EVALUATING THE PRESCRIBING AND MANAGEMENT PRACTICES OF VENLAFAXINE AT A PUBLIC SECTOR PSYCHIATRIC HOSPITAL

BAVIKA NAIDU

Evaluating the prescribing and management practices of venlafaxine at a public sector psychiatric hospital

Bavika Naidu
G13N0852

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Supervisor:	Prof J. Bodenstein (Rhodes University)
Co-supervisor 1:	Mrs M. Bodenstein (Rhodes University)
Co-supervisor 2:	Prof M.S. Lubbe (North-West University)

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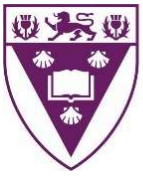

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DECLARATION

I, Ms Bavika Naidu (Rhodes University Student Number G13N0852), hereby declare that all the experimental work, planning, literature search, data capturing and interpretation, as well as writing the initial version of this dissertation was conducted by myself. My supervisor (Prof Johannes Bodenstein) and co-supervisors (Mrs Marisan Bodenstein and Prof Martie S. Lubbe) assisted in the interpretation of the results of the experimental work and proof read the dissertation in preparation for its final version. The work on which this dissertation is based is original (except where acknowledgements indicate otherwise) and that neither the whole work, nor any part thereof, has been or is being submitted for another degree at this or any other university.

_____ _____

Signature **Date**

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SUMMARY

Evaluating the prescribing and management practices of venlafaxine at a public sector psychiatric hospital

Key words: Drug utilisation, major depressive disorders, prescribing patterns, psychiatric hospital, anxiety disorders, public sector, South Africa, venlafaxine, anxiety-related disorders

Introduction: Neuropsychiatric conditions have been ranked third in South Africa according to some of the most recent reviews of disease burden, following human immunodeficiency virus/acquired immune deficiency syndrome and other infectious diseases (Bateman, 2012:70; South African Depression and Anxiety Group, 2018).

For depressive disorders, the conventional selective serotonin reuptake inhibitors (e.g. fluoxetine), are common first-step treatments due to their relatively low toxicity and high tolerability (Rush *et al*., 2006:1231). The class of selective noradrenaline reuptake inhibitors (e.g. venlafaxine) is relatively new on the market.

The first SNRI to be marketed in the United States was venlafaxine immediate-release (IR). It was approved by the United States FDA in 1993 (Sansone and Sansone, 2014:37) and was soon followed by the introduction of a micro-encapsulated extended-release (XR) formulation in 1997.

Currently there is no published or readily available information concerning the prescribing and management patterns of venlafaxine as well as the incidence and types of adverse effects experienced by patients in the public health sector of South Africa besides the established increased in blood pressure.

Aim and Objectives: The aim of the study was to evaluate the prescribing and management practices of venlafaxine to outpatients at a public healthcare sector psychiatric hospital.

The specific research objectives included the following:

- To determine the prescribing patterns of venlafaxine and compliance with the recommended treatment guidelines.

- To identify interactions and adverse effects associated with the use of venlafaxine.

Methodology: A retrospective DUR was conducted. Once ethical approval for the study was granted, data were collected from the files of 85 outpatients of 18 years and older who received venlafaxine treatment at Fort England Hospital for the period 1 January 2017-31 December 2017.

Results and Discussion: The sample size consisted of 85 patients (n=85). The patient sample consisted of 65 (76.47%) females and 20 (23.53%) males. The study results indicate that most of the patients in the study sample were diagnosed with either a depressive (n=53; 62.36%) or anxiety-related disorder (n=13; 15.29%). Therefore, venlafaxine was correctly indicated for most of the patients (n=66; 77.65%) in the study sample. Concerning initiation of therapy, results established that 78.82% (n=67) of the patients had their dose titrated from the initiation of venlafaxine treatment. The data analysis revealed that 74.12% (n=63) of patients did not experience any adverse effects from treatment with venlafaxine during the study period. The results indicated that blood pressure monitoring was conducted for 95.29% (n=81) of the patients in the sample, body weight monitoring was performed for 94.12% (n=80) of the patients, 95.29% (n=81) of the venlafaxine patient sample had their pulse rate monitored and 31.76% (n=27) of patients had their total cholesterol monitored. However, there was no information available in the majority of patient files of the patient sample (n=80; 94.12%) on venlafaxine treatment to ascertain whether triglyceride, low-density lipoproteins, high-density lipoproteins and sodium were monitored according to the recommended monitoring guidelines, suggesting target areas for improvement.

Conclusion: It was established that venlafaxine therapy was fairly monitored and in the majority of cases the initiation of venlafaxine was compliant with the recommended treatment guidelines. This drug utilisation study has provided valuable insight into the use of venlafaxine in the public sector of South Africa. Healthcare professionals should be trained and knowledgeable on the prescribing and monitoring guidelines to promote the rational and optimal use of venlafaxine.

LIST OF ABBREVIATIONS

A

AIDS Acquired Immunodeficiency Syndrome

ATC Anatomical therapeutic chemical

B

BMI Body mass index

BP Blood pressure

C

CBT Cognitive-behavioural therapy

D

DALYs Disability adjusted life years

DDD Defined daily dose

DSM Diagnostic and Statistical Manual of Mental Disorders

DUR Drug utilisation review

E

ECT Electroconvulsive therapy

EML Essential Medicines List

F

FDA United States Food and Drug Administration

G

GAD Generalised anxiety disorder

GBD Global burden of disease

GP General practitioner

H

HCl Hydrochloride

HDL High-density lipoproteins

HIV Human Immunodeficiency Virus

HT Hypertension

I

IPT Interpersonal therapy

IR Immediate-release

L

LDL Low-density lipoproteins

M

MAOI Monoamine oxidase inhibitor

MDD Major depressive disorder

O

ODV O-desmethylvenlafaxine

P

PD Panic disorder

PDD Prescribed daily dose

S

SA South Africa

SAD Social anxiety disorder

SADAG South African Depression and Anxiety Group

SASH South African Stress and Health

SASOP South African Society of Psychiatrists

SIADH Syndrome of inappropriate antidiuretic hormone secretion

SNRIs Serotonin-noradrenaline reuptake inhibitors

SSRIs Selective serotonin reuptake inhibitors

STGs Standard Treatment Guidelines

T

TCAs Tricyclic antidepressants

W

WHO World Health Organization

WMH World Mental Health

X

XR Extended-release

LIST OF DEFINITIONS

Agoraphobia: Is defined as a morbid fear of open spaces and/or of public places (Oxford, 2015:17).

Anxiety: A state which describes a generalised persistent fear. Anxiety disorders are defined in the Oxford Concise Colour Medical Dictionary as *"conditions in which anxiety dominates the patient's life or is experienced in particular situations: they include panic disorder, post-traumatic stress disorder and generalised anxiety disorders"* (Oxford, 2015:46).

Asthenia: Is described as a feeling of weakness or loss of strength (Oxford, 2015:61).

Autism: It is a psychiatric disorder of childhood, with an early age of onset before the age of 2 and a half years. The disorder is associated with severe difficulties in communicating and forming relationships with other individuals, in developing languages, and in using abstract concepts (Oxford, 2015:67).

Bipolar Disorder: Also referred to as bipolar affective disorder, is defined in the Oxford Concise Colour Medical Dictionary as a severe mental illness which results in repeated episodes of depression, mania, or mixed affective state. There are two types of bipolar affective disorders, namely type I and type II. Each type can be recognised by their characteristic episode (i.e. depression or mania) experienced (Oxford, 2015:87)

Bruxism: It is defined as a habit in which an individual grinds his or her teeth which may lead to excessive wear, this typically occurs during sleep (Oxford, 2015:106).

Burden: A term that is used to describe a heavy weight or a cause of destitution and grief (Hornby *et al*., 2010:189).

Depression: It is described as a mental state which is characterised by extreme melancholy or sadness (Oxford, 2015:205).

Dysthymia: It is defined as a permanent state of a mildly lowered mood, it never reaches the severity of clinical depression, however, it can impair the individual's quality of life (Oxford, 2015:235).

Ecchymosis: It is described as a bruise which is an initially bluish-black mark on the skin resulting from the release of blood into tissues caused by either an injury or spontaneous leaking of blood from the vessels (Oxford, 2015:238).

Eosinophil: It is a variety of white blood cells distinguished by a lobed nucleus and the presence of coarse granules in its cytoplasm (Oxford, 2015:257).

Eosinophilia: Refers to the increase in the number of eosinophils in the blood, it occurs in response to certain drugs and in a variety of diseases including allergies (Oxford, 2015:257).

Eructation: It is also referred to as belching which is the sudden raising of gas from the stomach (Oxford, 2015:264).

Hyperaesthesia: Describes a sensation of excessive sensibility especially of skin (Oxford, 2015:367).

Major depressive disorder (MDD): The diagnosis of MDD requires a distinct change of mood and is characterised by a depressed mood (sadness), accompanied by social withdrawal as well as loss of interest and reduced experience of pleasure (American Psychiatric Association, 2013:160; Belmaker and Agam, 2008:55; National Department of Health, 2015:15.8).

Melancholia: It is an obsolete name for depression which is not triggered by any stressors (Oxford, 2015:462).

Meta-analysis: It is a statistical technique for combining and analysing the results of a number of different studies focused on the same topic to enable identification of trends and patterns and more accurate estimation of significant effects (Oxford, 2015:471).

Multicentre study: It refers to a clinical trial that is conducted at more than one medical institution (National Cancer Institute, 2018).

Multidisciplinary: Describes a process involving numerous academic disciplines or professional specialisations (Hornby *et al*., 2010:970).

Mutism: It refers to the inability or refusal to speak which may be a result of brain damage or caused by depression, psychosis or psychological trauma (Oxford, 2015:492).

Mydriasis: Refers to the widening of the pupil which generally occurs in dim light (Oxford, 2015:493).

Myocardial Infarction: It is described as the death of a segment of heart muscle following an interruption of its blood supply, which is usually confined to the left ventricle (Oxford, 2015:496).

Myoclonus: It is defined as a sudden spasm of the muscles (Oxford, 2015:496).

Neuroleptic malignant syndrome: Refers to a life-threatening syndrome that appears after initiating antipsychotic drugs which is characterised by confusion, muscle rigidity, fever, sweating and urinary incontinence (Oxford, 2015:514). Indicated treatment usually takes places in a high-dependency unit with a high-dose of benzodiazepines and immediate cessation of antipsychotic drugs.

Off-label prescribing: It is defined as the prescribing or use of a drug for an indication different from that approved by the FDA (Stafford, 2008:1428).

Open-label study: Refers to a type of study in which both the healthcare providers and the patients are aware of the drug or treatment being given (National Cancer Institute, 2018).

Paraesthesia: Is a spontaneously occurring tingling sensation which is sometimes described as pins and needles, it may be due to partial and temporary damage to a peripheral nerve (Oxford, 2015:559).

Paternalism: Is defined as an attitude or policy that supersedes a person's own wishes in pursuit of his or her best wellbeing (Oxford, 2015:565).

Pharmacoepidemiology: Defined by the World Health Organization (WHO) as the study of the use and effects of drugs in large numbers of people aimed at supporting the rational and cost-effective use of drugs, thus improving health outcomes for the population (WHO Collaborating Centre for Drug Statistics Methodology and WHO

Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services, 2003:1).

Pharmacovigilance: Defined by the WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any drug-related problems (WHO, 2018).

Porphyria: A group of rare disorders which is due to inborn errors of metabolism in which there are deficiencies in the enzymes responsible for the biosynthesis of haem (Oxford, 2015:603).

Psychoanaleptic: It is a term used to describe a drug that has a stimulating effect on the mind, e.g. antidepressants and antipsychotics (Oxford, 2015:627).

Psychological: This term is used to describe the scientific study of behaviour and its related mental processes (Oxford, 2015:627).

Q-T Interval: Is the interval on an electrocardiogram between the beginning of ventricular depolarisation (Q wave) and the beginning of the repolarisation (T wave) (Oxford, 2015:638).

Rater-blinded study: In a study, bias occurs when there is knowledge of the treatment assignment which modifies the outcome of assessment (Marcus *et al*., 2006:2762). Therefore, blinding (keeping patients, healthcare providers, raters or data analysts unaware of treatment assignment) is one method to limit bias influencing assessment (Marcus *et al*., 2006:2763).

Remission: Defined by the Oxford Concise Colour Medical Dictionary as the diminishing in the severity of symptoms or their temporary vanishing during the course of an illness, or a reduction in the size of a cancer and its associated symptoms (Oxford, 2015:651).

Serotonin syndrome: It is a potentially life-threatening adverse drug reaction that results from therapeutic drug use, intentional self-poisoning, or inadvertent interactions between drugs (Boyer and Shannon, 2005:1112). The signs of excess serotonin differ from tremor and diarrhoea in mild cases to delirium, neuromuscular rigidity and hyperthermia in life-threatening cases.

Syncope: Refers to the loss of consciousness due to a sudden decrease in blood pressure, which results in a temporarily insufficient flow of blood to the brain (Oxford, 2015:735).

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH): It is a condition of inappropriately high plasma levels of antidiuretic hormone with associated water retention, dilutional hyponatraemia and the production of highly concentrated urine (Oxford, 2015:736).

Tachycardia: This term refers to an increase in the heart rate to above normal (Oxford, 2015:739).

Torsades de pointes: It is defined as a dangerous form of ventricular tachycardia characterised by a sinusoidal (twisting) pattern on the electrocardiogram due to a constantly shifting cardiac electrical vector (Oxford, 2015:762).

Trismus: It is described as a spasm of the jaw muscle, thus keeping the jaws tightly closed (Oxford, 2015:774).

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CHAPTER 1. INTRODUCTION AND PROBLEM STATEMENT

1.1 Introduction

Antidepressants are a class of drugs that are used to treat depression, anxiety, bipolar disorders and various pain syndromes (Cascade *et al*., 2007:25). The classes of antidepressants are: selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin-noradrenaline reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and some other antidepressants (Ciraulo and Shader, 2004:33).

Venlafaxine is classified as an SNRI and a central nervous system psychoanaleptic drug. Venlafaxine immediate-release (Effexor™) was the first SNRI to be marketed in the United States. It was approved by the United States Food and Drug Administration (FDA) in 1993 (Sansone and Sansone, 2014:37). The FDA has approved four clinical indications: MDD, generalised anxiety disorder (GAD), panic disorder (PD) and social phobia/ social anxiety disorder (SAD). Its pharmacological mechanism of action is to inhibit the reuptake of serotonin and noradrenaline into the presynaptic terminal. Reuptake is inhibited in a sequential manner, with initial serotonin reuptake inhibition followed by noradrenaline uptake inhibition (Sansone and Sansone, 2014:37). Results suggest that at high doses, venlafaxine may exhibit some degree of dopamine reuptake inhibition, whilst at lower doses it mainly affects serotonin reuptake, making it comparable to an SSRI (Ciraulo and Shader, 2004:77).

Pharmacological studies suggest that venlafaxine has minimal or no interaction with muscarinic, histaminic, or α-adrenergic receptors, which most likely accounts for its low incidence of adverse effects. It is an effective antidepressant and antianxiety agent (Ciraulo and Shader, 2004:77). The introduction of the venlafaxine immediate-release (IR) dose form, which was administered twice a day, preceded the improved micro-encapsulated extended-release (XR) formulation (Effexor XR™), which is administered once a day. The XR formulation has the advantage of a lower incidence of nausea and dizziness at the initiation of therapy. Both formulations are also available as generic and branded products with cost benefits for patients. In terms of its chemical properties, venlafaxine has a bicyclic chemical structure and is structurally different to the other SNRIs (Sansone and Sansone, 2014:37). The half-life of venlafaxine in the IR formulation is 5 hours. In comparison, the XR formulation has a longer half-life of 9-11 hours.

This chapter introduces the current pharmacoepidemiological study. A pharmacoepidemiological study is defined as the study of the use and effects of drugs in large numbers of people (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services, 2003:8). It is aimed at supporting the rational and cost-effective use of drugs and thereby improving health outcomes for the population (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services, 2003:8). Pharmacoepidemiology may be drug-oriented, placing an emphasis on the safety and effectiveness of individual drugs or drug groups, or utilisation-oriented aiming to improve the quality of drug treatments using educational interventions.

Specific emphasis was placed on the prescribing and management practices of venlafaxine at a public sector psychiatric hospital and current practices were evaluated against available local and international guidelines. In addition, the pharmacovigilance component of the study investigated the prevalence of drug interactions and adverse effects.

The background, problem statement, the aim and objectives, research methodology for the literature review and empirical study as well as ethical considerations are briefly outlined.

1.2 Background to the study

One of the major contributors to the burden of disease globally is mental disorders (Tomlinson *et al*., 2009:367). The World Health Organization (WHO) constitution states: *"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."* This statement implies that mental health is more than the absence of mental disorders or disabilities and is determined by a range of socioeconomic, biological and environmental factors (WHO, 2017). Mental health is essential for individuals to lead a healthy life, to be able to manage stressful situations and enjoy life.

In South Africa, studying some of the most recent reviews of disease burden, neuropsychiatric conditions have been ranked third, following human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and other

infectious diseases (Bateman, 2012:70; South African Depression and Anxiety Group, 2018). The lifetime prevalence of major depressive disorder (MDD) documented in the South African Stress and Health (SASH) survey, was found to be 9.8% across all age groups (Emsley *et al*., 2013:157; Seedat *et al*., 2009:377). The SASH survey was the first national epidemiological survey of common mental disorders in South Africa. The 12-month prevalence rate of MDD was 4.9%, and it was found that females were 1.75 times more likely to develop MDD than males (Emsley *et al*., 2013:157; Seedat *et al*., 2009:378-379). Compared to 14 other countries in the World Mental Health (WMH) survey, South Africa has the 7th highest life-time prevalence of mood disorders (9.8%), 2nd highest prevalence of substance abuse disorders (13.3%) and 6th highest prevalence for anxiety disorders (15.8%) (South African Depression & Anxiety Group, 2012).

Mental disorders not only have a substantial negative psychological, social and economic impact on society, but also increase the risk for physical illnesses. Furthermore, mental health and poverty are strongly related in South Africa. This association was one of the key findings in the Mental Health and Poverty Project (MHaPP) by the Department of Psychiatry and Mental Health at the University of Cape Town (UCT) Africa (Alan J Flisher Centre for Public Mental Health, 2011). Results from the MHaPP study suggest that mental disorders are associated with poverty and social deprivation, social circumstances such as living in poverty, exposure to stressful events such as crime and violence, inadequate housing, unemployment and social conflict (South African Depression and Anxiety Group, 2018).

There are many different mental disorders, each with a different clinical presentation. Mental disorders are generally characterised by a combination of abnormal thoughts, perceptions, emotions, behaviours and relationships with others (World Health Organization, 2016). These disorders include: depression, bipolar affective disorder, schizophrenia and other psychoses, dementia, intellectual disabilities and developmental disorders such as autism.

For depressive disorders, the conventional SSRIs, such as fluoxetine, are common first-step treatments due to their relatively low toxicity and high tolerability (Rush *et al*., 2006:1231). Due to the class of SNRIs being relatively new on the market as compared to the other antidepressant classes, there is limited research completed to

add to existing knowledge regarding its efficacy and to describe the extent of adverse effects experienced by patients on treatment with venlafaxine. Hence, it is commonly overlooked as a first-line measure for antidepressant treatment.

However, from the literature review the researcher was able to find a few randomised trials which compared the efficacy and tolerability of treatment with venlafaxine to at least two other active second-line drugs after initial treatment failure with an SSRI. The outcomes supported the use of venlafaxine (Baldomero *et al*., 2005; Fang *et al*., 2010; Rush *et al*., 2006).

A study was conducted by Rush and co-workers to investigate the viable options for switching therapy after unsuccessful treatment with an SSRI, as it was unknown whether switching within one antidepressant class is more advantageous and effective than switching to another class of antidepressants (Rush *et al*., 2006:1232). Their study compared the outcomes achieved from three second-step medications, namely sustained-release bupropion, sertraline and extended-release venlafaxine. The remission rates following the administration of these medications were chosen as the primary outcome. Results suggest that the remission rates, which were approximately one in four patients, were not drastically different from each other and they did not differ considerably with respect to tolerability or adverse effects. Therefore, the study concluded that after an unsuccessful treatment with an SSRI, any one of bupropion, sertraline and venlafaxine, would be a reasonable second-step choice for patients with depression (Rush *et al*., 2006:1240). The study included an important point concerning venlafaxine, namely it stated that *post hoc* analyses suggest slightly higher remission rates with venlafaxine than with SSRIs when used as a first-step treatment. However, in their study, higher remission rates were not established with extended-release venlafaxine compared to the other two drugs.

Results from a study by Baldomero and co-workers support the findings from the study of Rush and co-workers discussed above. Their study discovered that venlafaxine extended-release may be more effective than the conventional antidepressants when treating patients who do not tolerate or respond adequately to treatment with a conventional antidepressant (Baldomero *et al*., 2005:68-76). These findings highlight the need for more broadly effective antidepressant treatment. Venlafaxine is one of the favourable options from second step treatment and therefore should be further

investigated for its pharmacological properties to treat depressive disorders as a first-line treatment option.

1.3 Motivation and problem statement

A retrospective DUR involves reviewing drug therapy after the patient has received treatment. The aim of a retrospective DUR is to detect patterns in the prescribing, dispensing or administration of medication (Academy of Managed Care Pharmacy, 2009:1). DURs have been previously conducted in South Africa, but some date back to more than a decade ago. This could pose a challenge for comparison purposes (Kairuz *et al*., 2003; Truter and Kotze, 1996). Some of these studies were also restricted to data sourced from private medical aid schemes and were conducted based on a whole class of antidepressants as opposed to a specific anti-depressant (Truter and Kotze, 2006) or to data gathered from public sector institutions. Over the years, there have been new developments which led to the introduction of novel antidepressant classes such as the SNRIs, of which venlafaxine is an example. However, data relating to the prescribing and management practices of venlafaxine have been lacking, especially in South Africa. Therefore, there was a need to conduct a DUR study to understand the prescribing and management practices of venlafaxine in the public sector and to compare it to specific guidelines.

With regards to prescribing of venlafaxine, according to the South African Medicines Formulary (SAMF) and the South African Society of Psychiatrists (SASOP) Treatment Guidelines for Psychiatric Disorders, venlafaxine treatment should be initiated at 37.5 mg/day for 4-7 days especially for new patients to allow patients to adjust before increasing the dose to 75 mg/day (Cipla Medpro, 2006:1; Emsley *et al*., 2013:159-162; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:5). Dose titration should be planned in increments of 75 mg/day as needed and should be made at intervals of not less than 4 days. The maximum dose for moderately depressed patients is 225 mg/day and for severely depressed patients it is 375 mg/day. Elderly or anxious patients can use an initial dose of 37.5 mg/day (Cipla Medpro, 2006:1; Emsley *et al*., 2013:159-162; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:5).

Patients on venlafaxine treatment require regular blood pressure monitoring, especially for regimens with doses above 200 mg/day (Cipla Medpro, 2006:1; Emsley

et al., 2013:159-162; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:5). In addition, the weight of patients should be monitored regularly, especially for high-risk patients with co-morbid disorders such as diabetes or hypercholesterolemia (Wyeth Pharmaceuticals, 2003:14). Venlafaxine treatment is associated with an approximate increase of 4 beats/min in mean heart rate therefore it is a requirement that the patients' heart rate be monitored regularly (Cipla Medpro, 2006:1).

A few common adverse effects experienced by patients on treatment with venlafaxine include the following: Central nervous system effects such as headache, dizziness, insomnia, nervousness, somnolence and visual disturbances; gastrointestinal complaints such as anorexia, dry mouth, nausea, vomiting, constipation; sexual dysfunction; sweating and fatigue (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503). Venlafaxine has known drug interactions with MAOIs, SSRIs and lithium (Rossiter *et al*., 2016:503). The concurrent use of venlafaxine and either MAOIs, SSRIs or lithium may lead to the serotonin syndrome and should therefore be monitored and avoided.

In the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) for South Africa Hospital Level for Adults, with regards to the treatment of psychiatric disorders (including depressive and anxiety-related disorders), venlafaxine was not mentioned as a first, second or third-line treatment alternative (National Department of Health, 2015:15.1-15.23). However, according to the South African National Department of Health tertiary and quaternary level EML recommendations as of August 2018, venlafaxine is recommended for use as a third-line treatment of MDD and anxiety associated with depression (National Department of Health Republic of South Africa, 2018). Hence, the focus of the current study was to evaluate the prescribing and management practices of venlafaxine at a public sector psychiatric healthcare facility to assess the rational use of the drug.

This study was the first retrospective DUR on venlafaxine conducted at a public sector psychiatric healthcare facility. Currently there are no published data regarding the prescribing and management practices of venlafaxine as well as the incidence and types of adverse effects experienced by patients at the study site.

1.4 Primary aim and research objectives

The current study aimed to conduct a DUR on venlafaxine, a SNRI antidepressant by retrospectively evaluating its prescribing and management practices to outpatients at Fort England Hospital in Grahamstown (Makhanda), situated in the Cacadu District Municipality, Makana Local Municipality, Eastern Cape Province, South Africa.

The study determined whether venlafaxine was rationally used for its recommended indication at Fort England Hospital. This psychiatric hospital was the preferred setting to conduct the study, because the researcher was completing her practical hours as an academic pharmacist intern during the study period. A need was identified for the correct monitoring of psychiatric patients on treatment with venlafaxine and further supported the motivation for this study.

In order to achieve the aim of the current study, the study consisted of a literature review and an empirical investigation at the psychiatric hospital. The specific objectives of the study are discussed in the following section.

1.4.1 Specific objectives for the literature study

The specific research objectives of the literature review included the following:

- To describe the history of the development of venlafaxine.
- To discuss the pharmacological properties of venlafaxine (pharmacokinetics and pharmacodynamics) and compare it to other antidepressants.
- To discuss the toxicological properties of venlafaxine (adverse effects, interactions, safety in pregnancy and lactation, use in specific patient populations) and compare it to other antidepressants.
- To acquire knowledge on depressive and anxiety-related disorders and their prevalence in South Africa.
- To determine the drug treatment guidelines of depressive and anxiety-related disorders, where venlafaxine therapy can be considered as a treatment option.
- To determine what constitutes a drug utilisation review as well as the importance and objectives thereof.
- To discuss drug utilisation reviews on antidepressants in general and specifically on venlafaxine in the public and private sectors, locally and internationally.

1.4.2 Specific objectives for the empirical study

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

- To determine the prescribing patterns of venlafaxine and compliance with the recommended treatment guidelines (the pharmacoepidemiology component of this study).
- To identify medication problems associated with the use of venlafaxine (the pharmacovigilance component of this study).

1.5 Research methodology

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

1.5.1 Literature review

The literature (books, review and research journal articles, websites and dissertations/theses) that were included in the literature review were selected through a comprehensive Internet search and the following process was followed:

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

  - “Psychiatric disorders”.
  - “Definition of major depressive disorders”.
  - “Pathophysiology of major depressive disorders”.
  - “Prevalence of major depressive disorders”.
  - “Treatment of major depressive disorders”.
  - “Antidepressant”.
  - “Psychoanaleptic”.
  - “Venlafaxine”.
  - “History of venlafaxine”.
  - “Pharmacology of venlafaxine”.

- "Toxicology of venlafaxine".
- "Drug utilisation review".
- "Pharmacoepidemiology".
- "Pharmacovigilance".
- "Prescribing and management practices".
- "Public health sector".
- "Makana local municipality".
- "Cacadu district municipality".
- "Eastern Cape province".
- "Private health sector".
- "Descriptive statistics".
- "Inferential statistics".

The most appropriate and current literature from the data base searches were utilised. Where recent (dating back to 5 years or less) references could not be found, older references were consulted.

The literature review was conducted from January 2017 to December 2018. Chapter 2 provides a comprehensive outline of the literature review.

1.5.2 Empirical study

A pharmacoepidemiological study with a cross-sectional research approach was conducted. Methodological concepts of a retrospective drug utilisation review were also employed.

The research methodology employed in the empirical study on venlafaxine is discussed in-depth in Chapter 3.

1.5.2.1 Study population

The study sample included a total number of 85 patients who were 18 years and older, who had been diagnosed at any time with a depressive disorder and who were on treatment with venlafaxine at the outpatient clinic of Fort England hospital for the period 1 January 2017-31 December 2017.

1.5.2.2 Research instrument

The research instrument was a data collection tool. This comprised of a structured data collection form designed to record patient demographic data, social and medical circumstances, medication as well as parameters important to assess the monitoring of patients on venlafaxine treatment. A pilot study was conducted on five patient files to determine the workability of the data collection tool.

1.5.2.3 Data collection

The data collection tool in the form of a structured data collection form was designed to record patient demographic data, social and medical circumstances, as well as parameters important to assess the monitoring of patients on venlafaxine treatment. A pilot study was conducted on five patient files to determine the workability of the data collection tool.

1.5.2.4 Data analysis

Data captured from the collection forms was transferred onto a MS® Excel spreadsheet and was analysed using the computer software MS® Excel and Statistical Analysis System® (SAS Institute Inc.). Data were analysed according to the specific objectives of the study.

1.5.2.5 Study variables

The following variables were included in the study:

- Age.
- Gender.
- Race.
- Tobacco, alcohol and substance abuse.
- Social history.
- Medical history.

1.5.2.6 Study measurements

The following measurements were included in the study:

- Weight.
- Height.
- Co-morbid diseases.
- Diagnosis.
- History of venlafaxine use.
- Concomitant drug use.
- Venlafaxine dose and dose titration.
- Drug interactions.
- Adverse effects.
- Compliance with the recommended treatment and monitoring guidelines for blood pressure, weight, heart rate total cholesterol and sodium level monitoring.

1.5.2.7 Ethical aspects

Approval to commence with this study was granted by the Rhodes University Faculty of Pharmacy Higher Degrees Committee, Rhodes University Faculty of Pharmacy Research Ethics Committee **(PHARM-2018-05)**, the Fort England Hospital Research Committee **(PHARM-2018-05 continued)** as well as the Eastern Cape Department of Health Research Committee **(EC_201808_010)**. Ethical aspects are explained in more detail in CHAPTER 3.

1.6 Chapter layout

- **Chapter 1** introduces the study, describes the aim and objectives and briefly explains the research methodology.
- **Chapter 2** serves as a literature review. Psychiatric disorders with specific emphasis on the treatment of depressive disorders with venlafaxine as well as its pharmacological properties are discussed. In addition, drug utilisation studies are discussed and their purpose and applications mentioned.
- **Chapter 3** describes the methodology for the empirical study on venlafaxine. It explains obtaining, analysing and interpreting the data. Statistical terminologies that were relevant for the study are also discussed. Furthermore, the ethical considerations of the study are also discussed.
- **Chapter 4** is a report on the research findings and the discussion thereof.

- **Chapter 5** is a concluding chapter that summarises the main findings of the study, lists the study limitations and provides directions for future studies.
- The complete reference list of the dissertation is presented in-between the last chapter and the annexures. The reference manager that was used is Zotero (Corporation for Digital Scholarship and the Roy Rosenzweig Center for History and New Media).
- Annexures.

1.7 Chapter 1 Summary

A brief outline of the background of the study was provided. The aim and objectives of the literature review and empirical study on venlafaxine were discussed in detail and the research methodology and ethical aspects briefly explained. The following chapter provides an overview of the literature study conducted.

CHAPTER 2.
LITERATURE REVIEW

2.1 Depressive disorders, anxiety-related disorders and panic disorders

Mental health and neurological conditions are one of the biggest contributors to the global burden of disease (World Health Organization, 2002:1). These conditions are initially difficult to diagnose and require continuous monitoring, hence there is limited data to accurately represent the statistics of the population. In the 1990's, the WHO introduced the Global Burden of Disease (GBD) study that was aimed at providing a comprehensive summary, including information on disease and injury to inform global priority setting for health research and for international health policy and planning (Üstün *et al*., 2004:386-392). The results from the study showed that unipolar depressive disorders are a relative large problem and were ranked as the fourth leading cause of burden amongst all diseases (Üstün *et al*., 2004:386). Such disorders accounted for 3.7% of the total disability adjusted life years (DALYs).

In 2001, the WHO decided to undertake a new assessment of the GBD for the year 2000. Both the GBD 1990 and 2000 studies used the DALYs approach to quantify the GBDs. One DALY represents the loss of a healthy year of life and aggregates the years of life lived with disability (YLD) with the years of life lost due to premature death (YLL) (Ferrari *et al*., 2013:2). From the GBD 2000 study, depressive disorders were ranked the third leading cause of disease burden and accounted for 4.3% of all DALYs (Ferrari *et al*., 2013:2).

The most recent GBD study conducted was the GBD 2010 study, which encompassed an expansion of the initial GBD framework (Ferrari *et al*., 2013:2). This was used to quantify the direct burden of 291 diseases and injuries across 187 countries in both male and female patients in 20 different age groups (Ferrari *et al*., 2013:2). The GBD 2010 study was different from the previous GBD studies that assessed the burden of "unipolar depression" in the sense that it measured the disease burden for MDD and dysthymia separately to accommodate differences between the subtypes of depression. The results from the GBD 2010 study concluded that depressive disorders are a significant cause of disease burden and a global health priority (Ferrari *et al*., 2013:2). MDD was found to be a risk factor and burden contributor to suicide and ischaemic heart disease (Ferrari *et al*., 2013:2). The findings from the study further suggested that depressive disorders needed to be recognised as a public

health priority and require cost effective interventions to alleviate its burden (Ferrari *et al*., 2013:11).

According to information in a mental health fact sheet compiled by the South African Depression and Anxiety Group (SADAG) for South Africa (South African Depression & Anxiety Group, 2012):

- Mental health is the 3rd biggest contributor to the disease burden.
- 43.7% of people with HIV/AIDS have a mental health condition.
- 11% of all non-natural deaths is due to suicide (approximately 8000 South Africans commit suicide each year).
- 82.1% of the population cannot afford private healthcare.
- 50% of healthcare facilities do not meet quality standards.
- 50% of people believe that mental health is not a priority.

2.1.1 Depressive disorders

2.1.1.1 Definition

Depressive disorders comprise of disruptive mood dysregulation disorder, MDD (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/drug-induced depressive disorder, depressive disorder due to another medical condition, other specified disorder and unspecified depressive disorder (American Psychiatric Association, 2013:155). All of these disorders have the following common features: Presence of sad, empty or irritable mood, accompanied by somatic and cognitive changes that affect the individual's ability to function normally (American Psychiatric Association, 2013:155). The difference among these disorders is the duration, timing or aetiology of the disorder.

2.1.1.2 Major depressive disorder

Major depressive disorder represents the classic condition in the group of depressive disorders. The diagnosis of MDD requires a distinct change of mood and is characterised by a depressed mood (sadness), accompanied by social withdrawal as well as loss of interest and reduced experience of pleasure (American Psychiatric Association, 2013:160; Belmaker and Agam, 2008:55; National Department of Health,

2015:15.8). The presenting mood is described as irritability, both in association with sadness or as the principal feature, and is common in adolescents (Fava and Kendler, 2000:335). MDD is characterised by single or recurrent major depressive episodes (Emsley *et al*., 2013:157). Patients may experience several psychophysiological changes manifesting as disturbances or reduction in sleep, appetite, energy, motivation, concentration and memory as well suicidal thoughts (American Psychiatric Association, 2013:160-161; Belmaker and Agam, 2008:56; Emsley *et al*., 2013:157; Fava and Kendler, 2000:335; National Department of Health, 2015:15.8). The features of major depression are generally present for at least two weeks and influence the person's ability to function normally (American Psychiatric Association, 2013:155; Belmaker and Agam, 2008:55; Emsley *et al*., 2013:157; National Department of Health, 2015:15.8). In addition, MDD is frequently associated with co-morbid psychiatric and medical conditions accompanied by a high risk of morbidity and mortality (Emsley *et al*., 2013:157).

2.1.1.2.1 Aetiology

There are numerous proposed theories to describe and elucidate the aetiology of depression. However, medications that modify neurotransmitter action have become the primary therapies for depression since numerous neurotransmitter abnormalities have been uncovered in depression (Ciraulo and Shader, 2004:13). The monoamine hypothesis of depression postulates a deficiency in serotonin or noradrenaline neurotransmission in the brain (Belmaker and Agam, 2008:58; Ciraulo and Shader, 2004:14).

2.1.1.2.2 Prevalence and onset

MDD has a median lifetime prevalence of 16.1% with a range between 4.4-18% (Emsley *et al*., 2013:157). According to the DSM-5, a twelve-month prevalence of major depressive disorder in the United States is approximately 7%, with marked differences by age group such that the prevalence in 18-29-year old individuals is threefold higher than the prevalence in individuals aged 60 years or older (American Psychiatric Association, 2013:165). The DSM-5 also indicated that females experience 1.5 to 3-fold higher rates than males, emerging early in the adolescence (American Psychiatric Association, 2013:165). Additional studies conducted in the

United States discovered the lifetime incidence of depression specific to gender is more than 12% in men and 20% in women (Belmaker and Agam, 2008:55; Fava and Kendler, 2000:335). In South Africa, the lifetime prevalence of MDD documented in the SASH survey, was found to be 9.8% across all age groups (Emsley *et al*., 2013:157; Seedat *et al*., 2009:377). The 12-month prevalence rate of MDD was 4.9%, and it was found that females were 1.75-times more likely to develop MDD than males (Emsley *et al*., 2013:157; Seedat *et al*., 2009:378-379). Compared with 14 other countries in the WMH survey, South Africa has the 7th highest life-time prevalence of mental disorders such as mood disorders (9.8%) (South African Depression & Anxiety Group, 2012). The onset of MDD can occur at any age, however, studies suggest that there are two peaks in life, primarily in the twenties and forties with a mean age of onset estimated around the age of 30 (American Psychiatric Association, 2013:165; Emsley *et al*., 2013:157).

2.1.1.2.3 Risk factors

Studies have discovered that females, a previous episode of major depression and a positive first-degree family history of depression are the most consistently described risk factors for MDD (Emsley *et al*., 2013:157). A wide range of environmental adversities such as job loss, marital difficulties, major health problems, low social class, low levels of support, being in a more recently born age group and loss of close personal relationships are all associated with a substantial increase in the risk for the onset of MDD (Fava and Kendler, 2000:335).

2.1.1.2.4 Co-morbidity

Disorders with which MDD frequently co-occur are substance-related disorders, panic disorder, obsessive-compulsive disorder, anorexia nervosa, bulimia nervosa and borderline personality disorder (American Psychiatric Association, 2013:168). Anxiety disorders are highly co-morbid, with a prevalence in about 58% of patients with MDD. Anxiety symptoms which are highly prevalent in MDD occur in 80% of patients (Emsley *et al*., 2013:157).

2.1.1.2.5 Treatment

Important information regarding antidepressants (National Department of Health, 2015:15.8):

- All antidepressants take at least 4-6 weeks to achieve their maximum effect. Some patients may experience an initial response within the first 1-2 weeks. There is little evidence to support combination drug treatment.
- TCAs and SSRIs are of equal efficacy.
- The choice of therapy should be based on patient profile, adverse effect profile, drug availability, nature of prior response to drug, co-morbid psychiatric and medical conditions, patient preference, potential drug interactions and cost, e.g. in patients with cardiac disease, TCAs should be avoided and in elderly patients TCAs and SSRIs should be used with caution.
- Following remission, treatment should be continued for at least another 6 months. Thereafter, review the need for ongoing treatment.
- When discontinuing the drug, taper off slowly to avoid discontinuation symptoms. If there is a reoccurrence, reinstitute the drug at the same dose.
- Patients with 3 or more episodes may require maintenance therapy to be reviewed every 2 years.
- Due to the increased risk of suicidal thoughts and behaviour associated with SSRI treatment, adolescents with depression should be treated by a specialist only.

According to the STGs and EML for South Africa Hospital Level for Adults, the following steps should be followed for MDD treatment (Table 2–1) (National Department of Health, 2015:15.8-15.9):

Table 2–1. Treatment of major depressive disorders according to the Standard Treatment Guidelines and Essential Medicines List for South Africa Hospital Level for Adults (National Department of Health, 2015:15.8-15.9).

FIRST-LINE TREATMENT				
	Class of Antidepressant	**Name of Antidepressant**	**Dosing Instructions**	
	Selective serotonin reuptake inhibitor	Fluoxetine	Initial dose	20 mg
			Route of administration	Oral
			Dose titration	Start with 20 mg, then if there is no or limited response after 4-8 weeks, increase to 40 mg, if treatment is well tolerated
OR	Selective serotonin reuptake inhibitor	Citalopram	Initial dose	20 mg
			Route of administration	Oral
			Dose titration	If there is no or limited response after 4-8 weeks, increase to 40 mg, if it is well tolerated
Note: Adolescents with depression are at increased risk of suicidal ideation when initiated on SSRIs				
OR	Tricyclic antidepressant	Amitriptyline	Dose range	75-150 mg
			Route and time of administration	Oral at night
			Dose titration	Start with 25 mg, then increase by 25

FIRST-LINE TREATMENT				
	Class of Antidepressant	**Name of Antidepressant**	**Dosing Instructions**	
				mg/day at 3-4 day intervals
Second-line treatment alternatives				
• If patient is currently on a SSRI, change treatment to another SSRI (citalopram) or a TCA • If patient is currently on a TCA, switch to a SSRI • If patient was initially on fluoxetine, wait for seven days after stopping fluoxetine before starting citalopram (the other SSRI)				

Referral should be considered in the following circumstances (National Department of Health, 2015:15.9):

- A high suicide risk patient.
- A patient experiencing inadequate response to treatment.
- Patient displays psychotic features.

General measures for patient and family (National Department of Health, 2015:15.8):

- Counselling of patient and family members.
- A review of patient's supporting social factors.
- Beneficial supportive psychotherapy.
- In particular circumstances additionally involving a discussion with a specialist, electroconvulsive therapy (ECT) in indicated.

According to The SASOP Treatment Guidelines for Psychiatric Disorders, the following steps should be followed for MDD treatment (Table 2–2) (Emsley *et al*., 2013:159-162):

Table 2–2. Treatment of major depressive disorder according to the South African Society of Psychiatrists (Emsley *et al*., 2013:159-162).

	TYPE OF DEPRESSION	FIRST-LINE TREATMENT
1	Mild to moderate depression	Psychotherapy, cognitive-behavioural therapy (CBT) or interpersonal therapy (IPT) either alone or in combination with an SSRI, an SNRI (e.g. venlafaxine), bupropion, mirtazapine or agomelatine
2	Severe depression	Always consider an antidepressant as first-line (an SSRI, SNRI (e.g. venlafaxine), bupropion or mirtazapine) in combination with CBT or IPT, or alternatively consider ECT.
3	Severe major depression with psychotic features	A combination of an antidepressant with an antipsychotic. ECT should also be considered. Consider a combination of either a tertiary amine tricyclic antidepressant (amitriptyline or imipramine) with an antipsychotic agent (either a first- or second-generation antipsychotic), an SSRI in combination with an antipsychotic, or venlafaxine in combination with an antipsychotic
Note: If a patient presents without co-morbidities and has had a previous satisfactory response to an SSRI, consider initiating treatment with a SSRI. If a patient presents with a co-morbid anxiety or pain disorder, consider initiating treatment with an SSRI, SNRI or mirtazapine		
Treatment alternatives (for no response)		
• Switch to another first-line drug from a different pharmaceutical class • Augment with any one of the following: Lithium, triiodothyronine (T3), an antipsychotic agent, an anticonvulsant/mood stabiliser • Combine an SSRI with a TCA, an SSRI with bupropion, an SSRI with mirtazapine, or venlafaxine with mirtazapine		
Note: Venlafaxine starting dose – 37.5 mg/day, venlafaxine usual dose – 75-375 mg/day Venlafaxine XR starting dose – 37.5 mg/day, venlafaxine XR usual dose – 75-225 mg/day		

The SASOP Treatment Guidelines for Psychiatric Disorders draws on several international guidelines (Emsley *et al*., 2013:157):

- Practice Guidelines of the American Psychiatric Association (APA) for the Treatment of Patients with Major Depressive Disorder, 2nd edition.
- Clinical Guidelines for the Treatment of Depressive Disorders by the Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT).
- National Institute for Clinical Excellence (NICE) guidelines.
- Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression (RANZCAP).
- Texas Medication Algorithm Project (TMAP) Guidelines.
- World Federation of Societies of Biological Psychiatry (WFSBP) Treatment Guideline for Unipolar Depressive Disorder.
- British Association for Psychopharmacology Guidelines.

2.1.2 Anxiety disorders

2.1.2.1 Definition

Anxiety disorders include disorders that share features of excessive fear, anxiety and related behavioural disturbances (American Psychiatric Association, 2013:189). Fear is described as the emotional response to a real or perceived imminent threat, whereas anxiety is the anticipation of future threat (American Psychiatric Association, 2013:189). The anxiety disorders differ from each in the types of objects or situations that induce fear, anxiety or avoidance behaviour and the cognitive ideation. Several of the anxiety disorders develop in childhood and tend to persist if untreated (American Psychiatric Association, 2013:189). Generally, most anxiety disorders occur more frequently in females than in males with a ratio of 2:1 (American Psychiatric Association, 2013:189).

2.1.2.2 Generalised anxiety disorder

The key features of GAD are persistent and excessive anxiety as well as concerns about various areas, such as work and school which the individual finds challenging to control (American Psychiatric Association, 2013:190). Generalised anxiety disorder

is characterised by chronicity and is associated with high levels of psychiatric co-morbidity, such as MDD and other anxiety disorders, physical co-morbidity and a reduced quality of life (Emsley *et al*., 2013:175). It can be considered as a "tension disorder" due to the boundary cross between psychic symptoms (e.g. worries, irritability) and somatic complaints such as muscle tension, restlessness and insomnia (American Psychiatric Association, 2013:190; Emsley *et al*., 2013:175).

2.1.2.2.1 Diagnostic and clinical characteristics

GAD is characterised by chronic, excessive, difficult-to-control worry, a range of somatic symptoms and the presence of persistent intrusive thoughts or concerns, and is usually associated with compulsions, which are mental acts or behaviours related to the obsessions, e.g. excessive hand washing (Emsley *et al*., 2013:175; National Department of Health, 2015:15.10). It is essential to make the correct diagnosis of anxiety disorder. Therefore, it is important to establish that (Emsley *et al*., 2013:175):

- Difficulty in controlling the worries is concomitant with physical and psychic symptoms.
- The focus of anxiety and worry is not part of another axis I disorder (e.g. major depressive disorder, schizophrenia) or due to the direct physiological effects of a substance or a general medical condition.
- Clinically significant distress or functional impairment is evident.

2.1.2.2.2 Prevalence and onset

The 12-month prevalence of GAD is 0.9% among adolescents and 2.9% among adults in the United States. In other countries, the 12-month prevalence for the disorder ranges from 0.4% to 3.6% (American Psychiatric Association, 2013:223; Emsley *et al*., 2013:175). According to the Mental Health Fact Sheet 2012, compared with 14 other countries in the WMH survey, South Africa has the 6th highest incidence of anxiety disorders at 15.8% (South African Depression & Anxiety Group, 2012). Females are twice as likely as males to experience generalised anxiety disorder (American Psychiatric Association, 2013:223; Emsley *et al*., 2013:175). The prevalence of GAD diagnosis peaks in middle age and declines over the years. The age of onset for GAD is spread over a very broad range, however, the median age at

onset is 30 years which is later than that for other anxiety disorders (American Psychiatric Association, 2013:223; Emsley *et al*., 2013:175).

2.1.2.2.3 Risk factors

The contributing risk factors for GAD are categorised as follows (American Psychiatric Association, 2013:224):

- Temperamental: Behavioural inhibition, negative affectivity and harm avoidance have been associated with GAD.
- Genetic and physiological: One-third of the risk of experiencing GAD is genetic and these genetic factors overlap with the risk of negative affectivity and are shared with other anxiety and mood disorders, MDD in particular.

2.1.2.2.4 Co-morbidity

Individuals who meet the criteria for GAD are likely to have met or currently meet the criteria for other anxiety and unipolar depressive disorders (American Psychiatric Association, 2013:226). Co-morbidity with substance use, conduct, psychotic, neurodevelopmental and neurocognitive disorders is less common (American Psychiatric Association, 2013:226).

2.1.2.2.5 Treatment

According to the STGs and EML for South Africa, Hospital Level for Adults the following should be followed for the management of generalised anxiety disorder (Table 2–3) (National Department of Health, 2015:15.10). This is indicated for patients where symptoms are interfering with normal functions of their daily living. An antidepressant may be more appropriate when there is concomitant drug/alcohol dependence or a co-morbid major depressive episode is present:

Table 2–3. Generalised anxiety disorder treatment according to the Standard Treatment Guidelines and Essential Medicines List for South Africa, Hospital Level for Adults (National Department of Health, 2015:15.10).

ACUTE MANAGEMENT				
	Class of drug	**Name of drug**	**Dosing instructions**	
Acute episode or intense prolonged anxiety	Benzodiazepines	Diazepam	Dose range	2-5 mg as a single dose, repeat if required up to 12 hourly
			Route of administration	Oral
			Duration of therapy	Up to 2 weeks, tapering off dose to zero within 6 weeks
Maintenance therapy				
	Selective serotonin reuptake inhibitor	Citalopram	Initial dose	20 mg
			Route and time of administration	Oral, daily
OR	Selective serotonin reuptake inhibitor	Fluoxetine	Dose range	10-40 mg
			Route and time of administration	Oral daily
			Duration of therapy	Variable, although the condition tends to be chronic

General measures for patient and family (National Department of Health, 2015:15.10):

- Psychotherapy.
- Most of the patients can be treated as outpatients, but some may need to be admitted.

Referral should be considered when the patient experiences ongoing symptoms, despite receiving treatment (National Department of Health, 2015:15.10).

According to SASOP Treatment Guidelines for Psychiatric Disorders, the following steps should be followed for generalised anxiety treatment (Table 2–4) (Emsley *et al*., 2013:176-178):

Table 2–4. Generalised anxiety disorder treatment according to the South African Society of Psychiatrists (Emsley *et al*., 2013:176-178).

FIRST-LINE TREATMENT	
1	Both pharmacotherapy and psychotherapy are efficacious first-line approaches for GAD
2	First-line pharmacotherapy of uncomplicated GAD comprises the use of an SSRI or SNRI
3	A range of other psychotropic drugs are useful for the treatment of GAD
4	The response time to a first-line selective SSRI (e.g. fluoxetine, citalopram, escitalopram, paroxetine, sertraline) or SNRI (e.g. venlafaxine, duloxetine) is usually between 4 and 12 weeks
5	Benzodiazepines (e.g. lorazepam, alprazolam, diazepam) are best reserved for short-term use (2-4 weeks) in the early phase of treatment with an SSRI or SNRI to provide symptomatic relief
Note: Caution should be exercised in using atypical and typical antipsychotic drugs as monotherapy due to concerns about their tolerability and adverse effect profile	
6	CBT for GAD involves techniques of cognitive restructuring, worry exposure, and behaviour modification

Treatment alternatives
• Neither augmentation, nor switching strategies have been well researched in GAD • Where there is only a partial response to an optimal 12-week trial, consider switching to another antidepressant within the same class or to a different class (e.g. SSRI to SNRI or agomelatine, SNRI to SSRI or agomelatine)

2.1.3 Panic disorder

2.1.3.1 Definition

Panic disorder refers to recurrent unexpected panic attacks (American Psychiatric Association, 2013:209; Emsley *et al*., 2013:172). A panic attack is characterised by an abrupt surge of intense fear or discomfort accompanied by 4 or more of 13 somatic or cognitive panic symptoms which develop abruptly and reach a peak within 10 minutes (American Psychiatric Association, 2013:209; Emsley *et al*., 2013:172; National Department of Health, 2015:15.11). The term "unexpected" refers to a panic attack for which there is no evident cue or trigger (American Psychiatric Association, 2013:209). PD may occur with or without agoraphobia, a disorder which has been described as a "common, persistent and disabling condition" (Emsley *et al*., 2013:172). The presence of agoraphobia in patients with PD is associated with substantial severity, co-morbidity and functional impairment.

2.1.3.2 Clinical and diagnostic characteristics

During a panic attack, the patient experiences significant fear and emotional discomfort. In addition, there is accompanying physical symptoms such as rapid pulse/palpitations, shortness of breath, dizziness and sweating (National Department of Health, 2015:15.11). Panic attacks that occur with fewer than 4 of the 13 panic symptoms are referred to as limited panic attacks (Emsley *et al*., 2013:172). Panic disorder is diagnosed if panic attacks reoccur, with intervening periods of comparative freedom from anxiety between attacks (National Department of Health, 2015:15.11). Panic attacks are a core feature of PD, however, they are also experienced by patients with post-traumatic stress disorder, social anxiety disorder and other specific phobias. One type of unexpected panic attack is a "nocturnal" panic attack, which involves

waking from sleep in a state of panic as opposed to panicking after fully waking from sleep (American Psychiatric Association, 2013:210).

2.1.3.3 Prevalence and onset

The median age of onset for PD in the United States is 20 to 24-years-old, however, a few cases begin in childhood and some has an onset after the age of 45 although it is unusual (American Psychiatric Association, 2013:210). According to the SASOP Treatment Guidelines for Psychiatric Disorders, PD is an anxiety disorder with lifetime prevalence rates ranging from 1.1% to 3.7% in the general population and 3.0% to 8.3% in clinical settings (Emsley *et al*., 2013:172). The DSM-5 states that the 12-month prevalence estimate for PD across the US and several European countries is approximately 2-3% in adults and adolescents (American Psychiatric Association, 2013:210). The disorder is more common in women than in men, with a 3:1 ratio in patients with agoraphobia and 2:1 in patients without agoraphobia (American Psychiatric Association, 2013:210; Emsley *et al*., 2013:172).

2.1.3.4 Risk factors

The following are categorised contributing risk factors for PD (American Psychiatric Association, 2013:211):

- Temperamental-negative affectivity and anxiety sensitivity are risk factors for the onset of panic attacks.
- Genetic and physiological: Smoking is a risk factor for panic attacks as well as panic disorder. Studies have reported that childhood experiences of sexual and physical abuse are more common in panic disorder than in other anxiety disorders.
- Environmental: There is an increased risk for PD among children of parents whom have been diagnosed with depressive, bipolar and anxiety disorders. In addition, respiratory disturbances such as asthma is associated with panic disorder, concerning past history, family history and co-morbidity.

2.1.3.5 Suicide risk

According to the DSM-5, panic attacks and a diagnosis of PD in the past 12 months are related to a higher rate of suicide attempts and suicidal ideation (American Psychiatric Association, 2013:212).

2.1.3.6 Co-morbidity

Panic disorder rarely occurs in clinical settings in the absence of other psychopathologies. According to DSM-5, the prevalence of panic disorder is higher in individuals with other disorders, which is predominantly other anxiety disorders (especially agoraphobia), major depression, bipolar disorder and perhaps mild alcohol abuse disorder (American Psychiatric Association, 2013:213). The reported lifetime rates of co-morbidity between MDD and PD differ broadly, with a range from 10-65% in individuals with PD (American Psychiatric Association, 2013).

PD is considerably co-morbid with several common medical symptoms and conditions, including but not limited to: Dizziness, cardiac arrhythmias, hyperthyroidism, asthma, chronic obstructive pulmonary disease (COPD) and irritable bowel syndrome (IBS). However, the nature of the association is indistinguishable (American Psychiatric Association, 2013:214).

2.1.3.7 Treatment

According to the STGS and EML for South Africa, Hospital Level for Adults, the following steps should be followed for panic attack and panic disorder treatment (Table 2–5) (National Department of Health, 2015:15.12):

Table 2–5. Panic disorder treatment according to Standard Treatment Guidelines and Essential Medicines List for South Africa, Hospital Level for Adults (National Department of Health, 2015:15.12).

PANIC ATTACK				
Acute management (National Department of Health, 2015:15.12): The initial aim in panic attack management is to control the panic symptoms and exclude an underlying medical cause				
	Class of drug	**Name of drug**	**Dosing instructions**	
	Benzodiazepine (repeated as necessary to control symptoms)	Lorazepam	Initial dose	2 mg (immediately)
			Route of administration	Oral
OR	Benzodiazepine	Clonazepam	Immediate dose	1 mg
			Route of administration	Oral
OR	Benzodiazepine	Diazepam	Immediate dose	5 mg
			Route of administration	Oral
OR	Benzodiazepine	Midazolam	Immediate dose	7.5 mg
			Route of administration	Oral or buccal
NOTE CAUTION: Benzodiazepines, especially diazepam IV, can cause respiratory depression, therefore monitor patients closely (National Department of Health, 2015:15.4)				
PANIC DISORDER				
	Drug Class	**Drug Name**	**Dosing Instructions**	
		Citalopram	Dose range	10-40 mg

	Selective serotonin reuptake inhibitor		Route and time of administration	Oral daily
			Dose titration	Start with 25 mg, then increase by 25 mg/day at 3-4 day intervals
OR	Selective serotonin reuptake inhibitor	Fluoxetine	Dose range	20-40 mg
			Route and time of administration	Oral daily
			Dose titration	Initiated at low dose and gradually titrated to therapeutic doses according to patient tolerability

Points to note about SSRIs

- At least eight weeks of adequate dose treatment is required before efficacy can be assessed due to SSRIs' onset of action in panic disorder being relatively slow
- Duration of SSRI therapy: Variable, initially six months but up to one year
- Long-term drug treatment may be necessary
- Relapses may occur when treatment is discontinued
- Due to the slow onset of action and the potential for increased anxiety during the initial phase of treatment with antidepressants, short-term co-administration of a benzodiazepine should be considered

According to the SASOP Treatment Guidelines for Psychiatric Disorders, the following steps should be followed for panic disorder treatment (Table 2–6) (Emsley *et al*., 2013:172-174):

Table 2–6. Panic disorder treatment according to the South African Society of Psychiatrists (Emsley *et al*., 2013:172-174).

FIRST-LINE TREATMENT	
1	Both pharmacological therapies and CBT are considered first-line treatments for PD
2	Antidepressants have proven efficacy in the treatment of PD. Drugs from within the SSRIs and SNRIs are the preferred options, namely the SSRIs such as citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline and the SNRI venlafaxine
3	Adjunctive benzodiazepines have a role in treatment
Acute treatment	Combination treatment (pharmacotherapy + psychotherapy or pharmacotherapy + pharmacotherapy (e.g. antidepressant + benzodiazepine/sodium valproate)
Maintenance treatment	Combination treatment or psychotherapy alone
Note: For acute treatment, a combination of pharmacological treatment and CBT is likely to be more effective than either therapy alone	
Points to note about PD	
• In children and adolescents with PD, there are only non-randomised, controlled studies to support the utility of the SSRIs • CBT is a good alternative for women with PD who plan to become pregnant, and for pregnant women who need to discontinue the drug	

General measures for patient and family (National Department of Health, 2015:15.11):

- Psycho-education and reassurance.
- Psychotherapy, e.g. cognitive-behavioural therapy.
- Exclude an underlying medical condition, e.g. thyrotoxicosis.

Referral should be considered in the case of treatment-resistant panic disorder or where there is a need for benzodiazepine treatment beyond 6 weeks (National Department of Health, 2015:15.11).

2.1.4 Social anxiety disorder or social phobia

2.1.4.1 Definition

In SAD or social phobia, the person is fearful or anxious about or avoidant of social interactions and situations that involve the likelihood of being scrutinised (American Psychiatric Association, 2013:190; Emsley *et al*., 2013:192). These include social interactions such as meeting unacquainted people, situations in which the individual may be observed eating or drinking as well as situations in which the individual performs in front of others where the cognitive ideation is of being negatively evaluated by others, such as being embarrassed, humiliated or rejected (American Psychiatric Association, 2013:190).

2.1.4.2 Diagnostic and clinical characteristics

The essential feature of SAD is a marked or intense fear or anxiety of social situations in which the individual may be analysed by others. In children the fear or anxiety must occur in peer settings and not just during interactions with adults (American Psychiatric Association, 2013:203). For a diagnosis to be made, the social situations must almost always provoke fear or anxiety in the individual. SAD is characterised by an exaggerated and persistent fear of being negatively evaluated in social and performance situations and is associated with physical, cognitive and behavioural disturbances (Emsley *et al*., 2013:192). Studies have reported that more than 80% of patients with SAD have a lifetime history of at least one other psychiatric disorder with the most common disorders being major depression, panic disorder, generalised anxiety disorder, agoraphobia and substance abuse disorders (Emsley *et al*., 2013:192).

2.1.4.3 Prevalence and onset

Social phobia and specific phobias have an earlier age of onset than other anxiety disorders. The median age of onset for the disorder is 13 years with an onset after age 25 relatively uncommon (American Psychiatric Association, 2013:205; Emsley *et al*., 2013:192). In the United States, 75% of individuals have an age at onset between 8 and 15 years (American Psychiatric Association, 2013:205). SAD characteristically persists throughout adulthood and is associated with significant functional impairment (Emsley *et al*., 2013:192). According to the SASOP Treatment Guidelines for

Psychiatric Disorders, epidemiological studies report that the rates of social anxiety disorder range from 3% to 16% in the general population (Emsley *et al*., 2013:192). The DSM-5 states that the 12-month prevalence estimate for SAD in the United States is approximately 7% and that the prevalence rates decrease with age (American Psychiatric Association, 2013:204). Compared with 14 other countries in the WMH survey, according to the Mental Health Fact Sheet 2012, South Africa has the 6th highest incidence for anxiety disorders at 15.8% (South African Depression & Anxiety Group, 2012).

Individuals with SAD are more likely to be females, however, in clinical settings SAD appears more equally distributed amongst men and women (Emsley *et al*., 2013:192). Females with SAD report a greater number of social fears and co-morbid depressive, bipolar and anxiety disorders, whereas males are more likely to have a fear of dating and use alcohol and/or illicit drugs to relieve the symptoms of SAD (American Psychiatric Association, 2013:206).

2.1.4.4 Risk factors

The following are contributing risk factors for SAD (American Psychiatric Association, 2013:205):

- Temperamental: Fundamental traits that predispose individuals to SAD include behavioural inhibition and fear of negative evaluation.
- Genetic and physiological: Traits that predispose individuals to SAD are strongly genetically influenced.
- Environmental: Childhood maltreatment and adversity are risk factors for SAD.

2.1.4.5 Co-morbidity

SAD is often co-morbid with other anxiety disorders, MDD and substance abuse disorders. The onset of SAD precedes the other disorders, except for separation anxiety disorder and specific phobias (American Psychiatric Association, 2013:208). In adults, co-morbidity with depression is high and in children co-morbidities with high-functioning autism and selective mutism is common (American Psychiatric Association, 2013:208).

2.1.4.6 Treatment

There was no guidelines concerning social anxiety disorder treatment listed in The STGs and EML for South Africa, Hospital Level for Adults (National Department of Health, 2015).

According to the SASOP Treatment Guidelines for Psychiatric Disorders, the following steps should be followed for panic disorder treatment (Emsley *et al*., 2013:192-195):

Table 2–7. Social anxiety disorder treatment according to the South African Society of Psychiatrists (Emsley *et al*., 2013:192-195).

TREATMENT OPTIONS	
SAD is highly responsive to evidence-based acute treatments:	
1	Pharmacological: Most SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), venlafaxine, phenelzine, moclobemide, some benzodiazepines (clonazepam), anticonvulsants (gabapentin, pregabalin) and olanzapine
2	Psychological: CBT
3	Adjunctive benzodiazepines (e.g. alprazolam) have a role in treatment
Points to note about SAD treatment	
• Treatment duration of up to 12 weeks is needed to assess efficacy • Drug treatment should be continued for at least a further 6 months in patients who have responded later at 12 weeks • In the longer term, CBT should be considered as it may reduce relapse rates better than drug treatment • Monitor efficacy and tolerability regularly during long-term treatment • A drug combination and a psychological approach is recommended during the initial phase of treatment • Switching to venlafaxine (75-225 mg/daily) after a non-response to acute treatment with an SSRI should be considered	

2.2 Classes of antidepressants

Antidepressants comprises of drugs with a diversity of chemical structures and possess anxiolytic, antidepressant and impulse-reducing properties (Rossiter *et al*., 2016:493). The classes of antidepressants are categorised as follows: Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and other antidepressants. The category of other antidepressants encompasses the following classes: Tetracyclics, the noradrenergic and specific serotonin antagonists, the serotonin antagonists and reuptake inhibitors, the serotonin and noradrenaline reuptake inhibitors (SNRIs), the noradrenaline and dopamine reuptake inhibitors and lastly the selective noradrenaline reuptake inhibitors (Rossiter *et al*., 2016:493).

The first SNRI to be marketed in the United States was venlafaxine immediate-release (IR). It was approved by the United States FDA in 1993 (Sansone and Sansone, 2014:37). The debut of venlafaxine IR was soon followed by the introduction of a micro-encapsulated extended-release (XR) formulation in 1997. The XR formulation has the advantage of causing less nausea and dizziness at the commencement of therapy, however, the integrity of the capsule cannot be compromised prior to or during ingestion. This is to protect the release mechanism of the capsule (Sansone and Sansone, 2014:38). Conveniently, both venlafaxine IR and XR formulations are available as brand and generic formulations. This has potential for a cost advantage for the formulations.

Venlafaxine XR was the first SNRI that the FDA approved for the treatment of MDD (Goldenberg, 2008:233). The class of SNRIs are primarily used in the treatment of major depression. There are numerous additional uses of SNRIs, which include: treatment of pain disorders (neuropathies and fibromyalgia), generalised anxiety, menopausal vasomotor symptoms and stress urinary incontinence (Celikyurt *et al*., 2012:91).

A study by Gutierrez and co-workers (2003) aimed to focus on the latest trends related to the treatment of patients with extended-release venlafaxine as well as the treatment of resistant depression. Their results suggest that extended-release venlafaxine may

be more effective than SSRIs in achieving remission of major depressive symptoms and concluded that venlafaxine was a first-line drug.

A research report which aimed to study the mechanisms of action and clinical profiles of three atypical antidepressants established the following advantages for venlafaxine use: Rapid onset of antidepressant action (this is important for severely depressed hospitalised patients), superior efficacy in hospitalised patients with major depression and an ascending dose-antidepressant effect curve, suggesting potential superior efficacy at higher doses (Horst and Preskorn, 1998:251).

2.3 Clinical pharmacological profile of venlafaxine

2.3.1 Pharmacological classification

Venlafaxine is chemically a bicyclic, phenylethylamine compound (Figure 2–1) which displays a distinctive pharmacological profile with unique antidepressant properties compared to the other SNRIs and other antidepressant classes (Celikyurt *et al*., 2012:95; Horst and Preskorn, 1998:243; Rossiter *et al*., 2016:503).

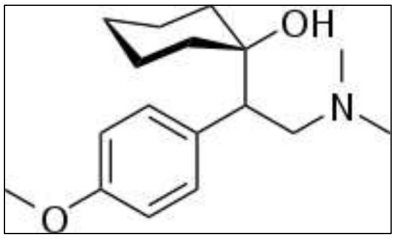

Figure 2–1. Structure of Venlafaxine from the SNRI class of antidepressants (Celikyurt *et al*., 2012:93).

Venlafaxine is pharmacologically classified as a SNRI (Gutierrez *et al*., 2003:2139; Rossiter *et al*., 2016:503; Sansone and Sansone, 2014:37).

2.3.2 Pharmacodynamics

The mechanism of action of venlafaxine is thought to be related to the potentiation of neurotransmitter activity in the central nervous (CNS) system (Wyeth Pharmaceuticals, 2003:2). SNRIs inhibit the reuptake of these neurotransmitters from the synaptic cleft by selectively binding to the serotonin and noradrenaline transporters (Celikyurt *et al*., 2012:92). Venlafaxine displays three properties accountable for its antidepressant activity, namely serotonin, noradrenaline and dopamine reuptake

inhibition (Horst and Preskorn, 1998:243). Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV) (also known as desvenlafaxine) are potent inhibitors of the reuptake of neuronal serotonin (most potent, at low doses), noradrenaline (moderate potency, at high doses >150 mg/d) and is a weak inhibitor of dopamine reuptake (Celikyurt *et al*., 2012:92; Gutierrez *et al*., 2003:2139-2140; Horst and Preskorn, 1998:243; Kent, 2000:912; Wyeth Pharmaceuticals, 2003:2).

The inhibition of the neurotransmitter reuptake by venlafaxine transpires in a disproportionate and sequential manner. Venlafaxine has a 30-fold higher affinity for the serotonin transporter than for the noradrenaline transporter (Celikyurt *et al*., 2012:92; Gutierrez *et al*., 2003:2140; Sansone and Sansone, 2014:39). Furthermore, neurotransmitter reuptake inhibition occurs initially for serotonin followed by noradrenaline. The suggested pharmacological mechanism of action is supported by clinical experience with venlafaxine, where the initial adverse effects experienced are related to serotonin reuptake inhibition (e.g. nausea and sexual dysfunction), whereas at higher doses the adverse effects are related to both serotonin- and noradrenaline reuptake inhibition (e.g. dry mouth and night sweats) (Sansone and Sansone, 2014:92). The inhibition of serotonin and noradrenaline reuptake by venlafaxine occurs at different doses, suggesting that venlafaxine may exhibit a clinical dose response curve for antidepressant efficacy (Horst and Preskorn, 1998:243; Preskorn, 1994:15).

Venlafaxine and its active metabolite ODV contrasts significantly from the tricyclic antidepressant (TCA) class, given that it has low affinity and therefore minimal or no activity on α- or β-adrenoceptors, as well as on benzodiazepine, opiate, muscarinic cholinergic or H_1-histaminergic receptors (Celikyurt *et al*., 2012:92; Gutierrez *et al*., 2003:2140; Horst and Preskorn, 1998:243; Kent, 2000:912; Stahl *et al*., 2005:732-747; Wyeth Pharmaceuticals, 2003:2). Pharmacological action at these receptors is theorised to be related to numerous anticholinergic, sedative and cardiovascular effects, therefore venlafaxine is unlikely to cause sedation, weight gain or orthostatic hypotension (Gutierrez *et al*., 2003:2140; Kent, 2000:914; Wyeth Pharmaceuticals, 2003:2).

Venlafaxine does not have the potential to inhibit monoamine oxidase (MAO) activity (Horst and Preskorn, 1998:243; Kent, 2000:912; Muth *et al*., 1986:4493-4497, 1991:191-199; Wyeth Pharmaceuticals, 2003:2).

Venlafaxine as compared to other antidepressants retains a unique ability to downregulate β-adrenoceptors after a single dose (Muth *et al*., 1986:4493-4497, 1991:191-199). This capability is speculated to be the reason for a more rapid onset of antidepressant activity over the other antidepressants (Horst and Preskorn, 1998:243).

2.3.3 Pharmacokinetics

Venlafaxine is available in IR and XR oral formulations. The IR formulation is a tablet dose form and the improved XR formulation is a capsule, that must not be broken or breached prior to ingestion (Sansone and Sansone, 2014:38). The XR formulation has the advantage of simpler dosing, with a once-daily dose achieving bioavailability equivalent to that of twice-daily dosing with the IR formulation (Kent, 2000:912).

Venlafaxine and its active metabolite ODV display linear pharmacokinetics (dose-independent and follows first-order kinetics) (Celikyurt *et al*., 2012:96; Wyeth Pharmaceuticals, 2003:3). Steady-state plasma concentrations of venlafaxine and ODV are achieved within 3 days of oral multiple dose therapy. The mean steady-state plasma clearance of venlafaxine and ODV is 1.3 and 0.4 L/h/kg respectively (Wyeth Pharmaceuticals, 2003:3).

Venlafaxine and ODV are widely distributed and have an apparent (steady-state) volume of distribution of 7.5 and 5.7 L/kg respectively (Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:3). The therapeutic effects of venlafaxine are usually achieved within 3 to 4 weeks after treatment has been initiated (Celikyurt *et al*., 2012:96).

The half-life of venlafaxine and ODV when administered as the IR formulation is 5 and 11 hours respectively (Rossiter *et al*., 2016:503; Sansone and Sansone, 2014:38; Wyeth Pharmaceuticals, 2003:3). As expected, the half-life of venlafaxine and ODV when administered as the XR formulation is 11 and 13 hours respectively (Sansone and Sansone, 2014:38).

At therapeutic plasma concentrations, venlafaxine and ODV are minimally (less than 50%) bound to plasma proteins at 27% and 30% respectively (Celikyurt *et al*., 2012:96; Wyeth Pharmaceuticals, 2003:3).

Venlafaxine is well absorbed from the gastrointestinal tract (Celikyurt *et al*., 2012:95; Wyeth Pharmaceuticals , 2003:3). From a single oral dose of venlafaxine, at least 92% is absorbed. The absolute bioavailability of venlafaxine is 45% (Wyeth Pharmaceuticals, 2003). The bioavailability of venlafaxine is not affected by food and the time of administration (morning or evening) (Wyeth Pharmaceuticals, 2003:3).

Venlafaxine undergoes the first-pass effect in the liver and is extensively metabolised to its pharmacologically active major metabolite, ODV (Celikyurt *et al*., 2012:95; Horst and Preskorn, 1998:243; Rossiter *et al*., 2016:503; Sansone and Sansone, 2014:38).

The primary route of excretion of venlafaxine and ODV is through renal elimination via the kidneys (Celikyurt *et al*., 2012:96; Wyeth Pharmaceuticals, 2003:3). Approximately 80% of the drug is removed through renal excretion (Rossiter *et al*., 2016:503).

The pharmacokinetic properties of venlafaxine and ODV can be summarised as follows (Table 2–8):

Table 2–8. Summary of the pharmacokinetic properties for venlafaxine and its active metabolite, O-desmethylvenlafaxine. IR = Immediate-Release, XR = Extended-Release, ODV = O-desmethylvenlafaxine. Data obtained from Kent, 2000:913; Sansone and Sansone, 2014:38.

PROPERTIES	INFORMATION
Year of FDA approval	IR: 1993, XR: 1997
Half-life (hours)	IR: 5, XR: 11
	ODV: IR: 11, XR: 13
Dosing interval	IR: Twice per day XR: Once per day
Serotonin to noradrenaline effects	30:1
Dopamine effects	Low affinity
Therapeutic dosing range	IR: 75-225 mg/day (divided dose) XR: 75-225 mg/day (single dose)
Bioavailability	45%
Metabolism	Hepatic
Elimination routes	Renal
Protein binding	Venlafaxine: 27% ODV: 30%

An important point to note is that the pharmacokinetics of both venlafaxine and ODV are significantly affected in patients with liver and renal disease, thus impacting on the optimal treatment of certain patients (Kent, 2000:912; Wyeth Pharmaceuticals, 2003:4). The elimination half-life of venlafaxine is extended by approximately 30% and clearance is reduced by 50% in patients with hepatic cirrhosis as compared to a healthy patient. In such patients, the half-life of ODV is prolonged by 60% and its clearance is decreased by 30% (Wyeth Pharmaceuticals, 2003:4). Therefore, dose adjustments in these patients are essential.

In renal impaired patients the elimination half-life of venlafaxine is extended by nearly 50% and clearance is reduced by 24% as compared to a healthy patient (Wyeth Pharmaceuticals, 2003:4). For patients receiving dialysis, the elimination half-life of venlafaxine is prolonged by almost 180% and clearance is reduced by 57%, whilst for ODV the elimination half-life is extended by almost 142% and clearance is reduced by

56%. The elimination half-life in renal impaired patients is prolonged by 40% for ODV, whilst the clearance rate remains unchanged (Wyeth Pharmaceuticals, 2003:4).

In elderly patients, clearance rates are reduced. Therefore, those patients with severe renal dysfunction and moderate to severe hepatic dysfunction will require dose adjustments (Celikyurt *et al*., 2012:96).

2.3.4 Venlafaxine preparations available in South Africa

The following venlafaxine preparations were currently available in South Africa during the time of the study (*Monthly Index of Medical Specialities (MIMS)*, 2018:23-24; Rossiter *et al*., 2016:503).

- Efexor XR® extended-release capsules 75 mg, 150 mg.
- Efegen XR® extended-release capsules 75 mg, 150 mg.
- Sandoz Venlafaxine® extended-release capsules 75 mg, 150 mg.
- Venlafaxine Unicorn® extended-release capsules 75 mg, 150 mg.
- Venlafaxine XR Adco® extended-release capsules 37.5 mg, 75 mg, 150 mg.
- Venlor® extended-release capsules 37.5 mg, 75 mg, 150 mg.
- Oviden® tablets (immediate-release) 37.5 mg, 75 mg.

The venlafaxine preparations used in Fort England Hospital consisted of the venlafaxine XR preparations only.

2.3.5 Clinical indications

The FDA has approved four clinical indications for the use of venlafaxine, namely (Sansone and Sansone, 2014:38):

- Major depressive disorder: For the treatment of MDD, the efficacy of venlafaxine XR was established in 8- and 12-week controlled trials of adult outpatients whose diagnoses corresponded to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) major depressive disorder category (Wyeth Pharmaceuticals, 2003:7).

- Generalised anxiety disorder: The efficacy of venlafaxine XR in the treatment of GAD was established in adult outpatients diagnosed according to the DSM-IV criteria in 8-week and 6-month placebo-controlled trials (Cipla Medpro, 2006:1; Wyeth Pharmaceuticals, 2003:8).
- Panic disorder: The efficacy of venlafaxine XR in the treatment of panic disorder was established in two 12-week placebo-controlled trials in adult outpatients diagnosed with panic disorder according to the DSM-IV criteria (Wyeth Pharmaceuticals, 2003:9).
- Social phobia: The efficacy of venlafaxine XR in the treatment of social anxiety disorder was established in two 12-week placebo-controlled trials in adult outpatients diagnosed with social anxiety disorder (DSM-IV criteria) (Cipla Medpro, 2006:1; Wyeth Pharmaceuticals, 2003:9).

According to the South African Medicines Formulary (SAMF), venlafaxine is additionally indicated for depression associated with anxiety (Rossiter *et al*., 2016:503).

According to the South African National Department of Health tertiary and quaternary level EML recommendations as of August 2018, venlafaxine is recommended for use as a third-line treatment of MDD and anxiety associated with depression (National Department of Health Republic of South Africa, 2018). However, in the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) for South Africa Hospital Level for Adults, with regards to the treatment of psychiatric disorders (including depressive and anxiety-related disorders) venlafaxine was not mentioned as a first, second or third-line treatment alternative (National Department of Health, 2015:15.1-15.23).

Other applications of venlafaxine include: Treatment of pain disorders (including neuropathies and fibromyalgia), vasomotor symptoms of menopause, stress urinary incontinence and to prevent the relapse of a depressive episode in patients that responded to an initial 6 to 8 week period of treatment (Celikyurt *et al*., 2012:91; Cipla Medpro, 2006:1; Gutierrez *et al*., 2003:2147; Sussman, 2003:19).

2.3.6 Contraindications

Venlafaxine therapy is contraindicated in the following cases (Cipla Medpro, 2006:1; Kent, 2000:916; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:9):

- Concomitant monoamine oxidase inhibitor therapy.
- Paediatric patients (children younger than 18 years).
- Hypersensitivity to venlafaxine HCl or any excipients in the formulation.
- Pregnancy and lactation (refer below).

2.3.7 Pregnancy and lactation

Globally, statistics suggest that approximately 10% of pregnant women and 13% of women who have recently given birth experience a mental disorder, predominantly depression (WHO, 2017). Studies suggest that in developing countries this incidence may be even higher, with as much as 15.6% of women during pregnancy and 19.8% after child birth. These statistics suggest that mental health treatments need to be investigated in terms of safety and tolerability during and after pregnancy for appropriate use in this patient population.

For women with pre-existing or severe mental illness, family planning and pregnancy are intricate matters that require challenging decision-making with careful consideration and planning (Jones, 2012:173). Women need to be knowledgeable about their treatment and its effect on pregnancy and lactation as well as the correct protocol to follow prior to becoming pregnant.

According to the SAMF and US FDA, venlafaxine is classified as a category C risk factor in pregnancy (Gutierrez *et al*., 2003:2148; Rossiter *et al*., 2016:503). The following are the FDA-assigned pregnancy categories as sourced from the SAMF (Table 2–9) (Rossiter *et al*., 2016:5-6):

Table 2–9. FDA-assigned pregnancy categories as listed in the South African Medicines Formulary (Rossiter *et al*., 2016:5-6).

CATEGORY	DESCRIPTION
A	In pregnant women, adequate and well-controlled studies have not shown an increased risk of foetal abnormalities
B	Animal studies have revealed no evidence of harm to the foetus, however, there are no adequate and well-controlled studies in pregnant women; or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the foetus
C	*Animal studies have shown an adverse effect or have not been conducted and there are no adequate and well-controlled studies in pregnant women. The drug should not be used unless the potential benefits outweigh the potential risk for the patient*
D	In pregnant women, adequate well-controlled or observational studies have demonstrated a risk to the foetus. However, the benefits of treatment may outweigh the potential risk
X	In pregnant women or in animals, adequate, well-controlled or observational studies have demonstrated a positive evidence of foetal abnormalities. The use of the drug is contraindicated in women who are, or may become pregnant

From the animal studies that tested venlafaxine for its potential teratogenic effects, it was established that venlafaxine did not cause malformations in offspring of rats and rabbits given doses up to 2.5 times for rats or 4 times for rabbits of the maximum recommended human daily doses. However, an important observation was noted in rats where there was an increase in the numbers of stillborn pups, a decrease in pup weight and an increase in pup deaths during the first 5 days of nursing (Wyeth Pharmaceuticals, 2003:23). Due to animal reproduction studies not being constantly predictive of human response, the use of venlafaxine in pregnancy should be reserved if evidently compulsory and if the benefits outweigh the risks.

In terms of non-teratogenic effects, studies have shown that where neonates were exposed late in the third trimester of pregnancy to venlafaxine, other SNRIs or SSRIs,

the patients developed complications which required respiratory support, tube feeding and prolonged hospitalisation (Wyeth Pharmaceuticals, 2003:24). Clinical findings have reported the following observations: Feeding difficulty, respiratory distress, apnoea, seizures, cyanosis, temperature instability, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. Therefore, it is important when treating a pregnant patient during the third trimester to carefully consider the potential benefits of treatment over adverse effects.

Concerning lactation, which is imperative for nursing mothers to be aware of, venlafaxine is excreted in human breast milk (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:24). Due to the potential for serious adverse effects in nursing infants, it should be carefully considered whether to discontinue lactation due to the importance of the drug to mother. If it is necessary for the mother to continue with venlafaxine drug treatment, then the infant should be monitored diligently for adverse effects such as agitation, insomnia, poor feeding and failure to thrive (Rossiter *et al*., 2016:503).

2.3.8 Dose and administration

The XR formulation of venlafaxine should be administered with food either in the morning or in the evening at about the same time every day (Cipla Medpro, 2006:1; Wyeth Pharmaceuticals, 2003:41. It should not be divided, crushed, chewed or placed in water. If the patient experiences difficulty with swallowing the dose form, then the capsule may be carefully opened and the contents sprinkled on a spoonful of applesauce or appropriate food (Wyeth Pharmaceuticals, 2003:24).

2.3.8.1 Recommended dosing frequency and period for venlafaxine

2.3.8.1.1 Major depressive disorder

Information obtained from (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:41)

- Immediate-release formulation:
  - Daily doses may be divided into 2 or 3 doses/day.

- Initial dose: 75 mg/day in two divided doses, increased if necessary to 150 mg/day in two divided doses.
- Dose titration (maintenance): Dose increases should be in increments of 75 mg/day as needed and should be made at intervals of not less than 4 days.
- Maximum dose (moderately depressed outpatients): 225 mg/day.
- Maximum dose (severely depressed inpatients): 375 mg/day.

- Extended-release formulation:

  - Initial dose: 75 mg/day as a single dose.
  - For some new patients it may be necessary to start treatment at 37.5 mg/day for 4-7 days to allow for patients to adjust before increasing the dose to 75 mg/day.
  - Dose titration (maintenance): Dose increases should be in increments of 75 mg/day as needed and should be made at intervals of not less than 4 days.
  - For patients that do not respond well to the 75 mg once daily dose, the dose can be increased to 150 mg once daily, with a maximum of 225 mg/day.
  - Maximum dose (moderately depressed patients): 225 mg/day.
  - Maximum dose (severely depressed patients): 375 mg/day.

2.3.8.2 Generalised anxiety disorder

Information obtained from (Wyeth Pharmaceuticals, 2003:42).

- Extended-release formulation:

  - Initial dose: 75 mg/day as a single dose.
  - For new patients it may be necessary to start treatment at 37.5 mg/day for 4-7 days to allow for patients to adjust to treatment before increasing the dose to 75 mg/day.
  - Dose titration: Dose increases should be in increments of 75 mg/day as needed and should be made at intervals of not less than 4 days.
  - Maximum dose: 225 mg/day.

2.3.8.3 Social anxiety disorder (social phobia)

Information obtained from (Wyeth Pharmaceuticals, 2003:42)

- Extended-release formulation:

  - Initial dose: 75 mg/day as a single dose.
  - It may be necessary for new patients to start treatment at 37.5 mg/day for 4-7 days to allow for patients to adjust before increasing the dose to 75 mg/day.
  - Dose titration: The dose should be increased if necessary in increments of 75 mg/day and should be made at intervals of not less than 4 days.
  - Maximum dose: 225 mg/day.

2.3.8.4 Panic disorder

Information obtained from (Wyeth Pharmaceuticals, 2003:42)

- Extended-release formulation:

  - Initial dose: 37.5 mg/day as a single dose for 7 days.
  - Initial dose may be increased to 75 mg/day for additional efficacy.
  - Dose titration (maintenance): Further dose increases should be implemented using increments of 75 mg/day as needed and must be in intervals of not less than 7 days.
  - Maximum dose: 225 mg/day.

2.3.8.5 Considerations for special populations

2.3.8.5.1 Patients with hepatic impairment

Patients who have hepatic cirrhosis experience a decrease in clearance and increase in elimination half-life for both venlafaxine and ODV as discussed above. Therefore it is recommended that patients with moderate hepatic impairment reduce their initial dose by 50% (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:43). Some patients may require individualisation of doses for improved efficacy of treatment.

2.3.8.5.2 Patients with renal impairment

Due to the decrease in clearance for venlafaxine and increase in elimination half-life for both venlafaxine and ODV in renal impaired patients as discussed above, the total daily dose should be reduced by 25-50% (Cipla Medpro, 2006:1; Rossiter *et al*.,

2016:503; Wyeth Pharmaceuticals, 2003:43). According to the SAMF, precise dose reductions can be made using the glomerular filtration rate (GFR) of patients as follows: patients with a GFR >50-70 mL/min should reduce the dose to 75%, patients with a GFR of 10-50 mL/min should reduce the dose to 50% (Rossiter *et al*., 2016:503).

For patients that undergo dialysis, it is suggested that the dose be withheld until the dialysis treatment is completed for at least 4 hours and the total daily dose be reduced by 50% (Wyeth Pharmaceuticals, 2003:43). Patients may require individualisation of doses for improved efficacy of treatment.

2.3.8.5.3 Pregnant patients during the third trimester

When neonates are exposed to venlafaxine, other SNRIs or SSRIs late in the third trimester of pregnancy, they develop complications which require hospitalisation, tube feeding and respiratory support (Wyeth Pharmaceuticals, 2003:43). The treatment of pregnant women with venlafaxine during the third trimester should be based on the risks and benefits of treatment. Dose tapering may be considered in the third trimester (Wyeth Pharmaceuticals, 2003;43).

2.3.8.5.4 Geriatric patients

Clearance rates are reduced in elderly patients. Therefore, those with severe renal dysfunction and moderate to severe hepatic dysfunction may require dose adjustments (Celikyurt *et al*., 2012:96). When treating the elderly, caution should be exercised, dose individualisation may be necessary and dose increases should be taken with utmost care. According to the SAMF, elderly patients can initiate treatment at a dose of 37.5 mg/day (Rossiter *et al*., 2016:503).

2.3.9 Overdose management

The most commonly reported symptom of venlafaxine overdose is somnolence. However, the occurrence of generalised convulsions has been reported as well (Cipla Medpro, 2006:1).

The following procedure should be completed in the case of a venlafaxine overdose (Cipla Medpro, 2006:1; Wyeth Pharmaceuticals, 2003:41):

- Ensure a satisfactory airway, oxygenation and ventilation.

- Vital signs and cardiac rhythm must be monitored.
- Supportive and symptomatic measures in general are guided.
- Emesis induction is not advised.
- Activated charcoal should be administered and/or a gastric lavage since venlafaxine-specific antidotes are unknown.

2.3.10 Special precautions

2.3.10.1 Elevated blood pressure

In some patients, venlafaxine treatment is associated with sustained increases in blood pressure. Sustained hypertension is defined as treatment-emergent supine diastolic blood pressure (SDBP) with a reading ≥ 90 mm Hg and ≥ 10 mm Hg above the baseline for 3 or more consecutive visits (Wyeth Pharmaceuticals, 2003:12). Increases in SDBP could result in adverse consequences such as subsequent coronary heart disease (Wyeth Pharmaceuticals, 2003:12). Reports on the effects of supine diastolic blood pressure display mean increases of 2 mm Hg (Cipla Medpro, 2006:1; Dierick, 1997:312). Blood pressure monitoring becomes clinically important at doses of 200 mg/day or more (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503). Therefore, it is advised that patients on venlafaxine treatment have regular compulsory blood pressure monitoring. Patients that experience a sustained blood pressure increase while on venlafaxine treatment should consider either a dose reduction or treatment discontinuation (Cipla Medpro, 2006:1).

2.3.10.2 Use in paediatric patients

In the paediatric population, the safety and efficacy has not been established yet (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:24). Therefore, when considering the use of venlafaxine in children or adolescents (children younger than 18), the potential risk must be balanced with the potential benefit prior to use.

2.3.10.3 Clinical deterioration and risk of suicide

There has been concern that antidepressants may exacerbate depression or result in the development of suicidality in some patients (Cipla Medpro, 2006:1; Wyeth Pharmaceuticals, 2003:9). Therefore, it is advised that all patients take precaution

when on antidepressant treatment and be aware of any signs and symptoms indicating worsening of the depressive disorder, such as the emergence of suicidal thoughts or unusual changes in behaviour. To reduce the possibility of overdose, venlafaxine prescriptions should include the minimum effective dose consistent with good patient management (Cipla Medpro, 2006:1).

2.3.10.4 Use in patients with co-morbidities

Venlafaxine should be used with caution in patients that present with the following disorders (Rossiter *et al*., 2016:503):

- Renal or hepatic impairment.
- History of epilepsy or myocardial infarction.
- Unstable heart disease.

Venlafaxine treatment is associated with an approximate increase of 4 beats/min in the mean heart rate (Cipla Medpro, 2006:1). Therefore, caution is advised when venlafaxine is prescribed to patients whose underlying medical conditions might be compromised by an increase in heart rate, e.g. in patients with hyperthyroidism, heart failure or recent myocardial infarction (Cipla Medpro, 2006:1).

2.3.10.5 Discontinuation of venlafaxine treatment

The sudden cessation of treatment or a reduction in the dose of venlafaxine is associated with the development of undesirable symptoms. Some of these reported symptoms include: agitation, anxiety, diarrhoea, dry mouth, fatigue, nausea, sweating and vomiting (Wyeth Pharmaceuticals, 2003:13). Therefore, abrupt withdrawal of venlafaxine should be avoided and when discontinuing venlafaxine treatment it is imperative that patients be monitored for these symptoms (Cipla Medpro, 2006:1; Wyeth Pharmaceuticals, 2003:13). A gradual dose reduction over at least 4 weeks is suggested (Rossiter *et al*., 2016:503). Tapering of the dose should be completed by reducing the daily dose by 75 mg at 1 week intervals (Wyeth Pharmaceuticals, 2003:13). Some patients may require individualisation of dose reduction, depending on the dose and duration of the treatment (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503).

2.3.10.6 Change in appetite

Appetite changes were one of the changes patients reported during short-term studies with venlafaxine. Treatment-emergent anorexia was commonly reported in 8% of the patients (Wyeth Pharmaceuticals, 2003:15). The discontinuation rate for anorexia associated with venlafaxine use was 1%, therefore patients should be advised of this effect (Cipla Medpro, 2006:1).

2.3.10.7 Change in weight

During short-term clinical trials with venlafaxine, some patients experienced changes in weight. For adults a loss of 5% or more in body weight occurred in 7% of the venlafaxine population. However, the discontinuation rate for weight loss associated with venlafaxine use was 0.1%. This suggests that the associated weight loss is not a major complication, but patients should be aware of it (Wyeth Pharmaceuticals, 2003:15). Furthermore, the safety and efficacy of venlafaxine used in combination with weight loss medication has not been established, therefore the co-administration of venlafaxine and weight loss medication is not advised.

2.3.10.8 Insomnia and nervousness

Patients that were previously treated with venlafaxine (XR formulation) commonly experienced treatment-emergent insomnia and nervousness (Wyeth Pharmaceuticals, 2003:13). Patients should be cautioned about such effects and the benefit-risk ratio should be evaluated to motivate treatment.

2.3.10.9 Seizures

In premarketing studies, no seizures occurred in the venlafaxine-treated patient population (Wyeth Pharmaceuticals, 2003:15). Patients that have a history of seizures should cautiously use venlafaxine as with other antidepressants. Venlafaxine use should be discontinued in any patient that develops seizures (Cipla Medpro, 2006:1).

2.3.10.10 Abnormal bleeding

Abnormal bleeding has been reported to be associated with venlafaxine use. The relationship is unclear, but impaired platelet aggregation may be a result of platelet serotonin depletion (Wyeth Pharmaceuticals, 2003:17). The risk of cutaneous or

mucus membrane bleeding may be increased, therefore venlafaxine should be used with caution in patients that are predisposed to bleeding from these sites (Cipla Medpro, 2006:1).

2.3.10.11 Activation of mania or hypomania

During premarketing MDD studies it was reported that mania or hypomania occurred in 0.3% of the venlafaxine treated population (Wyeth Pharmaceuticals, 2003:16). Therefore, venlafaxine and all other drugs used for MDD treatment should be used with caution in patients with a history of mania (Cipla Medpro, 2006:1).

2.3.10.12 Mydriasis

Venlafaxine use has been associated with mydriasis (Wyeth Pharmaceuticals, 2003:17). Therefore, it is crucial to monitor those patients who experience raised intraocular pressure or those at risk of acute narrow-angle glaucoma (Cipla Medpro, 2006:1).

2.3.10.13 Serum cholesterol elevation

In clinical trials, clinically relevant increases in serum cholesterol was recorded in 5.3% of patients (Wyeth Pharmaceuticals, 2003:17). Serum cholesterol increase have been reported in patients treated for at least 3 months (Cipla Medpro, 2006:1). Patients on long-term venlafaxine treatment should consider having their serum cholesterol levels measured regularly.

2.3.10.14 Hyponatraemia

Venlafaxine use may result in the occurrence of hyponatraemia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (Cipla Medpro, 2006:1; Wyeth Pharmaceuticals, 2003:16). This should be taken into consideration when treating patients who are using diuretics, dehydrated patients or the elderly.

2.3.10.15 Patients switching to or from a monoamine oxidase inhibitor

For those patients that have a change in treatment regimen, at least 14 days should lapse in between discontinuation of a MAOI and initiation of venlafaxine treatment

(Wyeth Pharmaceuticals, 2003:44). In addition, at least 7 days should lapse after terminating venlafaxine treatment and initiating treatment with a MAOI.

2.3.11 Adverse effects associated with the use of venlafaxine

An adverse effect is defined as an unwanted or undesirable effect produced by a drug in addition to its desired therapeutic effect (Oxford, 2015:699).

The mechanism of action of venlafaxine combines two therapeutic mechanisms which is the inhibition of the reuptake of both the neurotransmitters serotonin and noradrenaline. The anticholinergic and cardiotoxic adverse effects of venlafaxine are not as common as compared to TCAs (Celikyurt *et al*., 2012:97). At low doses, venlafaxine's serotonergic actions are noticeable and at higher doses the noradrenergic actions are enhanced.

Some common adverse effects experienced include the following: Central nervous system effects such as headache, dizziness, insomnia, nervousness, somnolence and visual disturbances; gastrointestinal complaints such as anorexia, dry mouth, nausea, vomiting, constipation; sexual dysfunction; sweating and fatigue (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503). Many of these adverse effects are dose-related and with prolonged treatment these effects generally decrease in frequency and intensity, thus not necessitating the discontinuation of treatment (Cipla Medpro, 2006:1).

Other adverse effects include cardiovascular effects such as hypertension, postural hypotension, palpitations and tachycardia. SIADH and hyponatraemia may occur. Some patients may experience hypersensitivity reactions such as skin rash, urticaria and pruritus (Rossiter *et al*., 2016:503).

The following adverse effects are frequently (≥ 1% of patients) reported with venlafaxine use (Table 2–10) (Cipla Medpro, 2006:1; Wyeth Pharmaceuticals, 2003:27-34):

Table 2–10. Adverse effects frequently reported with venlafaxine use (Cipla Medpro, 2006:1; Wyeth Pharmaceuticals, 2003:27-34).

CLASSIFICATION	FREQUENT	LESS FREQUENT
Haematological and lymphatic system	Ecchymosis	Mucous membrane bleeding, prolonged bleeding time, thrombocytopenia, agranulocytosis, aplastic anaemia, neutropenia and pancytopenia
Metabolic and nutritional	Changes in serum cholesterol (possibly dose related and after prolonged use), weight loss and weight gain	Hyponatraemia, abnormal liver function tests, hepatitis, increased prolactin and SIADH
Neuropsychiatric	Agitation, twitching, anxiety, nervousness, confusion, depersonalisation, depression, amnesia, somnolence, insomnia, abnormal dreams, abnormal thinking, emotional lability, hypertonia, hyperaesthesia, paraesthesia, dizziness, vertigo, decreased libido, tremor, dry mouth, urinary retention and sedation	Apathy, myoclonus, convulsion, neuroleptic malignant syndrome, serotonergic syndrome, extrapyramidal signs (e.g. dyskinesia, dystonia), tardive dyskinesia, delirium, hallucinations and manic reaction
Special senses	Abnormality of accommodation, abnormal vision,	

CLASSIFICATION	FREQUENT	LESS FREQUENT
	mydriasis, taste perversion and tinnitus	
Cardiovascular	Vasodilation (mostly flushes) and hypertension	Palpitations, tachycardia, postural hypotension, oedema, migraine, hypotension, syncope, QT prolongation, ventricular tachycardia and fibrillation
Respiratory	Yawning, dyspnoea, rhinitis, pharyngitis and bronchitis	Pulmonary eosinophilia
Gastrointestinal	Constipation, anorexia, nausea, vomiting, eructation, dyspepsia, flatulence, and diarrhoea. Dose-related nausea is common at the start of treatment. It decreases over the first few weeks of therapy	Increased appetite and pancreatitis
Skin and appendages	Rash, pruritus and sweating (including night sweats)	Alopecia, Stevens-Johnson syndrome
Musculoskeletal	Arthralgia and myalgia	Rhabdomyolysis
Urogenital	Urinary frequency, impotence, anorgasmia, impaired urination and erectile dysfunction	Abnormal orgasm/ejaculation, menorrhagia and urinary retention
General	Abdominal pain, chest pain, neck pain, back pain, headache, asthenia and chills	Anaphylaxis and photosensitivity reaction

2.3.12 Monitoring requirements

- According to the SAMF, patients on venlafaxine treatment require regular blood pressure monitoring, especially for regimens with doses above 200 mg/day (Rossiter *et al*., 2016:503). Acceptable blood pressure readings are systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg (National Department of Health, 2015:3.28).
- The patients' weight should be monitored regularly (Wyeth Pharmaceuticals, 2003:14). A Body Mass Index (BMI) of < 25 kg/m^2 should be maintained (National Department of Health, 2015:3.29).
- During lactation, venlafaxine is excreted in breast milk. Therefore, if the patient is pregnant or breastfeeding while on venlafaxine treatment it is essential to thoroughly monitor the infant for adverse effects such as poor feeding, agitation, insomnia and failure to thrive (Rossiter *et al*., 2016:503).
- It is advised that patients with MDD or co-morbid depression who are on venlafaxine treatment be monitored for clinical worsening or possible suicidality. This is especially important during the first few months of initial drug treatment or during periods of dose changes (both increases or decreases) (Wyeth Pharmaceuticals, 2003:10). Monitoring of the patients should include observations such as: Weekly face-to-face contact with patients, their family member or caregivers during the initial four weeks of treatment; then every other week for another 4 weeks; thereafter at 12 weeks of treatment and beyond 12 weeks as clinically indicated. Additional measures such as telephonic conversations in between direct visits may be beneficial.
- Patients who are on venlafaxine treatment for anxiety disorders should be monitored regularly for the occurrence of agitation and nervousness (Rossiter *et al*., 2016:503).
- Due to the potentiation of adverse effects through interaction with MAOIs (discussed further below), patients on venlafaxine treatment should be monitored for tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome as well as seizures that may cause death (Wyeth Pharmaceuticals, 2003:11).
- There are three changes that may occur with venlafaxine in terms of its adverse effects and should be monitored (Wyeth Pharmaceuticals, 2003:35):

- Vital sign changes: In a placebo-controlled MDD trial venlafaxine XR was associated with a mean final on-therapy increase in pulse rate of 2 beats per minute, compared to 1 beat per minute for the placebo. Patients should therefore be monitored for any significant changes in pulse rate.
- Laboratory test changes: From a placebo-controlled MDD trial it was observed that venlafaxine XR was associated with a mean final on-therapy increase in the serum cholesterol concentration of approximately 1.5 mg/dL compared to a mean final decrease of 7.4 mg/dL for the placebo. It is essential that patients' serum cholesterol concentration be monitored. According to the Heart and Stroke Foundation, the following normal cholesterol levels are appropriate for most healthy people (The Heart and Stroke Foundation, 2017): Total cholesterol < 5 mmol/L, LDL cholesterol level < 3 mmol/L, HDL cholesterol levels > 1.2 mmol/L for women or 1.0 mmol/L for men, and fasting triglyceride levels < 1.7 mmol/L. Patients diagnosed with diabetes, have kidney disease or who are overweight should have their cholesterol levels monitored frequently (The Heart and Stroke Foundation, 2017). If LDL cholesterol levels are high or the patient is at a high risk of heart disease, their cholesterol levels should be checked at least every six months.
- ECG changes: In a flexible dose study, venlafaxine doses in the range of 200-375 mg/day and a mean dose greater than 300 mg/day was associated with a mean change in heart rate of 8.5 beats per minute compared with 1.7 beats per minute for placebo. Therefore, patients should be informed about such changes and monitored for any significant changes in heart rate.

2.3.13 Possible drug-drug interactions associated with the use of venlafaxine

Venlafaxine has known interactions with the following drugs (Table 2–11) (Cipla Medpro, 2006:1; Leesette Turner, 2010:494; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:20).

Table 2–11. Known drug-drug interactions with venlafaxine (Cipla Medpro, 2006:1; Leesette Turner, 2010:494; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:20).

DRUG	EFFECT OF INTERACTION
Alcohol/CNS active drugs	Sedation is potentiated by most central nervous system depressants as well as alcohol. Patients should be advised to take care when driving, or when operating machinery, especially during the first few weeks of therapy. Additionally, alcohol consumption should be discouraged during venlafaxine treatment
Aripiprazole	Risk of neuroleptic malignant syndrome. Known occurrence of extrapyramidal effects
Aspirin	Use with caution as it may result in bleeding
Bupropion	Risk of convulsions and use is not recommended
Cimetidine	Use with caution in patients with pre-existing hypertension, elderly patients and patients with hepatic dysfunction
Drugs that prolong the QT interval	Additive effect. Causes Torsades de Pointes arrhythmias and use is not recommended
Duloxetine	Results in serotonin syndrome and use is not recommended
Haloperidol	Concurrent venlafaxine use results in raised levels of haloperidol
Indinavir	Concurrent venlafaxine use leads to reduced levels of indinavir
Linezolid	Concurrent use leads to serotonin syndrome
Lithium	Information is limited, however, there is the possibility that the combination may enhance serotonergic activity, leading to serotonin syndrome

DRUG	EFFECT OF INTERACTION
Monoamine oxidase inhibitors	Avoid concomitant use due to serotonin syndrome may occur
Moclobemide	Serotonin syndrome may occur, avoid concomitant use
Olanzapine	Concurrent use leads to raised levels of olanzapine
SSRIs	It is possible that concurrent use with venlafaxine may enhance serotonin activity, leading to serotonin syndrome
TCAs	Serotonin syndrome
Warfarin	Venlafaxine may result in increased anticoagulant effects in patients taking warfarin

Venlafaxine is an example of an enzyme-inhibiting drug. When one drug inhibits another drug's metabolism, it results in the accumulation of the second drug, thus causing prolonged and intensified activity (Leesette Turner, 2010:11). This inhibition may occur within 2-3 days, resulting in the rapid development of toxicity. The clinical significance of these drug interactions depends on the rate and extent to which the plasma concentrations of the drug rise (Leesette Turner, 2010:11). However, the interaction can be beneficial if the plasma concentrations remain within the therapeutic range for drugs having a broad therapeutic window.

The following drugs are commonly affected by enzyme-inhibiting drugs (Leesette Turner, 2010:11):

- Anticoagulants (oral).
- Beta blockers.
- Caffeine.
- Carbamazepine.
- Corticosteroids.
- Digoxin.
- Phenytoin.

- Rifabutin.
- Sulfonylurea-type oral antidiabetic agents.
- Suxamethonium.

2.4 Drug utilisation reviews

2.4.1 Background

In 1977, the WHO defined drug utilisation research as the marketing, distribution, prescription and use of drugs in a society with special emphasis on the resulting medical, social and economic consequences (Academy of Managed Care Pharmacy, 2009:215; Truter, 2010:91; WHO, 2003:85, 1992:67; WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:8). Drug utilisation research also provides insight into the efficiency of drug use (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:9).

Pharmacoepidemiology is the study of the use and adverse effects of drugs in a large population, with the aim of supporting cost-effective and rational use of drugs, thereby improving health outcomes (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:8). This concept emphasises the effectiveness and safety of individual drugs or groups of drugs.

In essence, a combination of drug utilisation research and pharmacoepidemiology can provide valuable insight into the following aspects of drug use and prescribing (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:8):

- **Pattern of use**: This describes the degree and profiles of drug use, including drug use trends and costs over time.

- **Quality of use**: This is determined using audits to compare actual use to national prescription guidelines or local drug formularies. Indices of quality of drug use may include the choice of drug, drug cost, drug, awareness of drug interactions and adverse drug reactions, and the proportion of patients who are aware of or unaware of the costs and benefits of the treatment.
- **Determinants of use**: These include user characteristics (e.g. sociodemographic parameters and attitudes towards drugs), prescriber characteristics (e.g. speciality, education and factors influencing therapeutic decisions) and drug characteristics (e.g. therapeutic properties and affordability).
- **Outcomes of use**: These refer to the health outcomes (i.e. the benefits and adverse effects), including the economic consequences.

Drug utilisation research may be separated into analytical or descriptive studies. Analytical studies attempt to link data on drug utilisation to figures on morbidity, outcome of treatment and quality of care with the ultimate goal of assessing whether drug therapy is rational or not (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:8). On the other hand, descriptive studies aim to describe patterns of drug utilisation and to identify problems eligible for more detailed studies.

There are three types of drug utilisation studies, namely cross-sectional studies, longitudinal studies and continuous longitudinal studies (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:17). Longitudinal studies are performed when public health authorities are interested in trends in drug use and require longitudinal data. Continuous longitudinal studies make use of data that can provide information about concordance with treatment based on the period between prescriptions, co-prescribing and duration of treatment. This drug utilisation study will be a cross-sectional one making use of cross-sectional data. Cross-sectional data provides a picture of drug use at a particular time, e.g. over a year (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:17). Such studies

can easily measure drug use or can be used to assess drug use in relation to guidelines or restrictions.

2.4.2 Classifications of drug utilisation reviews

A drug utilisation review (DUR) is defined as a system of continuous, systematic, criteria-based evaluation of drug use that ensures drugs are used appropriately (Academy of Managed Care Pharmacy, 2009:217; Truter, 2010:95; WHO, 2003:85). A DUR is drug- or disease-specific and can be designed to assess the actual process of prescribing, dispensing or administering a drug, such as indications, dose and dosing instructions (WHO, 2003:85). It is a dynamic process which encompasses a drug review against predetermined criteria or standards. DURs are classified in three categories (Academy of Managed Care Pharmacy, 2009:217-218; Truter, 2010:95; WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:23):

1. Prospective: Conducted to evaluate a patient's drug treatment before the drug is dispensed.

Issues commonly addressed by prospective drug utilisation reviews (Academy of Managed Care Pharmacy, 2009:217):

- Clinical abuse/misuse.
- Drug-disease contraindications (when a prescribed drug should not be used with certain diseases).
- Drug dose modification.
- Drug-drug interactions (when two or more different drugs interact and alter their intended effects, often causing adverse effects).
- Drug-patient precautions (due to age, allergies, gender, pregnancy, etc.)
- Formulary substitutions (e.g. therapeutic interchange, generic substitution).
- Inappropriate duration of drug treatment.

2. Concurrent: Continuous monitoring of drug treatment during the course of treatment.

Issues commonly addressed by concurrent drug utilisation reviews (Academy of Managed Care Pharmacy, 2009:218):

- Drug-disease interactions.
- Drug-drug interactions.
- Drug dose modifications.
- Drug-patient precautions (age, gender, pregnancy, etc.)
- Over and underutilisation.
- Therapeutic interchange.

3. Retrospective: A review of drug treatment after the patient has received the drug.

Issues commonly addressed by retrospective drug utilisation reviews (Academy of Managed Care Pharmacy, 2009:218):

- Appropriate generic use.
- Clinical abuse/misuse.
- Drug-disease contraindications.
- Drug-drug interactions.
- Inappropriate duration of treatment.
- Incorrect drug dose.
- Use of formulary drugs whenever appropriate.
- Over and underutilization.
- Therapeutic appropriateness and/or duplication.

A retrospective review aims to detect patterns in prescribing, dispensing or administering of drugs (Academy of Managed Care Pharmacy, 2009:218). From a comparison of patient records with current patterns of drug use, potential target interventions can be developed to avoid recurrence of inappropriate drug use. Retrospective drug utilisation studies are advantageous as they are inexpensive, can be conducted rapidly and have easily accessible data (Truter, 2010:95). Retrospective data are generally easier to collect and there may be fewer potential biases as compared to prospective data (INRUD/WHO, 1993). These are a few justifications for the chosen category of DUR for the current study.

2.4.3 Importance of drug utilisation reviews

DUR programs play a vital role in helping managed healthcare systems understand, interpret, evaluate and improve the prescribing, administration and use of drugs (Academy of Managed Care Pharmacy, 2009:215). The main aim of a DUR is to ensure that drug therapy meets the current standards of care. DURs provide an opportunity for healthcare professionals to work together and make a collaborate effort towards improving the health status of patients. Pharmacists have a key role in this process, due to their vast knowledge in the management of drug treatment. The DUR process allows pharmacists to identify patterns in prescribing within the patient population and thereafter consult prescribers and other healthcare professionals on collaborative methods to improve drug treatment for patients (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:23). DUR programs are thus valuable as they provide feedback to prescribers on their individual performance and prescribing behaviours as compared to pre-determined treatment protocols (Academy of Managed Care Pharmacy, 2009:215). Information obtained from DURs can assist healthcare professionals to design educational programs to improve rational prescribing and patient compliance. Data from DUR studies may also be used for comparison purposes with other local and international studies (WHO, 2003:85). DURs are significant and of immense importance as there are numerous new drugs in the market, a wide variation in the patterns of drug prescribing and consumption as well as an increase in drug costs (Truter, 2010:94).

2.4.4 Objectives of drug utilisation reviews

The primary goal of a DUR is to promote optimal drug treatment as well as ensuring that drug treatment is of suitable quality and meets the current standards of care (WHO, 2003:85). Additional objectives include (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:23):

- Evaluating the effectiveness of drug treatment.
- Enhancing the responsibility of healthcare professionals involved in the drug utilisation and treatment process.

- Controlling drug cost.
- Investigating and preventing drug related problems such as adverse drug reactions, over- and under-use of drugs, treatment failures and incorrect doses.
- Identifying areas in practice where healthcare professionals may require additional education and training.

2.4.5 Methodology of drug utilisation reviews

There are numerous methods that can be followed to conduct a drug utilisation study as described in the literature. Truter (2010) performed a valuable review of drug utilisation studies and methodologies. The review provided an overview of the countless methods that can be implemented (Truter, 2010:91-104). The different methods were divided into eight broad categories (Truter, 2010:96):

- Methods used in qualitative studies.
- Methods used in studies on prescription habits.
- Methods used in studies on patient compliance.
- Methods used in studies on drug effects.
- Methods used in studies on patients' knowledge about drugs.
- Methods used in ad hoc studies.
- Methods used in descriptive studies, determinants of drug use and impact of drug utilisation.
- Methods used in consumption studies.

The researcher needs to choose the most applicable method according to the specific type of DUR study, considering the study aim and objectives.

In addition, drug utilisation studies may be either quantitative or qualitative (Truter, 2010:96). Quantitative studies can be used to describe trends in prescribing and drug use, whilst qualitative studies assess the appropriateness of drug utilisation and link prescribing data to indications for prescribing (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:20). The current study aimed to firstly evaluate the usage of venlafaxine by analysing the prescribing patterns and management practices and secondly to compare the patterns of venlafaxine use in the

public sector with the current STGs. Therefore, a combined approach of both qualitative and quantitative methods was required to achieve the aims of this study. Quantitative data may be used to provide overall statistics with a detailed breakdown of specific data in a given situation, whereas qualitative data obtained is useful for international comparisons of drug use (Capella, 1993:55-65).

Data for drug utilisation studies may be acquired from various sources. The source of data is specific for each study and depends on the study design and study objectives. Some of these data sources include: Large databases, drug regulatory agencies, privately owned companies, health facility records and medical aid funds (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:20). The primary source of data for a DUR is patient files and/or prescriptions (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:20-24). An appropriate sample size should be determined prior to the data collection process. According to the WHO, a sample size with a minimum of 50-75 records per healthcare facility is considered acceptable (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:24). However, the number of records sampled would also depend on the size of the facility and the number of prescriptions available.

Once the data source for the DUR is identified, the next step is to identify a specific drug, class of drugs or disease state that will be the focus of the study (Truter, 2010:96-97). Data based on that subject area will be collected and analysed.

For comparison purposes, a drug classification system is essential as it represents a common language for describing the drug use pattern in a country or region and is a prerequisite for national and international comparisons of drug utilisation data (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:33). The standardisation of data results in efficient data analysis and allows for the comparison of data between countries. The WHO Collaborating Centre for Drug Utilisation Research and Clinical Pharmacological Services recommends the use of the

Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) system to standardise the data. The purpose of this classification system is to serve as a tool for drug utilisation studies to improve the quality of drug use (WHO Collaborating Centre for Drug Statistics Methodology, 2016:14). This system allows for the presentation and comparison of drug consumption statistics at international and other levels. The ATC classification system divides the drugs into different groups according to the organ or system on which they act and according to their chemical, pharmacological and therapeutic properties (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:33-34). However, the focus of the current study was on one specific drug (venlafaxine) therefore the ATC system was not necessary.

The DDD methodology was established to overcome the limitations of expressing consumption in terms of costs or units prescribed or sold. It is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults (Truter, 2010:99; WHO Collaborating Centre for Drug Statistics Methodology, 2016:22). Furthermore, the DDD is a unit of measurement and comparison which provides a rough estimate of the proportion of patients within a community that would receive the drug treatment but it does not essentially reflect the recommended or prescribed daily dose (Truter, 2010:99; WHO, 2003:79; WHO Collaborating Centre for Drug Statistics Methodology, 2016:22-23). Consumption in different geographic areas or hospitals may also be compared using this methodology (WHO, 2003:79). A study which aimed to perform a preliminary investigation into the use of the DDD as a unit to measure drug utilisation in South Africa showed that its methodology is a useful technique to enable drug consumption data to be measured and compared both nationally and internationally (Truter *et al*., 1996:675). In addition, it can be regarded as a valuable tool for the promotion of rational and cost-effective use of drugs in a future healthcare system for South Africa (Truter *et al*., 1996:678). Concerning the class of antidepressants their DDDs are based on the treatment of moderately severe depression (WHO Collaborating Centre for Drug Statistics Methodology, 2016:224). This unit of measure is limited as doses for individual patients and groups will differ and will necessarily have to be based on individual characteristics such as age and

weight, which may not be a true reflection of the actual prescribing patterns (Truter, 2010:100).

Due to the limitations of DDD, the Prescribed Daily Dose (PDD) was introduced. The PDD is the average daily dose of drug that is prescribed (Truter, 2010:101; WHO Collaborating Centre for Drug Statistics Methodology, 2016:31; WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services., 2003:14). The PDD can be determined from prescription studies, medical or pharmacy records and patient interviews (Truter, 2010:101; WHO Collaborating Centre for Drug Statistics Methodology, 2016:31). When there is a considerable discrepancy between the PDD and the DDD, caution is needed when comparison is made (Truter, 2010:101). PDDs may differ from one country to another and this is an important point to consider when making international comparisons (WHO Collaborating Centre for Drug Statistics Methodology, 2016:31).

2.4.6 Published literature on drug utilisation reviews on antidepressants

The following is a summary of published literature that was found regarding drug utilisation reviews conducted specifically on antidepressants.

The oldest review found by the researcher based on the availability of literature was conducted in 1978 (Trimble, 1978). This study reviewed the literature regarding the convulsant effects of the class of antidepressant drugs known as MAOIs. The conclusion made was that most of the drugs in this class lower the seizure threshold and even at standard therapeutic doses it may precipitate seizures (Trimble, 1978:241-250).

The second oldest review found was conducted in 1985, which aimed to evaluate the importance of doses in antidepressant prescribing (Quitkin, 1985). The doses of TCAs used was analysed with data from a few dose-response studies. Data from the study suggests that patients received inadequate doses during treatment (Quitkin, 1985:593).

Other published studies that were found are from the 1990's and more current. A study that aimed to review the results of previous placebo-controlled studies to determine the use of antidepressants in the treatment of chronic pain was found (Magni, 1991). The results of the review suggest that a variety of conditions are responsive to treatment with antidepressants. These conditions in particular include: Headache, migraine, facial pain, neurogenic pain, fibrosis and perhaps arthritis, however, more evidence is needed in terms of the efficacy of treatment for lower back pain and pain associated with cancer (Magni, 1991:730-748).

A study conducted in 1995 aimed to use a meta-analytic approach to review the efficacy of antidepressant treatment in obsessive-compulsive disorder (OCD) patients (Piccinelli *et al*., 1995). Results from the study suggest that antidepressant treatment is effective in the short-term treatment of OCD sufferers. With regards to the various classes of antidepressants, the TCA clomipramine showed a similar therapeutic efficacy compared to the SSRI class for the treatment of OCDs (Piccinelli *et al*., 1995: 424).

A review by Bollini and co-workers (Bollini *et al*., 1999) aimed to determine whether antidepressants are more effective at high doses compared to low doses as well as the association between the safety and doses of antidepressants. The results from the meta-analysis suggest that with a low dose of antidepressants, clinicians substitute a slightly reduced chance of improvement for a greater chance of evading adverse reactions (Bollini *et al*., 1999:297).

A DUR study investigated the association between trends in the prescribing of antidepressants and suicide rates in Australia for the years 1991-2000 according to patient age and gender (Hall *et al*., 2003). The study established that antidepressant prescribing is considerably associated with changes in suicide rates in Australia for that period. This trend was significant in older age groups and it was noted that suicide rates were largely decreased due to antidepressant use (Hall *et al*., 2003:1008). However, in clinical practice there has been concern that antidepressants may exacerbate depression or result in the development of suicidality in some patients (Cipla Medpro, 2006:1; Wyeth Pharmaceuticals, 2003:9). Therefore, it is advised that all patients take precaution when on antidepressant treatment and be aware of any signs and symptoms indicating worsening of the depressive disorder, such as the

emergence of suicidal thoughts or unusual changes in behaviour (Rossiter *et al*., 2016:493).

The study results from a retrospective analysis concluded that general practitioners (GPs) are the major providers of depression treatment in Australia (McManus *et al*., 2003). The study examined the antidepressant prescribing patterns of psychiatrists and GPs in Australia. It was also observed that for TCA prescriptions, GPs use lower doses than the recommended dose for major depression (McManus *et al*., 2003:184-189). Another study conducted in 2003 which included a systematic review and meta-analysis aimed to compare the efficacy and tolerability of TCAs with SSRIs for the treatment of depression in primary care settings (MacGillivray *et al*., 2003). Results from the study suggest that the data on the relative efficacy of SSRIs and TCAs is scarce and of inconstant quality (MacGillivray *et al*., 2003:1014).

A study conducted in 2011 aimed to determine the prevalence of psychotropic drug utilisation in Belgian nursing homes (Azermai *et al*., 2011). Psychotropic drugs were categorised into antidepressants, antipsychotics, benzodiazepines and anti-dementia drugs by using the ATC classification system. The results revealed that 40% (n=692) of the total sample population (n=1730) were prescribed antidepressants, two-thirds were indicated for depression and one third for insomnia (Azermai *et al*., 2011:12-20). Results from the study suggest that as seen in other European countries, the frequency of psychotropic drug utilisation in Belgian nursing homes was remarkably high and with unnecessary duplicate use (Azermai *et al*., 2011:12-20).

2.4.7 Published literature on drug utilisation reviews specifically on venlafaxine

The following is a summary of published literature that was found on DUR studies conducted on venlafaxine. The majority of the studies support the favourable clinical profile of venlafaxine.

Despite there being a shortage of literature to fully support the use of venlafaxine as a first-line treatment for MDD over the other antidepressant classes, a literature search led to the discovery of an old review study conducted on the efficacy and tolerability of venlafaxine (Dierick, 1997). The aim was to discuss the role of venlafaxine as first-line therapy for the treatment of MDD. Results from the review suggest that

venlafaxine presented with a favourable side-effect profile which was comparable to that of SSRIs, overall tolerability which appeared to exceed that of TCAs as well as the potential of achieving an early therapeutic response through rapid dose titration (Dierick, 1997:307s-313s). Venlafaxine was found to be well tolerated during short- and long-term treatment, therefore with these characteristics the review concluded that venlafaxine may be a logical first-line therapy in a broad range of patients with MDD. The review also considered the available evidence from previous placebo- and active-controlled trials concerning the adverse effects experienced with venlafaxine and found the most common adverse effects to be nausea, somnolence and dry mouth (Dierick, 1997:307s-313s). However, in clinical trials a slight but statistically significant rise in blood pressure (mean of < 2 mm Hg diastolic) was observed with venlafaxine at daily doses above 200 mg, although the incidence of elevated blood pressure at 75 mg daily was comparable to that with placebo. Despite this observation, there was no evidence to suggest that hypertensive patients were at greater risk for increased blood pressure (Dierick, 1997:307s-313s). On the other hand, the observation of slightly elevated blood pressure could be a possible reason as to why venlafaxine is not considered a first-line treatment option and the clinical significance of this observation needs to be further investigated along with other possible reasons.

The SSRIs are common first-step treatments for depression due to their relatively low toxicity and high tolerability (Rush *et al*., 2006:1231-1242). However, a few randomised trials have compared the efficacy and tolerability of treatment with at least two active second drugs of which one was venlafaxine after the initial treatment failure with an SSRI. The first was a randomised, open-label, multicentre study which aimed to compare the effectiveness of the venlafaxine extended-release formulation with that of conventional antidepressants. The study was conducted in patients who were referred to an outpatient psychiatric specialty care setting for treatment after failure to tolerate or respond to at least 4 weeks of treatment with conventional antidepressant in a primary care setting (Baldomero *et al*., 2005). Results from the study suggest that venlafaxine extended-release may be more effective than the conventional antidepressants (paroxetine, citalopram, sertraline, fluoxetine and mirtazapine) when treating patients who do not tolerate or respond adequately to treatment with a conventional antidepressant (Baldomero *et al*., 2005:68-76).

A second study by Rush and co-workers (2006) also supports the findings from the previously mentioned study by Baldomero and co-workers. The study was conducted to investigate the viable options for switching therapy after unsuccessful treatment with a SSRI. A comparison of the outcomes achieved from three second-step drugs was made, namely: Sustained-release bupropion, sertraline and venlafaxine XR (Rush *et al*., 2006:1231-1242). The resulting remission rates of the three drugs were not drastically different from each other and they did not differ considerably with respect to tolerability or adverse effects. Therefore, the study concluded that after an unsuccessful treatment with an SSRI, any one of the three drugs would be a reasonable second-step choice for patients with depression (Rush *et al*., 2006:1231-1242). The study stated that *post hoc* analyses suggest slightly higher remission rates with venlafaxine than with SSRIs when used as a first-step treatment. However, higher remission rates were not established with XR venlafaxine compared to the other two drugs (Rush *et al*., 2006:1231-1242).

From the literature survey, two other studies were found to additionally support the conclusions of the previously mentioned studies (Baldomero *et al*., 2005; Rush *et al*., 2006). Fang and co-workers (2010) aimed to compare the efficacy and tolerability of antidepressants switched with venlafaxine-XR, mirtazapine and paroxetine. The study was conducted in Chinese patients with MDD who had two consecutive unsuccessful antidepressant trials. Results suggest that venlafaxine was a successful treatment alternative for MDD after at least 2 failed previous antidepressant treatments (Fang *et al*., 2010:357-364). Papakostas and colleagues (2008) aimed to investigate two broad treatment options for switching antidepressants for depressed patients who failed to respond to a SSRI, either to therapy with a second SSRI or to a different class of antidepressants. The results of the study supported the use of venlafaxine as an alternative for SSRI-resistant depression (Papakostas *et al*., 2008:699-704).

The following is a summary of published literature that have compared the effectiveness of venlafaxine to other classes of antidepressants, but particularly with the SSRIs class.

Einarson and co-workers (1999) conducted a comparison study on the efficacy of venlafaxine XR, SSRIs and TCAs in the treatment of depression. This meta-analysis established that venlafaxine XR is clinically superior in efficacy to SSRIs and TCAs in

the treatment of depression (Einarson *et al*., 1999:296-308). The findings from a different study also conducted in 1999 suggested that venlafaxine was superior to paroxetine in the difficult-to-treat-patient (unresponsive to initial antidepressant therapy) population (Poirier and Boyer, 1999:12).

A study was conducted to investigate whether venlafaxine may result in better treatment outcomes compared to SSRIs (Thase *et al*., 2001). Data were sourced from eight comparable randomised, double-blind studies of MDD and their remission rates were compared. The SSRIs included were fluoxetine, paroxetine and fluvoxamine. The study concluded that remission rates were significantly higher with venlafaxine when compared to treatment with an SSRI (Thase *et al*., 2001:234-241).

The aim of a study by Smith and co-workers was to review if venlafaxine was more effective than comparator antidepressants of particularly the SSRI class as stated in individual studies and meta-analyses (Smith *et al*., 2002). The study conducted a systematic review of double-blind, randomised trials that compared venlafaxine with alternative antidepressants in the treatment of depression. The analysis concluded that venlafaxine does have a greater efficacy than SSRIs, but there is uncertainty compared with other antidepressants therefore, further studies are required (Smith *et al*., 2002:396-404). A different study conducted in 2002 by Stahl and co-workers supported the conclusion made by Smith and co-workers (2002), with findings that venlafaxine was significantly more effective than SSRIs in improving depression and proposed that this may be attributed to the dual-enhancing effect of both serotonin and noradrenaline (Stahl *et al*., 2002:1166-1174).

A study by Whyte and co-workers aimed to assess the toxicity in overdose of SSRIs and venlafaxine compared to TCAs, as well as of dothiepin compared to the other TCAs (Whyte *et al*., 2003). The results reported that there were no deaths from a total of 528 admissions. It was discovered that in the event of an overdose, venlafaxine and dothiepin are pro-convulsant. In addition, venlafaxine was observed to more likely cause serotonin syndrome but less likely to cause coma than TCAs (Whyte *et al*., 2003:369-374). The study concluded that antidepressant classes other than TCAs and venlafaxine should be carefully managed and monitored in patients with a risk of suicide or seizure (Whyte *et al*., 2003:369-374).

Antidepressants are the most frequently recommended treatment for atypical facial pain but only limited data are available to demonstrate their effectiveness. Atypical facial pain, recently defined as persistent idiopathic facial pain is a poorly understood condition, with pain described as "persistent facial pain that does not have the characteristics of cranial neuralgias and is not attributable to another disorder (Agostoni *et al*., 2005:s71-s72). The pain is confined to a limited area on one side of the face, often in the nasolabial fold or side of the chin and may spread to the upper or lower jaw or a wider area of the face of neck also it is deep and poorly localised (Agostoni *et al*., 2005:s73). A study by Forssell and associates (2004) aimed to determine the efficacy of venlafaxine in the treatment of atypical facial pain. It was concluded from the results that venlafaxine in comparison to the placebo given was only modestly effective in the treatment of atypical facial pain (Forssell *et al*., 2004: 131-137).

The objective of a study by Campagne was to review severe withdrawal symptoms that may occur with venlafaxine (Campagne, 2005). Clinical records and a search of PubMed and other databases was used as the data source. The review concluded that abrupt venlafaxine dose reduction or discontinuation can result in specific symptoms such as impaired coordination, dizziness, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor and vertigo that seriously impair driving abilities and should be avoided by adhering to strict dosing discipline and adequate warnings of symptoms (Campagne, 2005:22).

Papakostas and co-workers (2007) aimed to establish whether antidepressants that combine serotonergic and noradrenergic mechanisms of action (SNRIs) are more effective than the SSRIs in the treatment of MDD by performing a meta-analysis of studies of newer drugs. The study concluded that SNRIs appear to have a modest efficacy advantage compared with SSRIs in MDD treatment. However, further research is needed to investigate whether there are large differences between antidepressant classes in specific MDD sub-populations or for specific MDD symptoms (Papakostas *et al*., 2007:1217-1227).

A different study conducted by Kadiroglu and co-workers aimed to assess the efficacy of venlafaxine HCl amongst patients with type 2 diabetes mellitus (DM) in the

symptomatic treatment of painful peripheral diabetic neuropathy (PPDN) (Kadiroglu *et al*., 2008). This study was designed as a prospective, randomised and controlled trial using a sample size of 60 patients. It was concluded that venlafaxine HCl is a safe and well-tolerable analgesic drug in the symptomatic treatment of PPDN and its efficacy is noticeable in the second week of treatment (Kadiroglu *et al*., 2008:241-245). Besides the success in pain relief, minimal adverse effects were reported.

A study completed by Nemeroff and colleagues (2008) conducted a comprehensive analysis of remission with venlafaxine *versus* SSRIs. The findings from the study suggest that venlafaxine therapy is statistically superior to SSRIs as a class (Nemeroff *et al*., 2008:424-434).

Bauer and collaborators (2009) analysed the effect of venlafaxine compared with other antidepressants and placebo in the treatment of depression. The meta-analysis revealed that venlafaxine appeared superior to SSRIs for both response and remission with similar overall tolerability (Bauer *et al*., 2009). There was also evidence to support the superiority of venlafaxine over TCAs for the outcome of response. A crucial observation was noted for the important role venlafaxine has in the long-term prevention of depressive relapse and recurrence, also in patients with treatment resistant depression who have failed to respond to therapy (Bauer *et al*., 2009:172-185).

The objective of a different study completed by Machado and Einarson was to compare the clinical outcomes of adults treated with SSRIs or SNRIs for MDD under ideal clinical conditions i.e. 8 to12-week treatment duration for MDD (Machado and Einarson, 2010). The data were sourced from electronic databases such as Medline, Embase and the Cochrane Library. Results suggest that SNRIs showed a statistical but no clinical significance when compared with SSRIs for the treatment of MDD (Machado and Einarson, 2010:177-188).

A study compared the treatment outcomes with venlafaxine XR and the SNRIs with SSRIs in primary care patients with MDD (Thase *et al*., 2011). The study was designed as a randomised, open-label, rater-blinded, multicentre study which was initiated at 92 primary care sites but continued at 87 sites (5 sites were discontinued). The conclusion from the study was that remission rates for patients treated with

venlafaxine XR or an SSRI did not differ considerably after 6 months of continuous treatment (Thase *et al*., 2011: 1-12). Favourably, the results of secondary analyses suggest that SNRI treatment with venlafaxine had a superior antidepressant effect as compared to the SSRIs in this study (Thase *et al*., 2011:1-12).

The objective of a study by Gibbons and co-workers was to determine the short-term safety of antidepressants by performing standard assessments of suicidal behaviour and thoughts in youth, adult and geriatric populations as well as the mediating effect of changes in depressive symptoms (Gibbons *et al*., 2012). From the analysis of results, it was established that venlafaxine and fluoxetine reduced suicidal thoughts and behaviour for adult and geriatric patients (Gibbons *et al*., 2012:580-587). For the young population there was no significant effect of treatment on suicidal thoughts and behaviour, however, their depression did respond to treatment. There was no evidence of increased suicide risk witnessed in the youth who received active drugs (Gibbons *et al*., 2012:580-587).

The aim of a paper was to review the evidence pertaining to the safety of the SNRI class of antidepressants from a cardiovascular and safety in overdose perspective (Taylor *et al*., 2013). Based on the available evidence, the review concluded that when used to treat depression and generalised anxiety disorder in a primary care setting, SNRIs have a positive risk-benefit profile, particularly as second-line agents (Taylor *et al*., 2013:151-161).

The most recent study found aimed to evaluate the short-term efficacy of venlafaxine extended-release at 75-225 mg/day compared with placebo for treating adult patients with MDD (Thase *et al*., 2017). The study design was a meta-analysis which included published and unpublished short-term, double-blind, placebo controlled, studies sponsored by pharmaceutical companies Wyeth/Pfizer. The study concluded that venlafaxine effectively reduced the symptoms of depression in patients with MDD (Thase *et al*., 2017:317-326).

2.4.8 Published literature from South Africa

2.4.8.1 Introduction

In South Africa from some of the most recent reviews of disease burden, neuropsychiatric conditions have been ranked third in their contribution to the burden of disease following HIV/AIDS and other infectious diseases (South African Depression and Anxiety Group, 2018).

2.4.8.2 Drug utilisation reviews on antidepressants

The majority of the studies found date back to almost a decade ago. However, there were a few studies that were reasonably current, published and available for reviewing.

The oldest study available from the literature survey aimed to investigate the prescribing patterns of SSRIs that were used on a chronic basis in a distinct South African patient population and to calculate the average PDDs of selected SSRIs (Truter and Kotze, 1996). The study sourced data from various medical schemes and analysed it retrospectively. It was concluded that for treating chronic depression, the popular SSRI fluoxetine was the first choice in the patient sample and that the PDDs used were in agreement with local and internationally acceptable dose ranges (Truter and Kotze, 1996:237–242).

A study performed in 1997 was unavailable for review, however, the article citation was available (Truter and Kotze, 1997:42-47). The drug utilisation review was an investigation into chronic TCA prescribing in South Africa.

A study completed in 2003 aimed to explore the prescribing patterns of TCAs and SSRIs in an adolescent and young adult population regarding prescribing frequency, cost and dose (Kairuz *et al*., 2003:379–382). The study was a retrospective investigation and the study results stimulated prescribing patterns that contribute to the scarcity of data on antidepressants in such patients (Kairuz *et al*., 2003:381-382).

Truter and Kotze (2006) aimed to determine the prescribing patterns of TCAs in two private primary care patient populations in South Africa (Truter and Kotze, 2006:301-310). Data for the study was sourced from a private medical aid scheme. The study

concluded that TCAs are an essential therapeutic class and recommended that more studies linking dose to ages and specific diagnoses should be conducted (Truter and Kotze, 2006:307-310).

A different study which had the main objective to characterise the prescribing patterns of drugs classified as antidepressants in children and adolescents in the private healthcare sector of South Africa was completed in 2009 (Burger *et al*., 2009). The study used a retrospective drug utilisation design and the data were sourced from a South African pharmaceutical benefit management company database. This study provided valuable insight into the prescribing patterns of antidepressants in South African children and adolescents, however, it was recommended that additional research is needed to determine reasons why specific drugs are prescribed to this population (Burger *et al*., 2009).

In terms of current studies, Truter (2010) aimed to determine antidepressant prescribing and cost to patients aged 18-years and younger in a South African private healthcare sector population (Truter, 2010). The data for the study was sourced from a private pharmacy group. The study concluded that fluoxetine has a favourable risk-benefit balance (Truter, 2010:A384). The study also found that escitalopram and citalopram are not desirable in the age group of 18-years and younger (Truter, 2010:A384). A second study conducted in 2010 aimed to examine the prescribing patterns of SSRIs and SNRIs to a population sample consisting of children and adolescents younger than 19-years in a primary practice setting (Van Schalkwyk and Truter, 2010). Data from a private medical aid scheme was retrospectively analysed. The results indicated that 50.68% of the 440 patients in the study were prescribed SSRIs and SNRIs (Van Schalkwyk and Truter, 2010:A384). An interesting observation was made concerning venlafaxine, because it is contraindicated in this patient population, which 6.32% of the total prescriptions accounted for prescribed venlafaxine. The study concluded that prescribing to this age group should be further explored and studied over a longer period (Van Schalkwyk and Truter, 2010:A384).

A study performed in 1996 aimed to perform a preliminary investigation into the use of the DDD as a unit of measurement for drug utilisation in South Africa. The DDD methodology was applied in many countries, however, research using the DDD method at that stage was still deficient in South Africa despite the important role that

it had in economic planning and the improvement of prescribing practices (Truter *et al*., 1996). The study concluded that the DDD methodology is an effective technique to facilitate drug consumption data to be measured and compared both nationally and internationally. In addition, it was suggested as a valuable tool for the promotion of rational and cost-effective use of drugs in the future healthcare system for South Africa (Truter *et al*., 1996:678-679).

A study conducted by Sorsdahl and Stein (2010) aimed to evaluate the awareness of attitudes toward and stigma associated with psychiatric disorders in a South African community. The study revealed that the community sample displayed more stigmatising attitudes towards patients with schizophrenia and substance abuse, however, post-traumatic stress disorder was considerably less stigmatised as compared to the other conditions. A recommendation from the study was to educate the public about the psychobiological foundations of psychiatric disorders and the value of effective treatments (Sorsdahl and Stein, 2010).

The following is a summary of South African DURs conducted on antidepressants (Table 2–12).

Table 2–12. South African drug utilisation reviews conducted on antidepressants.

AUTHORS	GENDER (MOST FREQUENT ANTIDEPRESSANT USE)	MOST FREQUENTLY PRESCRIBED ANTIDEPRESSANT	AGE GROUP WITH MOST FREQUENT ANTIDEPRESSANT USE (YEARS)	DATA SOURCE
(Truter and Kotze, 1996)	Females (more than 70%)	Fluoxetine (63.3% (SSRI prescriptions)), 21.9% (antidepressant prescriptions)	48.1	Prescription data from medical schemes
(Truter and Kotze, 1997)	Females	Not available	Not available	Not available
(Kairuz *et al*., 2003)	Females	TCAs (amitriptyline)	Not available	Not available

AUTHORS	GENDER (MOST FREQUENT ANTIDEPRESSANT USE)	MOST FREQUENTLY PRESCRIBED ANTIDEPRESSANT	AGE GROUP WITH MOST FREQUENT ANTIDEPRESSANT USE (YEARS)	DATA SOURCE
(Truter and Kotze, 2006)	Females	Amitriptyline, dothiepin and imipramine	52.99	Prescription data from private medical aid scheme
(Burger *et al*., 2009)	Females	• SSRIs (43.0%) • TCAs (42.7%), with imipramine (22.04%) and amitriptyline (19%)	15-19	Pharmaceutical benefit management company database
(Truter, 2010)	Females (53.72%)	• SSRIs (55.91%) • TCAs (32.32%)	12-18	Prescription data of a private pharmacy group
(Van Schalkwyk and Truter, 2010)	Females (62.33%)	• Fluoxetine (36.50%) • Citalopram (22.14%) • Escitalopram (17.15%)	12-19	Data from private medical aid scheme

One of the motivations for the current research topic is attributed to the observation that in South Africa there seems to be a limited number of recent DURs on antidepressants. Most studies date back to almost a decade ago and the more recent studies analysed data sourced from private medical aid schemes in the private healthcare sector. To the best of knowledge, no specific South African studies on the use of venlafaxine in either the public or private healthcare sectors without data sourced from medical aid schemes could be found, suggesting a deficit of data specifically in the South African public sector.

2.4.9 Challenges experienced with venlafaxine treatment

The following is a summary of published literature that was found concerning possible challenges experienced with prescribing venlafaxine therapy.

The literature survey led the researcher to find an old review study on the efficacy and tolerability of venlafaxine (Dierick, 1997:307-313). The review aimed to discuss the role of venlafaxine as first-line therapy for the treatment of MDD. The review found that venlafaxine presented with a favourable side-effect profile comparable to that of SSRIs, overall tolerability which appeared to exceed that of TCAs and the potential of achieving an early therapeutic response through rapid dose titration (Dierick, 1997:307-313). However in clinical trials a slight but statistically significant rise in blood pressure (mean of < 2 mm Hg diastolic) was observed with venlafaxine at daily doses above 200 mg, although the incidence of elevated blood pressure at 75 mg daily was comparable to that with placebo (Dierick, 1997:312). Despite this observation, there was no evidence to suggest that hypertensive patients were at greater risk for increased blood pressure.

A study published in 1998 aimed to evaluate the effects of venlafaxine on blood pressure (Thase, 1998). The study was designed as a meta-analysis of original data from a sample of 3744 patients with depression. From the results it was concluded that venlafaxine has a dose-dependent effect on supine diastolic blood pressure (SDBP) that is clinically significant at high doses (Thase, 1998:502-508). However, apprehension regarding blood pressure effects should not deter first-line use, although more extensive studies of patients with cardiovascular diseases are still necessary.

Ciraulo and Shader, (2004) states that the most common adverse effects experienced with venlafaxine therapy include those associated with SSRIs such as nausea, vomiting, sexual dysfunction, somnolence and sweating, although the incidence of sexual dysfunction is suggested to be lower than that of SSRIs (Ciraulo and Shader, 2004:77). Most concern was placed on the elevated blood pressure, which occurred at higher doses of venlafaxine (between 101 and 300 mg/day) that returned to normal after drug discontinuation. Blood pressure changes were dose related, with an incidence of approximately 5% at doses under 200 mg/day and 13% at doses larger than 300 mg (Ciraulo and Shader, 2004:77). It was concluded that pre-existing

hypertension did not appear as a risk factor for the effect on blood pressure. It was suggested that if the dose cannot be reduced, the blood pressure should be treated pharmacologically with the use of an alternate hypertensive drug (Ciraulo and Shader, 2004:77).

A study completed in 2006 aimed to investigate the cardiovascular changes associated with venlafaxine in the treatment of late-life depression (Johnson *et al*., 2006). In the study, participants aged 60-years and older with a diagnosis of a major depressive episode without psychotic features were treated openly with venlafaxine XR for 12 weeks (Johnson *et al*., 2006:796-802). The study concluded that venlafaxine XR was well tolerated overall. However, similar to previous reports, venlafaxine XR was associated with some undesirable cardiovascular effects (blood pressure and pulse rate) in some of the participants, therefore systematic monitoring of cardiovascular parameters during treatment with venlafaxine XR is strongly recommended, especially in the elderly population (Johnson *et al*., 2006:796-802).

A different study aimed to review the adverse-effects of antidepressants (Khawam *et al*., 2006). The review of the adverse effects of antidepressants indicated that the most common adverse effects experienced with venlafaxine therapy were nausea, dizziness, insomnia, somnolence and dry mouth. The gastrointestinal adverse effects were less common with the XR preparation (Khawam *et al*., 2006:351-3, 356-61). Sexual dysfunction may occur, as with SSRIs. An important observation was made that hypertension could occur with venlafaxine XR, especially at higher doses (Khawam *et al*., 2006:351-3, 356-61). Therefore, prescribers should be cautious when prescribing venlafaxine to patients with pre-existing hypertension. In addition, it is imperative that blood pressure be monitored regularly, especially when using venlafaxine XR at doses of 225 mg or more per day.

All five of the SSRIs currently available as well as venlafaxine are associated with hyponatraemia. A study by Romero and co-workers aimed to evaluate the association between the syndrome of inappropriate secretion of antidiuretic hormone due to citalopram and venlafaxine (Romero *et al*., 2007:81-84). The study investigated the case of an 87-year-old male patient with depression who presented with hyponatremia after starting treatment with citalopram and venlafaxine on separate occurrences. The study concluded that prescribers should be aware of the risk of hyponatraemia when

prescribing SSRIs as well as venlafaxine in elderly patients with multiple drug therapies. It is imperative that sodium levels be monitored during treatment (Romero *et al*., 2007:81-84).

A recent study completed in 2017 aimed to determine the association of acute urinary retention after venlafaxine use (Demirdöğen *et al*., 2017). The study investigated the case of a 48-year-old male patient who presented with lower urinary system symptoms (LUSSs) and acute urinary retention that developed after treatment with a low dose of venlafaxine. After assessing the patient, the symptoms disappeared completely after venlafaxine was replaced with agomelatine and the study concluded that the LUSSs and urinary retention were due to the venlafaxine treatment (Demirdöğen *et al*., 2017:60-61).

2.4.10 Off-label prescribing

The following is a summary of published literature that was found with reference to the off-label prescribing of venlafaxine therapy.

A 12-week, double-blind, placebo-controlled study aimed to evaluate the efficacy and safety of venlafaxine as first-line therapy for the treatment of major depression and major depression associated with anxiety (Khan *et al*., 1998). The patient sample consisted of 384 adult outpatients and the study design encompassed fixed total daily doses of 75, 150, and 200 mg of venlafaxine which were administered in a twice a day regimen (Khan *et al*., 1998). The study results established that 75 to 200 mg/day of venlafaxine twice daily produced a dose-related improvement in the primary efficacy parameters and in the onset of significant antidepressant effects, which was noted at weeks 1 to 2 with the highest dose tested (200 mg/day) (Khan *et al*., 1998). The study concluded that those doses of venlafaxine were safe and effective as first-line therapy for major depression and depression associated with anxiety.

A different study conducted in 1998 aimed to conduct a meta-analysis on the effects of venlafaxine on anxiety associated with depression (Rudolph *et al*., 1998). The study design consisted of a pooled analysis of six short-term trials of venlafaxine retrospectively measuring anxiety in anxious depressed patients. From the study results it was concluded that venlafaxine was more effective than placebo in reducing symptoms of anxiety in depressed patients and suggested that venlafaxine may give

rise to a monotherapy option for treating patients who have a co-morbid diagnosis of depression with anxiety (Rudolph *et al*., 1998).

A double-blind, placebo-controlled, randomised trial was conducted on 191 patients over 4 weeks to assess the efficacy of venlafaxine in women with a history of breast cancer and who were reluctant to take hormonal treatment because of fear of breast cancer (Loprinzi *et al*., 2000). The study concluded that venlafaxine was an effective non-hormonal treatment option for hot flashes, although the efficacy needs to be balanced against the adverse effects (Loprinzi *et al*., 2000:2059-2063).

Malhotra and co-workers explored the effectiveness and tolerability of venlafaxine in binge-eating disorder (Malhotra *et al*., 2002). The study design followed a retrospective approach and the medical charts of 35 outpatients diagnosed with binge-eating disorder who received clinical treatment with venlafaxine at a weight management program were reviewed. The study concluded that venlafaxine may be an effective treatment for binge-eating disorder associated with (Malhotra *et al*., 2002: 802-806).

An open-label, single-centre study aimed to assess the long-term efficacy of venlafaxine XR in the treatment of chronic pain and depression in outpatients (Bradley *et al*., 2003). The patient sample consisted of patients who were diagnosed with MDD of various types, with or without chronic pain, and who had previously failed treatment with either TCAs or SSRIs. The results of the study demonstrated the long-term efficacy of venlafaxine XR that has besides antidepressant activity also analgesic properties (Bradley *et al*., 2003).

TCAs are conventionally used in the treatment of painful polyneuropathy. However, a study completed in 2003 aimed to test if venlafaxine would relieve painful polyneuropathy and compare its possible efficacy with that of the TCA imipramine (Sindrup *et al*., 2003). The study design was randomised, double blind, and placebo controlled, with a sample of 40 patients. Results suggest that venlafaxine relieved pain in polyneuropathy and may be as effective as imipramine in the treatment of the condition (Sindrup *et al*., 2003:1284).

A study aimed to evaluate the clinical efficacy of venlafaxine for Functional Chest Pain (FCP) in young adult patients (Lee *et al*., 2010). FCP is classified as chest pain that

is not explained by reflux disease or cardiac, musculoskeletal, mucosal, or motor oesophageal abnormalities (Remes-Troche, 2016:429). The study sample comprised of 43 patients. The study concluded that venlafaxine, an SNRI antidepressant, significantly improved symptoms in young adult patients with FCP (Lee *et al*., 2010:1504).

A study completed in 2014 aimed to review the efficacy of venlafaxine for the treatment of fibromyalgia (VanderWeide *et al*., 2014). A systematic review was conducted *via* a search of the PubMed, Web of Science and the Cochrane Database using the terms 'venlafaxine' and 'fibromyalgia'. The review concluded that studies assessing the efficacy of venlafaxine in the treatment of fibromyalgia were limited by small sample size, inconsistent venlafaxine dosing, lack of placebo control and lack of blinding (VanderWeide *et al*., 2014:1-6). Considering these limitations, venlafaxine appears to be at least modestly effective in treating fibromyalgia, however, larger randomised controlled trials are needed to further elucidate the full benefit of venlafaxine.

The objective of a paper published in 2017 was to investigate SNRIs and the influence of binding affinity (K_i) on receptors associated with analgesia (Raouf *et al*., 2017). The paper reviewed differences in receptor affinities and monoamine selectivity amongst SNRIs and the corresponding clinical impact. It was concluded that the SNRIs' varying selectivity for serotonin and noradrenaline could explain the therapeutic dosing required for neuropathic pain as well as their dose-related adverse effects (Raouf *et al*., 2017:513-517). It is therefore imperative to understand the pharmacological differences amongst the SNRIs, in addition to the data from clinical trials to monitor their safe and effective use.

2.4.11 International prescribing patterns of antidepressants

The following is a summary of published literature that investigated the prescribing patterns of venlafaxine in other countries.

A Danish study aimed to perform a prescription database analysis to describe the outpatient utilisation of antidepressants (Rosholm *et al*., 1993). The study results revealed that 1.62% of 3360 people in the sample were on antidepressant treatment, with females and patients aged over 70-years-old who contributed to an excessively

large part. It was also found that the use of TCAs was common in 75% of the patient sample (Rosholm *et al*., 1993:23-27).

A study conducted in 2001 aimed to evaluate the growth and change in the prescribing of antidepressants in New Zealand from 1993 to 1997 (Roberts and Norris, 2001). Results suggest that the overall size of the antidepressant market increased significantly over the study period, most of this was due to the growth in prescribing of newer generation antidepressants. The study concluded that as with other countries, the use of newer antidepressants was contributing to an increased overall use of antidepressants and resultant government expenditure in New Zealand. However, the use of older drugs was not reduced considerably (Roberts and Norris, 2001:25-27).

In 2004 a DUR of antidepressants in children and adolescents using the General Practice Research Database was conducted to describe the prescribing patterns of antidepressants to children and adolescents aged 18-years and younger in the UK (Murray *et al*., 2004). The study sample included a relatively large total of 24 976 patients with 93 091 prescriptions. The results of the study were as follows: 51 868 (55.7%); 38 429 (41.3%); and 2708 (2.9%) prescriptions were for TCAs, SSRIs and other antidepressants, respectively (Murray *et al*., 2004:1098). Furthermore, antidepressant prevalence increased 1.7-fold from 1992 to 2001.

A study entitled “Making new choices about antidepressants in Australia: The long view 1975–2002” examined trends in the types of antidepressants prescribed in Australia between the years 1975-2002 (Mant *et al*., 2004). The data source for the study was sales data from the Australian pharmaceutical industry (Mant *et al*., 2004:S21). The study concluded that the rapid growth in antidepressant prescribing that was characteristic of the early 1990s, and reflected the emergence of new antidepressants, did not continue into the late 1990s (Mant *et al*., 2004:S21). In Australia the prescribing of SSRIs dominates other antidepressant classes.

A study conducted in Southern Italy aimed to estimate the 1-year prevalence, 1-year incidence and indication of use of antidepressants in general practice during the years 2003-2004 (Trifirò *et al*., 2006). The study sample comprised of 142 346 individuals registered on the lists of 119 GPs. The results indicated that antidepressant use increased by 20% in 2004 and depressive disorders were the main indication (mostly

for SSRI users), followed by anxiety disorders (Trifirò *et al*., 2006:552-559). The study concluded that SSRIs, particularly those recently marketed, have been increasingly used during the years 2003-2004 to mainly treat affective disorders (Trifirò *et al*., 2006:552-559).

In 2008 the results from the Factors Influencing Depression Endpoints Research (FINDER) study was used to describe the prescribing patterns of antidepressants in Europe (Bauer *et al*., 2008). The study design was a prospective, observational study in 12 European countries with 3468 adults. The results presented SSRIs as the most commonly prescribed antidepressant (63.3% of patients), followed by SNRIs (13.6%), with substantial differences across countries (Bauer *et al*., 2008:66-73). Notably, in Germany, tricyclic and tetracyclic antidepressants were prescribed for 26.5% patients.

Sclar and co-workers aimed to distinguish ethnic-specific (black, Hispanic or white) population rates of US office-based diagnosis of depression, and the extent of the use of antidepressants (Sclar *et al*., 2008). Study data were sourced from the National Ambulatory Medical Care Survey for the time frames 1992-1997, and 2003-2004. The study results demonstrated that from 1992-1993 to 2003-2004, the annualised rate of visits supporting a diagnosis of depression increased from 10.9 to 15.4 per 100 US population for whites, from 4.2 to 7.6 for blacks, and from 4.8 to 7.0 for Hispanics (Sclar *et al*., 2008). A concomitant diagnosis of depression and antidepressant use increased from 6.5 to 11.4 per 100 for whites, from 2.6 to 5.2 for blacks, and from 3.0 to 5.6 for Hispanics (Sclar *et al*., 2008). From the results it was concluded that by 2003-2004, diagnostic and treatment rates were comparable amongst blacks and Hispanics, but were less than half the observed rates for whites.

The prevalence of major depression was reported as approximately 8% in Canada and 7.5% in Australia, suggesting the use of antidepressants is common (Smith *et al*., 2008). A study published in 2008 aimed to compare the use of antidepressants in Nova Scotia, Canada and Australia. Dispensing data for all publicly subsidised antidepressants obtained from the Nova Scotia Pharmacare Program and the Pharmaceutical Benefits Scheme in Australia was used (Smith *et al*., 2008:697-706). Results suggest that the use of antidepressants increased in both areas, however, the increase in Nova Scotia was at a significantly higher rate than in Australia.

Additionally, SSRIs were the most commonly prescribed class at 60% in both areas (Smith *et al*., 2008:697-706).

A study conducted by Sonnenberg and co-workers (2008) investigated trends of antidepressant use in the older population (Sonnenberg *et al*., 2008). The data were sourced from the Longitudinal Aging Study Amsterdam for the years 1992-2002 and the sample population was individuals aged 65-85 years. The results showed that antidepressant use increased from 2% to 6%, and in the group with MDD, treatment with antidepressants showed an increase from 15% to 30% (Sonnenberg *et al*., 2008:299-305). Furthermore, the increase was found to be mainly due to a rise in SSRI-use.

A study completed in 2011 aimed to compare antidepressant utilisation patterns and mortality in relation to antidepressant use in men and women aged 20-34 years in Sweden (Andersson Sundell *et al*., 2011). The data for the study was sourced from the Swedish Prescribed Drug Register. The study results displayed that the one-year prevalence of antidepressant use was 5.6% among all Swedes aged 20-34 years (n=94 239) and was higher among females than males (7.2% *versus* 4.0%, p< 0.001) (Andersson Sundell *et al*., 2011:169-178). SSRIs were the most common class of antidepressants at baseline and were more common amongst females than males (78.7 *versus* 71.7%, p<0.001). The study concluded that with a ratio of 2:1, Swedish females to males aged 20-34 years who acquired antidepressants in 2006 showed high discontinuation rates, suggesting that healthcare professionals and patients need to acquire an increased awareness on attitudes towards treatment (Andersson Sundell *et al*., 2011:169-178).

A study by Bae and co-workers (Bae *et al*., 2011) aimed to investigate antidepressant prescribing patterns, including initial choice, switching and combining, and concomitant use of non-antidepressant agents, for depressive disorders in clinical care settings in Korea. The patient sample comprised of patients with depressive disorder who were recruited from both outpatient and inpatient settings from 18 Korean hospitals. From the results, SSRIs were the most commonly prescribed initial antidepressant (48.9%), followed by newer dual-action antidepressants (45.8%) (Bae *et al*., 2011:234-244).

A study published in 2012 investigated trends in antidepressant utilisation in Taiwan between the years 2000-2009 (Wu *et al*., 2012). The data were sourced from the National Health Insurance Research Database of antidepressant use. The study results showed that the prevalence of antidepressant use per 1000 persons increased from 32.1 in 2000 to 46.3 in 2009 (Wu *et al*., 2012: 980-988). Regarding antidepressant classes, the prescriptions of SSRIs and other newer drugs increased. However, the use of TCAs, trazodone and MAOIs declined. Results suggest that there was an increasing trend of antidepressant use for sleep and adjustment disorders (e.g. adjustment disorder with depressed mood, or adjustment disorder with anxiety), but the rates of antidepressant use for mood disorder, anxiety disorders and other non-psychiatric conditions decreased (Wu *et al*., 2012:980-988).

A study analysed antidepressant use and off-label prescribing in children and adolescents in Germany by using results from a large population-based cohort study (Dörks *et al*., 2013). The study design was a retrospective study including cross-sectional analyses. The patient sample comprised of a large number of 2 599 685 patients up to 17-years of age (Dörks *et al*., 2013:511-518). In Germany, the use of SSRIs and other antidepressants is not licensed for the treatment of depressive disorders in children and adolescents, except for fluoxetine, which was approved in 2006. The study results revealed that from all prescribed antidepressants, 42.09% were tricyclic antidepressants, 34.58% were SSRIs, 16.47% were St John's Wort preparations and 6.86% were other antidepressants (Dörks *et al*., 2013:511-518). Approximately half of the patient sample who were treated with antidepressants were diagnosed with depressive disorders at 56.30%. Overall, 49.11% of all antidepressants were prescribed off-label (Dörks *et al*., 2013:511-518).

2.5 Chapter 2 summary

This concludes the literature review chapter. A comprehensive literature search was completed to acquire relevant information pertaining to the objectives of the literature study. This chapter provided a detailed overview of venlafaxine (history, pharmacological and toxicological properties); a brief overview of the disorders treated with venlafaxine (major depressive disorder, anxiety-related disorders and panic disorder); a summary of drug utilisation reviews (what drug utilisation reviews are and their use to assess the prescribing patterns and management of medication); as well

as drug utilisation reviews on antidepressants in general and specifically on venlafaxine (in the public and private sectors, locally and internationally). In the following chapter, a comprehensive description of the research methodology that was employed in this study will be described.

CHAPTER 3.
RESEARCH METHODOLOGY

3.1 Introduction

This chapter elucidates the methodology utilised to conduct the empirical study. The primary focus of this study was to retrospectively evaluate the prescribing and management practices of venlafaxine for patients who were on treatment with venlafaxine at a public sector psychiatric hospital.

The research methods utilised to achieve the study objectives are described in the following sections: Study design; study setting; study population; data source; development of the data collection tool; data collection process; statistical analysis, ethical considerations as well as limitations of the research method.

3.2 Study design

For the empirical study, a retrospective drug utilisation review was completed. This DUR implemented a cross-sectional research approach. Cross-sectional data provides a description of drug usage during a particular time frame, e.g. over a year which is valuable for comparative purposes (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services, 2003:17). Drug utilisation research can be separated into descriptive or analytical studies. The current DUR study utilised a combined descriptive and analytical approach to analyse the data. The emphasis of descriptive studies is to describe patterns of drug utilisation and to detect any problems in drug prescribing whereas analytical studies try to link data from DUR studies with the ultimate goal of assessing whether drug therapy is rational or not (WHO Collaborating Centre for Drug Statistics Methodology and WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services, 2003). A retrospective DUR utilises data that was previously recorded. In the current study, patient files were assessed. The retrospective data on venlafaxine was collected from the patient files and recorded onto a structured data collection form.

3.3 Study setting

The study was conducted at Fort England Hospital in Grahamstown (the name was recently changed to Makhanda by the Honourable Minister of Arts and Culture, Mr Nathi Mthethwa), Makana local municipality, Cacadu district municipality, Eastern

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

As part of their outreach programme, specialised medicine is sent from Fort England Hospital Pharmacy to four surrounding hospitals in the district (Table 3–1). The following list provides the names of hospitals to which patients in the study sample at Fort England Hospital were discharged or down referred to:

Table 3–1. Names of hospitals/clinics to which patients in the study sample were discharged or down referred to.

NAME OF HOSPITAL	NAME OF TOWN
Fort Beaufort Hospital (Provincial)	Fort Beaufort
Victoria Hospital (Provincial)	Alice
Adelaide Provincial Hospital	Adelaide
Settlers Day Hospital	Grahamstown (Makhanda)

The Makana Municipality is located in the Eastern Cape Province on the south-eastern seaboard of South Africa and in the western part of the Eastern Cape Province, falling under the Cacadu District Municipality. Makana (also spelt Makanda by his descendants) is most noted as the Xhosa warrior and prophet who led a massive attack against the British garrison at Grahamstown in 1819 (“Makana Municipality,” 2013). Makana Municipality is strategically situated between two of the province’s largest industrial centres, with the cities of Port Elizabeth 120km to the west and East London 180 km to the east. Apart from its natural, historical and cultural attractions, Makana is the home of the National Arts Festival and the seat of Rhodes University as well as other prominent and internationally acclaimed primary and high schools which are found in Grahamstown.

The City of Grahamstown together with the nearby towns of Alicedale and Riebeeck East and the quaint villages of Fort Brown, Salem, Seven Fountains and Sidbury comprise the Makana Municipality in the Eastern Cape, South Africa (Local Government Business Network, 2013).

The Cacadu District is the largest (58 243 km²) of the six districts in the Eastern Cape Province of South Africa, covers 34% of the entire Eastern Cape Province's geographical footprint, is situated in the western portion of the Eastern Cape and wholly surrounds Nelson Mandela Bay (Local Government Business Network, 2013). The Cacadu District Municipality focuses on creating projects to grow skills, employment and initiate sustainable economic development as well as elevating the quality of life in the District.

The Eastern Cape is South Africa's second largest province following the Northern Cape. The capital of the province is Bhisho (Integrated marketing, 2015). The majority of the Eastern Cape's population is black, and they are predominantly speakers of isiXhosa, a Nguni language. This province is one of natural beauty and diversity unmatched in another province (Integrated marketing, 2015).

3.4 Study population

This study was targeted at both male and female patients who were older than 18-years of age, who were diagnosed at any time with a depressive disorder and who were on treatment with venlafaxine at the outpatient clinic of Fort England hospital for the period 1 January 2017-31 December 2017. A total number of 85 patients were identified and included in the study sample.

3.5 Data source

The main data source for the current study was the patient files of patients who attended the study location during the period covered. A retrospective approach was followed for data collection. The patient file is a rich source of data. However, it is imperative that patient files be checked for accuracy, completeness and consistency. Data were recorded only once for each patient and a 12-month period was chosen to get a snapshot of the prescribing practices of venlafaxine and management of patients on venlafaxine treatment throughout one year. In addition, it provided sufficient patient numbers and rich data for the study. Data from patients who discontinued venlafaxine treatment during the period was also collected, as this could perhaps be due to adverse effects and therefore may contribute important information towards the pharmacovigilance component of this study.

All information acquired in the patient files were assessed, which included: Prescriptions, treatment summaries, clinical notes (doctor's, nurse's and other healthcare worker's) and laboratory test results. This information provided the researcher with a comprehensive treatment and monitoring history of the patient.

3.6 Data collection tool

The data collection tool was a data collection form designed to record relevant patient data sourced from the patient files.

3.6.1 Validity and reliability of research instruments

Validity and reliability are concerned with how specific measurements or indicators for the current study were developed since it may influence the conclusion based on the results.

The validity of the data collection tool is a measure of the accuracy of the tool used to collect the data (Bolarinwa, 2015). In this study, only content and face validity were applied. In face validity, the data collection tool was evaluated to determine whether it will be measuring what it is supposed to be measuring. Content validity was used to determine how well the data collection tool represents all the components of the variables to be measured and to ensure that it meets the study objectives.

Reliability is used to determine to what level the instrument can be depended on to provide consistent results if the study will be repeated (Bolarinwa, 2015). Reliability of the data were ensured as only the researcher made use of the data collection tool to minimise possible mistakes. The data collection tool was in the form of hard copies that was easy to complete and the data were captured afterwards on an electronic spreadsheet.

A pilot study was conducted to test the validity and reliability of the data collection tool designed for data collection process of the study. A comparison of information recorded on the data collection tool and the data source (patient files) exhibited that the data collection tool was an accurate and reliable method of data representation.

3.6.2 Pilot study

A pilot study was initially conducted at the study site by using five patient files that were randomly selected from the study population list. The pilot study served as a validity and reliability test for the data collection tool. The aim of the pilot study was to test the practical workability of the draft data collection form (ANNEXURE A) and the objective was to streamline it, making it user friendly and efficient for the data collection process. The revised data collection form (ANNEXURE B) was thereafter employed in the study.

3.6.3 Structure of data collection form

The data collection form was designed to record patient demographic data, social and medical circumstances, as well as important parameters to assess the monitoring of patients on venlafaxine treatment. Data were numerically coded. The specific criteria required to analyse the prescribing and management practices of venlafaxine are further discussed.

3.6.4 Patient subjective information

Patient Identification Number

To maintain patient confidentiality, each patient file identified for the study population list was assigned a distinctive number, i.e. from 1 to 85.

Age

The age of each patient was obtained from the patient file. In some files the age was calculated using the date of birth. The patients were classified and grouped according to their ages. The age groups were divided into the five main categories namely A, B, C, D and E to compare venlafaxine use between each major age group to assist in the data analysis process.

The age groups were classified and coded as follows (Table 3–2):

Table 3–2. Coding of age categories.

Group	Age (Years)	Code
Teenagers	< 20	0
Adults	≥ 20 and < 35	1
Middle aged adults	≥ 35 and < 50	2
Mature adults	≥ 50 and < 65	3
Elderly	≥ 65	4

It was considered important to include the age category of the patients, with emphasis placed on the elderly. This is due to the clearance rates being reduced in elderly patients, therefore requiring dose adjustments (Celikyurt *et al*., 2012:96). When treating the elderly, caution should be exercised, dose individualisation may be necessary and additional care must be taken when increasing the dose. Data regarding age was also important to ensure that the study sample excluded patients younger than 18-years old.

Gender

Information regarding the gender of each patient was obtained from the patient file. To assist with the data analysis of the spreadsheet, the two gender options available on the data collection form were given the following codes (Table 3–3):

Table 3–3. Coding of gender categories.

Gender	Code
Female	0
Male	1

The gender of the patient sample was an important demographic to record and analyse. The results from a South African Stress and Health study revealed that the female gender was associated with significantly higher odds of any mood and any anxiety disorder, but with significantly lower odds of any substance use disorder (Seedat *et al*., 2009:381). A comparison was therefore made with the results of the current study.

Weight, Height and Body Mass Index

Where the information was available, each patient's weight and height were recorded to calculate the BMI.

The following is the WHO's recommended body weight based on BMI values for adults (Table 3–4). It is used for both men and women, age 18-years or older (Maple Tech International, 2008):

Table 3–4. Coding of body weight categories.

Category	BMI Range (kg/m^2)	Code
Severe thinness	< 16	0
Moderate thinness	≥ 16 < 17	1
Mild thinness	≥ 17 < 18.5	2
Normal	≥ 18.5 < 25	3
Overweight	≥ 25 < 30	4
Obese class I	≥ 30 < 35	5
Obese class II	≥ 35 < 40	6
Obese class III	> 40	7
Unable to calculate	-	8

One of the monitoring requirements for venlafaxine is that the patient's weight should be regularly monitored (Wyeth Pharmaceuticals, 2003). A BMI < 25 kg/m^2 is ideal and should be maintained (National Department of Health, 2015:3.29).

Ethnicities

Information concerning each patient's race was coded as follows (Table 3–5):

Table 3–5. Coding of patient ethnicities.

Race	Code
White	0
African	1
Coloured	2
Indian	3
Other	4

Results from the South African Stress and Health study suggest that blacks and Indians were more likely than coloureds or whites to endorse greater exposure to global negative life events, social demands and economic stresses (Seedat *et al*., 2009:377).

Marital Status

Where the information was available, each patient's marital status was recorded to assess whether the patient's marital status was related to or influenced the diagnosis. The marital status options were coded as follows (Table 3–6):

Table 3–6. Coding of marital status.

Marital Status	Code
Single	0
Married	1
Unmarried	2
Divorced	3
Other	4
No data available	5

The marital status of the patient sample was an important demographic to record. Results from the South African Stress and Health study revealed that the marital status (separated, divorced, widowed, never married) is the only socio-demographic correlate of any 12-month or any lifetime disorder, consistent with other general population surveys (Seedat *et al*., 2009:380).

Pregnancy and Breastfeeding Status

Where the information was available in the files of female patients, the pregnancy and breastfeeding status was recorded. This information was important to obtain because when neonates are exposed to venlafaxine late in the third trimester, they develop complications which require hospitalisation, tube feeding and respiratory support (Wyeth Pharmaceuticals, 2003:43). These complications are considered dreadful and should be prevented. The following options were available on the data collection form and coded as follows (Table 3–7):

Table 3–7. Coding of pregnancy/breastfeeding status.

Pregnancy/Breast Feeding Status	Code
No	0
Yes	1
Not applicable	2

Tobacco Use

Information concerning each patient's tobacco use was important to record, especially to assess if tobacco use may have influenced their condition. A study discovered that the steady-state plasma concentration-to-dose ratio of desvenlafaxine (active metabolite) in patients who smoked was significantly lower than that in non-smoker patients (Oliveira *et al*., 2017). The following options were available on the data collection form and coded as follows (Table 3–8):

Table 3–8. Coding of tobacco use.

Tobacco Use	Code
No	0
Yes	1

Alcohol Use

Information concerning each patient's alcohol use was essential to record, especially to ascertain whether alcohol abuse may have influenced their condition. Sedation is one of the common adverse effects of venlafaxine which is potentiated by alcohol (Rossiter *et al*., 2016:503). Therefore, alcohol consumption should be discouraged during venlafaxine treatment. The following options were available on the data collection form and coded as follows (Table 3–9):

Table 3–9. Coding of alcohol use.

Alcohol Use	Code
No	0
Yes	1

A meta-analysis of depression and substance use amongst individuals with alcohol use disorders (AUDs), discovered that high rates of depression are common amongst individuals with AUDs, particularly alcohol dependence (Conner *et al*., 2009).

Substance/Drug Abuse

Information concerning each patient's substance/drug abuse was recorded because it is vital to know whether the use of such substances may have influenced their condition or the venlafaxine therapy as the substance could have an unwanted or potentially harmful interaction with venlafaxine. The following options were available on the data collection form and coded as follows (Table 3–10):

Table 3–10. Coding of substance/drug abuse.

Substance/Drug Abuse	Code
No	0
Yes	1

The results from a study which conducted a meta-analysis of depression and substance use amongst individuals supported the hypothesis of a positive association of depression and concurrent alcohol use and impairment as well as general drug use and impairment (Conner *et al*., 2009).

If the answer was "yes", a space was provided on the data collection form to record details of the substance/drug abuse. The information was grouped and were coded as follows (Table 3–11) to assist in the data analysis process:

Table 3–11. Coding of names of substances.

Name of Substance/Drug	Code
Cannabis (Dagga)	0
Codeine	1
Benzodiazepines	2
No data	3

Suicide Risk

There has been concern that antidepressants may exacerbate depression or result in the development of suicidality or suicidal idealisation in some patients (Cipla Medpro, 2006:1; Wyeth Pharmaceuticals, 2003:9). It was therefore important to obtain information concerning each patient's suicide risk to assess whether it may have been related to their venlafaxine therapy or not. In women, the risk for suicide attempts is higher, however, features associated with an increased risk for completed suicide include male gender, being single or living alone and having prominent feelings of worthlessness (American Psychiatric Association, 2013:167). The following options were available on the data collection form and coded as follows (Table 3–12):

Table 3–12. Coding of suicide risk.

Suicide Risk	Code
No	0
Yes	1
No data available	2

Social History

Information concerning each patient's social history included living conditions, education and employment status. This was documented to evaluate the patient's lifestyle and any changes that may have occurred due to venlafaxine, use as well as to assess whether the patient's social history influenced the patient's diagnosis or *vice versa*.

A study which aimed to analyse the relationship between employment status, anxiety and depression in a municipal context demonstrated that the prevalence of anxiety and depression was higher among those who were out of the labour market as compared to those who were employed (Hiswåls *et al*., 2017). In addition, people who were unemployed had a higher risk of anxiety and depression. A second study suggests that unemployment and disability rates in MDD are high, due to the presence of anhedonia. Medical co-morbidity significantly influenced the work status, emphasising the need for treatment strategies to alleviate the additional symptom burden in this subpopulation (Rizvi *et al*., 2015).

A space was provided on the data collection form to record the details of each patient's employment status. The information was grouped and coded as follows (Table 3–13):

Table 3–13. Coding of employment status.

Employment Status	Code
Employed	0
Unemployed	1
Unemployed – student	2
Unemployed – pension	3
Unemployed – disability grant	4
Other	5
No data available	6

Education

The highest level of education of the patient sample was an important piece of information to record. The results from a South African Stress and Health study discovered that, lower educational attainment was predictive of mood disorders but not other mental disorders (Seedat *et al*., 2009:379). This finding supports a study across three provinces in South Africa that found lower educational attainment, among other social and economic correlates, to predict depression scores in the general population (Seedat *et al*., 2009:381). Information on the data collection form was coded as follows (Table 3–14):

Table 3–14. Coding of highest level of education.

Highest Level of Education	Code
Undergraduate degree	0
Diploma/course	1
Grade 12	2
Grade 10/11	3
Other	4
No data available	5

Caregiver Support

Information concerning each patient's caregiver support was recorded to note if the patient did have family or some form of caregiver support, which is essential for patients presenting with psychiatric and mood disorders. The following options were available on the data collection form and coded as follows (Table 3–15):

Table 3–15. Coding of caregiver support.

Caregiver Support	Code
No	0
Yes	1
No data available	2

Medical Aid

The following information was obtained and were coded as follows (Table 3–15):

Table 3–16. Coding of medical aid.

Medical Aid	Code
No	0
Yes	1
No data available	2

Hospital History

Information concerning each patient's hospital history was obtained and coded on the data collection form as follows (Table 3–17):

Table 3–17. Coding of the number of previous hospital admissions.

Number of Previous admissions	Code
No previous admissions	0
One previous admission	1
Two previous admissions	2
More than two previous admissions	3
No data available	4

Family History of Psychiatric Illnesses

Information concerning each patient's family medical history was recorded to provide the researcher with more details of the family history of medical conditions, especially regarding genetic conditions that may be hereditary. The following options were available on the data collection form and coded as follows (Table 3–18):

Table 3–18. Coding of the patients' family history of psychiatric illness.

Family History of Psychiatric Illness	Code
No	0
Yes	1
Family history of psychiatric illness and other medical illnesses	1, 2
Other	2
No data available	3

Past/Current Co-morbid Diseases

Information concerning each patient's past/current co-morbid diseases was recorded to provide the researcher with more details of the patient's history of medical conditions. The following options were available and coded on the data collection form (Table 3–19). These were chosen specifically relating to the common adverse effects of venlafaxine (Rossiter *et al*., 2016:503):

Table 3–19. Coding of the patients' past/current co-morbid disorders.

Past/Current Co-morbid Diseases	Code
Hypertension	0
Hypertension & hypercholesterolaemia & other	0, 2, 5
Hypertension & diabetes	0, 3
Hypertension & diabetes & other	0, 3, 5
Hypertension & other	0, 5
Cardiovascular disease	1
Hypercholesterolaemia	2
Hypercholesterolaemia & diabetes & other	2, 3, 5
Hypercholesterolaemia & other	2, 5
Diabetes & other	3, 5
Glaucoma	4
Other	5
None	6

3.6.5 Patient objective information

Diagnosis

Information concerning each patient's diagnosis was documented to provide the researcher with details of the patient's current medical conditions. The following options were available on the data collection form. These were chosen according to the approved indications of venlafaxine and were coded as follows (Table 3–20):

Table 3–20. Coding of patients' diagnosis.

Diagnosis	Code
Major depressive disorder	0
Major depressive disorder & generalised anxiety disorder	0, 1
Major depressive disorder & panic disorder	0, 2
Major depressive disorder & social anxiety disorder	0, 3
Major depressive disorder & other	0, 4
Major depressive disorder & generalised anxiety disorder & panic disorder	0, 1, 2
Major depressive disorder & generalised anxiety disorder & social anxiety disorder	0, 1, 3
Major depressive disorder & generalised anxiety disorder & social anxiety disorder & other	0, 1, 3, 4
Major depressive disorder & generalised anxiety disorder & other	0, 1, 4
Generalised anxiety disorder	1
Generalised anxiety disorder & social anxiety disorder	1, 3
Generalised anxiety disorder & other	1, 4
Generalised anxiety disorder & social anxiety disorder & other	1, 3, 4
Panic disorder	2
Social anxiety disorder	3
Other	4

Concomitant Drug Use

Information concerning each patient's current medication was beneficial in identifying any possible drug-drug interactions that were present and may not have been acknowledged. The use of concomitant drugs was analysed and the most commonly prescribed drugs were identified. The information obtained was summarised, the following options were available on the data collection form and coded as follows (Table 3–21):

Table 3–21. Coding of the patients' most frequently prescribed concomitant drug.

Most Frequently Prescribed Concomitant Drug	Code
Quetiapine	0
Quetiapine & levothyroxine	0, 4
Quetiapine & levothyroxine & lorazepam	0, 4, 8
Quetiapine & lorazepam	0, 8
Levothyroxine	4
Levothyroxine & lorazepam	4, 8
Lorazepam	8
None	

Contraceptive Use

This sub-section aimed to extract information concerning each female patient's contraceptive use or lack thereof, as well as a possible reason for not using a contraceptive. This is important to note, as venlafaxine is a category C risk drug for birth abnormalities. Therefore, if the patient is of a child-bearing age they should be administered a contraceptive (Rossiter *et al*., 2016:503). It was also imperative to ensure that the patient was on the correct contraceptive that will not interact with their other medication. The following options were available on the data collection form and coded as follows (Table 3–22):

Table 3–22. Coding of patients' contraceptive use.

Contraceptive Use	Code
No	0
Yes	1
No data available	2
Not applicable	3

If "Yes" was recorded, a space was provided on the data collection form to record details of the contraceptive used.

Presence of Drug Interactions

This sub-section was included to extract information concerning each patient's drug-drug interactions. Details regarding drug interactions that were identified for the patient were noted. This was completed to provide more information with regards to the patient's treatment plan. The following options were available on the data collection form and coded as follows (Table 3–23):

Table 3–23. Coding of drug interactions identified.

Drug Interactions Identified	Code
No	0
Yes	1
No data available	2

Information about Identified Drug Interactions

The information obtained regarding each patient's current medication were further analysed to determine the following and coded (Table 3–24):

- The number of interactions present.
- The names of the drugs that interact with venlafaxine.

Table 3–24. Coding of the number of drug interactions identified.

Number of Drug Interactions	Code
1	0
2	1
Not applicable	2

Drug-drug interactions were further classified as follows:

Drug Interaction 1 – the first drug interaction identified (Table 3–25):

Table 3–25. Coding of first drug interaction identified.

First Drug Interaction	Code
Lithium carbonate	0
Amitriptyline	1
Risperidone	2

Clomipramine	3
Bupropion	4
Fluoxetine	5
Olanzapine	6
Aspirin	7
Not applicable	8

Drug Interaction 2 – the second drug interaction identified (Table 3–26):

Table 3–26. Coding of second drug interaction identified.

Second Drug Interaction	Code
Clozapine	0
Olanzapine	1
Aspirin	2
Risperidone	3
Not applicable	4

Adverse Effects

The adverse effects sub-section was incorporated to attain information concerning the adverse effects experienced by the patient. Information received from the doctors' clinical notes regarding any adverse effects experienced by the patient was noted. This was completed to acquire more information with regards to the success of each patient's treatment plan. The following options were available on the data collection form. These were chosen based on common adverse effects experienced (Rossiter *et al*., 2016:503) and coded as follows (Table 3–27):

Table 3–27. Coding of the adverse effects experienced by patients.

Adverse Effects Experienced	Code
No	0
Yes	1
No data available	2

If "Yes" was recorded, a space was provided on the data collection form to record details of the adverse effects experienced and were coded (Table 3–28):

Table 3–28. Coding of the types of adverse effects experienced by patients.

Adverse Effects Experienced	Code
Nausea	0
Somnolence	1
Dry mouth	2
Dizziness	3
Dizziness & other	3, 8
Yawn	4
Sexual dysfunction	5
Insomnia	6
Insomnia & other	6, 8
Constipation	7
Other	8
No data available	9

Treatment of Adverse Effects

If available, information regarding whether the patient's adverse effects were treated was noted. This segment was included as a way for the researcher to observe if the monitoring and follow-up of the patient's treatment plan was efficient. The following options were available on the data collection form and coded as follows (Table 3–29):

Table 3–29. Coding of the adverse effects treated.

Adverse Effects Treated	Code
No	0
Yes	1
No data available	2
Not applicable	3

If the patient's response was recorded as "Yes", then a space was provided to specify how the adverse effect was treated. This was done to establish if the monitoring and follow-up procedures were effective.

The following sub-sections were included in the data collection form to obtain detailed information regarding each patient's venlafaxine and previous antidepressant treatment.

History of Venlafaxine Use

Information concerning each patient's history of venlafaxine use was completed to acquire whether the patient was on venlafaxine treatment previously. The following options were available on the data collection form and coded as follows (Table 3–30):

Table 3–30. Coding of the patients' history of venlafaxine use.

Previous Venlafaxine Use	Code
No	0
Yes	1
No data available	2

Duration of Venlafaxine Treatment

The date of the first initiation of venlafaxine was recorded on the data collection form and used to calculate the number of years/months since the first initiation of venlafaxine. Treatment guidelines suggest that antidepressants should generally be continued for 6-12 months in order for an adequate treatment response to occur and to prevent relapse. However, longer maintenance periods may be required if the patient has had multiple episodes (Rossiter *et al*., 2016:493). The following categories were used for the time calculation and coded as follows (Table 3–31):

Table 3–31. Coding of the number of years/months since the first initiation of venlafaxine.

Number of Years/Months since First Initiation of Venlafaxine	Code
< 6 months	0
≥ 6 months and < 1 year	1
≥ 1 year and < 5 year	2
≥ 5 years and < 10 years	3
≥ 10 years	4
No data available	5

History of Antidepressant Use

This sub-section was included to access information concerning each patient's history of antidepressant use, including the classes of antidepressants used previously if venlafaxine was not the first antidepressant used. The following options were available on the data collection form and coded as follows (Table 3–32):

Table 3–32. Coding of the history of venlafaxine use.

Venlafaxine use as First Antidepressant	Code
No	0
Yes	1
No data available	2

The classes of previously used antidepressants were recorded on the data collection form. This information was obtained from the past prescriptions and medication history available in each patient's file. The following options were available on the data collection form and coded as follows (Table 3–33):

Table 3–33. Coding of the previously used classes of antidepressants.

Classes of Antidepressants	Code
Selective serotonin reuptake inhibitor	0
Tricyclic antidepressant	1
Another selective noradrenaline reuptake inhibitor	2
Monoamine oxidase inhibitor	3
Other antidepressant	4
No data available	5
Not applicable	6

Trials of Previous Antidepressants Used before Venlafaxine Therapy was Initiated

The information acquired for the previous question was analysed to determine which antidepressants and how many were used by the patient in the past. The information obtained was categorised into one of the following categories and coded as follows (Table 3–34):

Table 3–34. Coding of the trials of previous antidepressants used.

Trials of Previous Antidepressants before Venlafaxine was Initiated	Code
One previous antidepressant prescribed	0
Two previous antidepressants prescribed from the same class	1
Two previous antidepressants prescribed from different classes	2
Three previous antidepressants prescribed from the same class	3
Three previous antidepressants prescribed from different classes	4
Other	5
No data available	6
Not applicable	7

Venlafaxine Doses and Dose Titration

This sub-section was included to obtain information about each patient's venlafaxine treatment and compliance with the recommended guidelines.

Compliance with the recommended guidelines for the initiation of venlafaxine

According to the SAMF and the SASOP Treatment Guidelines for Psychiatric Disorders, venlafaxine treatment should be initiated at 37.5 mg/day for 4-7 days, especially for new patients, to allow patients to adjust before increasing the dose to 75 mg/day (Cipla Medpro, 2006:1; Emsley *et al*., 2013:159-162; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:5).

Information regarding the initiation of dose and increments of dose titration was noted on the data collection form and coded as follows (Table 3–35):

Table 3–35. Coding of the dose titration performed.

Dose Titration Performed from Initiation of Venlafaxine Treatment	Code
No	0
Yes	1
No data available	2

In order to determine the initial dose used for the patient, the following options were available on the data collection form which were chosen according to the dosing instructions available for venlafaxine (Cipla Medpro, 2006:1; Emsley *et al*., 2013:159-

162; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:5) and coded as follows (Table 3–36):

Table 3–36. Coding of the initial dose of venlafaxine used.

Initial Dose Used	Code
37.5 mg/day for 4 to 7 days before increasing to 75 mg/day	0
75 mg/day	1
Other	2
No data available	3

Details regarding the specific increments of venlafaxine dose titration used were also noted in terms of date, dose and treatment duration. This was an important source of data to investigate the prescribing patterns of venlafaxine, including each patient's tolerance to venlafaxine. The information obtained was summarised and the duration of dose titrations were coded as follows (Table 3–37):

Table 3–37. Coding for the duration of dose titrations performed.

Duration of Dose Titrations	Code
Weekly	0
Weekly (once)	1
1-2 weekly	2
2 weekly	3
Monthly	4
Monthly (once)	5
None	6
No data available	7

Maintenance Dose Used

The information obtained was summarised and the maintenance dose used was coded as follows (Table 3–38):

Table 3–38. Coding of the maintenance dose used.

Maintenance Dose Used	Code
75 mg	0

150 mg	1
225 mg	2
300 mg	3
Other	4
No data	5

Information available in each patient's file was obtained to determine whether monitoring procedures were conducted according to recommended guidelines.

- Blood pressure, weight and heart rate monitoring are a few of the essential monitoring guidelines for patients on venlafaxine treatment (Rossiter *et al*., 2016:503).
- According to the SAMF patients on venlafaxine treatment require regular blood pressure monitoring, especially for regimens with doses above 200 mg/day (Rossiter *et al*., 2016:503).
- Acceptable blood pressure readings are systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg (National Department of Health, 2015:3.28).
- Venlafaxine treatment is associated with an approximate increase of 4 beats/minute in mean heart rate (Cipla Medpro, 2006:1).
- The patient's weight should be monitored regularly (Wyeth Pharmaceuticals, 2003:14). A BMI < 25 kg/m^2 should be maintained (National Department of Health, 2015:3.29).

Therefore, a table was included in the data collection form to record the regularity of blood pressure, weight and pulse rate monitoring completed for each patient as follows (Table 3–39):

Table 3–39. Monitoring parameters.

Parameter Measured			
Date	Blood Pressure (mm Hg)	Weight (kg)	Pulse Rate (Beats/min)

Blood Pressure Monitoring

A summary was made for each patient based on the frequency of blood pressure monitoring and coded as follows (Table 3–40):

Table 3–40. Coding for the frequency of blood pressure monitoring.

Frequency of Blood Pressure Monitoring	Code
Twice a month	0
Monthly	1
1-2 monthly	2
2-3 monthly	3
3 monthly	4
6 monthly	5
Other	6
No data available	7
Not applicable	8

The same approach and steps were taken for weight and pulse rate monitoring.

Where applicable, using the laboratory results it was determined whether the following parameters were regularly monitored and whether the results fell within normal ranges:

- Total cholesterol.
- Triglycerides.
- Low-density lipoprotein (LDL).
- High-density lipoprotein (HDL).

Total Cholesterol Monitoring

A summary was made for each patient based on the frequency of total cholesterol (including HDL and LDL) monitoring and coded as follows (Table 3–41):

Table 3–41. Coding for the frequency of total cholesterol monitoring.

Frequency of Total Cholesterol (Including HDL and LDL) Monitoring	Code
Three times a year	0
Annually (once a year)	1
No data available	2

Not applicable	3

The following values were considered during data analysis, for most healthy people normal cholesterol levels are as follows (The Heart and Stroke Foundation, 2017):

- Total cholesterol < 5 mmol/L.
- LDL cholesterol level < 3 mmol/L.
- HDL cholesterol levels > 1.2 mmol/L for women or 1.0 mmol/L for men.
- Fasting triglyceride levels < 1.7 mmol/L.

Patients diagnosed with diabetes, have kidney disease or who were overweight should have their cholesterol levels monitored frequently (The Heart and Stroke Foundation, 2017). If LDL cholesterol levels were high or the patient is at a high risk of heart disease, their cholesterol levels should be checked every six months.

3.6.6 Summary of study variables and measurements

The following study variables and study measurements were included in the data collection form (Table 3–42):

Table 3–42. A summary of the study variables (patient demographics and subjective information) and study measurements (patient objective information and monitoring procedures) that were included in the data collection form.

Patient Demographics	**Subjective Information**	**Objective Information**	**Monitoring Procedures**
Age	Pregnant status	Blood pressure	Venlafaxine dose and dose titration
Gender	Breastfeeding status	Pulse rate	Blood pressure
Weight	Marital status	Weight	Total cholesterol
Height	Suicide risk	Height	LDL
Race	Education	Diagnosis	HDL
	Tobacco, alcohol, substance abuse	Co-morbid disorders	
	Hospital history		

	Surgical history		

3.7 Data collection process

The data collection process explains when, where and how the data were collected.

3.7.1 Permission

Prior to the commencement of the data collection process, approval from the following places were obtained:

- Rhodes University Faculty of Pharmacy Ethics Committee.
- Research Committee at Fort England Hospital.
- Eastern Cape Provincial Health Research Committee.

3.7.2 Dates and places

Once permission was granted, data collection took place from 15 August 2018 to 21 September 2018. Data collection utilising the patient files occurred at the study site and specifically the hospital pharmacy during office hours on Wednesdays and Fridays, or as per prior arrangement with the pharmacy manager. A total of 85 patient files were identified according to the study criteria.

The data recorded on the data collection tools were captured on a comprehensive Excel spreadsheet using the programme Microsoft Office Excel® 2016. The Excel spreadsheet included columns/headings for every criterion investigated and recorded on the data collection tool. The data were captured from 05 October 2018 to the 20 November 2018.

3.7.3 Responsibilities of the researcher

The roles and responsibilities of the researcher were as follows:

- Only the researcher was involved in collecting and capturing the data to avoid any possible errors that may occur if more people were involved, thus ensuring reliability.
- The researcher assigned a unique study number to each filled data collection form to avoid potential duplication of information.

- The researcher recorded the relevant information from the patient files directly onto the data collection forms.
- The researcher thoroughly checked the collected data for accurateness and completeness before returning the patient files to the filing cabinets in the pharmacy.
- The researcher collated the hard copy data and captured it electronically on a Microsoft® Excel 2016 spreadsheet.

3.8 Data analysis

The data were arranged, analysed, summarised and presented (tables and graphs) using Microsoft® Excel and Statistical Analysis System® (SAS Institute Inc.). Data were analysed according to the specific objectives of the study.

Descriptive statistics were mostly employed to describe and summarise the data of the patient characteristics of the study sample. Frequency distributions, measures of central tendency (e.g. means), and standard deviations were calculated to summarise the data. Cross-tabulations were prepared and the row percentage and column percentage were calculated.

Comparisons were made using inferential statistics by performing the Pearson chi-square test and calculating Cramér's V-value. The *p*-value was calculated to determine statistical significance. The *p*-value of an analysis is calculated in order to determine whether a result is statistically significant (Rosner, 2011:210). Therefore, the *p*-value can be used as a measure of the strength of the information obtained, the *p*-value was considered significant if < 0.05 and highly significant if < 0.001.

The DDD of venlafaxine for the main indication it was prescribed for was tabulated according to the literature and the actual PDD of each patient was calculated and compared with the DDD. This was then compared with the international guidelines for the DDD.

Statistical concepts related to the current study are explained in more detail below.

3.8.1 Statistical terminologies

3.8.1.1 Descriptive statistics

3.8.1.1.1 Discrete values

Variables are discrete if the possible values that it can attain are distinguishable from each other (Rosner, 2011:72). For example, the gender of a patient was categorised as “0” for male and “1” for female. There were no values in-between.

3.8.1.1.2 Continuous values

In contrast to discrete values, the different possible values of continuous variables are indistinguishable (Rosner, 2011:72). For example, the body weights of patients were measured and there can be additional values in-between two possible values.

3.8.1.1.3 Frequency

Frequency (f) is defined as the number of times that a specific value is obtained for a specific variable in the study population (Rosner, 2011:22). For example, substance abuse can be categorised as discrete data in terms of alcohol, tobacco and drug abuse and the number of occurrences expressed as relative percentage frequencies. In cases of data on an ordinal scale, cumulative frequencies are useful to answer questions such as:

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

The relative frequency and relative frequency density can also be determined from the frequency by deciding on class intervals and the length of such intervals (Rosner, 2011:39). A histogram can graphically represent the relative frequency density by plotting the relative frequency density on the left y-axis, the frequency on the right y-axis and the class ranges on the x-axis. Another method is to construct a frequency polygon by plotting the relative frequency densities against class middle points. In both graphic representations, the surface area above an interval will give the approximate proportion observations in the data with values falling inside such an interval. A relative accumulative frequency polygon can be constructed by plotting the relative accumulative frequency against the class ranges.

3.8.1.1.4 Median

The median ($\tilde{x}$, if x is the variable) for discrete data is a number in the middle of observations arranged in ascending order (Rosner, 2011:16). It divides the observations into two equal sides, one side to the left and one side to the right of the median. For an uneven number of observations (n) the median is the middle value and can be calculated as $\frac{n+1}{2}$, whilst for an even number there are two middle values calculated from $\frac{n}{2}$ and $\frac{n}{2}+1$ and the median is taken as the value in-between. A relative accumulative frequency polygon can also be constructed, and the median determined from $\frac{n}{2}$ irrespective if the observations are even or uneven in number.

3.8.1.1.5 Average (arithmetic mean)

The average ($\bar{x}$, if x is the variable) is one of the best-known and popular statistics and is calculated by the sum of all the observations in the data set, divided by the total number of measurements (Rosner, 2011:17). The data set needs to be in the form of an interval- or ratio scale. The average is calculated with (Rosner, 2011:18):

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

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

3.8.1.1.6 Standard deviation

The standard deviation is the measure of the spread of the data that is most commonly used (Rosner, 2011:18). It attempts to give the average distance of the observations from their arithmetic mean and is calculated with:

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

3.8.1.2 Inferential statistics

3.8.1.2.1 Pearson chi-square test

The Pearson chi-square test (χ^2) determines whether there is an association between proportions of two or more categorical variables (Rosner, 2011:177).

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

3.8.1.2.2 Cramér's V statistic

Tests of statistical significance, such as the chi-square, determine whether a relationship exists between variables, however, they do not measure the strength of that relationship (Rea and Parker, 2014:217). The strength of a relationship between two or more variables is reflected by the measures of association. Cramér's V-value can be calculated directly from the calculated chi-square statistic (Rea and Parker, 2014:217). The value can be interpreted as follows (Table 3–43):

Table 3–43. Interpretation of the calculated Cramér's V-value (Rea and Parker, 2014:219).

Measure	Interpretation
0.00 and under 0.10	Negligible association
0.10 and under 0.20	Weak association
0.20 and under 0.40	Moderate association
0.40 and under 0.60	Relatively strong association
0.60 and under 0.80	Strong association
0.80 to 1.00	Very strong association

3.9 Ethical considerations

The research project made use of clinical data obtained retrospectively from patient files. There was no interaction with patients and the project was unobtrusive and non-invasive in nature. It was imperative for the researcher to conduct the study in an ethical sound manner during all phases of the study. This includes the conceptualisation, research and development phase, through the implementation and data collection phase, to the dissemination of the results phase.

3.9.1 Permission and informed consent

Permission to commence with the study was first obtained from the following institutions prior to the commencement of the data collection process:

- Rhodes University Faculty of Pharmacy Higher Degrees Committee. The final letter of approval is attached as ANNEXURE C.
- Rhodes University Faculty of Pharmacy Ethics Committee (PHARM-2018-05). The final letter of approval is attached as ANNEXURE D.
- Permission from the Research Committee at Fort England Hospital (PHARM-2018-05 continued). The final letter of approval is attached as ANNEXURE E.
- Permission from the Eastern Cape Department of Health Research Committee (EC_201808_010). The final letter of approval is attached as ANNEXURE F.

3.9.2 Anonymity and confidentiality

- Patient anonymity was maintained at all times because no patient names or identity was captured by the researcher. A unique number was allocated to each data collection form. The patient file number was not captured.
- Only the researcher collected and analysed the necessary data from the patient file and data were depersonalised.
- No information was disseminated, published or presented that could result in the identification of any patients.
- Only information pertaining to the objectives of the study was collected and it was impossible to determine which prescriber and pharmacist (name and contact details) were involved in the prescribing and dispensing of the medication.

3.9.3 Data management and storage

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

3.9.3.1 During data collection

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

3.9.3.2 After study completion

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

3.10 Chapter 3 summary

This concludes the methodology chapter. The research methodology employed to conduct the retrospective drug utilisation review was discussed in detail as well as background about the study site. The ethical considerations as well as patient confidentiality were extensively explained. The results of the study will be presented in the following chapter.

CHAPTER 4.
RESULTS AND DISCUSSION

4.1 Introduction

In this chapter the results of the empirical study are reported. The results were obtained from the data collection tool employed to evaluate the prescribing patterns and management practices of venlafaxine at Fort England Hospital.

Results expressed as percentages in tables were rounded off to two decimal places. Results displayed as percentages in the graphs were rounded off to the nearest integer.

4.2 Patient demographics

This set of results outlines the demographical properties of the study sample.

4.2.1 Age

The age groups were divided into the five main categories, namely A (< 20 years old), B (≥ 20 and < 35 years old), C (≥ 35 and < 50 years old), D (≥ 50 and < 65 years old) and E (≥ 65 years old) to compare venlafaxine use between each major age group.

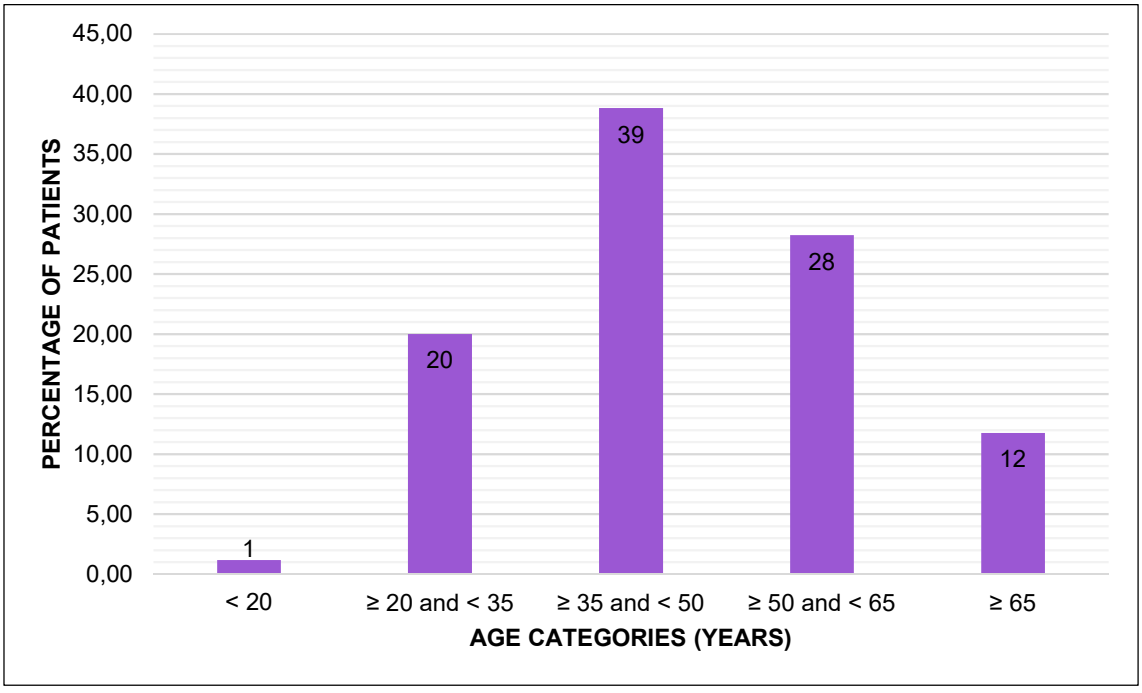

Figure 4–1. Age distribution according to age categories (n=85).

The analysis showed that there was only one patient in the age category A (teenagers) younger than 20-years. Most patients were in category C (middle aged adults)

between the ages of 35-50 years (n=33; 38.82%). This result is supported by the findings in the literature which suggests that MDD primarily occurs in the twenties and forties with a mean age of onset estimated around the age of 30 (American Psychiatric Association, 2013:165; Emsley *et al*., 2013:157).

The sample consisted of 10 elderly patients (65-years and older). Elderly patients should be carefully monitored due to the greater probability that clearance rates of venlafaxine may be reduced, therefore necessitating dose adjustments. In this instance, additional care must be taken concerning dose individualisation and when it may be necessary to increase the dose (Celikyurt *et al*., 2012:96).

Table 4–1. A summary of the age distribution (n=85).

Min Patient Age (Years)	Max Patient Age (Years)	Mean Age (Years)	Median (Years)	Standard Deviation (Years)
18 (n=1)	80 (n=2)	46.15	46	14.66

The mean age of the patient sample of 46.15 years was similar to the results from two DUR studies (Truter and Kotze, 2006, 1996) conducted in SA which suggested that 48.10 and 52.99 years were the mean ages of their patient samples receiving antidepressant treatment.

4.2.2 Gender

The following figure shows the results for the gender distribution of the study sample.

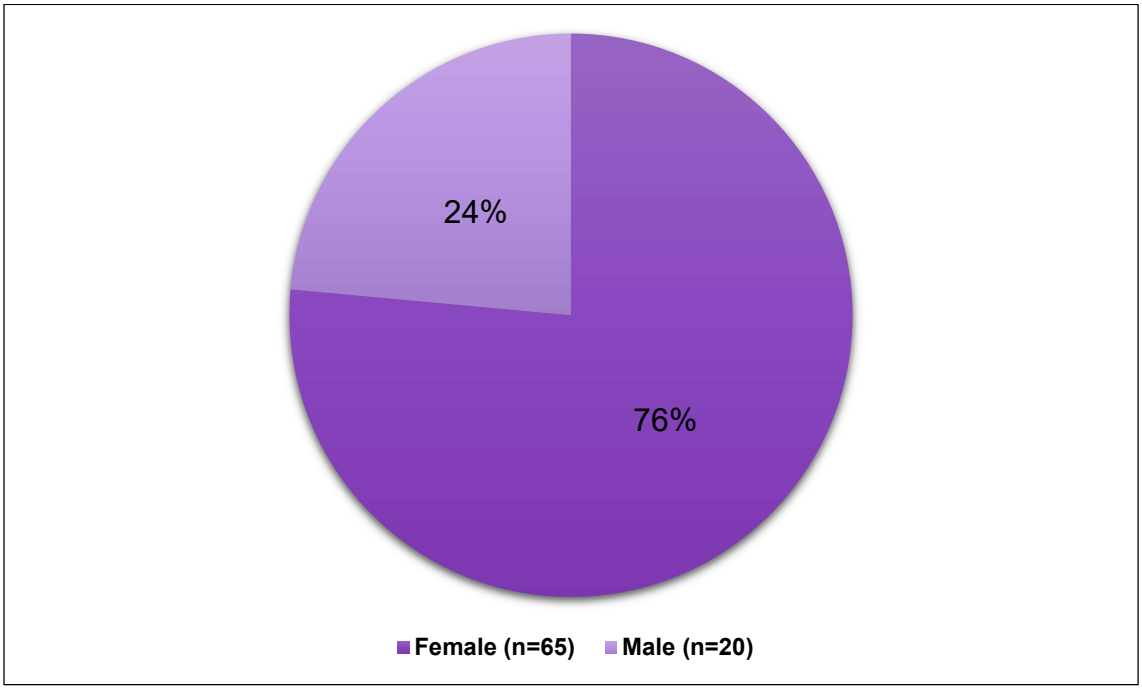

Figure 4–2. Gender distribution (n=85).

The results show that the majority of patients receiving treatment with venlafaxine were females (n=65; 24%).

The results of the current study correlate with the results from a South African Stress and Health study which demonstrated that the female gender was associated with significantly higher odds of any mood or anxiety disorder (Seedat *et al*., 2009:381). The DSM-5 also indicated that females experience 1.5 to 3-fold higher rates than males, emerging early in the adolescence (American Psychiatric Association, 2013:165).

From the DURs on antidepressants conducted in SA it was established that females were the gender with the most prescribed antidepressants, which is supported by the results of the current study (Burger *et al*., 2009; Kairuz *et al*., 2003; I Truter, 2010; Truter and Kotze, 2006, 1997, 1996; Van Schalkwyk and Truter, 2010).

4.2.3 Age by gender

The following table summarises the number and percentages of patients' age categories by gender.

Table 4–2. Age categories by gender (n=85).

	Gender		
Age Category (Years)	**Male n (%)**	**Female n (%)**	**TOTAL n (%)**
< 20	0 (0%)	1 (100%)	1 (100%)
≥ 20 and < 35	4 (23.53%)	13 (76.47%)	17 (100%)
≥ 35 and < 50	7 (21.21%)	26 (78.79%)	33 (100%)
≥ 50 and < 65	4 (16.67%)	20 (83.33%)	24 (100%)
≥ 65	5 (50%)	5 (50%)	10 (100%)
TOTAL	20 (100%)	65 (100%)	85 (100%)

The results show that most of the male (n=7; 35%) and female (n=26; 40%) patients were in the same age category of 35 to 50 years, suggesting that female patients between the ages 35 to 50 years were the majority of patients on venlafaxine treatment.

The statistical analysis performed with the chi-square test revealed that the association between age and gender in the patient sample that used venlafaxine was not statistically significant (p=0.2947)

4.2.4 Ethnic distribution

The patient sample consisted of various ethnic groups, of which one patient in the Other group was Asian (Chinese).

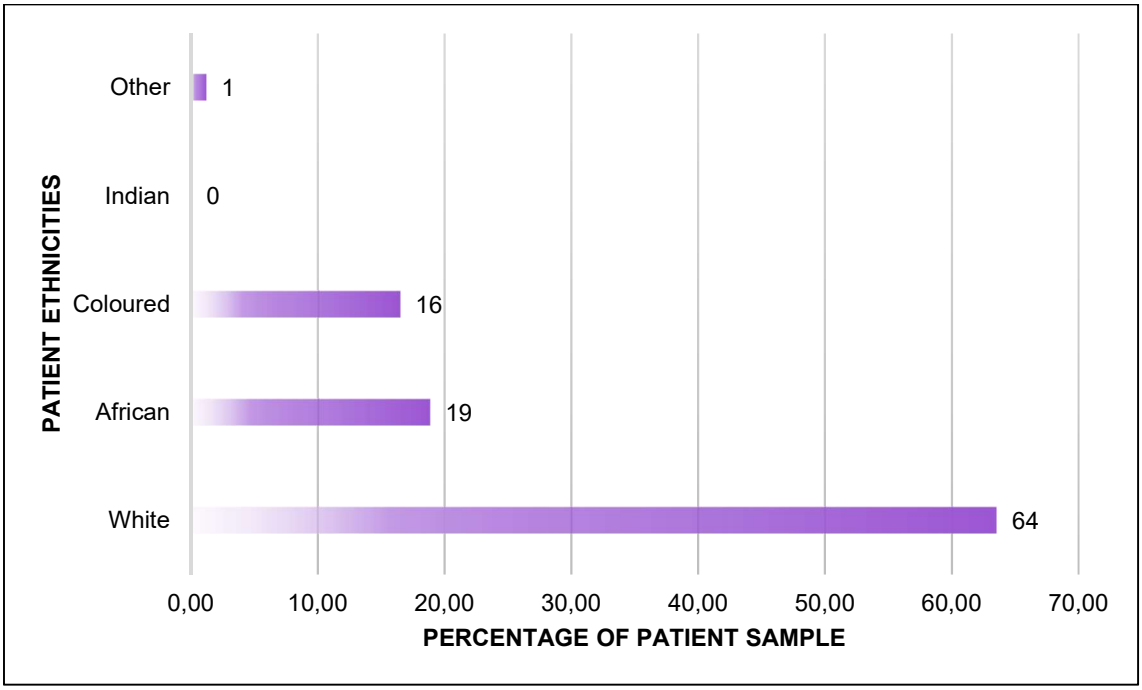

Figure 4–3. Percentage of patient ethnicities according to categories (n=85).

The results display that the majority of the patient sample were White (63.53%; n=54). There were no Indian patients in the patient sample.

The results from the SASH study suggested that Africans and Indians were more likely than coloureds or whites to endorse greater exposure to global negative life events, social demands and economic stresses implying that they would require medicinal treatment (Seedat *et al.*, 2009:377).

The demographic of our country which consists of 76.4% African, 9.1% white, 8.9% coloureds and 2.5% Indian individuals (Statistics South Africa, 2012) contrasts with the results of the current study where the majority of patients who received venlafaxine treatment were white (63.53%; n=54).

4.2.5 Age by ethnicity

The following table summarises the number and percentage of age categories by patients' ethnicities.

Table 4–3. Age categories by patient ethnicities (n=85).

Age category (Years)	Patient ethnicity				
	White n (%)	African n (%)	Coloured n (%)	Other n (%)	TOTAL n (%)
< 20	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
≥ 20 and < 35	8 (47.06%)	5 (29.41%)	3 (17.65%)	1 (5.88%)	17 (100%)
≥ 35 and < 50	17 (51.52%)	9 (27.27%)	7 (21.21%)	0 (0%)	33 (100%)
≥ 50 and < 65	19 (79.17%)	1 (4.16%)	4 (16.67%)	0 (0%)	24 (100%)
≥ 65	9 (90%)	1 (10%)	0 (0%)	0 (0%)	10 (100%)
TOTAL	54 (100%)	16 (100%)	14 (100%)	1 (100%)	85 (100%)

From the results it is evident that most White patients were in the age category 50 to 65 years (n=19; 35.19%) of age, most Coloured patients (n=7; 50.00%) were in the age category 35 to 50 years of age and African patients (n=9; 56.25%) were in the age group 35 to 50 years of age. The only patient in the Other patient ethnicity category was in the age group 20 to 35 years (n=1; 100%) of age. The results demonstrate that White patients between the ages 50 to 65 years were the majority of patients on venlafaxine treatment.

The statistical analysis performed with the chi-square test revealed that there is no statistically significant association between age and patient ethnicities in the patient sample that used venlafaxine (p=0.2106)

4.2.6 Ethnicity by gender

The following figure summarises the percentage of patients' ethnicities by gender.

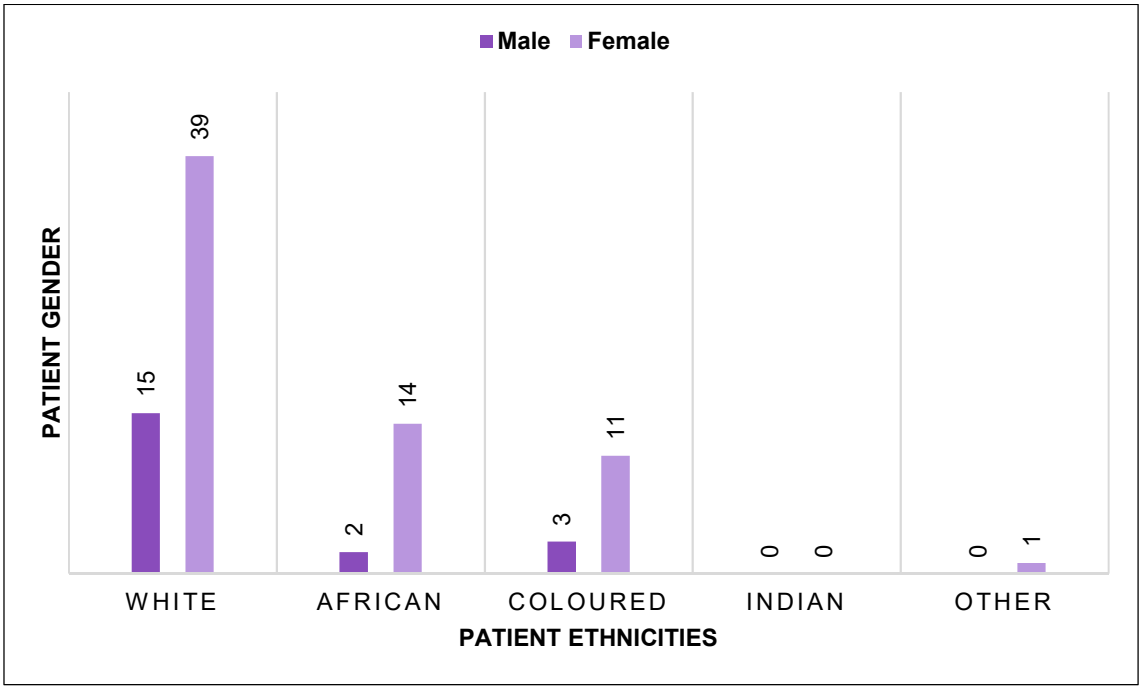

Figure 4–4. Percentage of patients' ethnicities by gender (n=85).

From the results it can be seen that for all the patient ethnicities, the female patients were greater than the male patients. There were no patients in the male category for other patient ethnicities. The results show that most female (n=39; 60%) and male (n=15; 75%) patients were in the same category of White ethnicity. From the results it is evident that white female patients were the majority on venlafaxine treatment.

The statistical analysis performed with the chi-square test revealed that the association between patient ethnicities and gender in the patient sample that used venlafaxine were not statistically significant (p=0.5796)

4.2.7 Weight categories

The following table summarises the number and percentage of patients' body weight according to the categories recommended by the World Health Organization (WHO).

Table 4–4. Body weight distribution (n=85).

Categories	BMI Range (kg/m^2)	n	%
Severe thinness	< 16	1	1.18
Moderate thinness	16-17	1	1.18
Mild thinness	17-18.5	1	1.18

Normal	18.5-25	16	18.82
Overweight	25-30	12	14.12
Obese class I	30-35	14	16.47
Obese class II	35-40	9	10.59
Obese class III	> 40	4	4.71
Unable to calculate	-	27	31.76
TOTAL		85	100.00

The average weight of the patient sample was 79.26 kg ± 23.57 kg. The analysis showed that the lightest patient in the sample was 42.30 kg and the heaviest patient was 129 kg.

Unfortunately, for some patients (n=27; 31.76%) the researcher was unable to calculate their Body Mass Index (BMI) due to the observation that height measurements were not recorded in the patient files. It is recommended by the South African National Department of Health that a BMI of < 25 kg/m^2 is ideal and should be maintained (National Department of Health, 2015:3.29). From the results it is evident that most patients were in the normal weight category with a BMI ranging from 18.5–25 kg/m^2 (n=16; 18.82%). The second highest weight category was the Obese Class I with a BMI range from 30-35 kg/m^2 (n=14; 16.47%), suggesting that lifestyle and dietary modifications may need to be implemented in this population.

4.2.8 Marital status

The following figure represents the results for the marital status for the patients in the study sample.

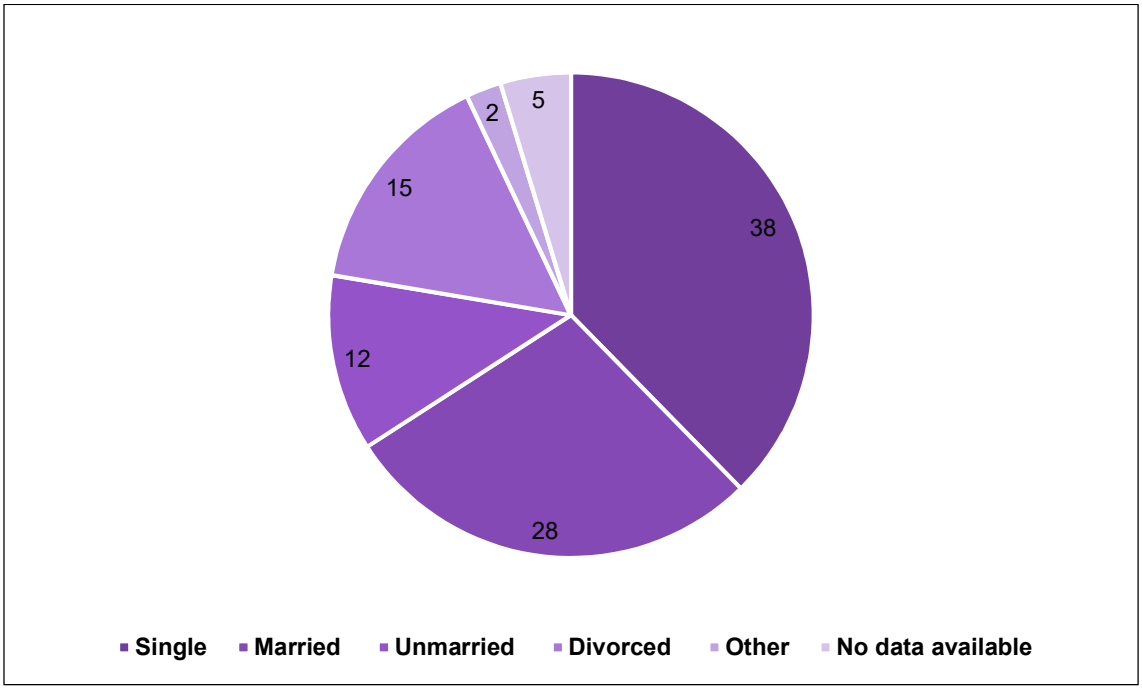

Figure 4–5. Marital status (n=85).

From the results it is evident that most patients included in the study were single. The Other category included patients who were separated or widowed.

4.2.9 Marital status by gender

The following figure summarises the number and percentage of patients' marital status by gender.

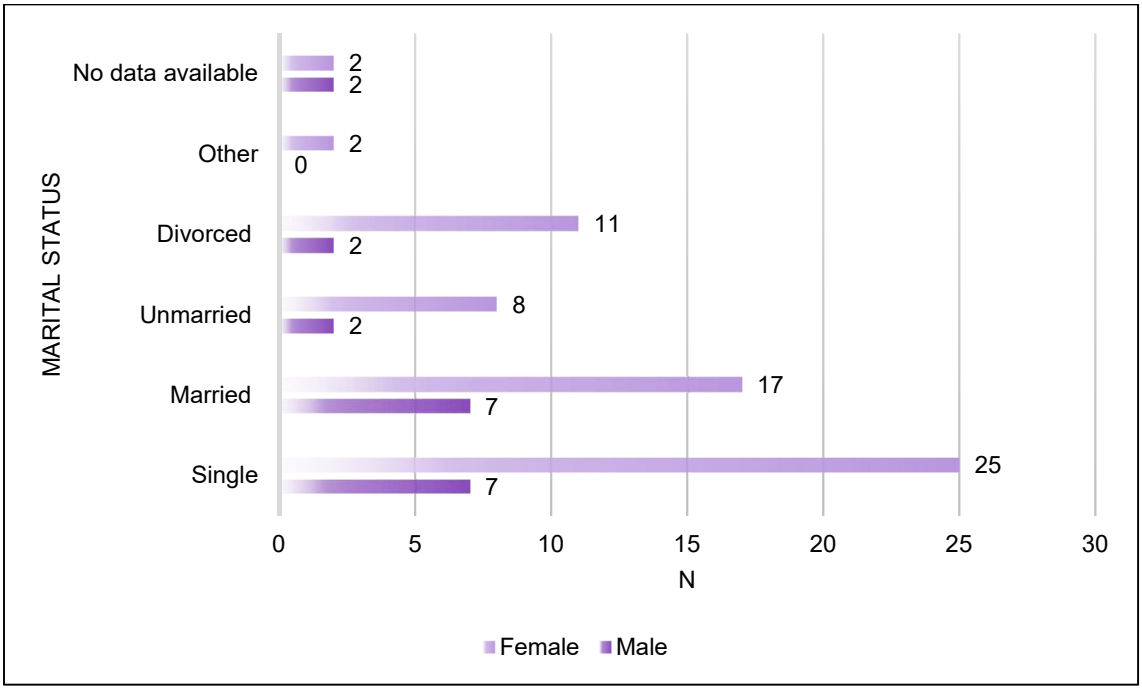

Figure 4–6. Numbers of patients' marital status by gender (n=85).

The results show that out of the female patients, single female patients were the majority of patients on venlafaxine treatment (n=25; 38.46%). This result is supported by the literature which suggests that the risk for suicide attempts is higher in women and being single is a feature associated with an increased risk for completed suicide (American Psychiatric Association, 2013:167).

The statistical analysis performed with the chi-square test revealed that there is no statistically significant association between marital status and patient gender in the patients that used venlafaxine (p=0.6701)

4.2.10 Pregnancy/breast feeding status

From the patient sample, males were not considered for this variable, therefore they were coded as not applicable (n=20, 23.53%).

Table 4–5. Pregnancy status (n=85).

Pregnancy/Breast Feeding Status	n	%
No	65	76.47
Yes	0	0.00
Not applicable	20	23.53
TOTAL	85	100.00

The results indicate that none of the patients included in the study sample were pregnant or breast feeding during the study period (n=65; 76.47%). This result is appropriate as venlafaxine therapy is contraindicated in pregnancy and lactation (Cipla Medpro, 2006:1; Kent, 2000:916; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:9).

According to the SAMF and US FDA, venlafaxine is classified as a category C risk factor in pregnancy which implies that venlafaxine should not be used unless the potential benefits outweigh the potential risk for the patient (Gutierrez *et al*., 2003:2148; Rossiter *et al*., 2016:503). When neonates are exposed to venlafaxine late in the third trimester, they develop complications which require hospitalisation, tube feeding and respiratory support (Wyeth Pharmaceuticals, 2003:43). These complications are dreadful and therefore venlafaxine use during pregnancy should be avoided or discussed with a doctor if is it necessary to continue treatment.

4.2.11 Tobacco use

The following table summarises the results for tobacco use of the patient sample.

Table 4–6. Tobacco use (n=85).

Tobacco Use	n	%
No	77	90.59
Yes	8	9.41
TOTAL	85	100.00

From the results it can be deduced that most of the patients did not use tobacco (n=77; 90.59%) during the study period. This was fortunate as it was established that the chemicals found in cigarettes reduces the concentration of antidepressant drugs in the

blood, thus resulting in a diminished antidepressant effect (Oliveira *et al*., 2017). Patients should be advised not to smoke while on venlafaxine therapy.

4.2.12 Alcohol use

The following table summarises the results for alcohol use of the patient sample.

Table 4–7. Alcohol use (n=85).

Alcohol Use	n	%
No	67	78.82
Yes	18	21.18
TOTAL	85	100.00

The results display that the majority of patients (n=67; 78.82%) did not use alcohol during the study period. Venlafaxine has an unwanted interaction with alcohol where the adverse effects experienced with venlafaxine therapy, e.g. sedation, is potentiated by the alcohol. Patients should be advised to take care when driving, or when operating machinery, especially during the first few weeks of venlafaxine therapy (Cipla Medpro, 2006:1; Leesette Turner, 2010:494; Rossiter *et al*., 2016:503). Additionally, alcohol consumption should be discouraged during venlafaxine treatment.

From a meta-analysis of depression and substance use amongst individuals with alcohol use disorders (AUDs), it was discovered that high rates of depression are common amongst individuals with AUDs, particularly alcohol dependence (Conner *et al*., 2009).

4.2.13 Substance abuse

The following table summarises the results for substance abuse of the patient sample.

Table 4–8. Substance abuse (n=85).

Substance/Drug Abuse	n	%
No	74	87.06
Yes	11	12.94
TOTAL	85	100.00

The results demonstrate that most of the patients did not abuse substances (n=74; 87.06%) during the study period.

However, it was of importance to classify what types of substances were abused by the remainder of the patients (n=11; 12.94%) as summarised in the following table. The results from a study which conducted a meta-analysis of depression and substance use amongst individuals supported the hypothesis of a positive association of depression and general drug use and impairment which is evident among the (n=11; 12.94%) patients who used substances (Conner *et al*., 2009).

Table 4–9. Types of substance abuse (n=11).

Name of Substance/Drug	n	%
Cannabis (Dagga)	6	54.55
Codeine	1	9.09
Benzodiazepines	3	27.27
No data	1	9.09
TOTAL	11	100.00

The results display that the majority of patients that did abuse substances during the study period (n=6; 54.55%) preferred cannabis (dagga).

4.2.14 Suicide risk

It was determined whether the patients in the sample size posed a suicide risk and the results are summarised in the following table.

Table 4–10. Patients with a suicide risk (n=85).

Suicide Risk	n	%
No	63	74.12
Yes	21	24.71
No data available	1	1.18
TOTAL	85	100.00

From the results it can be observed that the majority of patients in the sample size (n=63; 74.12%) did not pose a risk to commit suicide. However, there has been concern that venlafaxine may exacerbate depression or result in the development of

suicidality or suicidal idealisation in some patients therefore patients on venlafaxine therapy should be monitored for any signs of suicidality or suicidal idealisation especially during the first few weeks of therapy (Cipla Medpro, 2006:1; Wyeth Pharmaceuticals, 2003:9). To reduce the possibility of overdose, venlafaxine prescriptions should include the minimum effective dose consistent with good patient management (Cipla Medpro, 2006:1).

4.2.15 Employment status

The following table summarises the employment status of the patients in the study sample.

Table 4–11. Patient employment status (n=85).

Employment Status	n	%
Employed	28	32.94
Unemployed	15	17.65
Unemployed-student	8	9.41
Unemployed-pension	5	5.88
Unemployed-disability grant	5	5.88
Other	6	7.06
No data available	18	21.18
TOTAL	85	100.00

The results indicate that the majority of patients (n=28; 32.94%) in the sample size were employed. However, a summary of the results for unemployment status display that a bulk of the patient sample were unemployed (n=33; 38.82%) which correlated with the results of another study which aimed to analyse the association between employment status, anxiety and depression in a municipal context. The study demonstrated that the prevalence of anxiety and depression was higher among those who were out of the labour market as compared to those who were employed (Hiswåls *et al*., 2017).

4.2.16 Employment status by patient ethnicity

The following table summarises the number and percentage of patients' employment status by ethnicities.

Table 4–12. Patients' employment status by ethnicities (n=85).

Employment Status	Patient Ethnicities				
	White n (%)	African n (%)	Coloured n (%)	Other n (%)	TOTAL n (%)
Employed	15 (53.57%)	3 (10.71%)	9 (32.15%)	1 (3.57%)	28 (100%)
Unemployed	7 (46.67%)	5 (33.33%)	3 (20%)	0 (0%)	15 (100%)
Unemployed-student	4 (50%)	4 (50%)	0 (0%)	0 (0%)	8 (100%)
Unemployed-pension	4 (80%)	1 (20%)	0 (0%)	0 (0%)	5 (100%)
Unemployed-disability grant	3 (60%)	1 (20%)	1 (20%)	0 (0%)	5 (100%)
Other	5 (83.33%)	1 (16.67%)	0 (0%)	0 (0%)	6 (100%)
No data available	16 (88.89%)	1 (5.56%)	1 (5.56%)	0 (0%)	18 (100%)
TOTAL	54 (100%)	16 (100%)	14 (100%)	1 (100%)	85 (100%)

From the results it is can be seen that most White (n=15; 27.78%) and Coloured (n=9; 64.29%) patients were employed, whilst most African (n=5; 31.25%) patients were unemployed. The results demonstrate that white, employed patients were the majority of patients on venlafaxine treatment.

The statistical analysis performed with the chi-square test revealed that the association between employment status and patient ethnicities in the patients that used venlafaxine were not statistically significant (p=0.189)

4.2.17 Highest level of education

Unfortunately, almost half (n=41; 48.24%) of the patients in the sample size had no record concerning their highest level of education in their patient file. Results show that 20% (n=17) of the patients completed an undergraduate degree, 7.06% (n=6)

completed a diploma or other course, 11.76% (n=10) completed matric, 5.88% (n=5) completed grade 10 or 11 and 7.06% (n=6) completed some other form of education excluding the ones mentioned. Regarding education, the results from the SASH study found that lower educational attainment was predictive of mood disorders but not mental disorders (Seedat *et al*., 2009:379). However, in this study from the patients on venlafaxine therapy, almost 50% of the sample had completed some other form of education.

4.2.18 Caregiver support

The following table summarises the patients who received caregiver support.

Table 4–13. Patients who received caregiver support (n=85).

Caregiver Support	n	%
No	59	69.41
Yes	26	30.59
TOTAL	85	100.00

From the results it can be noted that most of the patients did have some form of caregiver support (n=59; 69.41%). It is important for patients on venlafaxine therapy or diagnosed with depressive disorders to have a good support system. It was established being single or living alone and having prominent feelings of worthlessness are features associated with an increased risk for completed suicide (American Psychiatric Association, 2013:167).

4.3 Patient past and current medical and drug use information

4.3.1 Medical aid

The patients' medical aid information was recorded as part of the required current medical information.

Table 4–14. Patients' medical aid information (n=85).

Medical Aid	n	%
No	31	36.47
Yes	9	10.59
No data available	45	52.94
TOTAL	85	100.00

The results display that 36.47% of the patients were not subscribed to a medical aid scheme (n=31). However, the majority (n=45; 52.94%) of patients did not have information about their medical aid recorded in the files.

4.3.2 Number of previous admissions

Information concerning the patients' hospital history was recorded as part of the required past and current medical and drug use information and summarised in the following figure

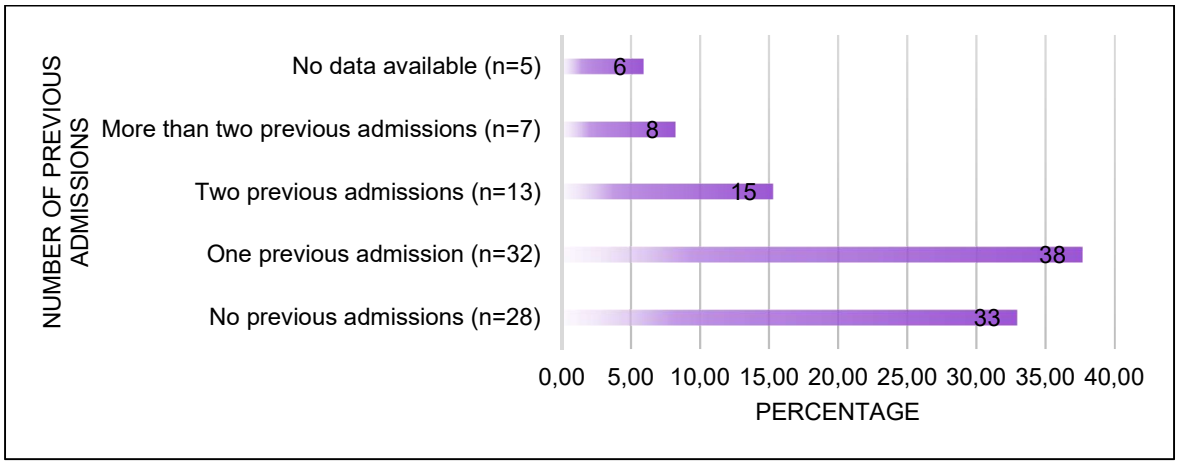

Figure 4–7. The hospital admission history of the patient sample (n=85).

From the results, it is evident that 32 patients (37.65%) had one previous hospital admission. 28 patients (32.94%) had one previous hospital admission which suggest that their current or previous diagnoses were not severe or life-threatening requiring hospital admission.

4.3.3 Number of previous admissions by age

The following table summarises the number and percentage of patients' number of previous admissions by age.

Table 4–15. Number of previous hospital admissions by age categories (n=85).

Number of Previous Admissions	Age Categories (Years)					
	< 20 n (%)	≥ 20 and < 35 n (%)	≥ 35 and < 50 n (%)	≥ 50 and < 65 n (%)	≥ 65 n (%)	TOTAL n (%)
No previous admissions	0 (0%)	7 (25%)	8 (28.57%)	9 (32.14%)	4 (14.29%)	28 (100%)
One previous admission	1 (3.13%)	7 (21.88%)	9 (28.13%)	10 (31.25%)	5 (15.62%)	32 (100%)
Two previous admissions	0 (0%)	3 (23.08%)	8 (61.54%)	2 (15.38%)	0 (0%)	13 (100%)
More than two previous admissions	0 (0%)	0 (0%)	5 (71.43%)	2 (28.57%)	0 (0%)	7 (100%)
No data available	0 (0%)	0 (0%)	3 (60%)	1 (20%)	1 (20%)	5 (100%)
TOTAL	1 (100%)	17 (100%)	33 (100%)	24 (100%)	10 (100%)	85 (100%)

The results show that in the oldest age category of 65 years and older (n=5; 50%) and in the youngest age category younger than 20 years old, the patient had one previous admission (n=1; 100%). From the results it can be seen that patients between the ages of 50 and 65 years with one previous hospital admission are the majority of patients on venlafaxine treatment.

The statistical analysis performed with the chi-square test revealed that in the patient sample that used venlafaxine the association between the number of previous admissions and patient age were not statistically significant (p=0.5408)

4.3.4 Family history of psychiatric illness

Information concerning each patient's family history of psychiatric illness was recorded and summarised in the following figure.

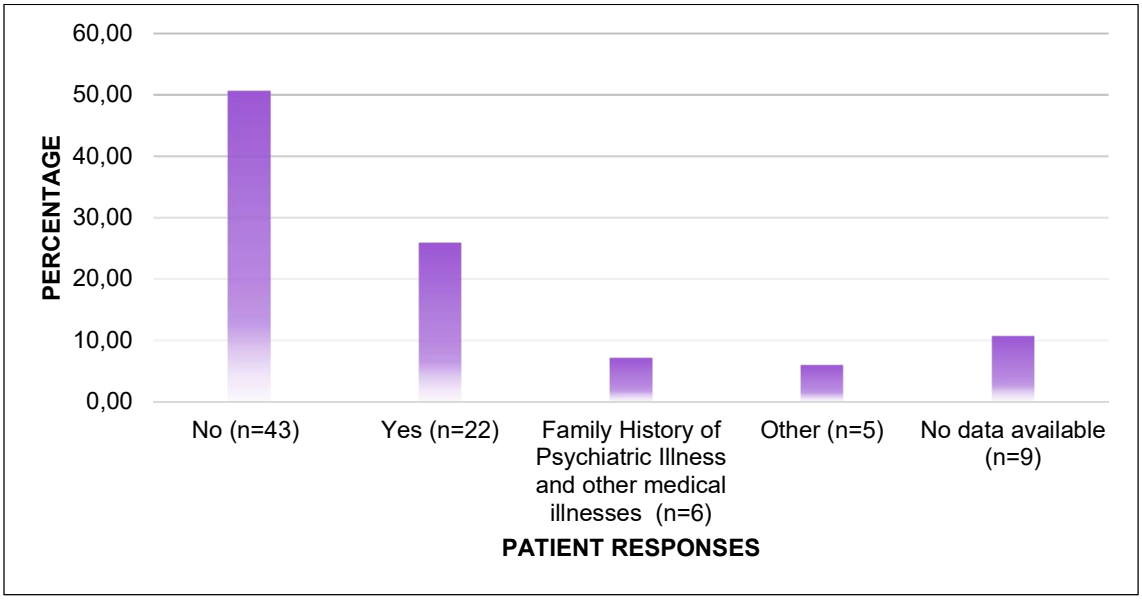

Figure 4–8. Family history of psychiatric illnesses (n=85).

From the results it can be seen that most of the patients did not have a family history of psychiatric illness (n=43, 50.59%), 25.88% (n=22) of patients did have a family history of psychiatric illness, whilst 7.06% (n=6) of patients had a family history of psychiatric illness and other medical illnesses. Unfortunately, there was limited information available in the patient files to specify which psychiatric illnesses were present.

4.3.5 Presence of past or current co-morbid diseases

Each patient's presence of past or current co-morbid diseases was recorded as part of the required past and current medical information and summarised in the following figure.

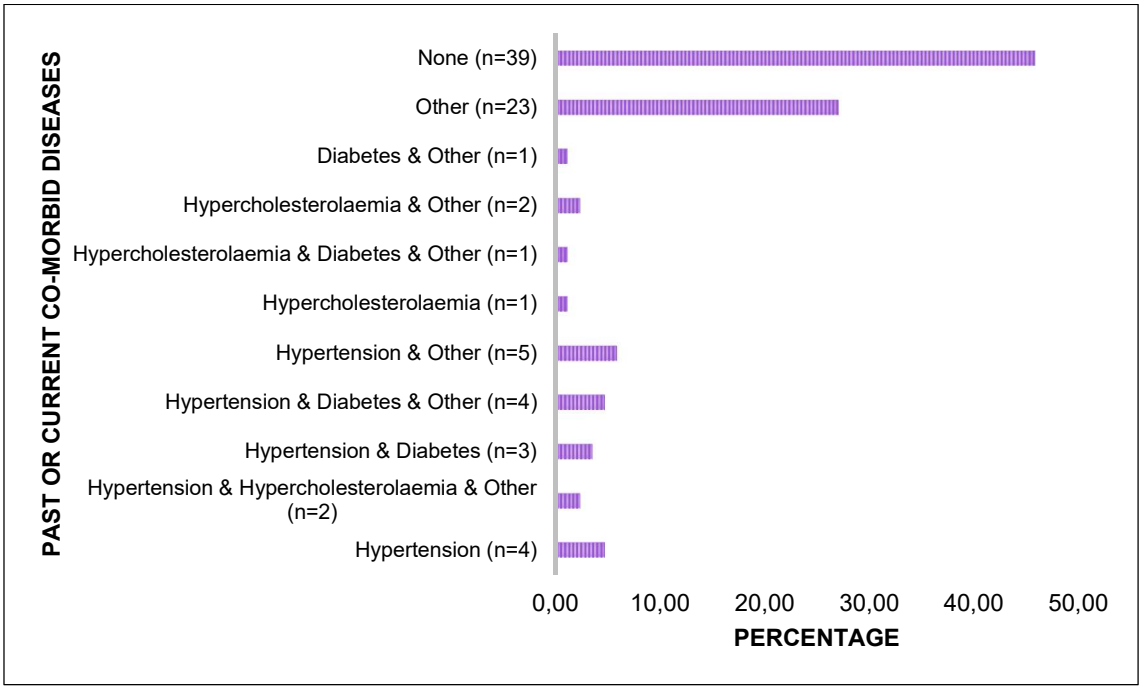

Figure 4–9. Percentage of patients with past or current co-morbid diseases (n=85).

The results revealed that surprisingly, 45.88% (n=39) had no other past or current co-morbid diseases present during the study period. Few patients (5.88%; n=5) had hypertension and one other disease, whilst 4.71% (n=4) had hypertension only as a co-morbid illness or hypertension, diabetes and one other disease.

It was essential to establish the presence of past or current co-morbid diseases for each patient since venlafaxine should be prescribed with caution to patients that present with the following disorders: Renal or hepatic impairment; history of epilepsy or myocardial infarction; unstable heart disease; hyperthyroidism; or heart failure (Rossiter *et al*., 2016:503).

4.3.6 Diagnosis

Information regarding the diagnosis was recorded and summarised in the following figure.

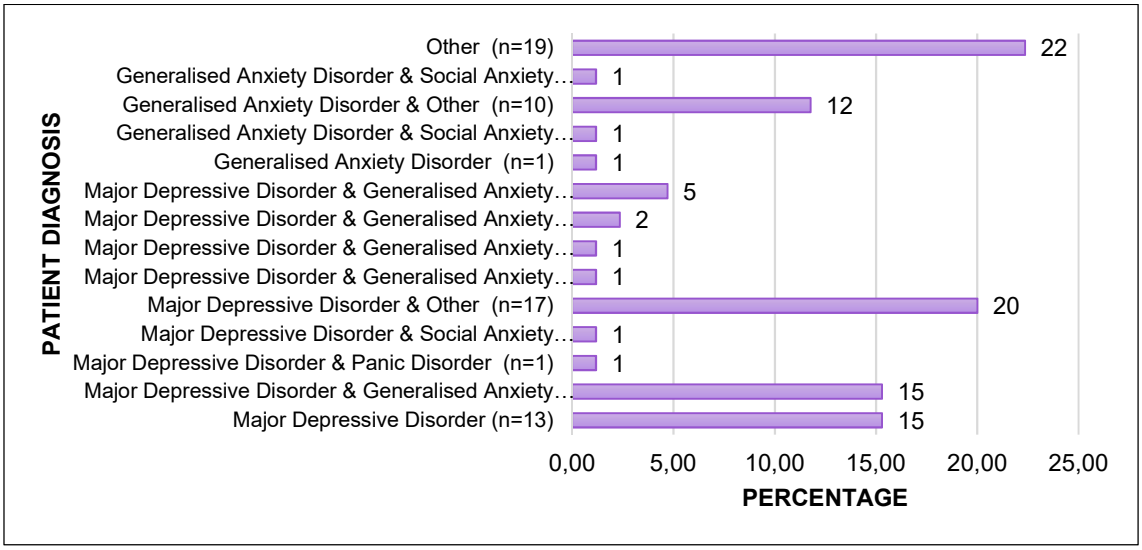

Figure 4–10. Percentage of patients with each diagnosis (n=85).

The results indicate that out of the patient sample, 22.35% of patients were using venlafaxine treatment for some other off-label use, other than the four FDA-approved indications. It was established that 15.29% of patients were diagnosed with either major depressive disorder or major depressive disorder and generalised anxiety disorder, and 20.00% diagnosed with major depressive disorder and some other disorder.

The results of the current study are supported by the literature which suggests that disorders with which MDD frequently co-occur are substance-related disorders, panic disorder, obsessive-compulsive disorder, anorexia nervosa, bulimia nervosa and borderline personality disorder (American Psychiatric Association, 2013:168). Anxiety disorders are highly comorbid, with a prevalence in about 58% of patients with MDD. Anxiety symptoms which are highly prevalent in MDD occur in 80% of patients (Emsley *et al*., 2013:157).

The use of venlafaxine treatment for off-label uses is supported by findings in the literature (Bradley *et al*., 2003; Khan *et al*., 1998; Lee *et al*., 2010; Loprinzi *et al*., 2000; Malhotra *et al*., 2002; Rudolph *et al*., 1998; Sindrup *et al*., 2003). It was discovered that there are numerous additional uses of SNRIs, which include: Treatment of pain disorders (neuropathies and fibromyalgia), generalised anxiety, menopausal vasomotor symptoms and stress urinary incontinence (Celikyurt *et al*., 2012:91).

4.3.7 Diagnosis and patient factors

The types of patient factors that may influence the patient diagnosis were analysed using the chi-squared test to establish if there were any statistically significant associations. Statistical significant associations were found between the following; Diagnosis and age categories (p=0.0382) (Table 4–16) and diagnosis and patient family history of psychiatric illness (p=0.0054) (Table 4–18).

Table 4–16. Comparison of patient diagnosis by age (n=85).

Diagnosis	Age Categories (Years)					
	< 20 n (%)	≥ 20 and < 35 n (%)	≥ 35 and < 50 n (%)	≥ 50 and < 65 n (%)	≥ 65 n (%)	TOTAL n (%)
MDD	0 (0%)	1 (7.69%)	5 (38.46%)	4 (30.77%)	3 (23.08%)	13 (100%)
MDD & GAD	0 (0%)	2 (15.38%)	6 (46.15%)	3 (23.08%)	2 (15.39%)	13 (100%)
MDD & PD	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
MDD & SAD	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
MDD & Other	0 (0%)	3 (17.65%)	9 (52.94%)	4 (23.53%)	1 (5.88%)	17 (100%)
MDD & GAD & PD	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)
MDD & GAD & SAD	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)
MDD & GAD & SAD & Other	1 (50%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	2 (100%)
MDD & GAD & Other	0 (0%)	0 (0%)	1 (25%)	2 (50%)	1 (25%)	4 (100%)
GAD	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)

Diagnosis	Age Categories (Years)					
GAD & SAD	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
GAD & Other	0 (0%)	3 (30%)	2 (20%)	4 (40%)	1 (1260%)	10 (100%)
GAD & SAD & Other	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)
PD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SAD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	5 (26.32%)	5 (26.32%)	7 (36.84%)	2 (10.52%)	19 (100%)
TOTAL	1 (100%)	17 (100%)	33 (100%)	24 (100%)	10 (100%)	85 (100%)

The results show that in the age category younger than 20 years, the most common diagnosis was MDD, GAD, SAD and one other (n=1; 100%). For the age category greater than 20 and younger than 35 years (n=5; 29.41%) and for greater than 50 and younger than 65 years (n=7; 29.17%), it was other diagnoses besides the ones mentioned. For the age category greater than 35 and younger than 50 years, the most common diagnosis was MDD and one other diagnosis (n=9; 27.27%) and for the elderly category (older than 65 years), the most common diagnosis was MDD (n=3; 30%).

The statistical analysis performed through the chi-square test revealed that diagnosis and age categories have a statistically significant association (p=0.0382) which is reinforced by the Cramér's V value (0.4583) which showed that there is a relatively strong association between diagnosis and age in patients that used venlafaxine. This result is supported by the literature which suggests that the onset of MDD can occur at any age, however, there are two peaks in life, primarily in the twenties and forties with a mean age of onset estimated around the age of 30 (American Psychiatric Association, 2013:165; Emsley *et al*., 2013:157). The results of the statistical analysis are summarised below.

Table 4–17. Statistical analysis for diagnosis by patient age (n=85).

Statistic	Value	Probability
Chi-Square	71.4132	0.0382
Cramér's V	0.4583	

Results for the comparison of diagnosis and family history of psychiatric illnesses are summarised in the following table (Table 4–18):

Table 4–18. Comparison of diagnosis and patient family history of psychiatric illness (n=85).

Diagnosis	Family History of Psychiatric Illness					
	No	Yes	Family History of Psychiatric Illness and other Medical Illnesses	Other	No data Available	TOTAL
MDD	10 (76.92%)	3 (23.08%)	0 (0%)	0 (0%)	0 (0%)	13 (100%)
MDD & GAD	6 (46.15%)	2 (15.39%)	1 (7.69%)	1 (7.69%)	3 (23.08%)	13 (100%)
MDD & PD	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
MDD & SAD	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)
MDD & Other	9 (52.94%)	3 (17.64%)	2 (11.77%)	1 (5.88%)	2 (11.77%)	17 (100%)
MDD & GAD & PD	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
MDD & GAD & SAD	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)
MDD & GAD & SAD & Other	0 (0%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)
MDD & GAD & Other	1 (25%)	3 (75%)	0 (0%)	0 (0%)	0 (0%)	4 (100%)
GAD	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)
GAD & SAD	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
GAD & Other	4 (40%)	1 (10%)	1 (10%)	1 (10%)	3 (30%)	10 (100%)
GAD & SAD & Other	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Other	12 (63.16%)	5 (26.32%)	1 (5.26%)	0 (0%)	1 (5.26%)	19 (100%)
TOTAL	43 (100%)	22 (100%)	6 (100%)	5 (100%)	9 (100%)	85 (100%)

From the results it is clear that most patients that had a family history of psychiatric illness and other medical illnesses were diagnosed with MDD and one other disorder (n=2; 33.33%). Most patients that had a family history of psychiatric illness only were diagnosed with a disorder other than the ones mentioned (n=5; 22.73%), indicating an off-label use.

The statistical analysis performed through the chi-square test revealed that there is a statistically significant association between diagnosis and patient family history of psychiatric illness (p=0.0054). Additionally, the Cramér's V value (0.49) showed that there is a relatively strong association between diagnosis and patient family history of psychiatric illness in patients that used venlafaxine. This correlates with the findings in the literature which suggests that a previous episode of major depression and a positive first-degree family history of depression are the most consistently described risk factors for MDD (Emsley *et al*., 2013:157). The results of the statistical analysis are summarised below.

Table 4–19. Statistical analysis for diagnosis by patient family history of psychiatric illness (n=85).

Statistic	Value	Probability
Chi-Square	81.6218	0.0054
Cramér's V	0.49	

The results of the statistical tests performed for the other patient factors that were discovered to be not statistically significant are summarised below.

Table 4–20. Statistical analysis for diagnosis by ethnicities (n=85).

Statistic	Value	Probability
Chi-Square	36.1648	0.5999

Table 4–21. Statistical analysis for diagnosis by marital status (n=85).

Statistic	Value	Probability
Chi-Square	82.7671	0.0678

Table 4–22. Statistical analysis for diagnosis by employment status (n=85).

Statistic	Value	Probability
Chi-Square	78.2407	0.4710

Table 4–23. Statistical analysis for diagnosis by previous venlafaxine use (n=85).

Statistic	Value	Probability
Chi-Square	23.8726	0.5832

4.3.8 Concomitant drug use

The concomitant drug use information of each patient was recorded and the list constructed according to the most commonly used concomitant drugs.

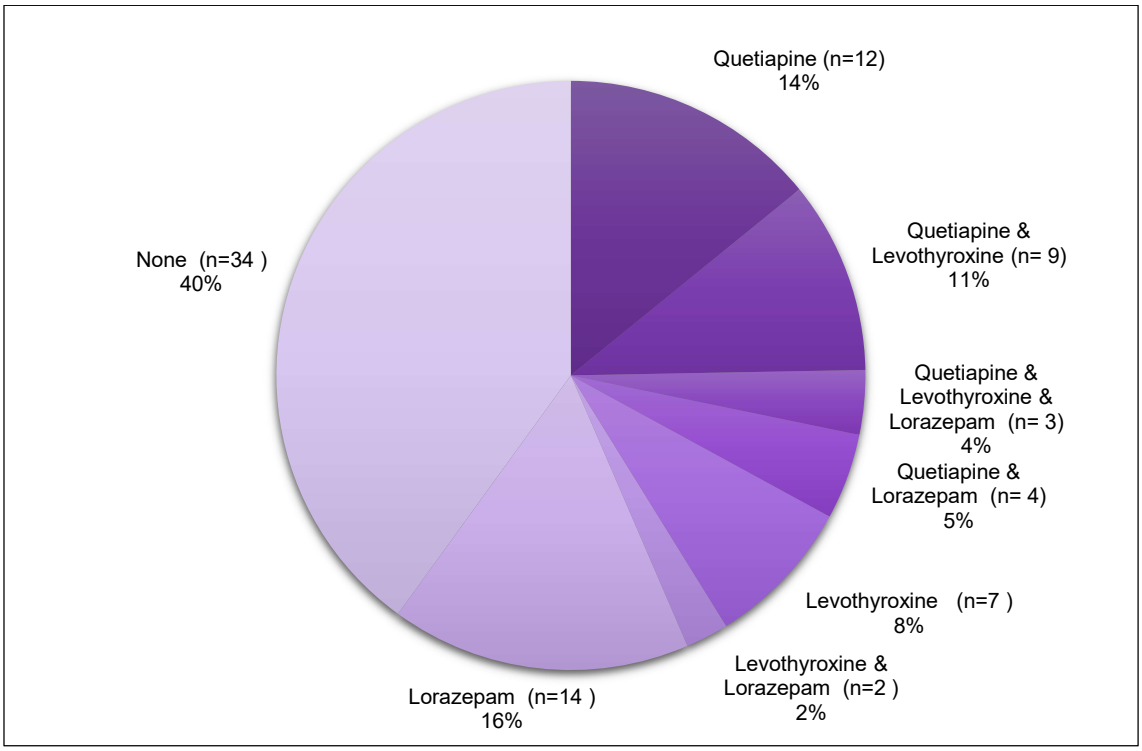

Figure 4–11. The most frequently prescribed concomitant drugs used by patients (n=85).

Besides venlafaxine treatment, the results showed that the most frequently prescribed concomitant drugs were the benzodiazepine lorazepam (n=14; 16.47%), followed by the antipsychotic quetiapine (n=12; 14.11%).

4.3.9 Contraceptive use

Information concerning each female patient's contraceptive use was recorded. Male patients were not considered for this variable, therefore they were coded as not applicable (n=20, 23.53%).

Table 4–24. Percentage of female patients that used contraceptives (n=85).

Contraceptive Use	n	%
No	62	72.94
Yes	3	3.53
No data available	0	0.00
Not applicable	20	23.53
TOTAL	85	100.00

From the results, it is evident that most female patients (n=62; 72.94%) on venlafaxine treatment did not use contraceptives. Venlafaxine is categorised as a category C risk factor drug in pregnancy and is excreted during breastfeeding (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503). Therefore, all female patients of child-bearing age on venlafaxine therapy should be encouraged to use contraceptive methods either the pill or the injectable form.

4.3.10 Names of contraceptives

Information concerning the names of the contraceptives used were recorded and from the patient sample only 3 patients used contraceptives. The results show that 2 patients used Depo-Provera® (medroxyprogesterone acetate) and 1 patient used Yaz® which is a combination of drospirenone and ethinyl oestradiol as their contraceptive.

Table 4–25. Names of contraceptives used by female patients (n=85).

Name of Contraceptives Used	n	%
Depo-Provera® (medroxyprogesterone acetate)	2	2.35
Yaz® (drospirenone and ethinyl oestradiol)	1	1.18
Not applicable	82	96.47
TOTAL	85	100.00

4.4 Presence of drug interactions

The following table reveals whether any drug interactions could be identified during the data analysis between venlafaxine and other drugs that the patients were taking.

Table 4–26. Percentage of drug interactions identified (n=85).

Drug Interactions Identified	n	%
No	59	69.41
Yes	26	30.59
No data available	0	0.00
TOTAL	85	100.00

The results show that in the majority of the patients on treatment with venlafaxine there were no drug interactions identified (n=59; 69.41%). However, drug interactions identified in the remainder of the patient sample were further investigated.

4.4.1 Number of drug interactions identified

The following table shows the number of drug-drug interactions identified between venlafaxine and other drugs (Cipla Medpro, 2006:1; Leesette Turner, 2010:494; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:20).

Table 4–27. Percentage of number of drug-drug interactions identified (n=26).

Number of drug-drug Interactions	n	%
1	22	84.62
2	4	15.38
TOTAL	26	100.00

From the results it is clear that from the 26 patients that had drug-drug interactions identified, 84.62% (n=22) had one drug-drug interaction identified in their treatment plan and 15.38% (n=4) had two drug interactions identified in their treatment plan.

4.4.2 Drug-drug interaction 1

The following figure displays the details of the first drug interaction identified between venlafaxine and the other drugs in the patients' treatment plan.

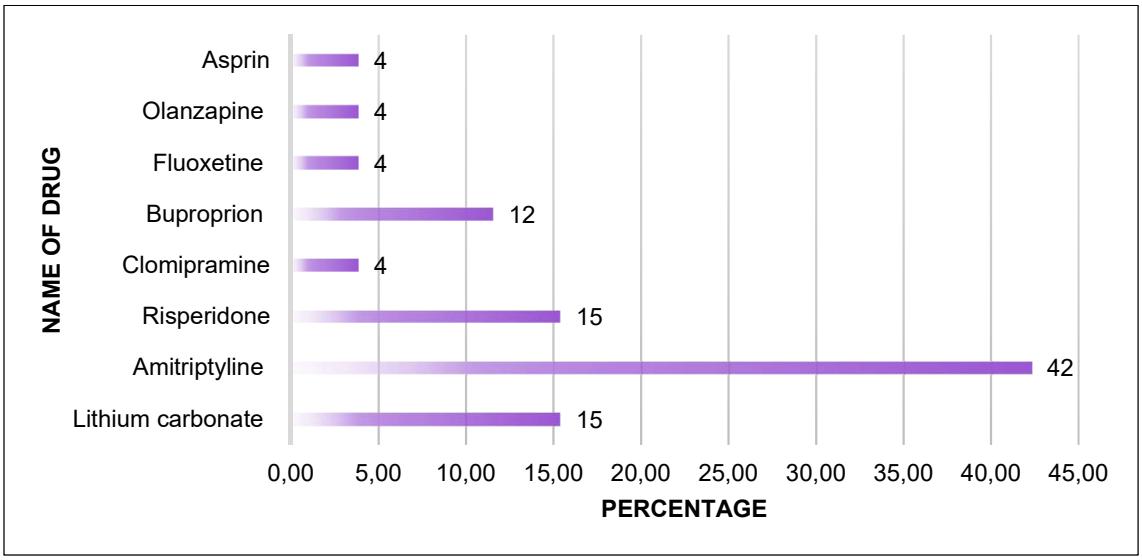

Figure 4–12. Drugs responsible for the first drug interaction (n=22).

The results of the drug-drug interactions identified showed that amitriptyline (n=11; 42.31%) was the drug most patients used, which has an unwanted reaction with venlafaxine (drug-drug interaction 1). Amitriptyline is classified as a TCA. Concurrent use of TCAs and venlafaxine enhances serotonin activity which may lead to serotonin syndrome (Cipla Medpro, 2006:1; Leesette Turner, 2010:494; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:20).

4.4.3 Drug-drug interaction 2

The following figure represents the details of the second drug interaction identified between venlafaxine and the other drugs in the patients' treatment plan.

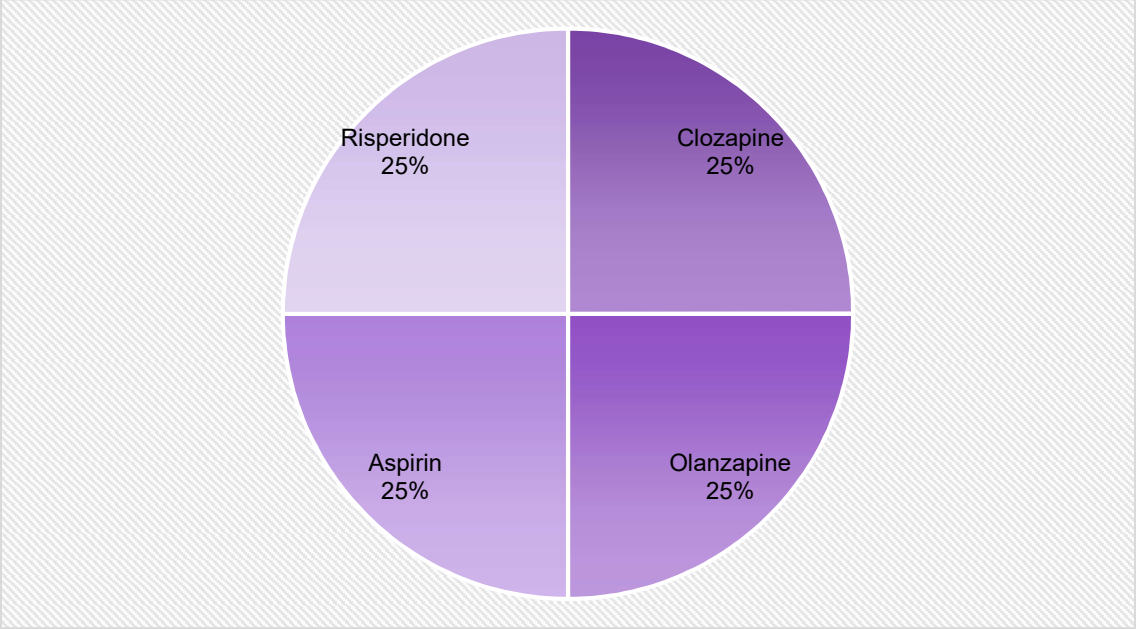

Figure 4–13. Drugs responsible for the second drug-drug interaction (n=4).

The results of the drug interactions identified showed that 3 out of the 4 drugs responsible for the second drug interaction were antipsychotics, which have an unwanted reaction with venlafaxine. Risperidone, clozapine and olanzapine are classified as antipsychotic drugs. Concurrent use of venlafaxine and risperidone, clozapine and olanzapine leads to raised levels of these drugs which could lead to toxicity (Cipla Medpro, 2006:1; Leesette Turner, 2010:494; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:20). Aspirin use while on venlafaxine therapy may result in bleeding and therefore should be avoided or used with caution only if necessary (Cipla Medpro, 2006:1; Leesette Turner, 2010:494; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:20).

4.5 Adverse effects experienced

The following table exhibits whether any adverse effects were experienced during the study period by the patients on venlafaxine treatment.

Table 4–28. Percentage of patients that experienced adverse effects (n=85).

Adverse Effects Experienced	n	%
No	63	74.12
Yes	21	24.71
No data available	1	1.18
TOTAL	85	100.00

The data analysis showed that fortunately the majority of patients (74.12%; n=63) did not experience any adverse effects from treatment with venlafaxine during the study period. However, the properties of adverse effects experienced by the remainder of the patient sample were further investigated.

4.5.1 Type of adverse effect experienced

The following figure describes the adverse effects that were experienced during the study period by patients on venlafaxine treatment. The options were available on the data collection form and were chosen based on common adverse effects experienced by patients as stated in the literature (Rossiter *et al*., 2016:503).

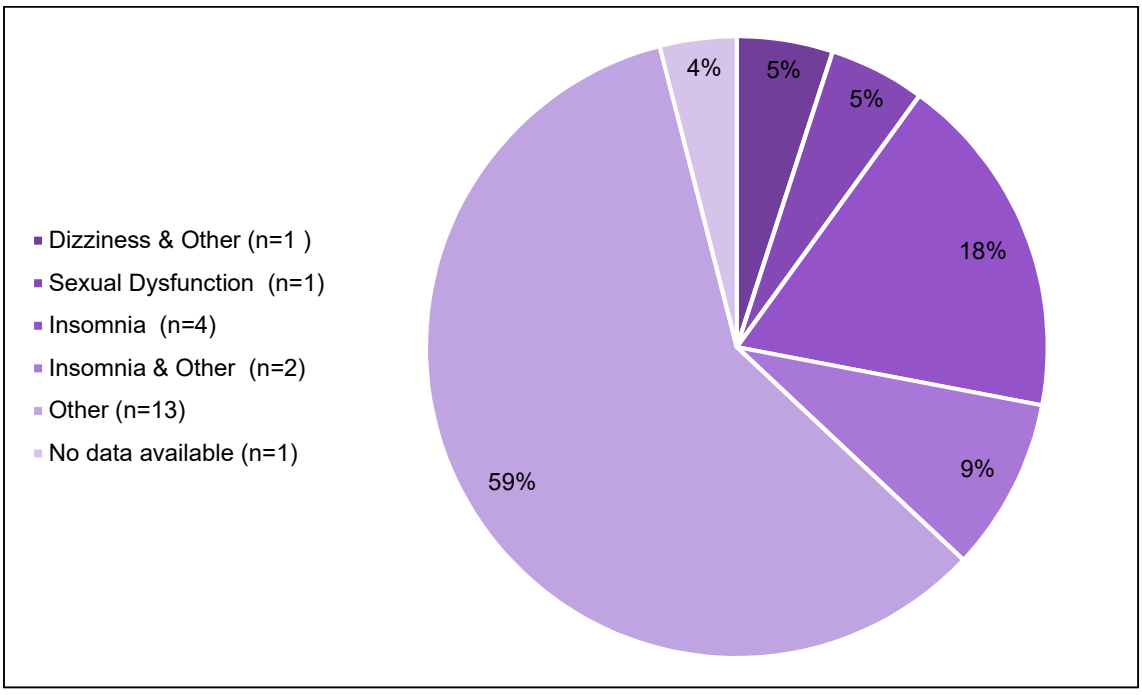

Figure 4–14. Common adverse effects experienced by patients (n=22).

The results suggest that the majority of patients on venlafaxine treatment experienced insomnia 18.18% (n=4) besides those patients that experienced other adverse effects compared to those stated in the literature 59.09% (n=13) during the study period. These results correlated with the literature which suggested that patients that were previously treated with venlafaxine commonly experienced treatment-emergent insomnia and nervousness therefore patients should be cautioned about such effects and the benefit-risk ratio should be evaluated to motivate treatment (Wyeth Pharmaceuticals, 2003:13).

Some of the other adverse effects experienced by patients on venlafaxine treatment are described in the figure below.

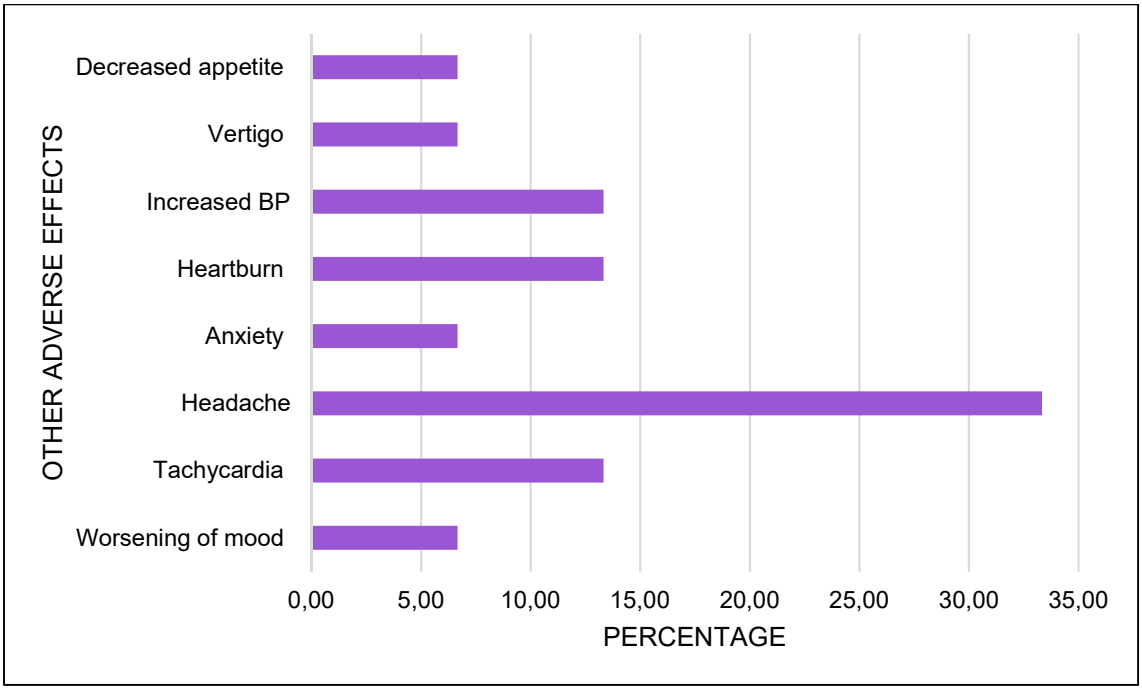

Figure 4–15. Percentage of patients with other adverse effects (n=13).

From the results it is clear that the most common other adverse effect experienced by patients was headaches (n=5; 33.33%). These results correlated with the literature which suggested that some common adverse effects experienced include the following: Central nervous system effects such as headache and other adverse effects include cardiovascular effects such as hypertension, postural hypotension, palpitations and tachycardia (Cipla Medpro, 2006; Rossiter *et al*., 2016). Many of these adverse effects are dose-related and with prolonged treatment these effects

generally decrease in frequency and intensity, thus not necessitating the discontinuation of treatment (Cipla Medpro, 2006:1).

From the literature, it was established that blood pressure changes were dose related, with an incidence of approximately 5% at doses under 200 mg/day and 13% at doses larger than 300 mg (Ciraulo and Shader, 2004:77). However, It was suggested that if the dose cannot be reduced, the blood pressure should be treated pharmacologically with the use of an alternate anti-hypertensive drug (Ciraulo and Shader, 2004:77).

4.5.2 Adverse effect treated

The following table indicates whether the adverse effects experienced were treated.

Table 4–29. Percentage of patients that had adverse effects treated (n=22).

Adverse Effects Treated	n	%
No	1	4.55
Yes	20	90.91
No data available	1	4.55
TOTAL	22	100.00

From the results it is evident that 90.91% (n=20) of patients that experienced adverse effects while on venlafaxine treatment was treated, suggesting that that the monitoring and follow up of patients' treatment plan at the study site were efficient and effective.

4.6 Monitoring procedures

The results acquired for monitoring procedures are described under the following headings: Blood pressure monitoring, weight monitoring, pulse rate monitoring and total cholesterol (including triglycerides, HDL and LDL) monitoring. Unfortunately, there were no information available in the patient files of the patient sample on venlafaxine treatment to ascertain whether sodium levels were monitored according to the recommended monitoring guidelines, suggesting a target area for improvement.

4.6.1 Blood pressure monitoring

Information was obtained from each patient's file to determine whether blood pressure monitoring was conducted according to recommended guidelines and summarised in the following table.

Table 4–30. Percentage of patients who had blood pressure monitoring conducted (n=85).

Blood Pressure Monitoring	n	%
No	0	0.00
Yes	81	95.29
No data available	1	1.18
Not applicable	3	3.53
TOTAL	85	100.00

The results indicate that blood pressure monitoring was conducted for 95.29% (n=81) of the patients in the sample. This suggests that the blood pressure monitoring procedures were conducted according to recommended guidelines. For one patient though there was no data available in the patient file regarding monitoring procedures and for three other patients, monitoring procedures were considered not applicable as they relocated and therefore no information was available for the study period.

It was established that it is imperative that blood pressure be monitored regularly, especially when using venlafaxine XR at doses of 225 mg or more per day (Cipla Medpro, 2006:1; Johnson *et al*., 2006: 796-802; Khawam *et al*., 2006: 351-3, 356-61; Rossiter *et al*., 2016:503).

4.6.1.1 Blood pressure monitoring frequency

Information obtained from each patient's file was utilised to summarise the frequency of blood pressure monitoring to determine whether blood pressure monitoring was compliant with the recommended guidelines.

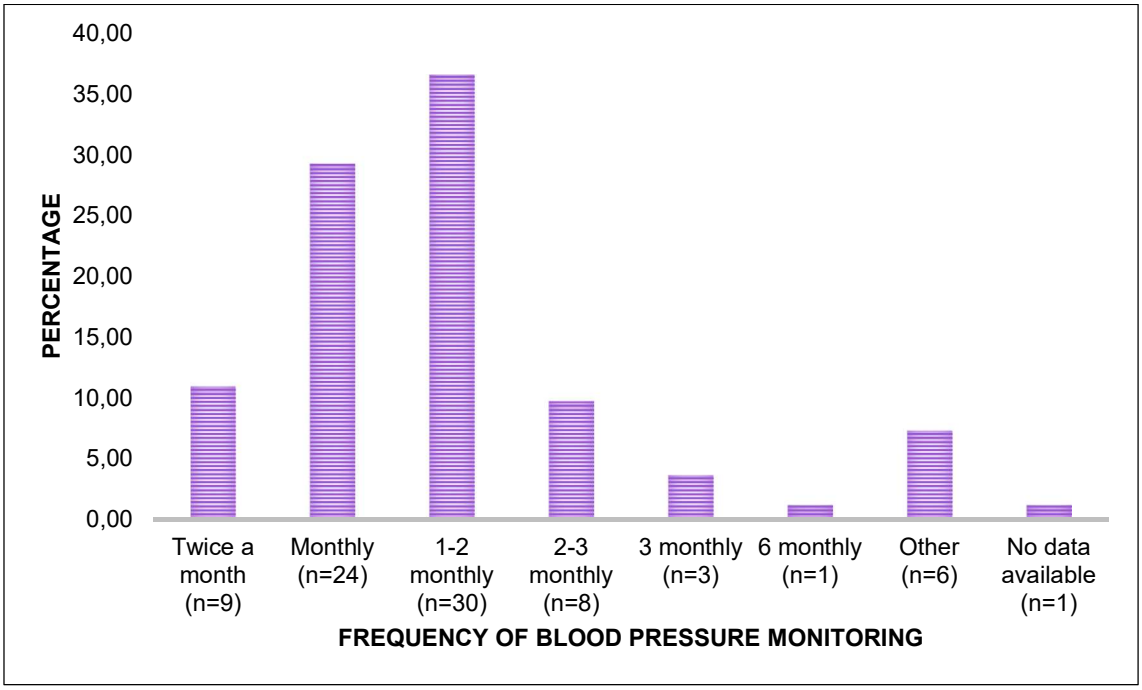

Figure 4–16. Frequency of blood pressure monitoring procedures (n=85).

The results indicate that blood pressure monitoring was conducted every 1 to 2 months for most of the patients (n=30; 36.59%) in the sample, followed by once every month for 29.27% (n=24) of the patients. The results suggest that the blood pressure monitoring frequency was compliant with the recommended guidelines.

4.6.1.2 Blood pressure results within range

Information was obtained from each patient's file to determine whether their blood pressure results from the monitoring conducted was within range according to the recommended guidelines and summarised in the following table.

Table 4–31. Percentage of patients who had blood pressure results within the normal range (n=82).

Blood Pressure Monitoring within Range	n	%
No	15	18.29
Yes	66	80.49
No data available	1	1.22
TOTAL	82	100.00

From the results it is evident that the majority of the patient sample (n=66; 80.49%) on venlafaxine treatment had blood pressure results within the safe range according to the recommended guidelines.

4.6.2 Weight monitoring

Information was obtained from each patient's file to determine whether body weight monitoring was compliant with the recommended guidelines and summarised in the following table.

Table 4–32. Percentage patients who had weight monitoring conducted (n=85).

Weight Monitoring	n	%
No	0	0.00
Yes	80	94.12
No data available	2	2.35
Not applicable	3	3.53
TOTAL	85	100.00

The results indicate that body weight monitoring was performed for the majority of the patient sample (n= 80; 94.12%), suggesting that the body weight monitoring procedures was compliant with the recommended guidelines.

Furthermore, information was obtained from each patient's file to determine whether their body weight was within range according to the recommended guidelines.

Table 4–33. Percentage patients who had body weight values within the normal range (n=82).

Weight Monitoring within Range	n	%
No	42	51.22
Yes	15	18.29
No data available	25	30.49
TOTAL	82	100.00

Results suggest that more than half of the patients (n=42; 51.22%) in the patient sample on venlafaxine treatment had body weight values that were not within a safe

range according to the recommended guidelines. Therefore, this is a target area for improvement.

4.6.3 Pulse rate monitoring

Information was obtained from each patient's file to determine whether pulse rate monitoring was compliant with the recommended guidelines and summarised in the following table.

Table 4–34. Percentage of patients who had pulse rate monitoring conducted (n=85).

Pulse Rate Monitoring	n	%
No	0	0.00
Yes	81	95.29
No data available	1	1.18
Not applicable	3	3.53
TOTAL	85	100.00

The results of the study indicate that the majority of patients (n=81; 95.29%) in the patient sample on venlafaxine treatment had their pulse rates monitored, therefore adhering to the recommended monitoring guidelines. It was established from the literature that venlafaxine XR was associated with some undesirable cardiovascular effects (blood pressure and pulse rate) in some of the participants, therefore systematic monitoring of cardiovascular parameters during treatment with venlafaxine XR is strongly recommended, especially in the elderly population (Johnson *et al*., 2006: 796-802).

In addition, information was obtained from each patient's file to determine whether their pulse rate results were within the normal range according to the recommended guidelines.

Table 4–35. Percentage of patients who had pulse rate values within the normal range (n=82).

Pulse Rate Monitoring within Range	n	%
No	25	30.49
Yes	56	68.29
No data available	1	1.22
TOTAL	82	100.00

It is evident from the results that the majority of patients (n=56; 68.29%) in the patient sample on venlafaxine treatment had pulse rate monitoring results within a safe range according to the recommended guidelines.

4.6.4 Total cholesterol monitoring

Information was obtained from each patient's file to determine whether total cholesterol monitoring was conducted according to the recommended guidelines and summarised in the following table.

Table 4–36. Percentage of patients who had total cholesterol levels monitored (n=85).

Total Cholesterol Monitoring	n	%
No	0	0.00
Yes	27	31.76
No data available	58	68.24
TOTAL	85	100.00

Unfortunately, there were no information available in the majority of patient files of the patient sample on venlafaxine treatment to ascertain whether total cholesterol levels were monitored according to the recommended monitoring guidelines, suggesting a target area for improvement.

4.6.4.1 Total cholesterol monitoring frequency

Information was further obtained from each patient's file to summarise the frequency of total cholesterol (including triglycerides, HDL and LDL) monitoring to determine whether monitoring was compliant with the recommended guidelines.

Table 4–37. Frequency of total cholesterol monitoring (n=85).

Frequency of Total Cholesterol Monitoring	n	%
Three times a year	1	1.18
Annually (once a year)	26	30.59
No data available	58	68.24
TOTAL	85	100.00

Again, there was no information available in the majority of patient files of the patient sample on venlafaxine treatment to ascertain whether total cholesterol levels were monitored according to the recommended monitoring guidelines, suggesting a target area for improvement.

The literature revealed that serum cholesterol increases have been reported in patients treated with venlafaxine for at least 3 months (Cipla Medpro, 2006:1). Therefore, patients on long-term venlafaxine treatment should consider having their serum cholesterol levels measured regularly.

4.6.4.2 Total cholesterol results within range

Information was further obtained from each patient's file that had total cholesterol monitored to establish whether the results were within the normal range according to recommended guidelines. The results are summarised in the table below.

Table 4–38. Percentage of patients who had total cholesterol monitored and had results within the normal range (n=27).

Total Cholesterol Monitoring Results within Range	n	%
No	11	40.74
Yes	16	59.26
TOTAL	27	100.00

From the results it is evident that the majority (n=16; 59.26%) of the patient sample on venlafaxine treatment who had their total cholesterol monitored, had levels within a safe range according to the recommended guidelines.

4.6.4.3 Triglycerides monitoring

Information concerning the triglyceride levels was obtained from each patient's file to determine whether monitoring was conducted according to the recommended guidelines.

Table 4–39. Percentage of patients who had triglycerides monitoring conducted (n=85).

Triglycerides Monitoring	n	%
No	0	0,00
Yes	5	5.88
No data available	80	94.12
TOTAL	85	100.00

The results show that unfortunately only 5.88% (n=5) of the patient sample had their triglyceride levels monitored, suggesting a target area for improvement.

It was furthermore established whether those patients who had their triglycerides monitored, had results within the normal range as summarised in the following table.

Table 4–40. Percentage of patients who had triglyceride monitoring had levels within the normal range (n=5).

Triglycerides Monitoring Results within Range	n	%
No	4	80.00
Yes	1	20.00
TOTAL	5	100.00

The results display that from the small proportion of patients on venlafaxine treatment that had their triglyceride levels monitored, the majority had results that were not within a safe range according to the recommended guidelines, further supporting a target area for improvement.

4.6.4.4 Low-density lipoproteins monitoring

Information was obtained from each patient's file to establish whether low density lipoproteins (LDL) monitoring was conducted according to recommended guidelines and summarised in the table below.

Table 4–41. Percentage of patients who had LDL monitoring conducted (n=85).

LDL Monitoring	n	%
No	0	0.00
Yes	8	9.41
No data available	77	90.59
TOTAL	85	100.00

Unfortunately, there were no information available in the majority of patient files of the patient sample on venlafaxine treatment to ascertain whether LDL levels were monitored according to the recommended monitoring guidelines, suggesting a target area for improvement.

It was further established whether the small proportion of patients who had their LDL monitored, had levels within the normal range as summarised in the following table.

Table 4–42. Percentage of patients who had their LDL monitored had results within the normal range (n=8).

LDL Monitoring Results within Range	n	%
No	3	37.50
Yes	5	62.50
TOTAL	8	100.00

From the results it is evident that the majority (n=5; 62.50%) of the small proportion of patients who had their LDL monitored had levels that were within a safe range according to recommended guidelines.

4.6.4.5 High-density lipoprotein monitoring

Information concerning the monitoring of high density lipoproteins (HDL) was acquired from each patient's file to establish whether monitoring was conducted according to the recommended guidelines and the results summarised in the following table.

Table 4–43. Percentage of patients who had HDL monitoring conducted (n=85).

HDL Monitoring	n	%
No	0	0.00
Yes	8	9.41
No data available	77	90.59
TOTAL	85	100.00

Likewise, there were no information available in the majority of patient files of the patient sample on venlafaxine treatment to ascertain whether HDL levels were monitored according to the recommended monitoring guidelines, suggesting a target area for improvement.

It was further established whether the small proportion of patients who had their HDL monitored, had levels within the normal range as summarised in the following table.

Table 4–44. Percentage of patients who had their HDL monitored had results within the normal range (n=8).

HDL Monitoring Results within Range	n	%
No	3	37.50
Yes	5	62.50
TOTAL	8	100.00

From the results it is evident that the majority (n=5; 62.50%) of the small proportion of patients who had their HDL monitored had levels that were within a safe range according to recommended guidelines.

4.7 Venlafaxine use

Results acquired concerning venlafaxine use are described below.

4.7.1 Previous venlafaxine use

Information concerning each patient's history of venlafaxine use is summarised in the table below.

Table 4–45. Patient sample history of venlafaxine use (n=85).

Previous Venlafaxine Use	n	%
No	21	24.71
Yes	62	72.94
No data available	2	2.35
TOTAL	85	100.00

The results reveal that 72.94% (n=62) of the patient sample used venlafaxine treatment previously prior to the study period.

4.7.2 Duration of venlafaxine treatment

The date (if available) of the first initiation of venlafaxine was recorded on the data collection form and used to calculate the number of years/months since then. The results are summarised in the following figure.

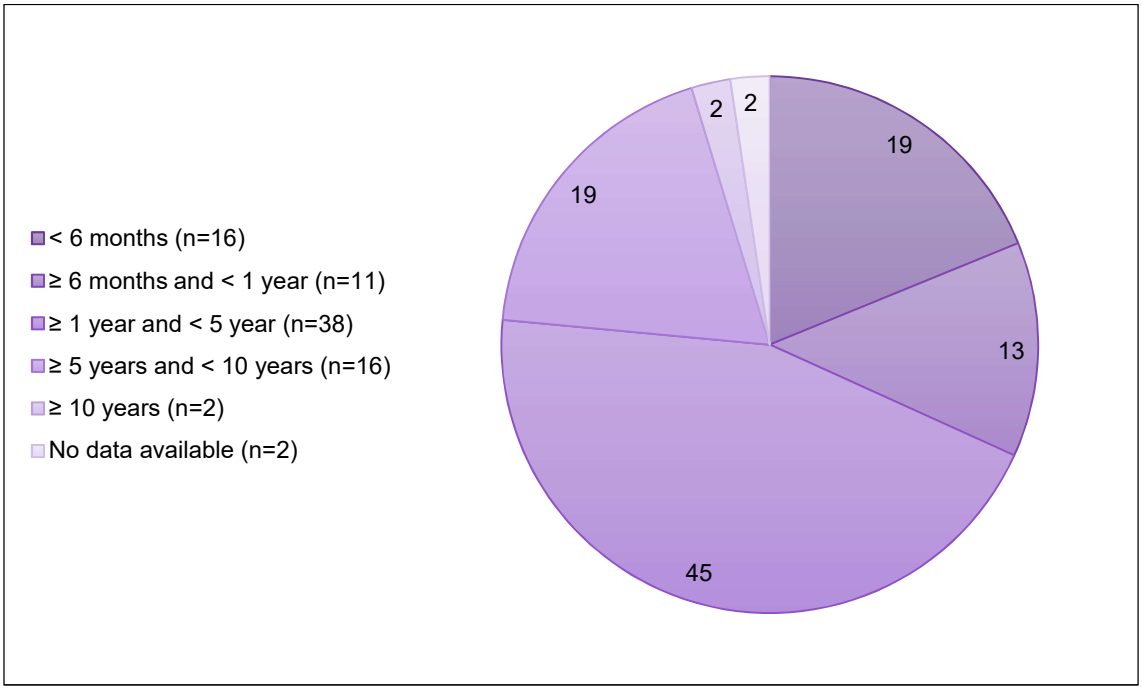

Figure 4–17. Years/months since first initiation of venlafaxine treatment (n=85).

From the results, it is evident that for most of the patients (n=38; 44.71%) that were on venlafaxine treatment during the study period, the first initiation of venlafaxine occurred between 1 and 5 years ago. Most of the patients were on long-term

venlafaxine therapy indicating that patients were satisfied with their treatment and venlafaxine was well-tolerated.

4.7.3 Venlafaxine use as first antidepressant

Information concerning each patient's history of other antidepressant use, including if venlafaxine was/was not the first antidepressant used, was acquired and summarised in the table below.

Table 4–46. Percentage of patients that used venlafaxine as their first antidepressant (n=85).

Venlafaxine Use as First Antidepressant	n	%
No	66	77.65
Yes	5	5.88
No data available	14	16.47
TOTAL	85	100.00

The results display that the majority of the patient sample (n=66; 77.65%) that were on venlafaxine treatment during the study period used a different antidepressant as their first antidepressant. This result corresponds with the findings from the literature which states that the SSRIs are common first-step treatments for depression due to their relatively low toxicity and high tolerability (Rush *et al*., 2006: 1231-1242).

4.7.4 Antidepressant names or classes used prior to venlafaxine

The classes and names of any previously used antidepressants prior to venlafaxine were recorded and summarised in the figure below.

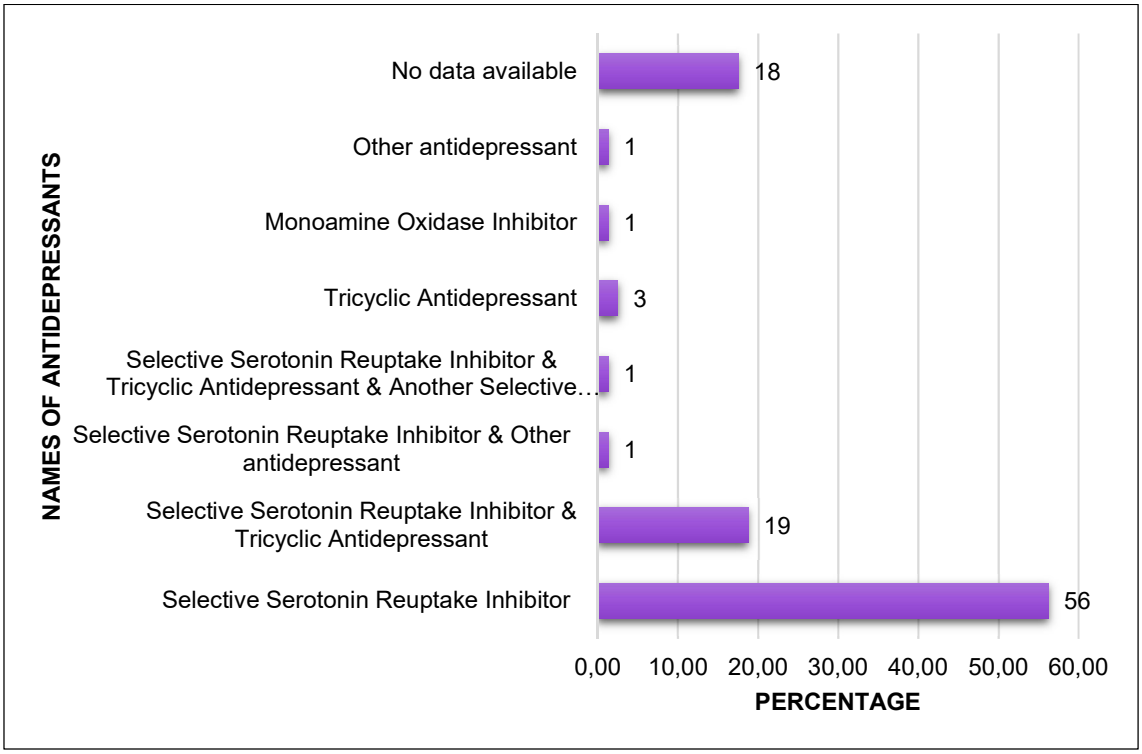

Figure 4–18. Percentage of previous antidepressants used other than venlafaxine (n=80).

From the results it is clear that most patients (n=45; 56.25%) used the selective serotonin reuptake inhibitor class of antidepressants prior to venlafaxine, followed by 18.75% (n=15) of patients who previously used both a selective serotonin reuptake inhibitor and a tricyclic antidepressant.

The results of the current study correspond with the findings from the previous DURs conducted in SA which suggests that SSRIs and TCAs are the most frequently prescribed antidepressant classes among the South African population (Burger *et al*., 2009; Kairuz *et al*., 2003; I Truter, 2010; Truter and Kotze, 2006, 1997, 1996; Van Schalkwyk and Truter, 2010).

The information acquired was further analysed to determine which antidepressants and how many were used by the patients in the past and summarised in the following figure.

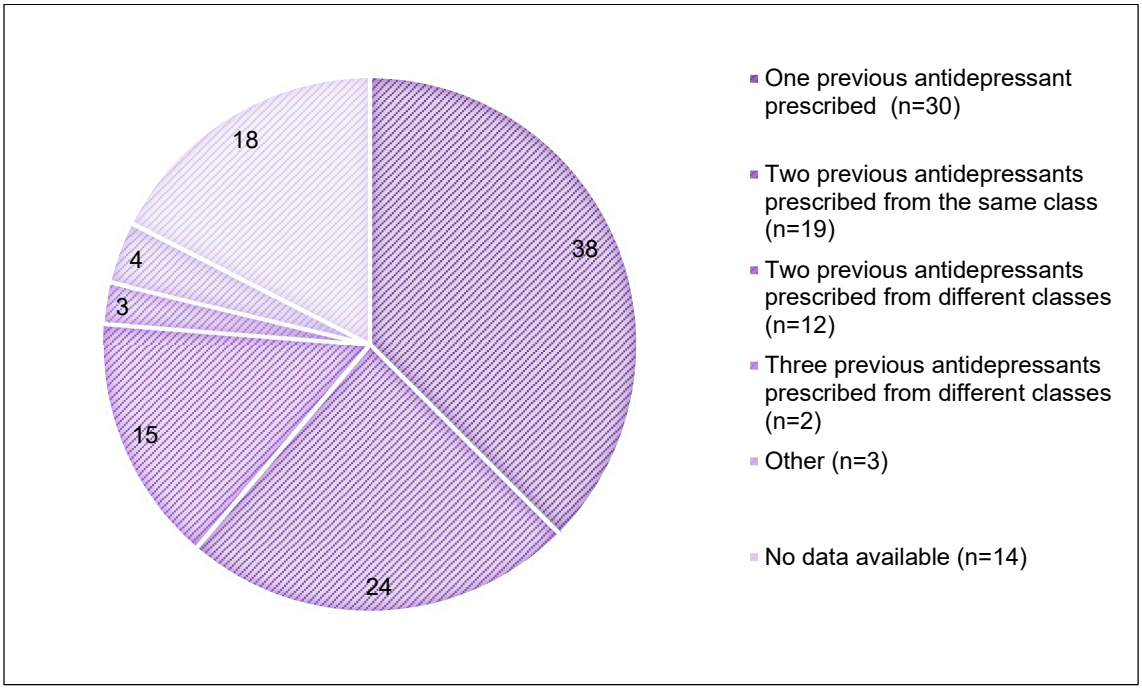

Figure 4–19. Trials of previous antidepressant classes (n=80).

The results show that 37.50% (n=30) of patients had one previous antidepressant prescribed prior to venlafaxine treatment being initiated, followed by 23.75% (n=19) of patients who had two previous antidepressants prescribed from the same antidepressant class prior to venlafaxine. This result implies that venlafaxine is a viable second line treatment option for depressive and anxiety-related disorders.

Findings from the local and international literature supported the use of venlafaxine as a MDD treatment alternative for those patients who are unresponsive to initial antidepressant therapy, or for SSRI-resistant depression (Baldomero *et al*., 2005; Fang *et al*., 2010; Papakostas *et al*., 2008; Poirier and Boyer, 1999; Rush *et al*., 2006; Thase *et al*., 2011).

4.7.5 Compliance with recommended guidelines for initiation and management of venlafaxine treatment

4.7.5.1 Dose titration performed from initiation of treatment

Information regarding the initiation of dose titration was recorded and analysed to understand the prescribing patterns at the study site. The results are summarised in the following table.

Table 4–47. Percentage of patients who had a dose titration performed from the initiation of venlafaxine treatment (n=85).

Dose Titration Performed from Initiation of Venlafaxine Treatment	n	%
No	1	1.18
Yes	67	78.82
No data available	17	20.00
TOTAL	85	100.00

The results demonstrate that the majority of patients (n=67; 78.82%) of the patient sample had their dose titrated from the initiation of venlafaxine treatment. This suggests that the prescribing of venlafaxine initiation was compliant with the recommended dosing guidelines at the study site which states that venlafaxine treatment should be initiated at 37.5 mg/day for 4-7 days before increasing the dose to 75 mg/day (Cipla Medpro, 2006:1; Emsley *et al*., 2013:159-162; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:5).

4.7.5.2 Initial dose used

Information regarding the initial dose of venlafaxine used was recorded and analysed to establish the prescribing patterns at the study site. The results are summarised in the following figure.

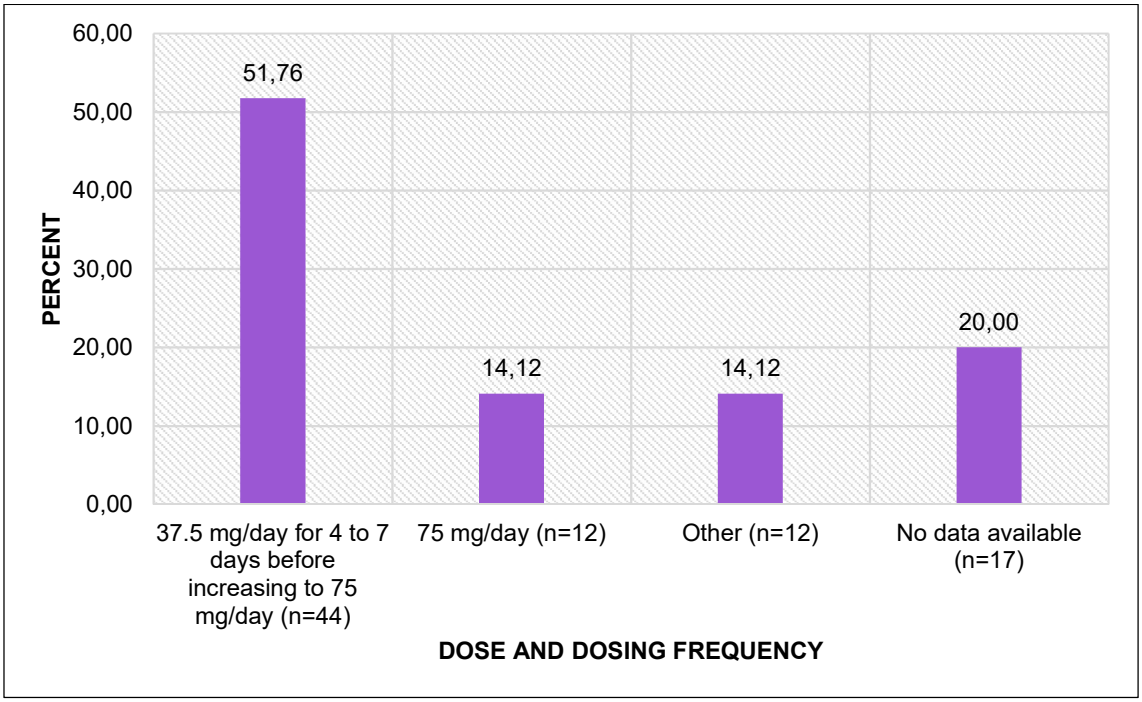

Figure 4–20. Initial dose of venlafaxine prescribed (n=85).

From the results it is evident that the initial dose used by most patients (n=44; 51.76%) was 37.5 mg/day for 4 to 7 days before increasing to 75 mg/day, which is compliant with the recommended prescribing guidelines for venlafaxine. However, 14.12% (n=12) of patients were prescribed a different dose from the initial recommended dose which could result in the emergence of adverse effects, especially in new patients. Therefore, venlafaxine treatment should be initiated at 37.5 mg/day for 4-7 days, especially for new patients, to allow patients to adjust before increasing the dose to 75 mg/day (Cipla Medpro, 2006:1; Emsley *et al*., 2013:159-162; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:5).

4.7.5.3 Duration of dose titration

Information regarding the specific increments of venlafaxine dose titration was noted to establish the prescribing patterns of venlafaxine at the study site, including patient tolerance to venlafaxine. The results are summarised in the following figure.

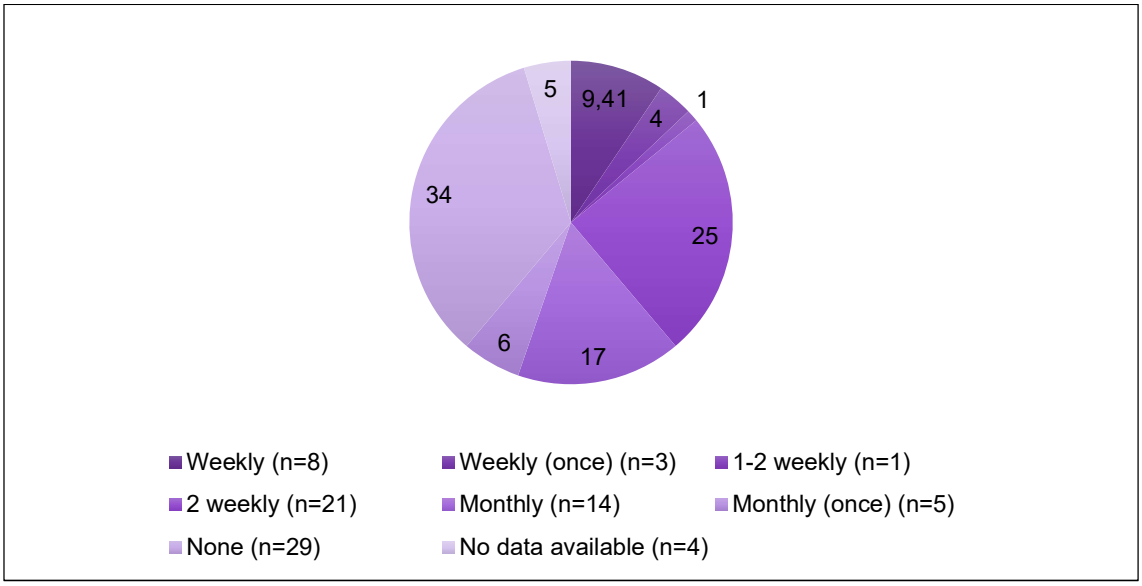

Figure 4–21. Percentage of dose titrations over specific periods (n=85).

The results show that 34.12% (n=29) of the patient sample had no dose titration performed to their venlafaxine treatment, indicating that they were well-controlled on the initial dose used. In addition, 24.71% (n=21) of patients received increments of dose titrations every 2 weeks, suggesting that their treatment was optimised and required check-ups every 2 weeks. None of the patients had a dose titration performed within 4 days, which is compliant with the guidelines which suggest that dose titration (maintenance) should be in increments of 75 mg/day as needed and should be made at intervals of not less than 4 days (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:41).

4.7.5.4 Maintenance dose used

Information regarding the maintenance dose of venlafaxine is summarised in the following figure.

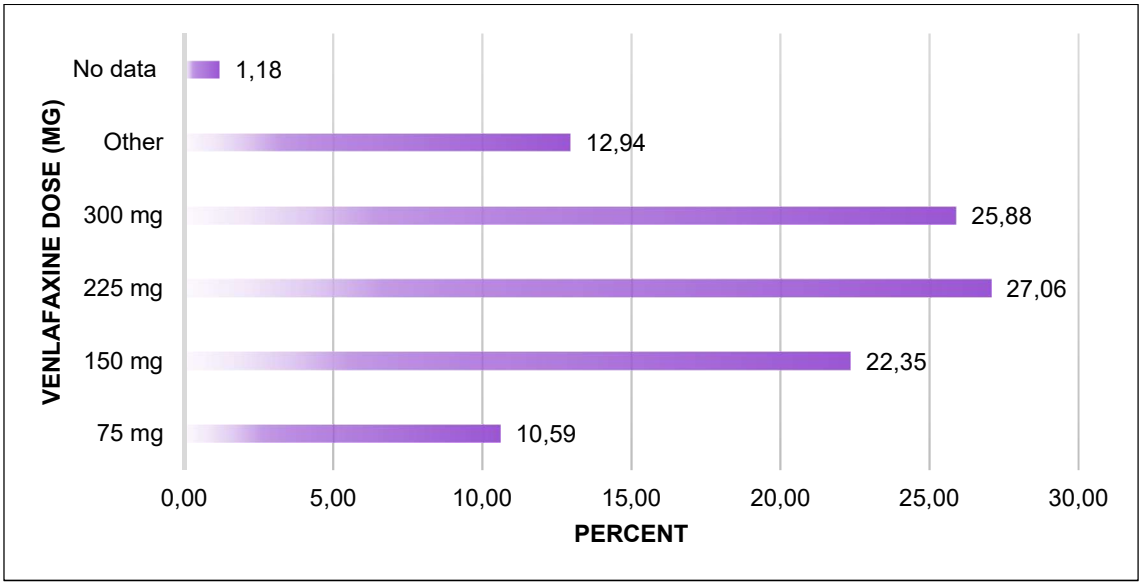

Figure 4–22. Maintenance dose of venlafaxine prescribed (n=85).

From the results it is clear that 225 mg was the maintenance dose prescribed to most patients in the study sample (n=23; 27.06%) which was closely followed by 300 mg (n=22; 25.88%). These results were compliant with the recommended guidelines which suggest that 225 mg venlafaxine per day is the maximum dose that can be used for moderately depressed patients and 375 mg per day is the maximum dose for severely depressed patients (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:41).

The following tables provide a summary of the venlafaxine doses prescribed at the study site.

Table 4–48. A summary of venlafaxine doses prescribed at the study site (n=85).

Antidepressant	Mean Dose (mg)	Standard Deviation (mg)	Range (mg)
Venlafaxine	213.53	84.65	75-375

Table 4–49. The PDD and DDD of venlafaxine for the patient sample (n=85).

Antidepressant	PDD (mg)	WHO DDD (mg)
Venlafaxine	213.53	100

A study based in New Zealand revealed that the PDD calculated in that patient population for venlafaxine ranged from 113-215 mg between the years 1999 to 2004 (Ministry of Health, 2007:14). The PDD calculated for the current study was 213.53 mg which is within the range that was calculated in the New Zealand-based study.

4.8 Change of antidepressant

During the study period, there were five patients who had their antidepressants changed. Two patients changed from venlafaxine to fluoxetine, the other two changed from venlafaxine to amitriptyline and the last one changed from venlafaxine to sertraline. From the five patients, four were females and one was a male.

4.9 Chapter 4 summary

This concludes the results of the empirical study. The results of the retrospective drug utilisation study conducted were presented, interpreted and discussed in this chapter under the following headings: Patient demographics, patient past and current medical and drug use information, monitoring procedures, details of venlafaxine use and compliance with the recommended guidelines for the initiation and management of venlafaxine treatment. The conclusions and recommendations of the study will be discussed in the next chapter.

CHAPTER 5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Introduction

The conclusions, recommendations and limitations of the current research study are discussed in this chapter.

5.2 Conclusions

The conclusions for this study will be discussed in relation to the specific research objectives stated in Chapter 1.

The aim of the current study was to evaluate the prescribing and management practices of venlafaxine to outpatients at Fort England Hospital in Grahamstown (Makhanda). A drug utilisation review was conducted to determine whether the initiation and monitoring of patients on venlafaxine at the study site complied with the recommended guidelines. The study revealed that the current practice of venlafaxine initiation and monitoring at the study site was appropriate and according to the recommended guidelines however it could be clinically enhanced.

The study results indicated that most of the patients in the study sample were diagnosed with either a depressive or anxiety-related disorder. Therefore, venlafaxine was correctly indicated for most (77.65%) of patients in the study. However, 22.35% of patients received venlafaxine treatment for diagnoses other than what venlafaxine is indicated for, suggesting that venlafaxine treatment was indicated for off-label purposes. These diagnoses included: Bipolar mood disorder, treatment of pain disorders (neuropathies and fibromyalgia), post-traumatic stress disorder and substance use disorder. In view of the above, it was established that in most cases venlafaxine was rationally utilised, nevertheless current practice needs to be revised in order to improve future clinical outcomes.

5.2.1 Literature review

The conclusions that were found from the literature study (CHAPTER 2) will be presented below. Each of the specific objectives for the literature review will now be discussed in detail.

The first specific research objective was to obtain information from the literature on the history of the development of venlafaxine:

- It was discovered that venlafaxine immediate-release (IR) was the first serotonin-noradrenaline reuptake inhibitor (SNRI) to be marketed in the United States (Sansone and Sansone, 2014:37).
- It was first approved by the United States Food and Drug Administration (US FDA) in 1993 (Sansone and Sansone, 2014:37).
- The debut of venlafaxine IR was soon followed by the introduction of a micro-encapsulated extended-release (XR) formulation in 1997, known as Effexor XR™.
- Venlafaxine XR was formulated for a convenient single daily dose as compared to the IR formulation which is a twice a day dose formulation.
- In addition, the XR formulation has the advantage of causing less nausea and dizziness at the initiation of therapy. However, the integrity of the capsule cannot be compromised prior to or during ingestion, and must be swallowed whole to protect the release mechanism of the capsule (Sansone and Sansone, 2014:38).
- Both the venlafaxine IR and XR formulations are conveniently available as brand and generic formulations which offers cost-effective treatment alternatives.
- Venlafaxine XR was the first SNRI that the FDA approved for the treatment of major depressive disorder (MDD) (Goldenberg, 2008:233).
- Venlafaxine has four approved clinical indications through the FDA: Major depression, generalised anxiety disorder, panic disorder and social phobia.

The second specific research objective was to acquire information from the literature on the pharmacological properties of venlafaxine, including the pharmacodynamics and pharmacokinetics in comparison to other antidepressants:

- Venlafaxine displays a distinctive pharmacological profile with unique antidepressant properties compared to the other SNRIs and other antidepressant classes (Celikyurt *et al*., 2012:95; Horst and Preskorn, 1998:243; Rossiter *et al*., 2016:503).

- Venlafaxine is pharmacologically classified as a SNRI antidepressant (psychoanaleptic) (Gutierrez *et al*., 2003:2139; Rossiter *et al*., 2016:503; Sansone and Sansone, 2014:37).
- The mechanism of action of SNRIs is to inhibit the reuptake of neurotransmitters from the synaptic cleft by selectively binding to the serotonin and noradrenaline transporters (Celikyurt *et al*., 2012:92).
- Serotonin, noradrenaline and dopamine reuptake inhibition are responsible for venlafaxine's antidepressant activity (Horst and Preskorn, 1998:243).
- The initial adverse effects experienced are related to serotonin reuptake inhibition (e.g. nausea and sexual dysfunction), and at higher doses the adverse effects are related to both serotonin- and noradrenaline reuptake inhibition such as dry mouth and night sweats (Sansone and Sansone, 2014:92).
- The inhibition of serotonin and noradrenaline reuptake occurs at different doses, suggesting that venlafaxine may exhibit a clinical dose response curve for antidepressant efficacy (Horst and Preskorn, 1998:243; Preskorn, 1994:15).
- Venlafaxine as compared to other antidepressants has a unique ability to downregulate β-adrenoceptors after a single dose, which is assumed to be the reason for a more rapid onset of antidepressant activity over the other antidepressants (Muth *et al*., 1986:4493-4497, 1991:191-199).
- Venlafaxine is unlikely to cause sedation, weight gain or orthostatic hypotension.
- Venlafaxine is widely distributed, therefore once treatment is initiated the therapeutic effects of venlafaxine are usually achieved within 3 to 4 weeks (Celikyurt *et al*., 2012:96).
- The half-life of venlafaxine is extended when administered as the XR formulation.
- Venlafaxine is extensively metabolised in the liver (Celikyurt *et al*., 2012:95; Horst and Preskorn, 1998:243; Rossiter *et al*., 2016:503; Sansone and Sansone, 2014:38).
- The primary route of excretion of venlafaxine and O-desmethylvenlafaxine (ODV) is via the kidneys through renal elimination (Celikyurt *et al*., 2012:96; Wyeth Pharmaceuticals, 2003:3).

The third specific research objective was to gain knowledge from the literature on the toxicological properties of venlafaxine (adverse effects, interactions, safety in pregnancy and lactation, use in specific patient populations) and compare it to other antidepressants:

- It was established that venlafaxine therapy is contraindicated in the following cases: Concomitant monoamine oxidase inhibitor therapy; paediatric patients; hypersensitivity to venlafaxine HCl or any excipients in the formulation; pregnancy and lactation (Cipla Medpro, 2006:1; Kent, 2000:916; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:9).
- According to the South African Medicines Formulary (SAMF) and US FDA, venlafaxine is classified as a category C risk factor drug in pregnancy (Gutierrez *et al*., 2003:2148; Rossiter *et al*., 2016:503). Therefore, the drug should not be used unless the potential benefits outweigh the potential risk for the patient.
- With reference to lactation, venlafaxine is excreted in human breast milk (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:24), therefore it should be carefully considered whether to discontinue lactation due to the importance of the drug to the mother or to continue with lactation, potentially causing serious adverse effects to the foetus.
- It is recommended that patients with moderate hepatic impairment (e.g. diagnosed with hepatic cirrhosis) reduce their initial venlafaxine dose by 50%.
- Elderly patients have reduced clearance rates, therefore caution should be exercised with their dose adjustments. According to the SAMF, elderly patients can start venlafaxine treatment at an initial dose of 37.5 mg/day (Rossiter *et al*., 2016:503).
- The total daily venlafaxine dose should be reduced by 25-50% for renal impaired patients (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:43).
- It is recommended that the total daily venlafaxine dose be reduced by 50% for patients that undergo dialysis, and be withheld until the dialysis treatment is completed for at least 4 hours (Wyeth Pharmaceuticals, 2003:43).
- The adverse effects experienced with venlafaxine therapy were not quite severe.

- According to the literature (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503), a few common adverse effects experienced by patients include the following: Central nervous system effects such as headache, dizziness, insomnia, nervousness, somnolence and visual disturbances; gastrointestinal complaints such as anorexia, dry mouth, nausea, vomiting, constipation; sexual dysfunction; sweating and fatigue. However, it was established that many of these are dose-related and decrease in frequency and intensity with prolonged treatment, therefore there is no need to discontinue treatment (Cipla Medpro, 2006:1).
- It was determined that venlafaxine has drug interactions with the following drugs: Alcohol/CNS active drugs, aripiprazole, aspirin, bupropion, cimetidine, duloxetine, haloperidol, indinavir, linezolid, lithium, MAOIs, moclobemide, olanzapine, SSRIs, TCAs and warfarin (Cipla Medpro, 2006:1; Leesette Turner, 2010:494; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:20).
- It was established that patients on venlafaxine therapy require regular blood pressure, weight and pulse rate monitoring.

The fourth specific research objective was to obtain information from the literature on depressive and anxiety-related disorders and their prevalence in South Africa:

- Depressive disorders are comprised of the following: Disruptive mood dysregulation disorder, dysthymia, premenstrual dysphoric disorder, substance/drug-induced depressive disorder, depressive disorder due to another medical condition, other specified disorder and unspecified depressive disorder.
- MDD is characterised by a single, or recurrent major depressive episodes, and the diagnosis requires a distinct change of mood that is characterised by a depressed mood accompanied by social withdrawal as well as loss of interest and reduced experience of pleasure.
- The lifetime incidence of depression specific to gender is more than 12% in men and 20% in women (Belmaker and Agam, 2008:55; Fava and Kendler, 2000:335).
- The lifetime prevalence of MDD in South Africa was found to be 9.8% across all age groups (Emsley *et al*., 2013:157; Seedat *et al*., 2009:377).

- It was established that female patients with a previous episode of major depression and a positive first-degree family history of depression are the most consistently described risk factors for MDD (Emsley *et al*., 2013:157).
- Anxiety disorders include disorders that share features of excessive fear, anxiety and related behavioural disturbances.
- Anxiety disorders differ from each in the types of objects or situations that induce fear, anxiety or avoidance behaviour and the cognitive ideation. It is important to make the correct diagnosis of anxiety disorder in order to provide the most appropriate treatment.
- GAD is characterised by key features such as chronic, excessive, difficult-to-control worry, a range of somatic symptoms and the presence of persistent intrusive thoughts or concerns, and is usually associated with compulsions, which are mental acts or behaviours related to the obsessions, e.g. excessive hand washing.
- The 12-month prevalence of GAD is 0.9% among adolescents and 2.9% among adults in the United States, and in other countries, the 12-month prevalence for the disorder ranges from 0.4% to 3.6% (American Psychiatric Association, 2013:223; Emsley *et al*., 2013:175).
- Panic disorder (PD) refers to recurrent unexpected panic attacks. A panic attack is characterised by an abrupt surge of intense fear or discomfort.
- PD is more common in women than in men with a ratio of 2:1 (American Psychiatric Association, 2013:210; Emsley *et al*., 2013:172)..
- The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) states that the 12-month prevalence estimate for PD across the US and several European countries is approximately 2-3% in adults and adolescents (American Psychiatric Association, 2013:210).
- It was discovered that smoking is a risk factor for panic attacks as well as panic disorder.
- The key feature of social anxiety disorder (SAD) is a marked or intense fear or anxiety of social situations in which the individual may be analysed by others.

- The median age of onset for SAD is 13 years of age (American Psychiatric Association, 2013:205; Emsley *et al*., 2013:192). SAD characteristically continues throughout adulthood and is associated with substantial functional impairment.
- The DSM-5 states that the 12-month prevalence estimate for SAD in the United States is approximately 7% (American Psychiatric Association, 2013:204).
- It was found that childhood maltreatment and difficulty are risk factors for SAD.

The fifth specific research objective was to gain knowledge from the literature on the drug treatment guidelines of depressive and anxiety-related disorders, where venlafaxine therapy can be considered as a treatment option:

- According to the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) for South Africa (SA) the following steps should be followed for MDD treatment (National Department of Health, 2015:15.8-15.9):

  - If patient is currently on a SSRI, change treatment to another SSRI (citalopram) or a tricyclic antidepressant (TCA).
  - If patient is currently on a TCA, switch to a SSRI.
  - If patient was initially on fluoxetine, wait for seven days after stopping fluoxetine before starting citalopram (the other SSRI).

- According to The SASOP Treatment Guidelines for Psychiatric Disorders, cognitive-behavioural therapy (CBT) or interpersonal therapy IPT either alone or in combination with an SSRI, a SNRI (e.g. venlafaxine), bupropion, mirtazapine or agomelatine should be considered for MDD treatment (Emsley *et al*., 2013:159-162).
- For the management of GAD, the STGs and EML for SA suggests using benzodiazepine treatment for acute management of GAD and SSRIs for the maintenance therapy of GAD (National Department of Health, 2015:15.10).

- The SASOP Treatment Guidelines for Psychiatric Disorders recommends that both pharmacotherapy and psychotherapy are efficacious first-line approaches for GAD (Emsley *et al*., 2013:176-178). First-line pharmacotherapy of uncomplicated GAD comprises the use of an SSRI (e.g. fluoxetine, citalopram) or SNRI (e.g. venlafaxine, duloxetine) drug. For short-term use, benzodiazepines are advised (Emsley *et al*., 2013:176-178).
- The STGs and EML for SA advises the use of benzodiazepine treatment for acute management of panic attacks. CBT and SSRI antidepressants are recommended for the treatment of PD (National Department of Health, 2015:15.12).
- Both pharmacological therapies and CBT are considered first-line treatments for PD by the SASOP Treatment Guidelines for Psychiatric Disorders. Antidepressants from within the SSRIs and SNRIs are the preferred, namely citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline and venlafaxine (Emsley *et al*., 2013:172-174).
- CBT is a good alternative for females diagnosed with PD who plan to become pregnant, and for pregnant women who need to discontinue medication (Emsley *et al*., 2013:172-174).
- The STGs and EML for SA did not have any information available concerning the treatment of SAD.
- The SASOP Treatment Guidelines for Psychiatric Disorders states that SAD is highly responsive to pharmacological treatment, mostly SSRIs (e.g. escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), venlafaxine, phenelzine, moclobemide, some benzodiazepines (clonazepam), anticonvulsants (gabapentin, pregabalin) and olanzapine. Psychological treatment such as CBT is also greatly effective (Emsley *et al*., 2013:192-195).
- It was established that the STGs and EML for SA did not recommend or list venlafaxine as a treatment option for MDD, GAD, SAD or PD.

The sixth specific research objective was to gain information from the literature to determine what constitutes a drug utilisation review as well as the importance and objectives thereof:

- Drug utilisation research may be separated into analytical or descriptive studies.

- It was discovered that a DUR is drug- or disease-specific and can be designed to assess the actual process of prescribing, dispensing or administering a drug, such as indications, dose and dosing instructions.
- DURs are classified in three categories: Prospective, concurrent and retrospective.
- The primary aim of a DUR is to promote optimal drug treatment as well as ensuring that drug treatment is of suitable quality and meets the current standards of care.
- The DUR process allows pharmacists to identify patterns in prescribing within the patient population and thereafter consult prescribers and other healthcare professionals on collaborative methods to improve drug treatment for patients.
- It was understood that there are numerous methods that can be followed to conduct a drug utilisation review and each is specific to the aims and objectives of the research.
- Data for drug utilisation studies may be acquired from various sources, the source of data is specific for each study and depends on the study design and study objectives.

The seventh and last specific research objective was to acquire information from the literature regarding drug utilisation reviews on antidepressants in general and specifically on venlafaxine in the public and private sectors, locally and internationally:

- Literature found regarding general DURs conducted on antidepressants from internationally published literature were included.
- Published literature that was discovered concerning DUR studies conducted specifically on venlafaxine was reviewed. The majority of these studies supported the favourable clinical profile of venlafaxine.
- An old review discovered that venlafaxine was well tolerated during short- and long-term treatment and concluded that venlafaxine may be a logical first-line therapy in a broad range of patients with MDD (Dierick, 1997:307s-313s)..
- The results of another study supported the use of venlafaxine as an alternative for SSRI-resistant depression (Papakostas *et al*., 2008:699-704).

- A fundamental observation was noted for the important role venlafaxine has in the long-term prevention of depressive relapse and recurrence, also in patients with treatment resistant depression who have failed to respond to initial therapy.
- A number of studies supported the efficacy of venlafaxine therapy for MDD treatment and several studies concluded that remission rates were similar or slightly higher with venlafaxine when compared to treatment with an SSRI.
- It was established that published drug utilisation reviews on antidepressants that were conducted in SA (included in the review) date back to more than a decade ago (e.g. conducted in 1996 and 2003). These studies were restricted to data sourced from private medical aid schemes and analysed classes of antidepressants as opposed to a specific antidepressant or to data gathered from public sector institutions.
- The studies suggest that SSRIs and TCAs are the most commonly prescribed antidepressants in SA. Females were the gender with the most prescribed antidepressants. The age group for which most antidepressants were prescribed to were between 12 and 19 years of age.
- To the best of the researcher's knowledge, no specific South African studies on the use of venlafaxine in either the public or private healthcare sectors without data sourced from medical aid schemes could be found, suggesting a deficit of data specifically in the South African public sector.
- From the summary of published literature that was found concerning possible challenges experienced with prescribing venlafaxine therapy, it was established that hypertension could occur with venlafaxine treatment, especially at higher doses (Khawam *et al*., 2006: 351-3, 356-61). However, apprehension regarding blood pressure effects should not deter first-line use but prescribers should be cautious when prescribing venlafaxine to patients with pre-existing hypertension. In addition, it is imperative that blood pressure be monitored regularly, especially when using venlafaxine XR at doses of 225 mg or more per day.
- It was additionally concluded that prescribers should be aware of the risk of hyponatraemia when prescribing venlafaxine in elderly patients with multiple drug therapies. It is imperative that sodium levels be monitored during treatment with venlafaxine.

- Off-label prescribing of venlafaxine was indicated for the following disorders: Depression associated with anxiety; non-hormonal treatment option for hot flashes; binge-eating disorder associated with obesity; treatment of painful polyneuropathy; symptoms in young adult patients with functional chest pain; and fibromyalgia (Bradley *et al*., 2003; Khan *et al*., 1998; Lee *et al*., 2010; Loprinzi *et al*., 2000; Malhotra *et al*., 2002; Rudolph *et al*., 1998; Sindrup *et al*., 2003).
- A review of the international prescribing patterns of antidepressants exhibited an overall increase in the number of antidepressant prescriptions over the years across countries. The studies showed a decline in the use of older generation antidepressants (e.g. TCAs) and an increase in the newer generation (e.g. SNRIs).
- In addition, the review presented SSRIs as the most commonly prescribed antidepressant class across countries.

5.2.2 Empirical study

The conclusions that were established from the empirical study (CHAPTER 4) will be stated below. For the empirical investigation each of the specific objectives will be discussed. The specific objectives were accomplished by performing a drug utilisation review through analysing data acquired from 85 patient files and prescriptions at the study site.

The first specific research objective for the empirical study was to determine the prescribing patterns of venlafaxine at Fort England Hospital:

- According to the patient demographics of the study sample, the average weight of the patient sample was 79.26 kg ± 23.57 kg. The results showed that the lightest patient in the sample was 42.30 kg and the heaviest patient was 129 kg.
- From the results it is evident that most patients were in the normal weight category with a body mass index (BMI) range from 18.5-25 kg/m^2 (n=16; 18.82%). This result was in accordance with the literature as it is recommended by the South African National Department of Health that a BMI of < 25 kg/m^2 is ideal and should be maintained (National Department of Health, 2015:3.29).

- The patient sample consisted of a higher number of female patients. From the 85 patients in the sample 65 (76.47%) were females and 20 (23.53%) were male patients.
- The result corresponds with the literature, which indicates that the female gender is associated with significantly higher odds of any mood or anxiety disorder (Seedat *et al*., 2009:381). Findings from other DURs also suggested a higher number of prescriptions for females (Burger *et al*., 2009; Kairuz *et al*., 2003; I Truter, 2010; Truter and Kotze, 1997, 1996; Van Schalkwyk and Truter, 2010).
- The patient demographics of the study sample indicated that most patients in the study were middle aged adults between the ages of 35 and 50 years (n=33; 38.82%). The average age of the patients were 46.15 years ± 14.66 years. The analysis showed that the youngest patient in the sample was 18 years old.
- The sample consisted of 10 elderly patients (65 years and older), this patient group should be monitored carefully as they may require dose adjustments to compensate for their reduced clearance rates (Celikyurt *et al*., 2012:96).
- The results exhibited that most male (n=7; 35%) and female (n=26; 40%) patients were in the same age category of 35 to 50 years. It can be concluded that female patients between the ages 35 to 50 years were the majority of patients on venlafaxine treatment at the study site.
- The majority of the patient sample were white patients (n=54; 63.53%) followed by African (n=16; 18.82%), coloured (n=14; 16.47%) and lastly patients of Asian (Chinese) (n=1; 1.18%) ethnicity.
- Most of the patients in the sample's marital status was single (n=32; 37.65%), followed by married (n=24; 28.24%), divorced (n=13; 15.29%), unmarried (n=10; 11.76%) and other (n=2; 2.35%) meaning either separated or widowed.
- A comparison of gender and marital status suggested that single female patients were the majority of patients on venlafaxine treatment (n=25; 38.46%).
- Fortunately, most of the patients did not use tobacco (n=77; 90.59%). The chemicals found in cigarettes decrease the concentration of antidepressant drugs in the blood, thus resulting in a diminished antidepressant effect (Oliveira *et al*., 2017).
- 78.82% (n=67) of patients did not consume alcohol during the study period.

- A total of 45.88% (n=39) of patients were unemployed during the study period. The result corresponds to the findings in the literature which demonstrated that the prevalence of anxiety and depression was higher among those who were out of the labour market as compared to those who were employed (Hiswåls *et al*., 2017).
- Regarding hospital history, 32 patients (37.65%) had one previous hospital admission, 28 patients (32.94%) did not have any previous hospital admissions.
- The results specified that 50.59% of patients on venlafaxine treatment did not have a family history of psychiatric illness.
- It was determined that 45.88% (n=39) of the patient sample had no other past or current co-morbid diseases present during the study period.
- From the results it was evident that 72.94% of patients did not use contraceptives.
- It was discovered that 22.35% of patients used venlafaxine treatment for some other off-label use other than the four FDA-approved indications. 15.29% of patients were diagnosed with major depressive disorder, 15.29% diagnosed with major depressive disorder and generalised anxiety disorder and 20.00% diagnosed with major depressive disorder and some other disorder.
- The high number of prescriptions for MDD suggest that venlafaxine treatment is a viable treatment option for MDD.
- The use of venlafaxine treatment for off-label uses is supported by the literature (Bradley *et al*., 2003; Khan *et al*., 1998; Lee *et al*., 2010; Loprinzi *et al*., 2000; Malhotra *et al*., 2002; Rudolph *et al*., 1998; Sindrup *et al*., 2003). It was discovered that there are numerous additional uses of SNRIs, which include: Treatment of pain disorders (neuropathies and fibromyalgia), generalised anxiety, menopausal vasomotor symptoms and stress urinary incontinence (Celikyurt *et al*., 2012:91).
- The results revealed that 72.94% of the patient sample had used venlafaxine treatment previously prior to the study period. For most of the patients (n=38; 44.71%) the first initiation of venlafaxine occurred between 1 and 5 years ago which indicates long-term use of venlafaxine by patients that were satisfied with their treatment.

- It was established that 37.50% (n=30) of patients had one previous antidepressant prescribed prior to venlafaxine treatment being initiated. This suggests that venlafaxine was used as second-line treatment in these cases.
- From the results it was clear that most patients (n=45; 56.25%) used the SSRI class of antidepressants prior to venlafaxine.
- Findings from the literature supported the use of venlafaxine as a MDD treatment alternative for those patients who are unresponsive to initial antidepressant therapy or for SSRI-resistant depression (Baldomero *et al*., 2005; Fang *et al*., 2010; Papakostas *et al*., 2008; Poirier and Boyer, 1999; Rush *et al*., 2006; Thase *et al*., 2011).
- The doses used at the initiation of venlafaxine treatment and for maintenance therapy were evaluated. From the results it is evident that the initial dose used by most patients (51.76%) was 37.5 mg/day for 4 to 7 days and 225 mg was the maintenance dose prescribed to most patients in the study sample (n=23; 27.06%).
- The PDD calculated for the patient sample was 213.53 mg, which is higher than the WHO DDD of venlafaxine at 100 mg.
- It was determined that venlafaxine is rationally used for the treatment of depressive disorders at Fort England Hospital.

The second specific research objective for the empirical study was to determine compliance with the recommended guidelines for the initiation and maintenance of venlafaxine treatment:

- According to the SAMF and the SASOP Treatment Guidelines for Psychiatric Disorders, venlafaxine treatment should be initiated at 37.5 mg/day for 4-7 days, especially for new patients, to allow patients to adjust before increasing the dose to 75 mg/day (Cipla Medpro, 2006:1; Emsley *et al*., 2013:159-162; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:5).
- The results demonstrated that 78.82% of the patients had their dose titrated from the initiation of venlafaxine treatment, suggesting that the prescribing of venlafaxine was compliant with the recommended initiation guidelines.

- It was established that the initial dose used by most patients (51.76%; n=44) was 37.5 mg/day for 4 to 7 days before increasing to 75 mg/day, which is compliant with the recommended initiation guidelines for venlafaxine. However, 14.12% (n=12) of patients were prescribed a different dose from the recommended doses.
- Dose titration (maintenance) should be in increments of 75 mg/day as needed and should be made at intervals of not less than 4 days (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:41).
- Regarding the frequency of dose titrations which was performed in 75 mg intervals, it was evident from the results that 34.12% of the patient sample had no dose titration performed to their venlafaxine treatment, suggesting that they were well-controlled on the initial dose prescribed. In addition, 24.71% of patients received increments of dose titrations every 2 weeks, suggesting that they received treatment optimisation therapy and required a check-up every 2 weeks. It can be concluded that the frequency and dose used for all dose titrations at the study site were according to the recommended guidelines.
- According to the prescribing guidelines, 225 mg venlafaxine per day is the maximum dose that can be used for moderately depressed patients and 375 mg per day is the maximum dose for severely depressed patients (Cipla Medpro, 2006:1; Rossiter *et al*., 2016:503; Wyeth Pharmaceuticals, 2003:41).
- The results indicated that 225 mg was the maintenance dose prescribed to most patients in the study sample (n=23; 27.06%) followed by 300 mg which accounted for 25.88% (n=22) of the patients.
- Doses prescribed to the patient sample ranged from 75-375 mg per day.
- Overall, it can be concluded that both the initiation and maintenance of venlafaxine therapy was fairly compliant with the recommended guidelines. However, additional emphasis should be placed on the correct dose for the initiation of venlafaxine treatment according to the patient's diagnosis to prevent dose-related adverse effects, thus causing unnecessary harm to the patient.

The third specific research objective for the empirical study was to identify drug-related problems such as drug interactions associated with the use of venlafaxine:

- The results exhibited that in the majority of the patients there were no drug interactions identified in their treatment plans (n=59; 69.41%).
- From the 26 patients that had drug interactions identified, 84.62% (n=22) had one drug interaction identified in their treatment plan. 15.38% (n=4) had two drug interactions identified in their treatment plan.
- Eight drugs were responsible for the first drug interaction, namely: Lithium carbonate, amitriptyline, risperidone, clomipramine, bupropion, fluoxetine, olanzapine and aspirin.
- The results displayed that amitriptyline had the greatest number of interactions with venlafaxine (n=11; 42.31%) for the first drug interaction.
- Four drugs were responsible for the second drug interaction, namely: Clozapine, olanzapine, aspirin and risperidone.
- Each of the four drugs had an equal number of interactions with venlafaxine (n=1, 25%) for the second drug interaction.

The fourth specific research objective for the empirical study was to investigate the presence of adverse effects possibly associated with the use of venlafaxine:

- The data analysis revealed that 74.12% (n=63) of patients did not experience any adverse effects from treatment with venlafaxine during the study period.
- From the 21 patients who experienced an adverse effect, it was found the most common adverse effect was insomnia 18.18% (n=4), notwithstanding those patients that experienced other adverse effects (59.09%, n=13) during the study period.
- The other adverse effects experienced by 59.09% (n=13) comprised of the following: Worsening of mood, tachycardia, headache, anxiety, heartburn, increased blood pressure (BP), vertigo and a decreased appetite. Headaches accounted for the majority (33.33%, n=5) of the other adverse effects experienced.

- From the results it is evident that 90.91% (n=20) of patients had their adverse effect treated. This implies that the monitoring and follow up of patients' treatment plan at the study site was effective.
- During the study period, five patients from the patient sample (n=85) had their treatment changed from venlafaxine to another antidepressant. The first patient experienced increased BP at extreme values, the second patient experienced vertigo and dizziness and therefore wanted to discontinue venlafaxine. The third patient was intolerable to venlafaxine treatment. The fourth patient experienced insomnia and the fifth patient experienced persistent headaches, prompting a change in antidepressant.

The fifth and last specific research objective for the empirical study was to assess the degree of compliance with the recommended guidelines for metabolic and general monitoring of venlafaxine:

- The results indicated that blood pressure monitoring was conducted for 95.29% of the patients in the sample, suggesting that the blood pressure monitoring procedures were conducted according to recommended guidelines.
- In terms of the frequency of blood pressure monitoring, the results indicated that monitoring was conducted once to twice a month for most of the patients (36.59%) in the sample, followed by once every month for 29.27% of the patients, suggesting that the blood pressure monitoring procedures was compliant with the recommended guidelines.
- From the results it was evident that 80.49% (n=66) of the patient sample on venlafaxine treatment had blood pressure readings within the safe range according to the recommended guidelines.
- It was determined that body weight monitoring was performed for 94.12% (n=80) of the patients in the sample.
- From the results it was found that 51.22% (n=42) of the patient sample on venlafaxine treatment had BMI values that were not within a safe range according to the recommended guidelines. This is a target area for improvement where simple lifestyle modifications can be introduced, e.g. appropriate diet and exercise plans.

- Unfortunately, 30.49% (n=25) of patients had no information available in their files regarding their height thus their BMI could not be calculated. It is suggested that weight and height recordings should be taken regularly.
- The results of the study indicated that 95.29% (n=81) of the venlafaxine patient sample had their pulse rate monitored, therefore adhering to the recommended monitoring guidelines.
- It was found that 68.29% of the patient sample on venlafaxine treatment had pulse rate readings within a safe range according to the recommended guidelines.
- The guidelines suggest that patients diagnosed with diabetes, have kidney disease or who are overweight, should have their cholesterol levels monitored frequently (The Heart and Stroke Foundation, 2017).
- Concerning lipid/lipoprotein monitoring, the majority of patients (n=58; 68.24%) did not have information available in their files, suggesting that monitoring was not conducted. This is one observation of poor compliance to the recommended monitoring guidelines.
- However, 31.76% of patients had their total cholesterol monitored, thus adhering to the recommended monitoring guidelines. The results indicated that total cholesterol monitoring was conducted annually for most patients (30.59%).
- The results of patients who had their total cholesterol monitored indicated that 59.26% had total cholesterol readings within a safe range according to the recommended guidelines.
- It was established that only 5.88% of the patient sample had their triglyceride levels monitored, 9.41% had their LDL monitored and 9.41% of patients had their HDL monitored.
- With regards to the monitoring of sodium levels, there was no information available in the patient files, suggesting that monitoring was not conducted especially for the elderly patients. This is a second observation of poor compliance to the recommended monitoring guidelines.

5.3 Recommendations

The current drug utilisation study generated beneficial information and the following recommendations can be made:

- An ongoing DUR programme should be implemented at Fort England Hospital to assist in identifying prescribing patterns and difficulties with venlafaxine therapy to promote the optimal use of the antidepressant.
- Patients with MDD or co-morbid depression who are on venlafaxine treatment need to be monitored for clinical worsening or possible suicidality.
- To promote the rational use of venlafaxine, all healthcare professionals need to be knowledgeable on the use of current treatment guidelines.
- During the data analysis the investigator observed that three patients had venlafaxine therapy abruptly withdrawn. Therefore, education needs to be provided about the steps for the discontinuation of venlafaxine therapy and symptoms of abrupt venlafaxine withdrawal. The sudden cessation of treatment or a reduction in the dose of venlafaxine is associated with the development of undesirable symptoms, such as agitation, anxiety, diarrhoea, dry mouth, fatigue, nausea, sweating and vomiting (Wyeth Pharmaceuticals, 2003:13). Therefore, a gradual dose reduction over at least 4 weeks is suggested (Rossiter *et al*., 2016:503). Tapering of the dose should be completed by reducing the daily dose by 75 mg at 1 week intervals (Wyeth Pharmaceuticals, 2003:13).
- Healthcare professionals need to be educated on the monitoring requirements of venlafaxine (blood pressure; pulse rate; body weight; sodium levels, especially in the elderly; and total cholesterol levels in patients with co-morbid disorders).
- Leaflets[1] can be designed for patients and healthcare professionals to contain useful information on the use of venlafaxine, e.g. indicated doses, common adverse effects and monitoring requirements. The leaflets can be distributed to patients who are prescribed venlafaxine from the doctors' rooms or the leaflets can be displayed in the foyer of the pharmacy at Fort England Hospital.
- Prescribers need to be educated on the use of current recommended treatment guidelines for venlafaxine initiation which can be promoted through educational workshops.
- Education on the effects of alcohol and smoking on venlafaxine therapy should be provided to healthcare professionals so that they can advise patients accordingly.

[1] A patient information leaflet on venlafaxine was created by the researcher and presented to the in-patients at Fort England Hospital on 14/06/2018, 06/08/2018 and 10/09/2018; and to nursing staff on 20/09/2018 (ANNEXURE G).

- The method of filing and recording information in the patient files at Fort England Hospital should be improved and follow a logical order, e.g. recent information should be available at the top of the file.
- A guideline for the initiation and monitoring of venlafaxine in the form of a simple guidance document should be developed. On initiation of therapy, a copy of this document should be placed in the patient files, designed to record the initial doses, details of dose titration, monitoring and counselling information. The dates and results of all monitoring procedures should also be recorded in this document, counselling provided to the patient as well as any experienced adverse effects or identified drug interactions. This will assist with record keeping of patient files at the study site, thus making it easier to access essential information amongst other information. This document will provide better understanding of patients' treatment plans, improve communication between the prescriber and the dispenser with regards to the health of the patient and enhance the provision of venlafaxine therapy according to recommended guidelines.
- Presentations should be performed to healthcare professionals to explain their role in the initiation and monitoring of venlafaxine therapy and how to use the document to efficiently record data, especially results of monitoring procedures.
- The STGs and EML for Hospital Level for Adults needs to be reviewed to include venlafaxine as a treatment option for MDD, GAD, PD and SAD according to the appropriate doses.
- Prescribers should be aware that patients switching to or from a MAOI should wait at least 14 days in between the discontinuation of a MAOI and initiation of venlafaxine treatment (Wyeth Pharmaceuticals, 2003:44). In addition, at least 7 days should lapse after terminating venlafaxine treatment and initiating treatment with a MAOI.
- Awareness on the use of contraception needs to be raised in female patients of child-bearing age on venlafaxine therapy and those who have not yet reached menopause. Venlafaxine is classified as a category C risk factor drug in pregnancy, therefore the drug should not be used unless the potential benefits outweigh the potential risk for the patient or foetus (Rossiter *et al*., 2016:503).

- There were incidences when healthcare professionals at Fort England Hospital removed information from patient files for use and did not return it to the correct file position. This resulted in confusion of records and sometimes loss of information. They should therefore refrain from removing information in patient files or follow a protocol in the pharmacy to return patient files as they were found to prevent such loss or confusion of information.
- Patient demographics (e.g. gender and height) should be recorded as detailed as possible in patient files, especially for new patients to provide the prescriber with a comprehensive profile of the patient.
- Family interventions and caregiver support is encouraged to improve adherence to therapy and positively influence the patient's mental health.
- Conveniently, both venlafaxine IR and XR formulations are available as brand and generic formulations for cost-effective treatment options for depressive or anxiety-related disorders.
- A document should be included and maintained in the patients' files to efficiently record the identification of drug interactions with treatment.
- Venlafaxine therapy should be considered in patients diagnosed with depressive or anxiety-related disorders, especially those who do not respond to initial antidepressant therapy or are treatment-resistant.

5.4 Recommendations for future studies

- The current study could be extended to include a patient questionnaire component to assess patient satisfaction or apprehensions about venlafaxine therapy.
- To implement drug utilisation reviews and related studies on venlafaxine at other institutions in other provinces in SA to determine a general overview of venlafaxine use in South Africa as well as to identify national prescribing trends.
- Future research studies similar to the current DUR can be performed using a larger sample size and additional study sites to evaluate the cost-effectiveness of venlafaxine treatment compared to other antidepressants.
- A possible future study could be to establish the cardiovascular effects associated with venlafaxine therapy in the wider South African population.

- To conduct a similar study to the current DUR, in which two or three groups of patients are assessed to determine whether venlafaxine has better remission rates as compared to a conventional antidepressant in the South African population. One group would be prescribed venlafaxine, the second group fluoxetine and the third group citalopram, thereafter their remission rates would be compared.
- Possible future studies could be to conduct DURs to compare the efficacy of venlafaxine therapy with other drugs used in the treatment of mental health disorders.

5.5 Research project limitations

The current DUR study had the following research limitations:

- Patient information in the files was often incomplete depending on the clinical documentation done by the healthcare professional, or when the patient was referred from other healthcare institutions. Some patients may have defaulted on their treatment and not returned to the hospital, which affected the completeness of the data.
- Limited literature was available for comparison because of little research on venlafaxine use in both the private and public healthcare sectors in SA.
- The researcher experienced difficulty with the interpretation of doctors' handwriting in the notes section of patient files and this restricted the information obtained from doctor consultations.
- The results of the current study are only a suggestion of the patterns in public practice of a patient sample, therefore, may not be representative of the trends and patterns of bigger groups such as the entire population in the Eastern Cape. In view of the fact that the data were collected at one psychiatric hospital in the Eastern Cape, caution needs to be exercised when generalising the results as it may not be reflective of the scenario throughout South Africa.
- The current DUR could have been conducted on a larger patient sample to achieve a result that would be of greater statistical significance.
- The study sample for the current DUR was restricted to outpatients who attended Fort England Hospital as opposed to the inpatients and the data source was limited to outpatient files.

5.6 Chapter 5 summary

The conclusions, recommendations and limitations of the study were discussed in this chapter. This DUR study is a valuable addition to the limited literature available relating to the prescribing and management practices of venlafaxine, especially in the public sector in South Africa. It is hereby concluded that all the objectives of the study were achieved.

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ANNEXURE A.
INITIAL DATA COLLECTION FORM

DATA COLLECTION FORM

PATIENT SUBJECTIVE INFORMATION

Patient Identification Number																			
Age	*Yrs*	**Gender**	M	F	**Weight**	*kg*	**Height**	*cm*	**BMI**	*kg/m²*									
Date of Birth					**Race**	W	A	C	I	*Other*									
Marital Status	*single*		*married*		*unmarried*		*divorced*												
Pregnancy Status	N	Y	*Wks*		**Breast Feeding**	N	Y	*Details*											
Tobacco Use	N	Y	*Duration, Frequency*		**Alcohol Use**	N	Y	*Duration, Frequency*											
Substance/Drug Abuse	N	Y	*Details*		**Suicide Risk**	N	Y	*Details*											
Allergies	N	Y	Medication	√	*Drug, Timing, Reaction*														
			Other	√	*Substance, Timing, Reaction*														
Porphyria	N	Y	*Details*																
Social History	*Living conditions, exercise, diet, education*																		
Surgical History	N		Y		*Details*														
Hospital History	N		Y		*Details*														
Medical Alerts																			
Caregiver Support																			
Chief Complaint																			

PATIENT OBJECTIVE INFORMATION

Vital Signs	Temp	*°C*	BP	*mm Hg*	RR	*Breaths/min*	Pulse	*Beats/min*

PATIENT MEDICAL HISTORY						
Family History	HT	Cardiovascular Disease	Hypercholesterolaemia	Diabetes	Glaucoma	
Other (specify)						
Past/Current Co-morbid diseases	HT	Cardiovascular Disease	Hypercholesterolaemia	Diabetes	Glaucoma	
Other (specify)						
Initial Episode	N	Y	*Details (Age, Circumstances)*			
Diagnosis (current)	Major Depressive Disorder	Generalised Anxiety Disorder	Panic Disorder	Social Anxiety Disorder	Other	

History of Venlafaxine Use			
Was the patient on venlafaxine previously?	N	Y	No data
Available date for first initiation of venlafaxine	N	Y	*Details*
Number of years since first initiation of venlafaxine			

Other Medicines and Medicine History			
Was venlafaxine the first antidepressant prescribed?	N	Y	No Data
Use an (X) to mark the antidepressant classes used previously			
Previous treatment with other antidepressant classes used before venlafaxine initiation			

A Selective Serotonin Reuptake Inhibitor	A Tricyclic Antidepressant	Another Serotonin and Noradrenaline Reuptake Inhibitor
Monoamine oxidase inhibitor	Other antidepressant	Specify

Other Medication and Medication History Continued			
Contraceptive(s) use by female patients	N	Y	No data
If yes, please record the name(s)			
If no, possible reason for not using a contraceptive			

Current Medication							
Drug	***Dose Form***	***Route***	***Dose***	***Interval***	***Date started***	***Date Stopped***	***Reason***

***Reason for Stopping Medication Codes: ST** = Successful Therapy; **FT** = Failed Therapy; **AL** = Allergy; **Saf** = Safety; **DxC** = Change in Diagnosis*
***Generation Antipsychotic Drugs: 1** = First; **2** = Second; **3** = Third; **O** = Other*

Drug Interactions			
Any drug interactions identified	N	Y	No Data
If yes, provide details of drug interactions			

Adverse Effects							
Adverse effects experienced					N	Y	No data
If yes, specify which adverse effects were experienced					nausea	somnolence	
dry mouth	dizziness	yawn	sexual dysfunction		insomnia	constipation	
Other							

Adverse Effects Continued			
Were the adverse effects treated	N	Y	No data
If yes, specify how the adverse effects were treated			

Venlafaxine Dose and Dose Titration

Was dose titration performed from initiation of venlafaxine	N	Y	No data
Mark (X) the appropriate choice for initial dose used			
37.5 mg/day for 4 to 7 days before increasing to 75 mg/day	75 mg/day	Other: Details	
Increments of dose increase	Details		
Maintenance dose used		Maximum dose	

Monitoring Procedures				
Parameter	Yes	No	Frequency	Result
Metabolic Monitoring				
Blood Pressure (mm Hg)				
Reading 1				
Reading 2				
Reading 3				
Fasting plasma glucose (mmol/L)				
Pulse Rate (beats/min)				
Reading 1				
Reading 2				
Laboratory Results				
Serum cholesterol (mmol/L)				
Total cholesterol (mmol/L)				
Triglycerides (mmol/L)				
LDL (mmol/L)				
HDL (mmol/L)				

ANNEXURE B.
REVISED DATA COLLECTION FORM

DATA COLLECTION FORM PATIENT SUBJECTIVE INFORMATION										
Patient Identification Number										
Age	*Yrs*	**Gender**	M	F	**Weight**	*kg*	**Height**	*cm*	**BMI**	*kg/m^2*
Date of Birth		**Race**	W	A	C	I	*Other*			
Marital Status	*single*	*married*	*unmarried*	*divorced*						
Pregnancy Status	N	Y	*Wks*	**Breast Feeding**	N	Y	*Details*			
Tobacco Use	N	Y	*Duration, Frequency*	**Alcohol Use**	N	Y	*Duration, Frequency*			
Substance/Drug Abuse	N	Y	*Details*	**Suicide Risk**	N	Y	*Details*			
Allergies	N	Y	Medication	√	*Drug, Timing, Reaction*					
			Other	√	*Substance, Timing, Reaction*					
Porphyria	N	Y	*Details*							
Social History	*Living conditions, exercise, diet, education*									
Surgical History	N	Y	*Details*							
Hospital History	N	Y	*Details and No. of Admissions*							
Medical Alerts										
Caregiver Support										
Chief Complaint										
Diagnosis (current)	Major Depressive Disorder	Generalised Anxiety Disorder	Panic Disorder	Social Anxiety Disorder						
	Other (specify)									

PATIENT MEDICAL HISTORY						
Family History of Psychiatric Illness	N	Y	*Details*			
Other (specify)						
Past/Current Co-morbid diseases	HT	Cardiovascular Disease	Hypercholesterolemia	Diabetes	Glaucoma	
Other (specify)						
Initial Episode	N	Y	*Details (Age, Circumstances)*			

History of Venlafaxine Use			
Was the patient on venlafaxine previously?	N	Y	No data
Available date for first initiation of venlafaxine	N	Y	*Details*
Number of years since first initiation of venlafaxine			

Other Medicines and Medicine History			
Was venlafaxine the first antidepressant prescribed?	N	Y	No Data
Use an (X) to mark the antidepressant classes used previously			
Previous treatment with other antidepressant classes used before venlafaxine initiation			

A Selective Serotonin Reuptake Inhibitor	A Tricyclic Antidepressant	Another Serotonin and Noradrenaline Reuptake Inhibitor
Monoamine oxidase inhibitor	Other antidepressant	Specify

Other Medication and Medication History Continued			
Contraceptive(s) use by female patients	N	Y	No data
If yes, please record the name(s)			
If no, possible reason for not using a contraceptive			

Venlafaxine Dose and Dose Titration			
Was dose titration performed from initiation of venlafaxine	N	Y	No data
Mark (X) the appropriate choice for initial dose used			
37.5 mg/day for 4 to 7 days before increasing to 75 mg/day	75 mg/day	Other: Details	

Venlafaxine Dose Titration		
Date	*Dose*	*Duration*

PATIENT OBJECTIVE INFORMATION						
Vital Signs (Current)	BP	*mm Hg*	Pulse	*Beats/min*	Weight	*kg*

Current Medication							
Drug	***Dose Form***	***Route***	***Dose***	***Interval***	***Date started***	***Date Stopped***	***Reason***

Drug Interactions			
Any drug interactions identified	N	Y	No Data
If yes, provide details of drug interactions			

Adverse Effects						
Adverse effects experienced				N	Y	No data
If yes, specify which adverse effects were experienced				Nausea/vomiting	somnolence	
dry mouth	dizziness	yawn	sexual dysfunction	insomnia	constipation	
Other						

Adverse Effects Continued			
Were the adverse effects treated	N	Y	No data
If yes, specify how the adverse effects were treated			

MONITORING PROCEDURES			
Metabolic Monitoring			
Parameter measured			
Date	Blood Pressure (mm Hg)	Weight (Kgs)	Pulse Rate (Beats/min)

Laboratory Results			
	Result	**Expected Range**	**Comment**
Total cholesterol (mmol/L)		< 5 mmol/l	
LDL cholesterol level		< 3 mmol/L	
HDL cholesterol levels		> 1.2 mmol/L for women or 1.0 mmol/L for men	
Fasting triglyceride levels		< 1.7 mmol/L	

ANNEXURE C.
LETTER OF APPROVAL FOR STUDY FROM RHODES UNIVERSITY FACULTY OF PHARMACY HIGHER DEGREES COMMITTEE

RHODES UNIVERSITY
Where leaders learn

Faculty of Pharmacy
Artillery Road, Grahamstown, 6139, South Africa
PO Box 94, Grahamstown, 6140, South Africa
t: +27 (0)46 603 8381
f: +27 (0)46 603 7506
e:dean.pharmacy@ru.ac.za

www.ru.ac.za

19 July 2018

Professor J. Bodenstein
Faculty of Pharmacy
Pharmacology Division
Rhodes University
Grahamstown
6139

Dear Professor Bodenstein

HDC APPROVAL: MS BAVIKA NAIDU (STUDENT NUMBER 613N0852)

The Faculty of Pharmacy Higher Degrees Committee has approved the project proposal of Ms Bavika Naidu, entitled "Evaluating the prescribing and management practices of Venlafaxine at a public sector Psychiatric Hospital".

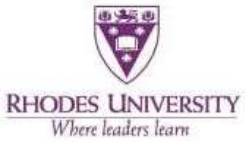
Thank you.

Yours sincerely

PROFESSOR S. DAYA
HEAD AND DEAN: FACULTY OF PHARMACY

FACULTY OF PHARMACY
RHODES UNIVERSITY
GRAHAMSTOWN 6139
SOUTH AFRICA

ANNEXURE D.
LETTER OF ETHICAL APPROVAL FOR STUDY FROM RHODES UNIVERSITY FACULTY OF PHARMACY RESEARCH ETHICS COMMITTEE



Faculty of Pharmacy
Artillery Road, Grahamstown, 6139, South Africa
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t: +27 (0) 46 603 8381
f: +27 (0) 46 603 7506
e: dean.pharmacy@ru.ac.za

www.ru.ac.za

Grahamstown 19th August 2018

From:
Associate Professor Roman Tandlich, PhD
Chairperson of the Faculty of Pharmacy Ethics Committee
Faculty of Pharmacy
Rhodes University
P.O. Box 94
Grahamstown 6140
South Africa
e-mail: r.tandlich@ru.ac.za

To:
Professor Johannes Bodenstein, PhD and collaborators

Re: Conditional Approval Letter on Ethics Committee Application PHARM-2018-05.

Dear Professor Johannes Bodenstein, Mrs. Mari-san Bodenstein, Professor Martie S. Lubbe and Ms. Bavika Naidu,

Thank for your application for ethical approval entitled: "Evaluating the prescribing and management practices of venlafaxine at a public sector psychiatric hospital". This application was considered by the Faculty of Pharmacy Ethics Committee under the tracking number: PHARM-2018-05. After reviewing the application and after the receipt of the necessary gatekeeper approvals, you have submitted to the Faculty of Pharmacy Ethics Committee I am happy to inform you the Faculty of Pharmacy Ethics Committee grants final approval for your study.

You can proceed with making any necessary arrangements for your project. Please ensure that the Faculty of Pharmacy Ethics Committee is notified should any substantive changes(s) be made, for whatever reason, during the research process.

Yours sincerely,

Roman Tandlich, PhD

CHAIRPERSON: FACULTY OF PHARMACY ETHICS COMMITTEE

ANNEXURE E.
APPROVAL LETTER FOR STUDY FROM FORT ENGLAND HOSPITAL RESEARCH COMMITTEE

FORT ENGLAND HOSPITAL

Private Bag X1002, Grahamstown, 6140. Tel: +27 (0)46 622 7003. Fax: +27 (0)46 622 7630. clinicalsecfeh@gmail.com

RESEARCH PROPOSAL APPROVAL

Date: 02-August-2018

Dear Ms. B. Naidu

Thank you for your application to conduct research at Fort England Hospital. We are pleased to inform you that your research proposal has been approved by the Academic and Research Committee of Fort England Hospital (as indicated below). A copy of our Research Policy is included herewith, for your information. Please do not hesitate to contact us should you require any further information or assistance.

Yours sincerely,

Mo Nagdee
Chair: Academic and Research Committee

Primary Investigator	Name	Ms. B. Naidu		
	Position	M. Pharm. (Pharmacology Student)		
	Student or staff number	G13N0852		
	Address	Artillery Road, Grahamstown, 6139		
	Telephone	046-603 8381		
	Email	Johannes.Bodenstein@ru.ac.za		
Research project	Title	Evaluating the prescribing and management practices of Venlafaxine at a Public Sector Psychiatric Hospital		
	Supervising University / Institution	Rhodes University		
	Supervisor	Prof. J. Bodenstein		
	Ethics Approval from Supervising University / Institution	~~**No**~~	**Yes** (insert ethics clearance reference no.) PHARM-2018-05	
Fort England Hospital Approval	Academic and Research Committee Chair / Clinical Head (M. Nagdee)	~~**No**~~	**Yes** (insert date) 02-August-2018	**Signature**
	Head: Psychology (I. Reid)	~~**No**~~	**Yes** (insert date) 02-August-2018	**Signature**
	Acting CEO (Mr. M. Dyalvane)	~~**No**~~	**Yes** (insert date) 02-August-2018	**Signature**
	Co-Opt Member Head: Pharmacy (S. Willows)	~~**No**~~	**Yes** (insert date) 02-August-2018	**Signature**
Additional comments				

ANNEXURE F.
APPROVAL LETTER FOR STUDY FROM EASTERN CAPE DEPARTMENT OF HEALTH RESEARCH COMMITTEE

Province of the
EASTERN CAPE
HEALTH

Enquiries: Zonwabele Merile Tel no: 083 378 1202

Email: zonwabele.merile@echealth.gov.za Fax no: 043 642 1409

Date: 28 August 2018

RE: EVALUATING THE PRESCRIBING AND MANAGEMENT PRACTICES OF VENLAFAXINE AT A PUBLIC SECTOR PSYCHIATRIC HOSPITAL. (EC_201808_010).

Dear Prof J. Bodenstein

The department would like to inform you that your application for the abovementioned research topic has been approved based on the following conditions:

1. During your study, you will follow the submitted amended protocol with ethical approval and can only deviate from it after having a written approval from the Department of Health in writing.

2. You are advised to ensure, observe and respect the rights and culture of your research participants and maintain confidentiality of their identities and shall remove or not collect any information which can be used to link the participants.

3. The Department of Health expects you to provide a progress update on your study every 3 months (from date you received this letter) in writing.

4. At the end of your study, you will be expected to send a full written report with your findings and implementable recommendations to the Eastern Cape Health Research Committee secretariat. You may also be invited to the department to come and present your research findings with your implementable recommendations.

5. Your results on the Eastern Cape will not be presented anywhere unless you have shared them with the Department of Health as indicated above.

Your compliance in this regard will be highly appreciated.

SECRETARIAT: EASTERN CAPE HEALTH RESEARCH COMMITTEE

ANNEXURE G.
PATIENT INFORMATION LEAFLET ON VENLAFAXINE

Can I use venlafaxine while *pregnant or breastfeeding?*

Venlafaxine is classified as a **Category C** drug.

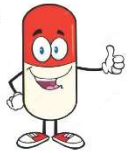
Venlafaxine should not be used unless the potential benefits outweigh the potential risk for the patient.

Venlafaxine is excreted in human breast milk which could be harmful to the baby therefore **DO NOT BREAST-FEED** while on venlafaxine treatment.

Important to remember when taking venlafaxine

The following must be monitored regularly: blood pressure, pulse rate, body weight, sodium levels especially in the elderly, and total cholesterol levels in patients with co-morbid disorders i.e. diabetes.

Venlafaxine needs 2-4 weeks to work before patients can feel better, but side -effects may appear immediately. Do not stop treatment due to no immediate effect, be patient.



References

Rossiter, D. 2016. South African Medicines Formulary, 12th ed. Health and Medical Pub. Group of the South African Medical Association, Rondebosch, South Africa.

Sansone, R.A., Sansone, L.A. 2014. Serotonin Norepinephrine Reuptake Inhibitors: A Pharmacological Comparison. Innovations in Clinical Neuroscience 11, 37–42

Turner, L. (2010). Daily drug use. 9th ed. [Cape Town]: Cape Western Branch of the Pharmaceutical Society of South Africa, p.494.

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Compiled by Bavika Naidu MPharm candidate in collaboration with Pharmaceutical Services at Fort England Hospital

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VENLAFAXINE

What is it?

Venlafaxine is an antidepressant that is classified as a serotonin and noradrenaline reuptake inhibitor (SNRI).

What is it used for?

It is used to treat the symptoms of major depressive disorder, generalized anxiety disorder, panic disorder and social anxiety disorder.

WHAT DO I NEED TO KNOW ABOUT VENLAFAXINE?

How does it work?

Venlafaxine works by increasing the level of chemical messengers' serotonin and noradrenaline in the brain thereby elevating one's mood.

How does it look?

Venlafaxine is available as capsules in three different strengths, 37.5 mg; 75 mg and 150 mg each with an assigned colour.

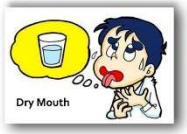
How do I take me medicine?

Venlafaxine should be taken either in the morning or in the evening at about the same time every day. It should not be divided; crushed; chewed or placed in water.

If it is hard to swallow, then the capsule may be carefully opened and the contents sprinkled on a spoonful of yogurt or appropriate food.

What are the side-effects that may occur?

NOTE: NOT ALL SIDE-EFFECTS WILL APPEAR



Dry mouth

Insomnia

Sleepiness

Fatigue

Sedation

Sweating

Nausea

Constipation

Sexual dysfunction

Vomiting

Should be taken with food to reduce stomach irritation

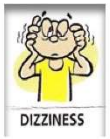
Venlafaxine indicated doses:

Initial dose: 37.5 mg/day for 4-7 days before increasing the dose to 75 mg/day

Dosing range: 75-225 mg/day (do not take more than the prescribed dose)

Can I use *alcohol, substances or smoke* while on venlafaxine treatment?

The sedative (dizzy and drowsy) effect of venlafaxine will be increased by the alcohol, substances and smoke which could be very dangerous for patients health.



Patients must be warned not to drive or operate heavy or dangerous machinery while on antidepressant treatment.