopharmacological prescribing patterns, private sector, South Africa

1. INTRODUCTION

Bipolar disorder is a recurrent psychiatric disorder characterised by uncommon fluctuations in mood, energy, activity levels and ability to carry out daily tasks as well as neuro-psychosocial deficit and functional impairment in memory, attention and executive functions.[1-6] Diagnosis of bipolar disorder varies from mania, hypomania, depression and unspecified bipolar and related disorders[5,6] with frequent recurrence that requires long-term management using various combinations of psychotropic drugs from different psychopharmacological groups.[6] Revision of medication therapy on a six-monthly basis is recommended.[6]

Based on prevalence, bipolar disorder is currently one of the top 10 chronic disease list conditions in South Africa, and has increased from 1.2 to 2.9 per 1 000 medical scheme beneficiaries at an average growth of 15.8% between 2010 and 2015.[7] The chronic disease list conditions are a list of 26 chronic diseases that are covered in the prescribed minimum benefits, meaning that medicine treatment, doctor consultations and laboratory tests should be covered by their medical schemes, independent of available benefits of the patient. To manage risk and ensure appropriate standards of healthcare, so-called treatment algorithms were developed for all chronic disease list conditions.[8] These algorithms are regarded as benchmarks or minimum standards for the treatment of the chronic disease list conditions, including bipolar disorder, in the private health sector in South Africa[8] and is similar to international treatment guidelines based on drugs and psychosocial treatments.[6, 9, 10, 11]

The treatment of bipolar disorder generally involves drugs from different psychopharmacological groups and non-pharmacological treatments, for example healthy diets, physical exercise, sleep hygiene, electroconvulsive therapy, cognitive behaviour, psycho-education, interpersonal- and social rhythm and family-focused therapies.[6,9-15] Recommended psychopharmacological treatments are categorised based on either therapeutic actions (i.e. antimanic agents, antidepressant agents and maintenance agents) or drug groups (mood stabilisers including anticonvulsants, antidepressants, antipsychotics, benzodiazepines and stimulants)[6,13,14] as mono- or combination therapy.[13]

Psychopharmacological treatment of bipolar disorder seems to be complicated due to its fluctuating nature. Because most bipolar disorder patients cannot tolerate the untoward effects of the therapy, treatment guidelines should be adaptable, with consideration of the individual patient characteristics, sociocultural context of the patient and the availability of treatment resources.[6,12-14,16,17] For acute symptoms of mania, treatment should be initiated with an antimanic agent, which includes lithium, anticonvulsants (e.g. valproate), atypical antipsychotics (e.g. olanzapine, aripiprazole, quetiapine, risperidone, ziprasidone, paliperidone), and to a lesser extent carbamazepine.[10] In comparison to monotherapy with either lithium or valproate alone, recent studies have shown superior efficacy of lithium or valproate in combination with the short-term administration of an atypical antipsychotic.[6,18,19] Gabapentin, lamotrigine, topiramate, phenytoin and oxcarbamazepine are not commended for the treatment of acute mania.[6,10] In the case of acute agitation and behavioural control, an injectable atypical antipsychotic or a combination of an injectable typical antipsychotic and a benzodiazepine is recommended.[6]

First-line monotherapy treatment choices for bipolar depression include quetiapine, lamotrigine, olanzapine, lithium, or valproate.[10,11,20] Suggested second-line options for bipolar depression include adjunctive risperidone, lithium and antidepressant combinations, olanzapine and fluoxetine combination, valproate and lithium combination, and lamotrigine as an add-on to lithium.[10] For concurrent psychotic symptoms, both in bipolar mania and depression, atypical antipsychotics can be used simultaneously;[20-24] however, combination of two antipsychotics drugs should be avoided.[6,10]

The benefits of conventional antidepressants (e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin and noradrenalin reuptake inhibitors) in the treatment of bipolar disorder are uncertain.[10] It is recommended that a conventional antidepressant should be administered concurrently with an antimanic maintenance agent to reduce the possibility of switching of moods.[6,10] Antidepressants should not be prescribed in rapid-cycling bipolar disorder;[10, 25] valproate, lithium, olanzapine, lamotrigine or quetiapine should rather be considered.[26, 27]

Maintenance treatment must be considered under the following conditions: i) if there has been a mood episode in the past five years; ii) if there have been two previous mood episodes over any time period; iii) severe acute episodes with psychotic features, or a suicide risk; and iv) ongoing functional disability.[6] Maintenance psychotherapy include lithium (mainly to prevent manic episodes), lamotrigine (mainly for preventing depressive episodes), valproate and atypical antipsychotics (e.g. olanzapine, aripiprazole, and quetiapine adjunctive to lithium or valproate).[10,11] Monotherapy is again the preferred choice of treatment modality.[10]

With the exception of a recent study[28] conducted at an outpatient clinic at a specialised psychiatric hospital in South Africa, little is known regarding medicine prescribing patterns for the treatment of private-insured bipolar disorder patients in South Africa. This study by Holzaphel and Szabo[28] also only included bipolar disorder patients diagnosed and treated in the public health sector. As such, there is a need to investigate changes in psychopharmacological prescribing patterns in bipolar disorder in the South African private health sector to ascertain the degree of consistency between psychopharmacological treatment patterns locally and internationally. The main objective of this study was, therefore, to investigate, over a six-year period, possible changes in the psychopharmacological prescribing patterns among patients diagnosed with only bipolar disorder in a section of the private health sector of South Africa.

2. METHOD

2.1 Research design

We employed a longitudinal open cohort design to analyse retrospective medicine claims data over a six-year period (1 Jan. 2010 to 31 Dec. 2015).

2.2 Data source

Nationally-representative medicine claims data were acquired from a privately-owned South African pharmaceutical benefit management company. This pharmaceutical benefit management

company is a large independent company that has been providing medicine claims processing services to approximately 1.8 million beneficiaries from 42 medical schemes in South Africa for over 25 years. There is continuously an enrolment and resignation of patients on the database because of changes in membership of patients on different medical schemes contracted with the pharmaceutical benefit management company for service delivery, and therefore the number of patients included each year is dependent on the patient combination. The reliability and validity of the data obtained from the pharmaceutical benefit management company were ascertained by the company's internal validation processes, such as gate-keeping services, eligibility services, utilisation management services, clinical management services and pricing management along with real-time benefit management.

The dataset consisted of patient demographics, and medication- and disease-related information. Patient demographics included the gender and date of birth, together with an encrypted medical scheme membership number that was used to follow-up patients' prescriptions over the six-year period. Information on the dispensed medication included the prescription number and date, the National Pharmaceutical Product Index (NAPPI) code of each medication, and the active pharmaceutical ingredient. Bipolar disorder patients were identified using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)[29] code, F31. The code on the database did not differentiate between the different types of bipolar disorders.

2.3 Study population

The open cohort consisted of all patients identified with the diagnosis code ICD-10[29] 'F31' for bipolar disorder on a medicine claim, reimbursed at least once per annum, during the six-year study period (1 Jan. 2010 to 31 Dec. 2015). These bipolar disorder patients did not have any of the other coexisting chronic disease list conditions that are covered through the prescribed minimum benefits as indicated in the South Africa Medical Scheme Act (131 of 1998).[8.]

2.4 Study variables

Independent variables for the study included the patient's gender and age. Patients' age was determined based on the date of the first prescription for medicine for a patient with the diagnosis code F31, and divided into two age groups: ≤18.2 years and >18.2 years, based on the results of the national comorbidity survey in the USA[30] showing that bipolar disorder initially occurred at an average age of 18.2 years (Bipolar disorder -I) and 20.3 years (Bipolar disorder -II).[30,31]

Dependent variables consisted of the medicine prescribing measures. Medication, according to active ingredients, was classified in different psychopharmacological groups as indicated in the Monthly Index of Medical Specialties (MIMS).[32]

In South Africa, a prescription can contain one or more medicine items; and a patient can receive more than one prescription in a month. Combination therapy was therefore defined as one or more psychopharmaceutic item(s) per prescription, or more than one prescription with a different active pharmaceutical ingredient during a month period. Change in medicine prescribing patterns

was therefore assessed by measuring change over the study period or between 2010 and 2015 in the: i) different types of active pharmaceutical ingredients according to pharmacological groups; ii) frequency of monotherapy (includes only one active pharmaceutical ingredient per prescription) or combination therapy (includes more than one active pharmaceutical ingredients in therapy, based on the last month's prescription(s) of a patient in 2010 and 2015); iii) average number of medicine items per prescription per patient per year; and iii) average number of prescriptions per patient per year, stratified per age and gender group.

2.5 Statistical analysis

Data were analysed using the SAS 9.4® (Statistical Analysis System®) program.[33] Variables were expressed using descriptive statistics, which include frequencies (*n*) presented as percentages (%), arithmetic means, standard deviations (SD) and 95% confidence intervals (CI). A *p*-value of .05 or less was considered statistically significant at a two-sided α-level. Practical significance of results was computed when the *p*-value was statistically significant.

The chi-square (χ^2) test was used to establish whether an association existed between proportions of two or more groups. The Cramér's *V* statistic was used to test the practical significance of association (practical significance was interpreted as follows: effect size of .1 was small; .3 effect size was medium and an effect size of .5 was large).[34]

One-way analysis of variance (ANOVA) was used to test for significant differences between: i) average number of prescriptions per patient for the different years; and ii) average number of medicine items per prescription per patient for the different years. If a difference was detected, *post-hoc* tests were used to determine where the differences lie. [35]

A two-sample *t*-test was used to compare the number of prescriptions per patient per year between the different gender and age groups. Cohen's *d*-value was considered for practical significance; the magnitude of the *d*-values was interpreted as follows: .2 a small effect, with no significant difference, > .2 and ≤ .8 a medium effect with an observable significance, > .8 a large effect and significant difference.[36]

McNemar's test[37] was used to measure whether there were statistically significant differences in the proportions of patients receiving the different psychopharmacological groups and active pharmaceutical ingredients in 2015 compared to 2010.

Table 1 depicts the demographic characteristics of the study population. Table 2 presents the medicine items and prescription information of psychopharmacological treatment for patients over the six-year study period. Differences in means in this table were calculated between 2010 and 2015 only. Table 3 illustrates the proportion of the psychopharmacological groups accounting for the top 90% in prescribing volume in 2010 and 2015. Table 4 then presents the sub-psychopharmacological groups and combinations included in bipolar disorder therapy accounting for 70% of the prescribing volume in 2010 *vs.* 2015, whereas Table 5 lists the psychopharmacological active pharmaceutical ingredients and combinations accounting for 50% of the prescribing volume in 2010 *vs*. 2015. Figure 1 shows the frequency of monotherapy and combination therapy in 2010 *vs*. 2015.

2.6 Ethical considerations

This study was approved by the Health Research Ethics Committee of North-West University (NWU-00179-14-A1) and the board of directors of the pharmaceutical benefit management company.

3. RESULTS

3.1 Patient demographics

The study population consisted of 3 627 bipolar disorder patients in 2010 and increased to 4 332 in 2015. This increase is the result of the addition of a constant number of *newly registered* bipolar disorder patients from 2011 to 2015. The majority of *newly registered* patients were older than 18.2 years old, and female (Table 1).

Table 1 Demographic characteristics of the study population

Variables	*Year*	2010	2011	2012	2013	2014	2015	*P*-value
BD patients n		3627	3851	4053	4380	4572	4332	
Newly registered BD patients n			1387	1379	1391	1267	1180	
Gender n (%)	Male	1094 (30.2)	464 (33.5)	479 (34.7)	482 (34.7)	450 (35.5)	409 (34.7)	.0005†
	Female	2533 (69.8)	923 (66.6)	900 (65.2)	909 (65.4)	817(64.5)	771 (65.3)	.
Age group (Year) n (%)	≤18.2	185 (5.1)	116 (8.4)	94 (6.8)	111 (8.0)	95 (7.5)	86 (7.3)	.0005‡
	>18.2	3442 (94.9)	1271 (91.6)	1285 (93.2)	1280 (92.0)	1172 (92.5)	1094 (92.7)	
Average age (Year) Mean (SD) [95% Cl]		38.3 (13.9) [37.8 – 38.8]	35.5 (13.7) [34.9 – 36.3]	35.6 (12.9) [34.9 – 36.3]	35.1 (13.1) [34.4 – 35.8]	35.1 (13.2) [34.4 – 35.9]	35.4 (12.9) [34.7 – 36.2]	.0001§

BD: Bipolar disorder

† Chi-square (χ^2) test, Cramér's V = .0464)

‡ Chi-square (χ^2) test, Cramér's V = .0509)

§ ANOVA, Tukey multiple comparison test, Cohen's d-value < .8 for all possible combinations

SD: Standard deviation; Cl: Confidence interval

3.2 Prescription information

The average (SD) [95% CI] number of items per prescription per patient per year did not change significantly from 2010 (1.90(0.93) [1.90-1.92]) to 2015 (2.01(0.98) [1.99-2.03]). The average number of prescriptions per patient increased observably from 7.08 (5.63) [6.94-7.23] in 2010 to 7.50 (5.59) [7.37-7.63] in 2015 (P < .0001, Cohen's d-value = .4). The average number of prescriptions per patient also increased observably from 2010 to 2015 in patients aged ≥18 years, and in both male and female groups (P < .0001, Cohen's d-value = .4) (Table 2).

Only for 2010 and 2011, an observable significantly higher average number of prescriptions per patient was found for patients older than > 18 years than for those ≤18.2 years (P < .05, Cohen's d > .2). No observable gender differences were found between the average number of prescriptions per patient per year (P <.05; Cohen's *d-value* < .2) (Table 2).

Figure 1 illustrates the number of active pharmaceutical ingredients per prescription (last prescription) as indication of monotherapy or combination therapy for 2010 *vs*. 2015. The results reveal that 55.4% (n = 2008) of patients received monotherapy in 2010 and 51.3% (n = 2221) in 2015. Combination therapy increased from 44.6% (n = 1619) in 2010 to 48.7% (n = 2111) in 2015.

Table 2 Medicine items and prescription information of psychopharmacological treatment of bipolar disorder patients: 2010-2015

		2010	2011	2012	2013	2014	2015	*P*-value† 2010 *vs*. 2015
Items per prescription per patient	N_{Items}	83 152	96 107	105 973	112 808	126 250	111 591	
	Mean (SD) 95% CI	1.90(0.93) [1.90-1.92]	1.90(0.93) [1.88-1.93	1.92(0.94) [1.90-1.94-]	1.96(0.96) [1.94-1.98]	1.98(0.97) [1.96-2.00]	2.01(0.98) [1.99-2.03]	< .0001 .0
Prescriptions per patient	$N_{Prescriptions}$	42 413	48 086	52 903	56 042	61 243	53 554	
	Mean (SD) 95% CI	7.08(5.63) [6.94-7.23-]	7.25(5.71) [7.11-7.39-]	7.42(5.75) [7.29-7.55-]	7.35(5.48) [7.22-7.47-]	7.78(5.72) [7.65-7.91]	7.50(5.59) [7.37- 7.63]	< .0001 .4
Gender $n_{Prescriptions}$ Mean (SD) 95% CI	Male	11 603	13 727.00	15 946.00	16 340.00	17 708.00	16 372.00	
		6.79(5.10) [6.55-7.03]	7.07(5.42) [6.83-7.31]	7.39(5.75) [7.15-7.63]	7.05(5.31) [6.83-7.26]	7.39(5.52) [7.18-7.62]	7.33(5.06) [7.12-7.54]	<.0001 .4
	Female	30 810	34 359	36 957	39 702	43 535	37 182	
		7.21(5.82) [7.03-7.38]	7.32(5.82) [7.16-7.49]	7.43(5.74) [7.27-7.59]	7.48(5.54) [7.33-7.63]	7.95(5.79) [7.79-8.10]	7.58(5.81) [7.41-7.74]	<.0001 .3
	P–value‡	.0092 .1	.1016	.0001 .0	.0014 .1	.0001 .1	.0816	
Age group (years) $n_{Prescriptions}$ Mean (SD) 95% CI	≤18.2	1 561	2 432	2 783	3 030	3 194	2 778	
		5.15(4.08) [4.69-5.61]	6.11(5.25) [5.59-6.62-]	6.87(5.84) [6.30-7.44-]	6.46(5.59) [5.95-6.97]	6.78(5.47) [6.28-7.28]	6.57(5.14) [6.07-7.05]	<.0001 .2
	>18.2	40 852	45 654	50 120	53 012	58 049	50 776	
		7.19(5.68) [7.04-7.33]	7.32(5.73) [7.18-7.46-]	7.45(5.74) [7.31-7.59]	7.41(5.47) [7.28-7.53]	7.84(5.73) [7.97-7.71]	7.56(5.61) [7.69-7.42]	< .0001 .4
	P–value‡	< .0001 .4	<.0001 .2	.0473 .1	0.0003 .2	<.0001 .2	.0004 .2	

† ANOVA, Tukey multiple comparison test, Cohen's *d*-value.
‡ Two-sample *t*-test, Cohen's *d*-value.
SD: Standard deviation; CI: Confidence interval

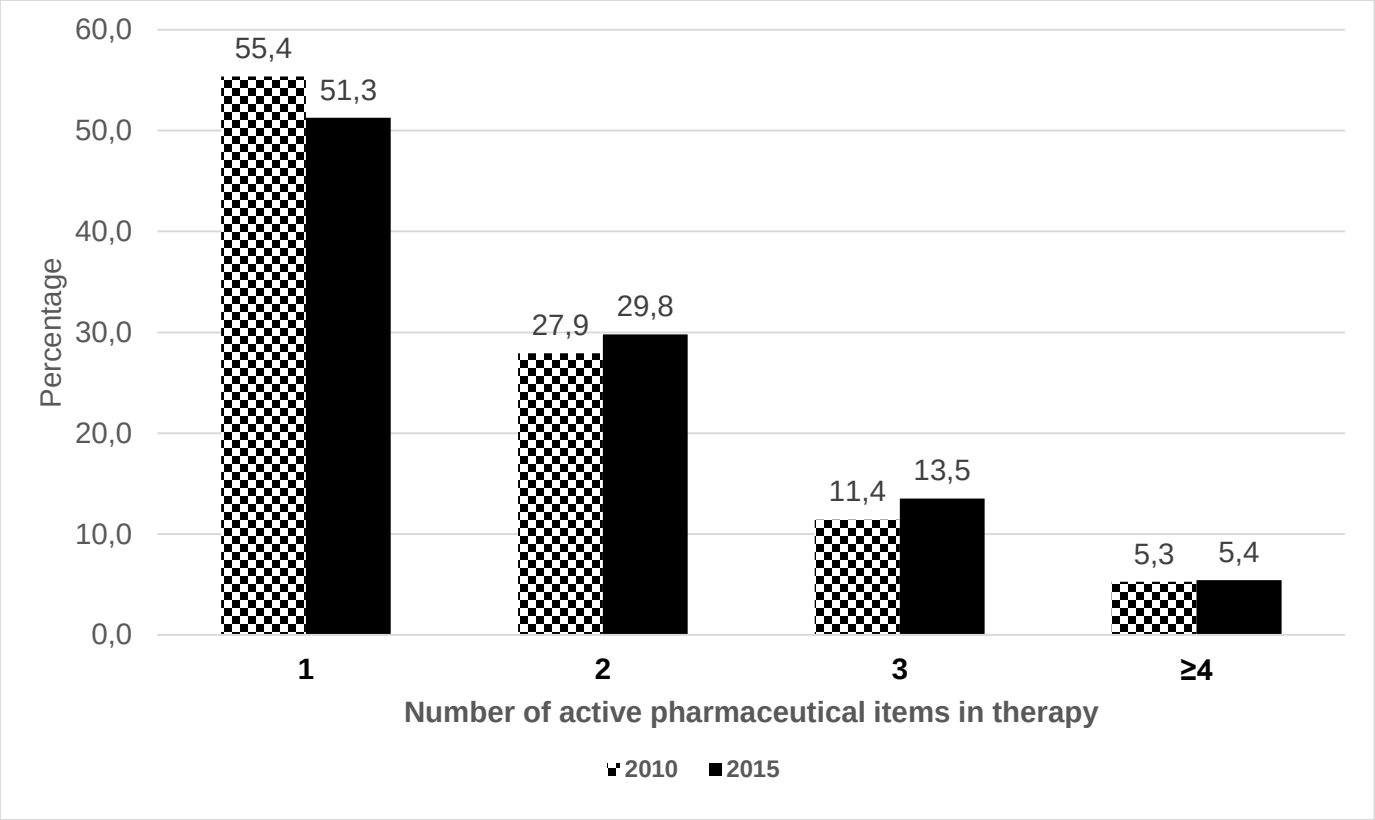

Fig 1. Number of active pharmaceutical ingredients in therapy: 2010 vs. 2015

Table 3 illustrates the psychopharmacological groups prescribed to patients in 2010 and 2015 accounting for 90% of the prescribing volume. The majority of patients on monotherapy received prescriptions containing an anticonvulsant (35.4% *vs*. 34.7%), antidepressant (31.9% *vs*. 36.1%), or antipsychotics drug (16.2% *vs*. 23.2%) in 2010 and 2015, respectively. McNemar's test confirmed a significant difference, with an increasing trend in the proportion of patients treated with antidepressants ($P < .0001$), antipsychotics ($P < .0001$) and anticonvulsants ($P < .0001$) as monotherapy in 2010 *vs*. 2015 (Table 3).

The most prevalent combination therapy for both 2010 and 2015 consisted of an antidepressant with an anticonvulsant drug (22.0% *vs.* 22.4%), an antipsychotic with an anticonvulsant drug (9.9% *vs*. 14.6%); two anticonvulsants (11.1% *vs.* 12.7%) and an antidepressant with an antipsychotic and anticonvulsant drug (9.0% *vs.* 11.5%) (Table 3). The proportions of patients who received these four top combinations were significantly higher in 2015 than in 2010 ($P < .0001$). The results in Table 5 indicate the specific active pharmaceutical ingredients involved in these four top combinations, including: i) serotine- and noradrenaline re-uptake inhibitors (SSRIs) (e.g. escitalopram, sertraline, citalopram) in combination with lamotrigine; ii) norepinephrine-dopamine reuptake inhibitors (NDRIs), namely bupropion in combination with lamotrigine; iii) the antipsychotic, quetiapine, in combination with anticonvulsant, lamotrigine; and iv) lamotrigine and valproate.

Table 3: Top 90% of psychopharmacological groups and combinations in bipolar disorder therapy: 2010 *vs.* 2015

Psychopharmacological group	2010				2015				*P*-value†
	Patients (N = 3627)		Prescriptions (N = 42 413)		Patients (N = 4332)		Prescriptions (N = 53 554)		
	n	%	n	%	n	%	n	%	
AC	1283	35.4	6930	19.8	1505	34.7	6390	15.1	<.0001
AD	1156	31.9	6051	17.3	1562	36.1	6663	15.7	<.0001
AD/AC	797	22.0	4251	12.2	1058	24.4	4723	11.1	<.0001
AP	587	16.2	2680	7.7	1005	23.2	3834	9.0	<.0001
AC/AC	401	11.1	1845	5.3	549	12.7	2166	5.1	<.0001
AP/AC	358	9.9	1538	4.4	632	14.6	2487	5.9	<.0001
AD/AP/AC	326	9.0	1505	4.3	497	11.5	2094	4.9	<.0001
AD/AP	326	9.0	1438	4.1	525	12.1	2044	4.8	<.0001
AD/AC/AC	222	6.1	1072	3.1	351	8.1	1470	3.5	<.0001
AD/AD	242	6.7	986	2.8	327	7.5	1050	2.5	<.0004
AD/AD/AC	205	5.7	865	2.5	263	6.1	1094	2.6	.0073
AP/AC/AC	142	3.9	585	1.7	245	5.7	930	2.2	<.0001
AD/AP/AC/AC	133	3.7	525	1.5	217	5.0	894	2.1	<.0001
AD/AD/AP/AC	110	3.0	441	1.3	137	3.2	604	1.4	.0858
AD/AD/AP	87	2.4	374	1.1	155	3.6	576	1.4	<.0001
AC/AC/AC	97	2.7	389	1.1	124	2.9	526	1.2	.0693

AC= Anticonvulsants; AD= Antidepressants; AP= Antipsychotics
†-McNemar test on patient data

Lithium was only prescribed to 4.9% of patients in 2010 and to 4.2% of patients in 2015. No significant difference was found in the proportion of patients who used lithium as monotherapy in 2010 *vs*. 2015 (Table 4).

The results in Table 5 indicate that the most prescribed anticonvulsant as monotherapy for both 2010 and 2015 consisted of lamotrigine (21.7% *vs.* 22.3%), followed by valproate (9.8% *vs.* 12.5%), and topiramate (2.6% *vs*. 0.7%) (Table 5). The proportion of patients treated with lamotrigine or valproate in 2010 changed significantly, with an increasing tendency in 2015 ($P < .0001$). The proportion of patients who received topiramate in 2010 decreased significantly towards 2015 ($P < .0001$).

Table 4 shows that, on sub-pharmacological level, the atypical antipsychotic drugs were the second most frequently prescribed monotherapy in both 2010 (14.9%) and 2015 (23.0%) (Table 4). The most prescribed atypical antipsychotic drug was quetiapine-containing items presenting 8.5% in 2010 and 14.2% in 2015 (Table 5). The proportion of patients who received quetiapine as monotherapy was significantly higher in 2015 than in 2010 ($P < .0001$) (Table 5). Although less prescribed, similar trends were observed with the other atypical antipsychotics, olanzapine and risperidone (Table 5).

Selective serotonin re-uptake inhibitors (SSRIs) (e.g. escitalopram, citalopram, fluoxetine, and sertraline) were the most prevalent antidepressant group prescribed as monotherapy for both years, with the proportion of patients in 2015, significantly higher than the proportion in 2010 ($P < .0001$) (Table 4). There was no difference in the proportion of patients who received escitalopram,

and citalopram in 2010 *vs*. 2015 (*P* < .0001). The proportion of patients who received fluoxetine and sertraline increased significantly from 2010 to 2015.

The other antidepressants that were prescribed as monotherapy were the SNRIs (e.g. venlafaxine, duloxetine), NDRIs (e.g. bupropion) and tetracyclic (e.g. trazodone). The proportion of patients receiving the SNRIs as monotherapy decreased significantly from 2010 to 2015 (*P* < .0001) (Table 4), confirmed by the prescribing patterns of venlafaxine and duloxetine (*P* < .0001) (Table 5). The results in Table 4 confirmed that the proportion of patients receiving the antidepressants, NDRIs and tetracyclic antidepressants, increased significantly from 2010 to 2015 (*P* < .0001).

Table 4: Top 70% of sub-psychopharmacological groups and combinations included in bipolar disorder therapy: 2010 vs 2015

Sub-psychopharmacological group	2010				2015				*P*-value†
	Patients (N =3627)		Prescriptions (N = 42 413)		Patients (N = 4332)		Prescriptions (N = 53 554)		
	n	%	n	%	n	%	n	%	
AC	1283	35.4	6930	19.8	1504	34.7	6387	15.0	<.0001
AA	542	14.9	2485	7.1	996	23.0	3788	8.9	<.0001
SSRI	583	16.1	2356	6.8	779	18.0	2697	6.4	<.0001
SSRI/AC	444	12.2	2302	6.6	561	13.0	2493	5.9	.0002
AC/AC	401	11.1	1845	5.3	549	12.7	2166	5.1	<.0001
AA/AC	331	9.1	1449	4.2	622	14.4	2448	5.8	<.0001
SNRI	264	7.3	1244	3.6	286	6.6	1267	3.0	<.0001
L	178	4.9	1021	2.9	198	4.6	883	2.1	.3023
T	201	5.5	844	2.4	406	9.4	1358	3.2	<.0001
SSRI/AA/AC	143	3.9	730	2.1	260	6.0	1128	2.7	<.0001
SNRI/AC	140	3.9	694	2.0	161	3.7	666	1.6	.2261
SSRI/AA	133	3.7	593	1.7	260	6.0	954	2.3	<.0001
AA/AC/AC	133	3.7	562	1.6	243	5.6	926	2.2	<.0001
T/AC	109	3.0	534	1.5	242	5.6	1028	2.4	<.0001
SSRI/AC/AC	116	3.2	179	0.5	191	4.4	799	1.9	<.0001
NDRI	6	0.2	11	0.03	198	4.6	883	2.1	<.0001

AC= Anticonvulsant; SSRI= Selective serotonin re-uptake inhibitors; SNRI= Serotonine and noradrenaline re-uptake inhibitors; NDRI= Noradrenaline (and dopamine) re-uptake inhibitors; T= Tetracyclic;
L= Lithium; AA= Atypical antipsychotics
†-McNemar test on patient data

Table 5: Top 50% of active pharmaceutical ingredient and combination in bipolar disorder therapy: 2010 vs 2015

Active pharmaceutical ingredient	2010				2015				*P*-value†
	Patients (N = 3627)		Prescriptions (N = 42 413)		Patients (N = 4332)		Prescriptions (N = 53 554)		
	n		n	%	n		n	%	
Lamotrigine	787	21.7	5229	14.3	964	22.3	5265	12.4	<.0001
Valproate	356	9.8	1702	4.9	541	12.5	1740	4.1	<.0001
Quetiapine	310	8.5	1321	3.8	616	14.2	2301	5.4	<.0001
Lithium	178	4.9	1021	2.9	198	4.6	883	2.1	.3023
Venlafaxine	158	4.4	780	2.2	175	4.0	823	1.9	.3515
Lamotrigine/quetiapine	112	3.1	466	1.3	217	5.0	836	2.0	<.0001
Escitalopram	201	5.5	749	2.1	216	5.0	780	1.8	.4626
Bupropion	149	4.1	595	1.7	232	5.4	765	1.8	<.0001
Escitalopram/lamotrigine	97	2.7	535	1.5	110	2.5	559	1.3	.3662
Fluoxetine	123	3.4	526	1.5	178	4.1	564	1.3	.0015
Bupropion/lamotrigine	64	1.8	370	1.1	128	3.0	565	1.3	<.0001
Citalopram	122	3.4	465	1.3	120	2.8	364	0.9	.8977
Olanzapine	100	2.8	461	1.3	140	3.2	494	1.2	<.0098
Citalopram/lamotrigine	71	2.0	453	1.3	65	1.5	354	0.8	.6069
Risperidone	91	2.5	334	1.0	134	3.1	470	1.1	<.0041
Duloxetine	110	3.0	446	1.3	89	2.1	364	0.9	.1366
Lamotrigine/valproate	75	2.1	368	1.1	11	0.3	240	0.6	<.0001
Topiramate	96	2.6	359	1.0	32	0.7	111	0.3	<.0001
Carbamazepine	80	2.2	290	0.8	95	2.2	363	0.9	.2586
Trazodone	87	2.4	305	0.9	103	2.4	309	0.7	.2457
Sertraline	88	2.4	296	0.9	215	5.0	780	1.8	<.0001
Sertraline/lamotrigine	44	1.2	219	0.6	110	2.5	456	1.1	<.0001
Aripiprazole	105	2.9	137	0.4	325	7.5	326	0.8	<.0001

†McNemar test on patient data

DISCUSSION

This is the first longitudinal study on prescribing patterns among patients diagnosed with bipolar disorder in the medical scheme environment in the private health sector of South Africa. With continuous registration and deregistration of patients, the number of patients included in this study increased from 3 627 in the index year (2010) to 4 332 in 2015. The increased trend in the number of bipolar disorder patient is in accordance with national trends reported by the Research and Monitoring Unit of the Council for Medical Schemes.[7]

The current study has shown a predominantly female population, with an increasing trend in the proportion of new male patients per year over the study period, with a male:female ratio of 1:2.3 in 2010 and 1:1.88 in 2015 (P = .0005, Cramér's V = .1). Females, in general, have a higher susceptibility to bipolar disorder as a result of female hormones and reproductive factors[30] with a tendency to ask more readily for help for healthcare problems than male patients[38]. The majority of patients in this study were older than 18.2 years; however, the average age of newly registered patients decreased from 2011 to 2015 (P < .0001). This is comparable to studies conducted in Denmark,[39] the United States of America (26 years)[40], the north-eastern part of Nigeria (25 to 34 years)[41] and Cairo, Egypt (18 to 55 years).[42]

Major changes took place in the type of psychopharmacological prescribing during the study period. Although the average numbers of medicine items per prescription stay constant at two

medicine items per prescription through the study years, the number of prescriptions per patient increased observably from 7.08 (5.63) [6.94-7.23-] to 7.50 (5.59) [7.37- 7.63] (*P* = .0001, Cohen's *d*-value = .4).

The current study confirmed a substantial increase in combination therapy from 44.6% in 2010 to 48.7% in 2015. These results are lower compared to international studies that estimate combination therapy prevalence between 50% and 60%.[39,43] A recent study, performed in an outpatient clinic at a specialised psychiatric hospital in South Africa, indicates that 93% of bipolar disorder patients received combination therapy, which is higher than our study.[28] This difference can be explained by a study that indicates that bipolar disorder patients managed in a specialist psychiatric setting, have a greater chance of being managed with combination therapy than in a general practice[44]. The acceptability of prescribing combination therapy based on the severity of the illness is supported by the South African and international treatment guidelines;[6,11,45,46] however, there is controversy in the literature regarding the standard of clinical trials that support the use of combination treatment.[47]

The most prevalent combinations consisted of: i) the antipsychotic, quetiapine in combination with anticonvulsant, lamotrigine; ii) SSRIs (e.g. escitalopram, sertraline, citalopram) in combination with lamotrigine; iii) NDRIs, namely bupropion in combination with lamotrigine; and iv) lamotrigine and valproate. The proportions of patients who received the combination quetiapine with lamotrigine, or sertraline in combination with lamotrigine, or the combination bupropion with lamotrigine in 2010, changed observably towards 2015, with an increasing trend (*P* > .0001). The proportions of patients who received a combination of escitalopram or citalopram with lamotrigine in 2010 did not change towards 2015. No combination with lithium was prevalent in the top 50% of active pharmaceutical ingredients based on prescription volume.

Various treatment guidelines recommend that the first-line monotherapy treatment choices for bipolar depression should include quetiapine, lamotrigine, olanzapine, lithium, or valproate.[6,10,11] The majority of patients on monotherapy in the current study received an anticonvulsant, or antidepressant, or antipsychotic drug. The proportions of patients who received these items in 2010 increased significantly towards 2015 (*P* > .0001). The anticonvulsants moved from the first monotherapy position in 2010 to the second position in 2015. In contrast, antidepressants moved from the second position in 2010 to the most prevalent prescribed monotherapy in 2015. Although there was an increase in the prescribing of antipsychotics through the study years, they stayed, as a group, in the fourth position. The combination therapy consisting of an antidepressant with an anticonvulsant was in the third position.

Among the anticonvulsants, lamotrigine was prescribed most in both 2010 and 2015 at 21.7% vs. 22.3%, followed by valproate (9.8% vs. 12.5%) and topiramate (2.6% vs. 0.7%), respectively. The proportion of patients treated with lamotrigine or valproate also increased significantly from 2010 to 2015 (*P* < .0001), whereas that for topiramate decreased significantly (*P* < .0001). Prescribing of lithium as monotherapy decreased marginally from 4.9% in 2010 to 4.2% in 2015. Although this decrease was not found statistically significant, the trend observed is in accordance with the overall results of a large population-based, national study in Denmark that observed an increase in the use of lamotrigine and valproate and a decrease in the use of lithium.[39]

Lamotrigine is recommended for the management of bipolar depression and bipolar maintenance, whereas valproate is indicated for patients with a manic/mixed episode in accordance with the treatment guidelines.[6, 11,45,46,48] Lamotrigine does not require blood level monitoring, which may be a preferred choice by clinicians for patients on an outpatient basis.

The prescribing trends of atypical antipsychotic drugs found in our study is similar to trends observed in various other international studies.[39,49] The atypical antipsychotic drugs were the second most frequent prescribed monotherapy in 2010 (14.9%) and 2015 (23.0%). No typical antipsychotics contributed to the top 50% of active pharmaceutical ingredients prescribed in 2010 or 2015 in our study population. The South African bipolar disorder treatment guidelines[6] include the use of typical (haloperidol) as well as atypical antipsychotics for manic/hypomanic episodes; however, most international guidelines only refer to atypical antipsychotics as monotherapy or combination therapy with standard mood stabilisers (e.g. anticonvulsants or lithium).[45,46] This increase in the atypical antipsychotic drugs was mostly the result of an observable significant increase in the prescribing of quetiapine-containing items from 2010 to 2015 ($P < .0001$). Although the other atypical antipsychotics, olanzapine and risperidone, were less prescribed in our study, the same increasing trends were observed.

International and national bipolar treatment guidelines suggest careful use of antidepressants in bipolar disorder patients[6,11,45,46] Antidepressants should be used in combination with an antimanic medication (standard mood stabilizer, antipsychotic) to prevent a manic switch or rapid cycling.[6,11] The current study found that 31.9% of patients received an antidepressant as monotherapy in 2010 and 36.4% in 2015. A further 22.0% and 24.4% of patients received a combination of antidepressant with an anticonvulsant in 2010 and 2015, respectively.

The SSRIs were the most prevalent antidepressant group prescribed as monotherapy for both years (16.1% *vs*. 18.0%), with an increasing trend from 2010 to 2015. Other antidepressants prescribed as monotherapy included the SNRIs (e.g. venlafaxine, duloxetine), NDRIs (e.g. bupropion) and tetracyclics (e.g. trazodone). The prescribing of SNRIs as monotherapy decreased, whereas that of the NDRIs and tetracyclic antidepressants increased significantly from 2010 to 2015 ($P < .0001$). This decrease in the prescribing of SNRIs may be due to a relatively higher risk of inducing a manic switch than the SSRIs[12]. However, because of a lack of clinical data, it was not possible to distinguish between the episodes of bipolar disorder.

Our study has a number of limitations, which should be taken into account by the reader. First and foremost, this study included only private-insured bipolar disorder patients enrolled in a nationally-representative medicine claims database that was acquired from a South African PBM company. Therefore, the findings cannot be generalised to bipolar disorder patients who received their medication from public health facilities in South Africa or private patients who are responsible for their own medical expenses. The pharmaceutical benefit management company that provided the medicine claims data for the study, furthermore does not include prescription data during hospital admissions. There is also a small possibility that patients may be taking medication that was not claimed through their medical scheme, and therefore is not included in the database.

Secondly, we could not differentiate between the prescribing patterns for the different types of bipolar disorders because of a lack of clinical information. Patients were identified using the ICD-

10 code, F31, which did not distinguish between the different types of bipolar disorders (e.g. bipolar I disorder, bipolar II disorder, cyclothymic disorder and rapid cycling).[7] We also could not exclude the possibility that the proportion of the different subtypes changed during the study period or between 2010 and 2015, which could have an influence on prescribing patterns.

Thirdly, the prescribed daily doses of the active pharmaceutical ingredients and the possible influence of the type of prescribing practitioner on prescribing patterns were not included in this study. Therefore, it should be included in further investigations. The possible influence of coexisting chronic disease list conditions on prescribing patterns was discounted by excluding patients with any registered chronic disease list conditions that are covered through the prescribed minimum benefits as indicated in the South Africa Medical Scheme Act (131 of 1998).[8]

Despite the limitations outlined, our findings suggest a number of important trends in the psychopharmacological treatment of bipolar disorder in private-insured patients in South Africa, which should further be investigated. The increase in combination therapy and the constantly high use of antidepressants as monotherapy should be further investigated in the private-insured bipolar disorder population in South Africa.

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CHAPTER 4: CONCLUSION AND RECOMMENDATIONS

4.1 Introduction

The purpose of this chapter is to review how the research objectives, as outlined in Chapter 1, were met, as well as to discuss the results that were reported in two manuscripts in Chapter 3. Finally, it identifies the limitations and strengths of the study and also provides recommendations for future research studies.

4.2 Conclusion derived from the literature study

The literature objectives include the following:

- To conceptualise the prevalence of BD and its comorbidities, nationally and internationally.
- To identify current treatment guidelines of BD by focusing on both national and international published consensus treatment guidelines from the literature.

The following conclusions were drawn after meeting the literature objectives:

4.2.1 Conceptualisation of the prevalence of BD and its comorbidities, nationally and internationally

Bipolar disorder is defined as a recurrent and chronic mental disorder, characterised as mania, major depression and hypomania and associated with a decline in functional and cognitive capacity (memory, attention and executive functions) as a result of lack of stability in mood, energy and activity levels as well as neuropsychosocial deficit (Bauer *et al.,* 2001:231; Best *et al*., 2017:406; Cardoso *et al.,* 2016:225; Goodwin, 2016:661; Goodwin *et al.*, 2016:508; Kilbourne, 2005:471; Malhi *et al.,* 2007:114; Samame *et al*., 2017:17). The following types of BD exist: bipolar I disorder (BD-I), bipolar II disorder (BD-II), cyclothermic disorder and rapid cycling (Goodwin *et al*., 2016:508,511).

Various factors may influence the prevalence of BD, e.g. gender, socio-economic status, family status, age, marital status, educational background and race (Blanco *et al.,* 2017:310; Kwajaffa *et al.*, 2016:16; Schoeyen *et al*., 2011:68).

The 2015 Global Burden of Disease (GBD) study highlighted that BD affects approximately 44 million (95% CI 38.2-50.9) people worldwide (Global Burden of Disease 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). The lifetime population prevalence differs between BD-I and BD-II (Dell'Osso *et al.,* 2015:257). In the USA, the lifetime prevalence of mania and depression is 0.6% and 0.4%, respectively, while the 12-month prevalence of BD-I and BD-II is 0.4% and 0.3%, respectively (Merikangas *et al.,* 2011:241). The prevalence in Europe and Asia was similar. The lifetime prevalence of all subtypes of BD in the USA was found to be 6.5% (Fovet *et al.*, 2015:348). A recent study reported the 12-month and lifetime prevalence of BD-I in the USA to be 1.5% and 2.1%, respectively (Blanco *et al.,* 2017:310). A study conducted in China showed that the prevalence of BD is lower in China compared to Western countries of the world, with 12-month and lifetime prevalence of BD-I of 0.06% and 0.09%, respectively, while both the 12-month and lifetime prevalence of BD-II was 0.04% (Zhang *et al.,* 2016:413). Singapore has a lifetime and 12-month prevalence of BD-II of 0.06% and 0.04%, respectively.

Studies have also shown the prevalence of BD in some African countries to be similar to that in the USA, for example Esan and Esan (2015:28) reported the lifetime prevalence of BD in Nigeria and Ethiopia to be 0.1% to 0.6%, respectively. Bipolar II disorder is the most prevalent type of BD in the northern part of Nigeria (Aiyeloro *et al*., 2011:94). A study in Kenya reported the prevalence of BD to be 9% (Jean-Louis *et al*., 2014:1257).

The Research and Monitoring Unit of the Council for Medical Scheme (2018:7,24) in SA reported the prevalence of BD to be 0.31% between 2015 and 2016. The South African Stress and Health (SASH) study showed that policies centred on racism/racial oppression, gender inequality, crime, lack of adequate number of psychiatrists, psychiatry nurses and social workers, unequal distribution of mental health services and political and non-political violence and victimization, among others, were responsible for the high prevalence of mental disorders in South Africa (Williams *et al*., 2008:211-217).

Comorbidity is the coexistence of one or more additional diseases or specific disease with the disease of interest in an individual patient in a particular period of time (Krishnan, 2005:1; Sin *et al*., 2006:1245; Surendran & Chakrabarti, 2016:1). Studies have shown that BD patients may have one or two comorbid conditions (Beyer *et al.*, 2005:401,402; Yasseen *et al*., 2010:30). Age and psychosocial stress have been shown to have a direct impact regarding susceptibility to comorbidities among BD patients (Beyer *et al.,* 2005:401,402).

Anxiety disorder, substance use disorder and eating disorders are the major comorbidities associated with BD; however, the coexistence of non-communicable diseases such as cardiovascular, endocrine, and blood-related diseases, among others, are also implicated as BD comorbidities (Prince *et al.,* 2007:859; Wildes *et al.,* 2008:51). Individuals with BD have a substantial burden of coexisting non-communicable diseases, suggesting the need for earlier detection and treatment of these conditions. (Kilbourne *et al.,* 2004:1399; Kilbourne, 2005:471).

The under listed diseases are some of the common comorbid conditions associated with BD: generalised anxiety disorder (GAD), panic disorder, obsessive compulsive disorder (OCD), post-traumatic stress disorder, and social anxiety, as are substance abuse (e.g. stimulants, sedatives, cocaine, opiates, marijuana and hallucinogens), anxiety disorders (e.g. panic disorder (PD) with agoraphobia, PD without agoraphobia, social phobia, specific phobia, OCD, GAD and post-traumatic stress disorder (PTSD), personality disorders (e.g. dependent, avoidant, paranoid, schizoid, histrionic, antisocial, and conduct disorder), attention deficit hyperactive disorders (ADHD), shoplifting, overspending, gambling, conduct disorders, eating disorders (e.g. bulimia nervosa and anorexia nervosa), alcohol abuse and dependence (Blanco *et al.,* 2008:911; Bolyan *et al*., 2004:1106; Fovet *et al*., 2015:351; Goodwin *et al*., 2016:512; Grant *et al*., 2005: 1205,1207,1210; Jones *et al.,* 2015:328; Klassen *et al.,* 2010:1; Subramaniam *et al.,* 2013:191; McElroy *et al.,* 2001:420,423; Nabavi *et al*., 2015:1405).

Cardiovascular diseases (hypertension, hyperlipidaemia and congestive heart failure), endocrine-related diseases (e.g. diabetes, hypothyroidism), liver diseases (e.g. such as hepatitis C), chronic obstructive pulmonary disease (COPD), blood-related diseases, musculoskeletal diseases, tuberculosis, HIV/AIDS, malaria, headache, allergic rhino-conjunctivitis, obesity, chronic constipation, irritable bowel syndrome, metabolic syndrome, hiatus hernia, dysmenorrhea, urticaria, atopic dermatitis, psoriasis, seborrheic dermatitis, bronchial asthma, biliary lithiasis and injuries are medical comorbidities reported in BD (Beyer *et al.,* 2005:401; Kilbourne, 2005:473; Perugi *et al.,* 2015:95; Prince *et al*., 2007:862-866; Rej *et al*., 2015:528).

These coexisting diseases may influence the optimal outcomes of pharmacological treatment of the BD patients (Kilbourne *et al.,* 2004:1399; Kilbourne, 2005:471). Recent evidence suggests that antipsychotics, antidepressants and mood stabilisers (e.g. lithium and anticonvulsants) used in treating BD may be associated with an increased risk of metabolic syndrome, e.g. impaired glycaemic control and weight gain (Palmiere *et al.,* 2016; Masand & Gupta, 2002). Therefore, the coexistence of non-communicable diseases in BD patients may be a threat to patients and third-

party payers, since more resources will be needed to treat these coexisting chronic conditions (Guo *et al.,* 2008; Kilbourne *et al.,* 2004:1399; Peele *et al.,* 2003:1286).

4.2.2 Identification of current treatment guidelines of BD by focusing on both national and international published consensus treatment guidelines

Treatment of BD is complex as it involves pharmacological (drug use) (also referred to as psychopharmacological) and non-pharmacological (psychosocial or psychotherapy) treatments, as well as choice of healthy diets, and physical exercise (Chen *et al.,* 2010:512-521; Jann, 2014:498; McIntyre, 2015; Miklowitz *et al.,* 2008:77). This study mainly focused on the psychopharmacological treatment of the BD patient.

The success of the treatment of BD patients is dependent on the following (Goodwin, 2009:348; Seedat *et al*., 2002:483; Wang *et al.,* 2000:926; Kessler *et al*., 2007:168):

- An increased awareness of mental diseases;
- Effective communication between prescribers and BD patients;
- Prescribing of appropriate doses of indicated drugs;
- Ongoing monitoring for positive and negative effects of drugs; and
- Early identification and treatment of BD are necessary towards preventing its severity.

Positive treatment outcomes are also not guaranteed due to side effects, non-compliance, other unmet needs and susceptibility to other medical comorbidities that could negatively impact the productive life activities of BD patients (Fountoulakis *et al.,* 2012:S1,S2; Kilbourne, 2005:471).

The treatment of BD can be divided into the following components (Collin, 2013:165; Yatham *et al*. 2018:97-170):

- Acute treatment of mania and hypomania
- Acute treatment of depression
- Maintenance treatment

- Bipolar II disorder
- Treatment of complex situation (e.g. rapid cycling and mixed stages)
- Partially or no treatment response
- Treatment when comorbidities (e.g. anxiety disorders and substance-use disorder) occur.
- Management of BP in specific populations (e.g. women in different stages of the reproductive cycle, children and adolescents; older age groups); and
- Safety and monitoring of side-effects.

The pharmacological treatment of bipolar disorder was discussed in section 2.4 of the literature review. According to Colin (2013:165-167), the South African Society of Psychiatrists' guidelines for the treatment of BD in South Africa advocate both pharmacological and non-pharmacological treatment guidelines. The South Africa treatment guidelines and algorithm (Appendix A to E) are mostly aligned with the following international guidelines and recommendations:

- Consensus Group of the British Association for Psychopharmacology (Goodwin, 2009:351).
- Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines (Yatham *et al*., 2009:225-255; Yatham *et al*., 2018:97-170).
- Clinical practice recommendations for mood disorders (Malhi *et al*., 2009:27-46), and
- The National Institute for Health and Care Excellence (NICE) Clinical Guideline for bipolar disorder (NICE, 2015).

The non-pharmacological treatment recommended in the bipolar treatment guideline of the South African Society of Psychiatrists (Colin, 2013:170) is also in accordance with international treatment guidelines and recommendations (Frank *et al.,* 2005:996; Goodwin, 2009:366,367; Goodwin *et al*., 2016:503,504,528; Miklowitz *et al.,* 2008:77; Pina *et al.,* 2016:23; Reinares *et al.,* 2008:511; Scott, 2001:s164; Valenti *et al.,* 2008:54,55; Yatham *et al*., 2009:225-255; Yatham *et al*. 2018:97-170). The non-pharmacological treatment of BD should recognise the monitoring of moods and early warning signs, identifying and managing factors that trigger stress and

interpersonal conflicts, and stabilising sleep/wake rhythms and daily responsibilities, among other factors, as suggested Miklowits *et al. (*2008:77). The benefits of psychosocial treatments' addition to pharmacological treatment in BD patients should be kept in mind during the treatment process (Miklowitz *et al.*, 2008:511; Yatham *et al.,* 2009:227; Yatham *et al*., 2018:97-170).

4.3 Conclusions derived from the empirical study

The objectives of the empirical study, written in the format of two manuscripts, were to:

- Determine trends, over a six-year period, in the prevalence and incidence of BD.
- Determine possible changes, over a six-year period, in the prevalence of coexisting CDL conditions in patients with BD.
- Investigate possible changes, over a six-year period, in the medicine prescribing patterns for patients with only BD.

4.3.1 Determining trends over a six-year period in the prevalence and incidence of BD and the prevalence of coexisting CDL conditions in patients with BD

The empirical objective to ascertain the incidence and prevalence of BD and its coexisting chronic disease list conditions was achieved and reported in manuscript 1, titled: "**Trends in the incidence and prevalence of bipolar disorder and its coexisting chronic disease list conditions in the private health sector of South Africa, 2010-2015".** This manuscript was prepared for submission to the "*International Journal of Methods in Psychiatric Research"* (refer to Annexure G for the author guidelines).

In this cohort study, retrospective medicine claims data from 2010 to 2015 were analysed to achieve the aforementioned objective. The incidence and prevalence rate of BD (ICD-10 code F31), and the number and type of CDL conditions coexisting in individual BD patients were determined. The incidence rate per 1 000 beneficiaries was determined using 2010 as index year.

Bipolar disorder patients represented 0.6% (N = 968 131) and 0.8% (N = 843 792) of the total patient population on the database in 2010 and 2015, respectively. The majority of BD patients were females, representing 0.8% (2010) (N = 521 387) to 1.0% (2015) (N = 445 626) of the total number of female patients on the database. The mean age of the BD patients was 43.6 (15.8)

years (95% CI 43.2-44.0), with the majority (96.4%, n = 5 471) older than 18.2 years in the index year (2010).

The prevalence rate of BD increased from 5.9 (2010) to 7.9 (2015) per 1 000 beneficiaries, whereas the incidence rate per 1 000 beneficiaries was 2.3 in 2011 vs. 2.1 in 2015. The prevalence rate found in this study agrees with that reported by a South African pharmaceutical benefit management company that indicated a prevalence rate of 6.9 per 1 000 beneficiaries in 2015 (Bester *et al.,* 2015:25). The study results, however, are higher than the estimated BD prevalence rate (1.9 to 3.9 per 1 000 beneficiaries per year) as indicated by the Research and Monitoring Unit of the Council for Medical Schemes (2017:8,35) in the medical scheme environment of South Africa. This may be as a result of the uniqueness of characteristics of medical scheme members and medical schemes included in the different databases and reports. Information on patients' medical scheme and benefit options were not available for research purposes and could therefore not be controlled for. Female BD patients have higher incidence rates (2.9 in 2011 *vs*. 2.6 in 2015) than males (1.7 in 2011 *vs*. 1.6 in 2015). Females, in general, have a higher susceptibility to BD as a result of female hormones and reproductive factors (Kennedy *et al.,* 2005)

The number of BD patients in the closed cohort (N = 1 228) with one or more coexisting CDL condition increased by 20.5% from 2010 (n = 594) to 2015 (n = 716); however, the increase in the mean number of coexisting CDL conditions per BD patient was practically insignificant ($P > 0.01$; Cohen's d-value < 0.8). The high level of coexisting CDL conditions observed may have been due to the majority of BD patients in the closed cohort being adults (mean age of 43 years). These results agree with the results of a study conducted in the USA, which indicates that the number of coexisting chronic conditions in BD patients increases with age (Beyer *et al.,* 2005:401). The increase in coexisting chronic conditions was independent of gender.

Evans-Lacko *et al.* (2009:1462) emphasise that various factors predispose BD patients to additional chronic conditions, *inter alia*, medication side effects, unhealthy lifestyles, deprived access to healthcare services, socioeconomic status and biological predisposition. Bipolar disorder patients can be predisposed to hypertension, type 2 diabetes mellitus and hyperlipidaemia as a result of possible sub-optimal psychosocial activities in BD patients and antipsychotic medications that have the potential to cause significant increases in weight gain, and negatively influence insulin sensitivity and lipid metabolism (Hajek *et al*., 2015: 296; Palmiere *et al.,* 2016:33; Masand & Gupta, 2002:175; Yumru *et al*., 2007:247). Hypothyroidism is the most

common thyroid dysfunction in BD patients (Kilbourne *et al*., 2004:1399; Martino & Strejilevich, 2015:167); however, it may also be the result of the side-effects of lithium (Zhang *et al.,* 2006). In this study, the most prevalent coexisting CDL conditions in BD patients over the six-year study period were hypertension, hypothyroidism, hyperlipidaemia, type 2 diabetes mellitus, asthma and epilepsy. A statistically significant increase was also found in the proportion of BD patients from 2010 to 2015 who were newly registered with hypertension ($P < .0001$), hypothyroidism ($P < .0001$), hyperlipidaemia ($P < .0001$) and type 2 diabetes mellitus ($P < 0.0001$). No statistically significant increases in patients with epilepsy ($P = .0065$) or rheumatoid arthritis ($P = .0253$) was found.

Hypertension, hyperlipidaemia and hypothyroidism combined was the most prevalent three chronic conditions-combination in BD patients. This is similar to studies conducted in northern Taiwan, Canada and Poland (Chen *et al.*, 2017:65; Hajek *et al.*, 2015: 295; Wysokiński *et al*., 2015:168)

Concisely, this section has achieved the first and second objectives of the empirical investigation as related to the incidence and prevalence of BD and the coexisting chronic disease list conditions in BD patients.

4.3.2 Investigation of possible changes, over a six-year period, in the medicine prescribing patterns among patients with only BD

The empirical objective, to investigate possible changes, over a six-year period, in the medicine prescribing patterns for patients with only BD, in the private health sector of South Africa was achieved and reported in manuscript two, titled: "**Trends in the psychopharmacological prescribing patterns among bipolar disorder patients in the South African private health sector".** This manuscript was prepared for submission to the journal "*Bipolar Disorder"* (refer to Annexure H for the author guidelines).

The study followed a longitudinal open cohort design. Retrospective medicine claims data of patients identified with the diagnosis code ICD-10, F31, for bipolar disorder, on reimbursed medicine claims, from 1 Jan. 2010 to 31 Dec. 2015 were analysed. The study population consists of bipolar patients who did not have any of the other coexisting chronic disease list (CDL) conditions that are covered through the prescribed minimum benefits as indicated in the South Africa Medical Scheme Act (131 of 1998).The study population consists of bipolar patients who

did not have any of the other coexisting chronic disease list (CDL) conditions that are covered through the prescribed minimum benefits as indicated in the South Africa Medical Scheme Act (131 of 1998). Changes in the medicine prescribing patterns through the study period and between 2010 and 2015 were assessed by using the following measurements: i) different types of active pharmaceutical ingredients according to pharmacological groups; ii) frequency of monotherapy (includes only one active pharmaceutical ingredient per prescription) or combination therapy (includes more than one active pharmaceutical ingredients in therapy, based on the last month's prescription(s) of a patient in 2010 and 2015; iii) average number of medicine items per prescription; and iii) average number of prescriptions per patient per year, stratified per age and gender group.

A total of 3 627 bipolar disorder patients complied with the inclusion criteria in the index year (2010) and increased to 4 332 in 2015. This increase is the result of the addition of *newly registered* bipolar disorder patients from 2011 to 2015. The majority of *newly registered* patients were older than 18.2 years old, with the male to female ratios 1:2.3 and 1:1.88 in 2010 and 2015, respectively.

The following trends were identified during the study period:

- The average number of items per prescription per patient did not change significantly from 2010 (1.90(0.93) [1.90 – 1.92]) to 2015 (2.01(0.98) [1.99-2.03]).

- The average number of prescriptions per patient increased observably from 7.08 (5.63) [6.94-7.23] in 2010 to 7.50 (5.59) [7.37-7.63] in 2015 ($P < .0001$, Cohen's d-value = .4). The same trends were experienced in patients aged ≥18 years, and in both male and female groups ($P < .0001$, Cohen's d-value = .4).

- The proportion of patients on combination therapy increased from 44.6% in 2010 to 48.7% in 2015.

- The most prevalent combination therapy in 2010 and 2015 was lamotrigine in combination with quetiapine or with a selective serotonin re-uptake inhibitor, or with bupropion or with valproate. These findings are similar to studies conducted in the USA (Fornaro et al., 2016:719), South African public health sector (Holzapfel & Szabo, 2016:1,9,10) and Denmark (Kessing et al.,2016:174).

- The proportion of patients receiving anticonvulsants (35.4% vs. 34.7%), antidepressants (31.9% vs. 36.1%) and atypical antipsychotics (16.2% vs. 23.2%) as monotherapy increased significantly (P = .0001) from 2010 to 2015.

- The proportion of patients receiving lithium decreased marginally (4.9% vs. 4.2%) (P = .302) from 2010 to 2015. Similar results were found in various longitudinal studies (Kessing et al., 2016:174; Bjørklund et al., 2016:75).

- Among the anticonvulsants, lamotrigine was prescribed most in both 2010 and 2015 at 21.7 % vs. 22.3%, followed by valproate (9.8% vs. 12.5%) and topiramate (2.6% vs. 0.7%), respectively. The proportion of patients treated with lamotrigine or valproate also increased significantly from 2010 to 2015 (P < .0001), whereas that for topiramate decreased significantly (P < .0001). Similar results were found by Kessing et al. (2016:174).

- The atypical antipsychotic drugs were the second most frequent prescribed monotherapy in 2010 (14.9%) and 2015 (23.0%). No typical antipsychotics contributed to the top 50% of active pharmaceutical ingredients prescribed in 2010 or 2015. The prescribing trends of atypical antipsychotic drugs found in this study are similar to results observed in various other international studies (Kessing et al., 2016:174; Bjørklund et al., 2016:78).

- An observable significant increase in the prescribing of quetiapine-containing items was found from 2010 to 2015 (P < .0001). The other atypical antipsychotics, olanzapine and risperidone were less prescribed, but have the same increasing trends.

- The percentage of patients who received an antidepressant as monotherapy increased from 31.9% of patients in 2010 to 36.4% in 2015.

- The SSRIs were the most prevalent antidepressant group prescribed as monotherapy for both years (16.1% vs. 18.0%), with an increasing trend from 2010 to 2015 (P < .0001).

- Other antidepressants prescribed as monotherapy included the SNRIs (e.g. venlafaxine, duloxetine), NDRIs (e.g. bupropion) and tetracyclics (e.g. trazodone).

In summary, this section has fulfilled the third objective of the empirical study as per investigation of possible changes in the medicine prescribing patterns for patients with BD over a six-year period.

4.4 Strengths and limitations

The empirical study has a number of limitations, which should be taken into account by the reader:

- The study included only privately-insured bipolar disorder patients enrolled in a nationally-representative medicine claims database that was acquired from a South African PBM company. Therefore, the findings cannot be generalised to bipolar disorder patients who received their medication from public health facilities in South Africa or patients who are responsible for their own medical expenses.

- The medicine claims database does not include prescription data during hospital admissions.

- There is also a small possibility that patients may be taking medications that were not claimed through their medical scheme, and therefore not included in the database.

- Patients were identified using the ICD-10 code, F31, which did not distinguish between the different types of bipolar disorders (e.g. bipolar I disorder, bipolar II disorder, cyclothymic disorder and rapid cycling), which makes comparison with international epidemiological studies problematic.

- It was also not possible to differentiate between the prescribing patterns for the different types of bipolar disorders because of a lack of clinical information.

- This lack of clinical data also made it difficult to determine whether medications used to treat BD resulted in the development of coexisting CDL conditions.

- It was not possible to determine whether the increase in prevalence of coexisting CDL conditions in BD patients occurred as a result of improved documentation and management of health information of CDL conditions by medical schemes and healthcare providers in South Africa.

This study established base-line information on the incidence and prevalence and coexisting chronic disease list conditions of privately-insured BD patients in South Africa.

4.5 Recommendations

The following recommendations are proposed from the study:

Further research should be conducted, which should include, *inter alia*, the following analyses:

- The prescribed daily doses of the active pharmaceutical ingredients and its influence on changes in therapy.
- The possible influence of the type of prescribing practitioner on psychopharmacological prescribing patterns.
- Evaluation of the psychopharmacological prescribing patterns in children and adolescents.
- Evaluation of the psychopharmacological prescribing patterns in patients with specific chronic disease list conditions.
- The increase in combination therapy and the constant high use of antidepressants as monotherapy should be further investigated.

Although the incidence of BD remained nearly the same through the study years, the medical scheme environment in South Africa should take notice of an increased trend in the prevalence of BD as well as an increased trend in coexisting CDL conditions in the BD patient.

This study advises healthcare practitioners on the need to pay utmost attention to hypertension, hyperlipidaemia, and type 2 diabetes mellitus among other comorbidities common in BD patients, as well as the psychopharmacological treatment guidelines for the management of BD.

4.6 Chapter summary

This final chapter aligns the objectives of the study with the final outcomes. The strengths and limitations were highlighted and discussed, and recommendations were proposed for further research.

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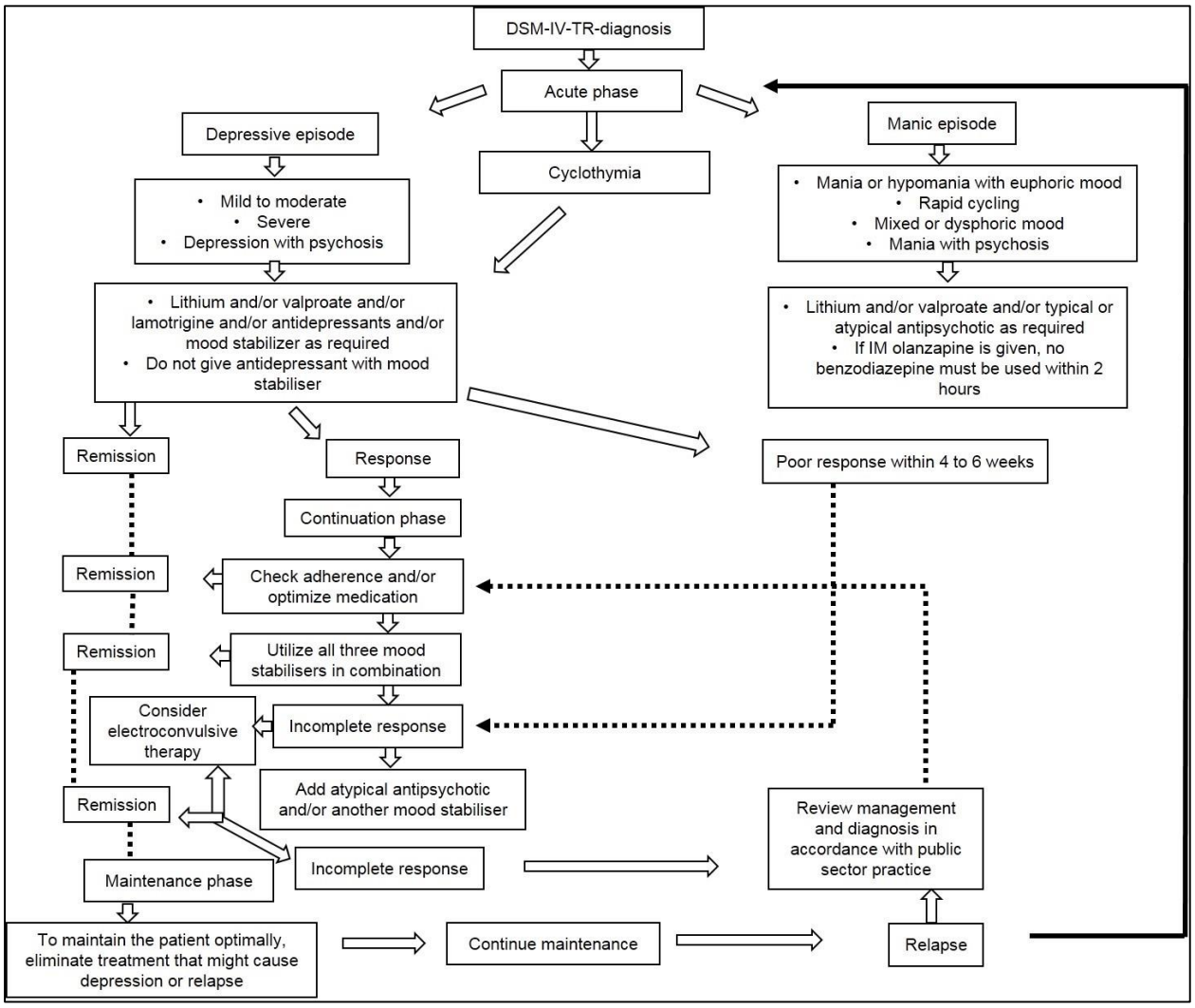
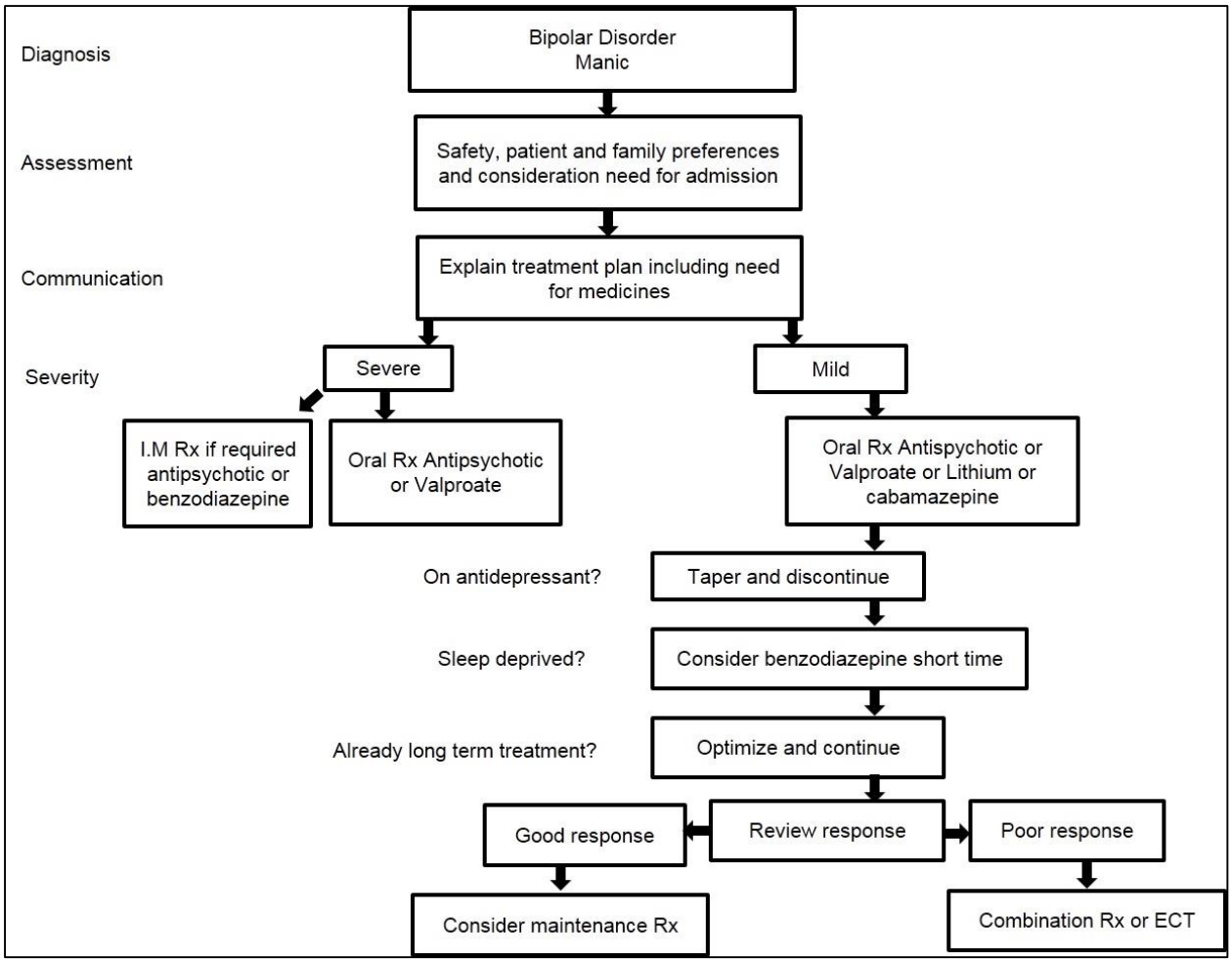
ANNEXURE A: BIPOLAR DISORDER ALGORITHM (BDA)



ANNEXURE B: MAJOR GROUPS OF PSYCHOTROPIC MEDICINE

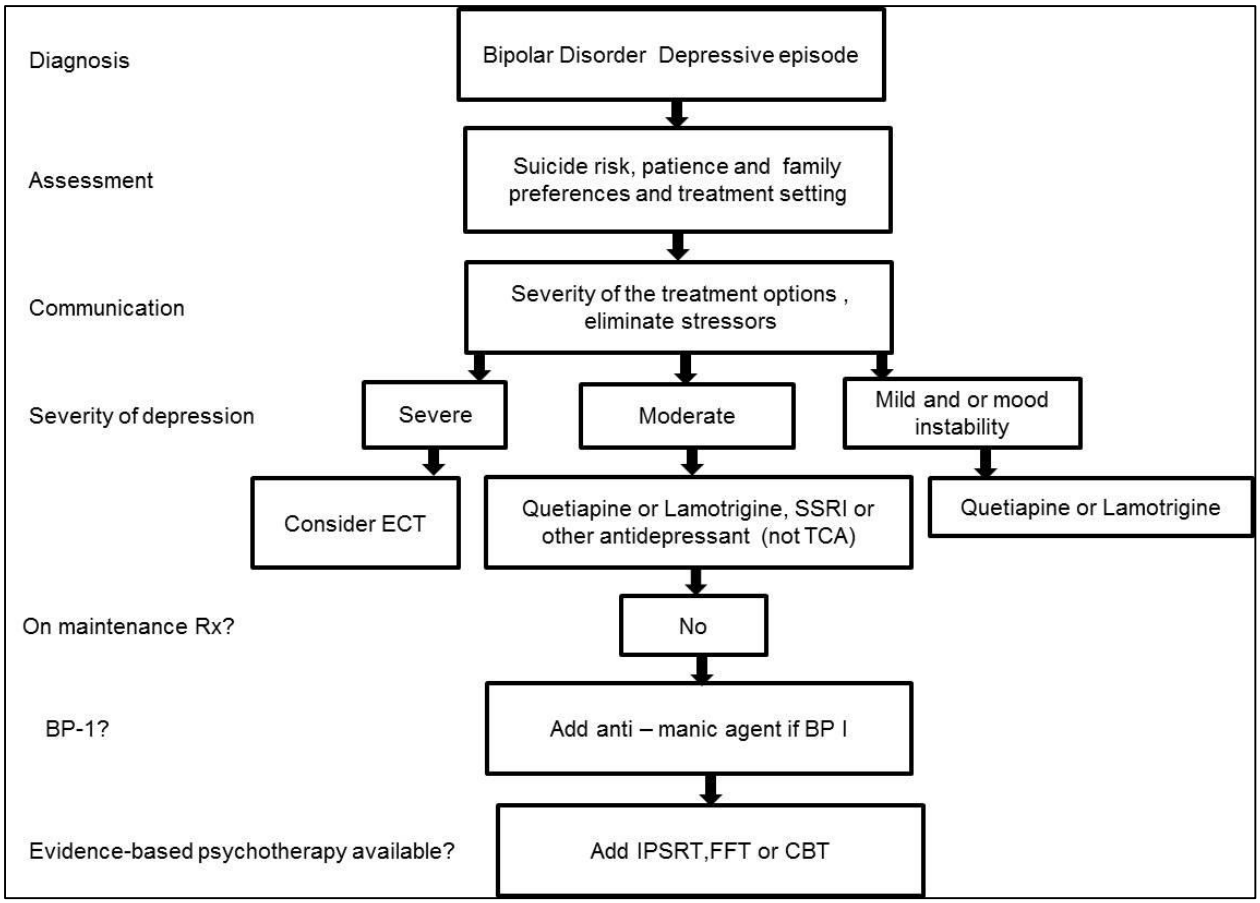
Group **Major groups of psychotropic medicine**	**Medicines**
Antidepressants (tetracyclic and tricyclics, selective serotonin reuptake inhibitors)	Sertraline hydrochloride, fluoxetine hydrochloride, paroxetine hydrochloride, citalopram hydrobromide etc.
Second generation antipsychotics	Clozapine, olanzapine, quetiapine fumarate, aripiprazole, risperidone and ziprasidone hydrochloride etc.
Mood stabilisers and anticonvulsants	Lithium citrate or carbonate, valproate, carbamazepine, lamotrigine, gabapentin, topiramate etc.
Benzodiazepines	Diazepam, lorazepam etc.
Stimulants	Amphetamine, methylphenidate hydrochloride etc.

ANNEXURE C: INITIAL TREATMENT SCHEME-MANIA/MIXED EPISODE



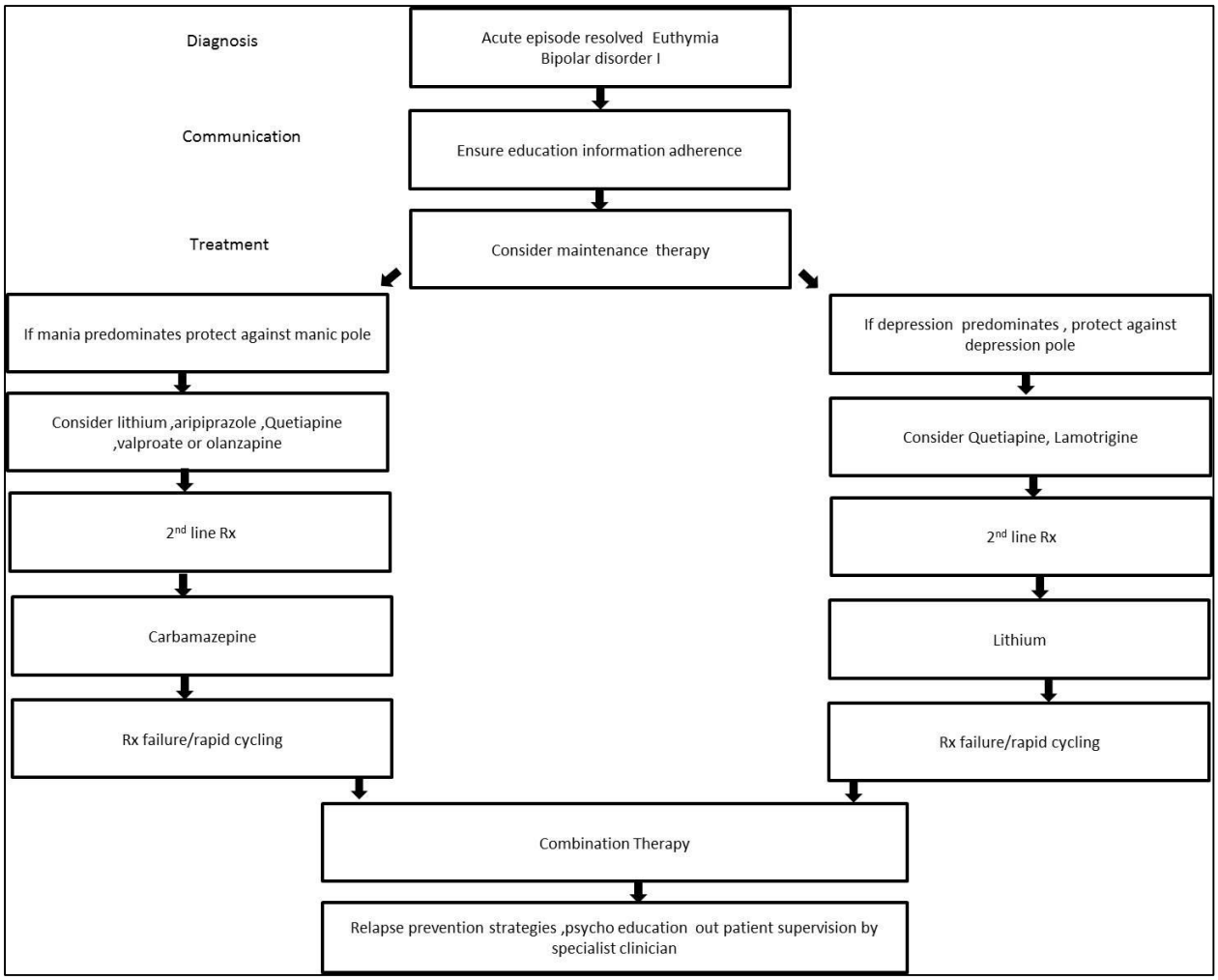
Adapted from Goodwin (2009:351)

ANNEXURE D: INITIAL TREATMENT SCHEME-DEPRESSIVE EPISODE



Adapted from Goodwin (2009: 353)

ANNEXURE E: LONG-TERM TREATMENT SCHEME-MAINTENANCE THERAPY



Adapted from Goodwin (2009: 354)

ANNEXURE F: ETHICS APPROVAL CERTIFICATE

NORTH-WEST UNIVERSITY
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Institutional Research Ethics Regulatory Committee

Tel: +27 18 299 4849

Email : Ethics@nwu.ac.za

2016-07-19

ETHICS APPROVAL CERTIFICATE OF STUDY

Based on approval by **Health Research Ethics Committee (HREC)** on **13/07/2016**, the North-West University Institutional Research Ethics Regulatory Committee (NWU-IRERC) hereby **approves** your study as indicated below. This implies that the NWU-IRERC grants its permission that provided the special conditions specified below are met and pending any other authorisation that may be necessary, the study may be initiated, using the ethics number below.

Study title: Medicine prescribing patterns in a section of the private health sector utilising data from a Pharmaceutical Benefit Management company in South Africa

Sub-study title: Bipolar disorder in the South African private health sector: Longitudinal analysis of prevalence, comorbidities and prescribing patterns

Study Leader/Supervisor: **Prof MS Lubbe**
Student: **AP Akinragunde**

Ethics number: N W U - 0 0 1 7 9 - 1 4 - A 1
(Institution – Study Number – Year – Status)

Status: S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation

Application Type: Sub-study

Commencement date: 2016-07-13 **Risk:** **Minimal**

Continuation of the study is dependent on receipt of the annual (or as otherwise stipulated) monitoring report and the concomitant issuing of a letter of continuation up to a maximum period of three years.

Special conditions of the approval (if applicable):

- Translation of the informed consent document to the languages applicable to the study participants should be submitted to the HREC (if applicable).
- Any research at governmental or private institutions, permission must still be obtained from relevant authorities and provided to the HREC. Ethics approval is required BEFORE approval can be obtained from these authorities.

General conditions:

While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, please note the following:

- *The study leader (principle investigator) must report in the prescribed format to the NWU-IRERC via HREC:*
  - *annually (or as otherwise requested) on the monitoring of the study, and upon completion of the study*
  - *without any delay in case of any adverse event or incident (or any matter that interrupts sound ethical principles) during the course of the study.*
- *Annually a number of studies may be randomly selected for an external audit.*
- *The approval applies strictly to the proposal as stipulated in the application form. Would any changes to the proposal be deemed necessary during the course of the study, the study leader must apply for approval of these amendments at the HREC, prior to implementation. Would there be deviated from the study proposal without the necessary approval of such amendments, the ethics approval is immediately and automatically forfeited.*
- *The date of approval indicates the first date that the study may be started.*
- *In the interest of ethical responsibility the NWU-IRERC and HREC retains the right to:*
  - *request access to any information or data at any time during the course or after completion of the study;*
  - *to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process.*
  - *withdraw or postpone approval if:*
    - *any unethical principles or practices of the study are revealed or suspected,*
    - *it becomes apparent that any relevant information was withheld from the HREC or that information has been false or misrepresented,*
    - *the required amendments, annual (or otherwise stipulated) report and reporting of adverse events or incidents was not done in a timely manner and accurately,*
    - *new institutional rules, national legislation or international conventions deem it necessary.*
- *HREC can be contacted for further information or any report templates via Ethics-HRECApply@nwu.ac.za or 018 299 1206.*

The IRERC would like to remain at your service as scientist and researcher, and wishes you well with your study. Please do not hesitate to contact the IRERC or HREC for any further enquiries or requests for assistance.

Yours sincerely

Prof LA Du Plessis

Digitally signed by Prof LA Du Plessis
Date: 2016.07.19 16:19:49 +02'00'

Prof Linda du Plessis
Chair NWU Institutional Research Ethics Regulatory Committee (IRERC)

ANNEXURE G: AUTHOR GUIDELINES ARTICLE 1

Sections

1. SUBMISSION

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

Data Protection

By submitting a manuscript to or reviewing for this publication, your name, email address, and affiliation, and other contact details the publication might require, will be used for the regular operations of the publication, including, when necessary, sharing with the publisher (Wiley) and partners for production and publication. The publication and the publisher recognize the importance of protecting the personal information collected from users in the operation of these services, and have practices in place to ensure that steps are taken to maintain the security, integrity, and privacy of the personal data collected and processed. You can learn more at https://authorservices.wiley.com /statements/data-protection-policy.html

Once the submission materials have been prepared in accordance with the Author Guidelines, manuscripts should be submitted online at https://mc.manuscriptcentral.com/ijmpr.

For help with submissions, please contact the Editorial Office: IJMPReditorialoffice@wiley.com

2. AIMS AND SCOPE

The *International Journal of Methods in Psychiatric Research* (IJMPR) publishes high-standard original research of a technical, methodological, experimental and clinical nature, contributing to the theory, methodology, practice and evaluation of mental and behavioural disorders. The journal targets in particular detailed methodological and design papers from major national and international multicentre studies.

3. MANUSCRIPT CATEGORIES AND REQUIREMENTS

The main document should be supplied as a Word Document (.doc, .docx). Manuscripts should be written in English (UK). All tables, figures, supporting information and bibliographic entries must have a reference in the text. Tables should be included in the main document after the reference list, each on an individual page alongside their legend. Figures should not be included in the main document and should instead be uploaded as individual files. Word limit excludes title page, tables, figure legends and references.

• Original Articles – *Manuscript structure*: Structured Abstract (Objectives, Methods, Results, Conclusions) of up to 200 words, together with three to five keywords; Introduction; Method; Results; Discussion; Conflict of Interest Statement; References. Word limit: 5,000 words.

• Invited Review – *Manuscript structure*: Abstract of up to 200 words, together with three to five keywords; Content-appropriate headings; Conflict of Interest Statement; References. Word limit: 5,000 words.

• Letters to the Editor – *Manuscript Structure*: no set format.

4. PREPARING YOUR SUBMISSION

Cover Letters

Cover letters are not mandatory; however, they may be supplied at the author's discretion as a separate file or via the cover letter section of the submission process.

Parts of the Manuscript

The manuscript should be submitted in separate files: main text file (including tables at the end; figures.

Main Text File

The text file should be presented in the following order:

i. A short informative title containing the major key words. The title should not contain abbreviations (see Wiley's best practice SEO tips);
ii. A short running title of less than 40 characters;
iii. The full names of the authors;
iv. The author's institutional affiliations where the work was conducted, with a footnote for the author's present address if different from where the work was conducted;
v. The name and email of the corresponding author
vi. Acknowledgments (including the names of any sponsors and grant numbers);
vii. Abstract and keywords;
viii. Main text;
ix. References;
x. Tables (each table complete with title and footnotes);

Authorship

Please refer to the journal's authorship policy the Editorial Policies and Ethical Considerations section for details on eligibility for author listing.

Acknowledgements

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. See section on Authorship for more detail. Financial and material support should also be mentioned Thanks to anonymous reviewers are not appropriate.

Conflict of Interest Statement

You will be asked to provide a conflict of interest statement during the submission process. See the section 'Conflict of Interest' in the Editorial Policies and Ethical Considerations section for details on what to include in this section. Please ensure you liaise with all co-authors to confirm agreement with the final statement.

Abstract

Abstract should be divided into the following sections: 'Objectives', 'Methods', 'Results' and 'Conclusion'; it should not exceed 200 words.

Keywords

Please provide between 3 and 5 keywords.

Main Text

See Section 3: Manuscript categories and requirements for information on manuscript types, structure, word limit and other requirements. Footnotes to the text are not allowed and any such material should be incorporated into the text as parenthetical matter.

References

References

References should be prepared according to the Publication Manual of the American Psychological Association (6th edition). This means in text citations should follow the author-date method whereby the author's last name and the year of publication for the source should appear in the text, for example, (Jones, 1998). The complete reference list should appear alphabetically by name at the end of the paper.

A sample of the most common entries in reference lists appears below. Please note that a DOI should be provided for all references where available. For more information about APA referencing style, please refer to the APA FAQ. Please note that for journal articles, issue numbers are not included unless each issue in the volume begins with page one.

Journal article

Beers, S. R. , & De Bellis, M. D. (2002). Neuropsychological function in children with maltreatment-related posttraumatic stress disorder. The American Journal of Psychiatry, 159, 483–486. doi:10.1176/appi.ajp.159.3.483

Book

Bradley-Johnson, S. (1994). Psychoeducational assessment of students who are visually impaired or blind: Infancy through high school (2nd ed.). Austin, TX: Pro-ed.

• **Numbers:** numbers under 10 are spelt out, except for: measurements with a unit (4mmol/l); age (6 weeks old), or lists with other numbers (11 dogs, 9 cats, 4 gerbils).

• **Trade Names:** Chemical substances should be referred to by the generic name only. Trade names should not be used. Drugs should be referred to by their generic names. If proprietary drugs have been used in the study, refer to these by their generic name, mentioning the proprietary name and the name and location of the manufacturer in parentheses.

Wiley Author Resources

Manuscript Preparation Tips: Wiley has a range of resources for authors preparing manuscripts for submission available here. In particular, authors may benefit from referring to Wiley's best practice tips on Writing for Search Engine Optimization.

Editing, Translation and Formatting Support: Wiley Editing Services can greatly improve the chances of your manuscript being accepted. Offering expert help in English language editing, translation, manuscript formatting and figure preparation, Wiley Editing Services ensures that your manuscript is ready for submission.

5. EDITORIAL POLICIES AND ETHICAL CONSIDERATIONS

Editorial Review and Acceptance

The acceptance criteria for all papers are the quality and originality of the research and its significance to journal readership. Manuscripts are single-blind review. Papers will only be sent to review if the Editor-in-Chief determines that the paper meets the appropriate quality and relevance requirements.

Wiley's policy on confidentiality of the review process is available here.

Supporter Journal

IJMPR works together with Wiley's Open Access Journal, Health Science Reports to enable rapid publication of good quality research that is unable to be accepted for publication by our journal. Authors may be offered the option of having the paper, along with any related peer reviews, automatically transferred for consideration by the Editor of *Health Science Reports*. Authors will not need to reformat or rewrite their manuscript at this stage, and publication decisions will be made a short time after the transfer takes place. The Editor of Health Science Reports will accept submissions that report well-conducted research that reaches the standard acceptable for publication. Health Science Reports is a Wiley Open Access journal and article publication fees apply. For more information please go to http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2398-8835.

Data Sharing and Accessibility

The journal encourages authors to share the data and other artefacts supporting the results in the paper by archiving it in an appropriate public repository. Authors should include a data accessibility statement, including a link to the repository they have used, in order that this statement can be published alongside their paper.

Human Studies and Subjects

For manuscripts reporting medical studies involving human participants, we require a statement identifying the ethics committee that approved the study, and that the study conforms to recognized standards, for example: Declaration of Helsinki; US Federal Policy for the Protection of Human Subjects; or European Medicines Agency Guidelines for Good Clinical Practice.

Images and information from individual participants will only be published where the authors have obtained the individual's free prior informed consent. Authors do not need to provide a copy of the

Endnotes

Endnotes should be placed as a list at the end of the paper only, not at the foot of each page. They should be numbered in the list and referred to in the text with consecutive, superscript Arabic numerals. Keep endnotes brief; they should contain only short comments tangential to the main argument of the paper.

Footnotes

Footnotes should be placed as a list at the end of the paper only, not at the foot of each page. They should be numbered in the list and referred to in the text with consecutive, superscript Arabic numerals. Keep footnotes brief; they should contain only short comments tangential to the main argument of the paper and should not include references.

Tables

Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Figure Legends

Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement.

Figures

Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted. Click here for the basic figure requirements for figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements.

Additional Files

Appendices

Appendices will be published after the references. For submission they should be supplied as separate files but referred to in the text. Supporting Information

Supporting Information

Supporting information is information that is not essential to the article but that provides greater depth and background. It is hosted online, and appears without editing or typesetting. It may include tables, figures, videos, datasets, etc. Click here for Wiley's FAQs on supporting information.

Note, if data, scripts or other artefacts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

General Style Points

The following points provide general advice on formatting and style.

• **Abbreviations:** In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Initially, use the word in full, followed by the abbreviation in

The journal requires that clinical trials are prospectively registered in a publicly accessible database and clinical trial registration numbers should be included in all papers that report their results. Authors are asked to include the name of the trial register and the clinical trial registration number at the end of the abstract. If the trial is not registered, or was registered retrospectively, the reasons for this should be explained.

Research Reporting Guidelines

Accurate and complete reporting enables readers to fully appraise research, replicate it, and use it. Authors are encouraged to adhere to the following research reporting standards.

- CONSORT
- SPIRIT
- PRISMA
- PRISMA-P
- STROBE
- CARE
- COREQ
- STARD and TRIPOD
- CHEERS
- the EQUATOR Network
- Future of Research Communications and e-Scholarship (FORCE11)
- ARRIVE guidelines
- National Research Council's Institute for Laboratory Animal Research guidelines: the Gold Standard Publication Checklist from Hooijmans and colleagues
- Minimum Information Guidelines from Diverse Bioscience Communities (MIBBI) website; Biosharing website
- REFLECT statement

Genetic Nomenclature

Sequence variants should be described in the text and tables using both DNA and protein designations whenever appropriate. Sequence variant nomenclature must follow the current HGVS guidelines; see varnomen.hgvs.org, where examples of acceptable nomenclature are provided.

Sequence Data

Nucleotide sequence data can be submitted in electronic form to any of the three major collaborative databases: DDBJ, EMBL, or GenBank. It is only necessary to submit to one database as data are exchanged between DDBJ, EMBL, and GenBank on a daily basis. The suggested wording for referring to accession-number information is: 'These sequence data have been submitted to the DDBJ/EMBL /GenBank databases under accession number U12345'. Addresses are as follows:

- DNA Data Bank of Japan (DDBJ): www.ddbj.nig.ac.jp
- EMBL Nucleotide Archive: ebi.ac.uk/ena
- GenBank: www.ncbi.nlm.nih.gov/genbank

Proteins sequence data should be submitted to either of the following repositories.

- Protein Information Resource (PIR): pir.georgetown.edu
- SWISS-PROT: expasy.ch/sprot/sprot-top

Conflict of Interest

directly related to the work that the authors describe in their manuscript. Potential sources of conflict of interest include, but are not limited to: patent or stock ownership, membership of a company board of directors, membership of an advisory board or committee for a company, and consultancy for or receipt of speaker's fees from a company. The existence of a conflict of interest does not preclude publication. If the authors have no conflict of interest to declare, they must also state this at submission. It is the responsibility of the corresponding author to review this policy with all authors and collectively to disclose with the submission ALL pertinent commercial and other relationships.

Funding

Authors should list all funding sources in the Acknowledgments section. Authors are responsible for the accuracy of their funder designation. If in doubt, please check the Open Funder Registry for the correct nomenclature: https://www.crossref.org/services/funder-registry/

Authorship

The list of authors should accurately illustrate who contributed to the work and how. All those listed as authors should qualify for authorship according to the following criteria:

1. Have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

2. Been involved in drafting the manuscript or revising it critically for important intellectual content;

3. Given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and

4. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section (for example, to recognize contributions from people who provided technical help, collation of data, writing assistance, acquisition of funding, or a department chairperson who provided general support). Prior to submitting the article all authors should agree on the order in which their names will be listed in the manuscript.

Additional Authorship Options: Joint first or senior authorship: In the case of joint first authorship, a footnote should be added to the author listing, e.g. 'X and Y should be considered joint first author' or 'X and Y should be considered joint senior author.'

ORCID

As part of the journal' commitment to supporting authors at every step of the publishing process, the journal encourages the submitting author (only) to provide an ORCID iD when submitting a manuscript. This takes around 2 minutes to complete. Find more information here.

Publication Ethics

IJMPR is a member of the Committee on Publication Ethics (COPE). Note this journal uses iThenticate's CrossCheck software to detect instances of overlapping and similar text in submitted manuscripts. Read Wiley's Top 10 Publishing Ethics Tips for Authors here. Wiley's Publication Ethics Guidelines can be found here.

6. AUTHOR LICENSING

If a paper is accepted for publication, the author identified as the formal corresponding author will receive an email prompting them to log in to Author Services, where via the Wiley Author Licensing Service (WALS) they will be required to complete a copyright license agreement on behalf of all authors

General information regarding licensing and copyright is available here. To review the Creative Commons License options offered under OnlineOpen, please click here. (Note that certain funders mandate a particular type of CC license be used; to check this please click here.)

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7. PUBLICATION PROCESS AFTER ACCEPTANCE

Accepted article received in production

When your accepted article is received by Wiley's production production team, you (corresponding authors) will receive an email asking you to login or register with Author Services. You will be asked to sign a publication licence at this point.

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The journal offers rapid publication via Wiley's Early View service. Early View (Online Version of Record) articles are published on Wiley Online Library before inclusion in an issue. Note there may be a delay after corrections are received before the article appears online, as Editors also need to review proofs. Once the article is published on Early View, no further changes to the article are possible. The Early View article is fully citable and carries an online publication date and DOI for citations.

8. POST PUBLICATION

Access and sharing

When the article is published online:
• You receive an email alert (if requested).
• You can share your published article through social media.
• The author will have free access (after accepting the Terms & Conditions of use, you can view the article).
• The corresponding author and co-authors can nominate up to ten colleagues to receive a publication alert and free online access to the article.

Wiley also helps authors measure the impact of their research through specialist partnerships with Kudos and Altmetric.

9. DATA PROTECTION AND PRIVACY

By submitting a manuscript to, or reviewing for, this publication, your name, email address, institutional affiliation, and other contact details the publication might require, will be used for the regular operations of the publication, including, when necessary, sharing with the publisher (Wiley) and partners for production and publication. The publication and the publisher recognize the importance of protecting the personal information collected from users in the operation of these services, and have practices in place to ensure that steps are taken to maintain the security, integrity, and privacy of the personal data collected and processed. You can learn more at https://authorservices.wiley.com/statements/data-protection-policy.html.

9. EDITORIAL OFFICE CONTACT DETAILS

For any queries or issues, please contact the Editorial Office: IJMPReditorialoffice@wiley.com.

ANNEXURE H: AUTHOR GUIDELINES ARTICLE 2

BIPOLAR DISORDERS
AN INTERNATIONAL JOURNAL OF PSYCHIATRY AND NEUROSCIENCES

Author Guidelines

Sections

1. SUBMISSION

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

Once the submission materials have been prepared in accordance with the Author Guidelines, manuscripts should be submitted online at https://mc.manuscriptcentral.com/bdi

Click here for more details on how to use ScholarOne.

Data protection

By submitting a manuscript to or reviewing for this publication, your name, email address, and

protecting the personal information collected from users in the operation of these services, and have practices in place to ensure that steps are taken to maintain the security, integrity, and privacy of the personal data collected and processed. You can learn more at https://authorservices.wiley.com/statements/data-protection-policy.html.

Preprint policy

This journal will consider for review articles previously available as preprints on non-commercial servers such as ArXiv, bioRxiv, psyArXiv, SocArXiv, engrXiv, etc. Authors may also post the submitted version of a manuscript to non-commercial servers at any time. Authors are requested to update any pre-publication versions with a link to the final published article.

For help with submissions, please contact: BDIedoffice@wiley.com

2. AIMS AND SCOPE

Bipolar Disorders is an international journal that publishes all research of relevance for the basic mechanisms, clinical aspects, or treatment of bipolar disorders and related illnesses. It intends to provide a single international outlet for new research in this area and covers research in the following areas:

- biochemistry
- physiology
- neuropsychopharmacology
- neuroanatomy
- neuropathology
- genetics
- brain imaging
- epidemiology
- phenomenology
- clinical aspects
- and therapeutics of bipolar disorders

Bipolar Disorders also contains papers that form the development of new therapeutic strategies for these disorders as well as papers on the topics of schizoaffective disorders, and depressive disorders as these can be cyclic disorders with areas of overlap with bipolar disorders.

3. MANUSCRIPT CATEGORIES AND REQUIREMENTS

Bipolar Disorders - An International Journal of Psychiatry and Neurosciences will consider for publication submissions within the domain of: Perspectives, Research Articles, Correspondence, Clinical Corner, and Reflections. Within these there are a number of types of articles: invited editorials, debates, review articles, original articles, commentaries, letters to the editors, clinical conundrums, clinical curiosities, clinical care, and musings.

PERSPECTIVES			
Editorial	2000	5	No
Debate	1200	5	No
RESEARCH ARTICLES			
Review Article	4000-7500	100	Yes
Original Article	5000	50	Yes
CORRESPONDENCE			
Commentary	800	5	No
Letter	400	3	No
CLINICAL CORNER			
Clinical Conundrum	800-1500	5	No
Clinical Curiosity	800-1500	5	No
Clinical Care	800-1500	5	No
REFLECTIONS			
Musing	600	3	No

Editorial: These should address contemporary topics of interest and provide thought-provoking discussion. The presentation of new hypotheses and novel ideas pertaining to psychiatry are welcome.

Debate: These are brief provocative accounts that provide differing perspectives on a single shared issue or topic of discussion. Their focus may be similar to that of editorials but these are generally shorter pieces that make one or two salient points.

Original Articles: These are papers that report original high quality research. Articles illustrating novel findings, innovation and clinical trials will be given priority.

Commentary: This is correspondence typically pertaining to a recent or concurrently published article within Bipolar Disorders. Usually comments and critiques will be passed on to the authors of the original article; however, this will not determine the outcome of review and publication. Commentaries may also address topical issues that have been considered in the journal.

Letter: Correspondence to the Editor is welcomed and encouraged on any aspect of psychiatry within the scope of the journal.

Clinical Conundrum: This Clinical Corner article is a brief case report that illustrates contentious clinical issues in psychiatry and aims to provide advice to practicing clinicians. The article should follow the following structured template:

- Key Message (50 words)
- Case Presentation
- Discussion
- Learning points (2-3 bullet points) - *optional*
- 1 life chart and/or 1 supporting figure

Clinical Curiosity: This Clinical Corner article is a brief case report detailing rare or unusual clinical cases and their management. The structure for this article is as follows:

- Key Message (50 words)
- Case Presentation
- Discussion
- Learning points (2-3 bullet points) - *optional*
- 1 life chart and/or 1 supporting figure

Clinical Care: This Clinical Corner article addresses new or updated standards of optimal care. It is aimed at informing clinicians of current diagnostic, treatment or management standards. This article must include:

- Key Message (50 words)
- Detailed discussion
- Learning points (2-3 bullet points)
- 1 supporting figure

Musing: This is a brief narrative article of interest or one relating to a matter of historical or future interest. It may include a figure/picture.

Editor's Choice and Key Review

Each issue one article is selected as the 'Editor's Choice' and one review paper is selected as the 'Key Review'. These selections are made by the Editor and are based on quality, scientific impact and scope. The articles chosen as Editor's Choice and Key Review will be published as Free Access.

4. PREPARING THE SUBMISSION

Cover Letters

Cover letters are not mandatory; however, they may be supplied at the author's discretion.

Parts of the Manuscript

The manuscript should be submitted in separate files: main text file; figures.

Main Text File

The text file should be presented in the following order:

i. A short informative title that contains the major key words. The title should not contain abbreviations (see Wiley's best practice SEO tips);
ii. A short running title of less than 40 characters;
iii. The full names of the authors;
iv. The author's institutional affiliations where the work was conducted, with a footnote for the author's present address if different from where the work was conducted;
v. Acknowledgments;
vi. Abstract and keywords;
vii. Main text;
viii. References;
ix. Tables (each table complete with title and footnotes);
x. Figure legends;
xi. Appendices (if relevant).

Figures and supporting information should be supplied as separate files.

Authorship

Please refer to the journal's authorship policy the Editorial Policies and Ethical Considerations section for details on eligibility for author listing.

Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

Conflict of Interest Statement

Authors will be asked to provide a conflict of interest statement during the submission process. For

Abstract

An abstract is only required for Review Articles and Original Articles. The abstract should not exceed 250 words and should be arranged in a structured fashion to include objectives, methods, results, and conclusions. It should state the purpose of the study, basic procedures (study subject /patients / animals, and methods), main findings (specific data and statistical significance), and principal conclusions. For Clinical Corner articles, a 50-word key message should be provided.

Keywords

Please provide 3-10 keywords. Keywords should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at www.nlm.nih.gov/mesh.

Main Text

- **Introduction:** Present the background briefly, but do not review the subject extensively. Give only pertinent references. State the specific questions you want to answer.
- **Patients and methods / Materials and methods:** Describe selection of patients or experimental animals, including controls. Do not use patients' names or hospital numbers. Identify methods, apparatus (manufacturer's name and address), and procedures in sufficient detail to allow other workers to reproduce the results. Provide references and brief descriptions of methods that have been published. When using new methods, evaluate their advantages and limitations. Identify drugs and chemicals, including generic name, dosage and route(s) of administration.
- **Results:** Present results in logical sequence in tables and illustrations. In the text, explain, emphasize, or summarize the most important observations.
- **Discussion:** Do not repeat in detail data given in the Results section. Emphasize the new and important aspects of the study. Relate the observations to other relevant studies. On the basis of your findings (and others') discuss possible implications / conclusions. When stating a new hypothesis, clearly label it as such.

References

All references should be numbered consecutively in order of appearance and should be as complete as possible. In text citations should cite references in consecutive order using Arabic superscript numerals. For more information about AMA reference style please consult the AMA Manual of Style

Sample references follow:

Journal article

1. King VM, Armstrong DM, Apps R, Trott JR. Numerical aspects of pontine, lateral reticular, and inferior olivary projections to two paravermal cortical zones of the cat cerebellum. J Comp Neurol 1998;390:537-551.

Book

2. Voet D, Voet JG. Biochemistry. New York: John Wiley & Sons; 1990. 1223 p.

Tables

Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Figure Legends

Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement.

Figures

All figures should clarify the text and their numbers kept to a minimum.Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted.

Click here for the basic figure requirements for figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements.

Colour Figures. Figures submitted in colour may be reproduced in colour online free of charge. Please note, however, that it is preferable that line figures (e.g. graphs and charts) are supplied in black and white so that they are legible if printed by a reader in black and white.

Data Citation

In recognition of the significance of data as an output of research effort, Wiley has endorsed the FORCE11 Data Citation Principles and is implementing a mandatory data citation policy. Wiley journals require data to be cited in the same way as article, book, and web citations and authors are required to include data citations as part of their reference list.

Data citation is appropriate for data held within institutional, subject focused, or more general data repositories. It is not intended to take the place of community standards such as in-line citation of GenBank accession codes.

When citing or making claims based on data, authors must refer to the data at the relevant place in the manuscript text and in addition provide a formal citation in the reference list. We recommend the format proposed by the Joint Declaration of Data Citation Principles:

> [dataset] Authors; Year; Dataset title; Data repository or archive; Version (if any); Persistent identifier (e.g. DOI)

Additional Files

Appendices

Supporting Information

Supporting information is information that is not essential to the article, but provides greater depth and background. It is hosted online and appears without editing or typesetting. It may include tables, figures, videos, datasets, etc.

Click here for Wiley's FAQs on supporting information.

Note: if data, scripts, or other artefacts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

General Style Points

The following points provide general advice on formatting and style.

- **Abbreviations:** Should be standardized and in accordance with ELLIS G (ed.). Units, symbols and abbreviations. The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE, 1975. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Initially, use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation only.
- **Units of measurement:** Measurements should be given in SI or SI-derived units. Visit the Bureau International des Poids et Mesures (BIPM) website at www.bipm.fr for more information about SI units.
- **Numbers:** numbers under 10 are spelt out, except for: measurements with a unit (8mmol/l); age (6 weeks old), or lists with other numbers (11 dogs, 9 cats, 4 gerbils).
- **Trade Names:** Chemical substances should be referred to by the generic name only. Trade names should not be used. Drugs should be referred to by their generic names. If proprietary drugs have been used in the study, refer to these by their generic name, mentioning the proprietary name and the name and location of the manufacturer in parentheses.

Resource Identification Initiative

The journal supports the Resource Identification Initiative, which aims to promote research resource identification, discovery, and reuse. This initiative, led by the Neuroscience Information Framework and the Oregon Health & Science University Library, provides unique identifiers for antibodies, model organisms, cell lines, and tools including software and databases. These IDs, called Research Resource Identifiers (RRIDs), are machine-readable and can be used to search for all papers where a particular resource was used and to increase access to critical data to help researchers identify suitable reagents and tools.

Authors are asked to use RRIDs to cite the resources used in their research where applicable in the text, similar to a regular citation or Genbank Accession number. For antibodies, authors should include in the citation the vendor, catalogue number, and RRID both in the text upon first mention in the Methods section. For software tools and databases, please provide the name of the resource followed by the resource website, if available, and the RRID. For model organisms, the RRID alone is sufficient.

Additionally, authors must include the RRIDs in the list of keywords associated with the manuscript.

To Obtain Research Resource Identifiers (RRIDs)

more information).

3. Click on the "Cite This" button to obtain the citation and insert the citation into the manuscript text.

If there is a resource that is not found within the Resource Identification Portal, authors are asked to register the resource with the appropriate resource authority. Information on how to do this is provided in the "Resource Citation Guidelines" section of the Portal.

If any difficulties in obtaining identifiers arise, please contact rii-help@scicrunch.org for assistance.

Example Citations

Antibodies: "Wnt3 was localized using a rabbit polyclonal antibody C64F2 against Wnt3 (Cell Signaling Technology, Cat# 2721S, RRID: AB_2215411)"

Model Organisms: "Experiments were conducted in c. elegans strain SP304 (RRID:CGC_SP304)"

Cell lines: "Experiments were conducted in PC12 CLS cells (CLS Cat# 500311/p701_PC-12, RRID:CVCL_0481)"

Tools, software, and Databases: "Image analysis was conducted with CellProfiler Image Analysis Software, V2.0 (http://www.cellprofiler.org, RRID:nif-0000-00280)"

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5. EDITORIAL POLICIES AND ETHICAL CONSIDERATIONS

Peer Review and Acceptance

The acceptance criteria for all papers are the quality and originality of the research and its significance to journal readership. Manuscripts are single-blind peer reviewed. Papers will only be sent to review if the Editor-in-Chief determines that the paper meets the appropriate quality and relevance requirements.

Wiley's policy on the confidentiality of the review process is available here.

Human Studies and Subjects

For manuscripts reporting medical studies that involve human participants, a statement identifying the ethics committee that approved the study and confirmation that the study conforms to recognized standards is required, for example: Declaration of Helsinki; US Federal Policy for the Protection of

identifiable body parts are used that may allow identification, authors should obtain the individual's free prior informed consent. Authors do not need to provide a copy of the consent form to the publisher; however, in signing the author license to publish, authors are required to confirm that consent has been obtained. Wiley has a standard patient consent form available for use.

Animal Studies

A statement indicating that the protocol and procedures employed were ethically reviewed and approved, as well as the name of the body giving approval, must be included in the Methods section of the manuscript. Authors are encouraged to adhere to animal research reporting standards, for example the ARRIVE guidelines for reporting study design and statistical analysis; experimental procedures; experimental animals and housing and husbandry. Authors should also state whether experiments were performed in accordance with relevant institutional and national guidelines for the care and use of laboratory animals:

- US authors should cite compliance with the US National Research Council's Guide for the Care and Use of Laboratory Animals, the US Public Health Service's Policy on Humane Care and Use of Laboratory Animals, and Guide for the Care and Use of Laboratory Animals.
- UK authors should conform to UK legislation under the Animals (Scientific Procedures) Act 1986 Amendment Regulations (SI 2012/3039).
- European authors outside the UK should conform to Directive 2010/63/EU.

Clinical Trial Registration

The journal requires that clinical trials are prospectively registered in a publicly accessible database and clinical trial registration numbers should be included in all papers that report their results. Authors are asked to include the name of the trial register and the clinical trial registration number at the end of the abstract. If the trial is not registered, or was registered retrospectively, the reasons for this should be explained.

Research Reporting Guidelines

Accurate and complete reporting enables readers to fully appraise research, replicate it, and use it. Authors are encouraged to adhere to recognised research reporting standards. The EQUATOR Network collects more than 370 reporting guidelines for many study types, including for:

- Randomised trials : CONSORT
- Observational studies : STROBE
- Systematic reviews : PRISMA
- Case reports : CARE
- Qualitative research : SRQR
- Diagnostic / prognostic studies : STARD
- Quality improvement studies : SQUIRE
- Economic evaluations : CHEERS
- Animal pre-clinical studies : ARRIVE
- Study protocols : SPIRIT
- Clinical practice guidelines : AGREE

We also encourage authors to refer to and follow guidelines from:

- Minimum Information Guidelines from Diverse Bioscience Communities (MIBBI) website
- FAIRsharing website

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Upon its first use in the title, abstract, and text, the common name of a species should be followed by the scientific name (genus, species, and authority) in parentheses. For well-known species, however, scientific names may be omitted from article titles. If no common name exists in English, only the scientific name should be used.

Genetic Nomenclature

Sequence variants should be described in the text and tables using both DNA and protein designations whenever appropriate. Sequence variant nomenclature must follow the current HGVS guidelines; see varnomen.hgvs.org, where examples of acceptable nomenclature are provided.

Sequence Data

Nucleotide sequence data can be submitted in electronic form to any of the three major collaborative databases: DDBJ, EMBL, or GenBank. It is only necessary to submit to one database as data are exchanged between DDBJ, EMBL, and GenBank on a daily basis. The suggested wording for referring to accession-number information is: 'These sequence data have been submitted to the DDBJ/EMBL /GenBank databases under accession number U12345'. Addresses are as follows:

- DNA Data Bank of Japan (DDBJ): www.ddbj.nig.ac.jp
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- GenBank: www.ncbi.nlm.nih.gov/genbank

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ANNEXURE I: PROOF OF LANGUAGE EDITING

To whom it may concern

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

20 November 2018

Dear Mr / Ms

Re: Language editing of dissertation (**Bipolar disorder in the South African private health sector: Longitudinal analysis of prevalence, comorbidities and prescribing patterns**)

I hereby declare that I language edited the above-mentioned dissertation by Mr Adebayo Paul Akinrogunde (student number: 26870630).

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

Kind regards

Cecile van Zyl

Language practitioner

BA (PU for CHE); BA honours (NWU); MA (NWU)
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ANNEXURE J: PROOF OF TECHICAL EDITING

TO WHOM IT MAY CONCERN

I hereby declare that the dissertation titled:

Bipolar disorder in the South African private health sector: Longitudinal analysis of prevalence, comorbidities and prescribing patterns

by

AP Akinrogunde

26870630

has been technically edited by myself, which includes all tables and figures as well as the layout of the document's contents.

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March 2019