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A DRUG UTILIZATION REVIEW

ON ANTIDEPRESSANTS

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A dissertation submitted to the Faculty of Health Sciences, University of Witwatersrand, in fulfilment of the requirements for the degree of Master of Science in Medicine

Johannesburg

September 2013

DECLARATION

I, Safiyyah Laher, declare that this dissertation is my own work. It is being submitted for the degree of Master of Science in Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

..... [Safiyyah Laher]

.....day of .....,.. 2013

ABSTRACT

The introduction of Selective Serotonin Reuptake Inhibitors (SSRIs) has lead to a considerable increase in global antidepressant prescriptions. This increase has been driven by the SSRIs favourable adverse effect profile and increased safety in overdose compared to the older generation of drugs. This increase has created substantial controversies. Questions have been raised on the efficacy of treatment of depression and anxiety, suicidality rates and tolerability of drugs. Despite these controversies, usage of antidepressants remains high. This research aims to shed light on current antidepressant prescriptions and compare these to local and international usage patterns and treatment guidelines. Differences in usage between antidepressants are also assessed.

Two datasets (A and B) were acquired from different medical data warehousing companies. Each dataset comprised of 1 year's medical records from healthcare practitioners subscribed to the respective company (Dataset A from 2009, Dataset B from 2011). Data included a unique patient number, age, gender, treatment code, ICD-10 code and treatment date. Microsoft Excel was used to filter the data and isolate patients treated with an antidepressant and a cluster analysis was performed to group antidepressants together. Simple descriptive statistics were determined. Data was analysed using STATA (v10.0). Statistical significance was determined using Pearson's chi-squared tests, theMann Whitney U test and logistic regression. Significance levels were set at $p<0.05$.

For dataset A, n=9213 and B, n=1244. The most frequently dispensed antidepressant was amitriptyline (A:67.75%, n=6 242, B: 64.06% n=797). The mean age of patients was 43.86±13.81 and 46.27±13.07 respectively. The type of antidepressant used was significantly associated with ICD-10 code, psychiatric condition and categorical age ($p<0.0001$). The mean number of antidepressant prescriptions per patient were A:2.95±3.77 and B:2.57±2.47. Duration of treatment was related to age, ICD-10 code and psychiatric condition ($p<0.0001$).

This research shows that amitriptyline accounts for a majority of prescriptions because of its varied indications for use. The determinants of the type of antidepressant used showed that patients with a psychiatric condition were more likely to receive a newer antidepressant and patients with a pain condition were more likely to receive an older antidepressant. Reasons for poor adherence to treatment and determinants of duration of treatment are discussed.

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LIST OF PRESENTATIONS ARISING FROM THIS RESEARCH

YEAR	CONFERENCE/SYMPOSIUM	PRESENTATION TYPE
2009	University of Witwatersrand Cross-Faculty Postgraduate Symposium	Poster
2009	University of Witwatersrand Faculty of Health Sciences Research Day	Poster
2010	South African Congress for Pharmacology and Toxicology	Oral
2012	South African Society of Psychiatrists Annual Conference	E-Poster
2012	University of Witwatersrand Faculty of Health Sciences Research Day	Poster
2012	University of Witwatersrand Cross-Faculty Postgraduate Symposium	Poster
2012	Annual Congress of the South African Society of Basic and Clinical Pharmacology	Poster

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ABBREVIATIONS

APA	American Psychiatric Association
ATC	Anatomical Therapeutic Chemical
CPA	Consumer Protection Act
DBS	Deep Brain Stimulation
DDD	Defined Daily Dose
DOH	Department of Health
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4)
DUR	Drug Utilization Review
ECT	Electroconvulsive Therapy
ESEMED	European Study of the Epidemiology of Mental Disorders
FDA	United States Food and Drug Administration
ICD-10	International Classification of Diseases
MAOIs	Monoamine Oxidase Inhibitors
MDD	Major Depressive Disorder
NAPPI	South African National Pharmaceutical Product Index
NICE	National Institute for Health and Clinical Excellence
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
OR	Odds Ratio

P	Probability
PDD	Prescribed Daily Dose
SAMF	South African Medicines Formulary
SASH	South African Stress and Health Study
SNRIs	Serotonin Noradrenaline Reuptake Inhibitors
SSRIs	Selective Serotonin Reuptake Inhibitors
TCAs	Tricyclic Antidepressants
STG	Standard Treatment Guidelines
TMS	Transcranial Magnetic Stimulation
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WHOCC	World Health Organization Collaborating Centre for Drug Statistics and Methodology
95%CI	95% Confidence Interval

CHAPTER ONE: INTRODUCTION

1.1 STIMULUS FOR RESEARCH

Local and international studies have added to the body of knowledge available on antidepressant usage patterns. At present the only comparison for South African usage patterns is limited to a few studies conducted in the late 90s to mid 2000s and confined to one province. Since the completion of these studies, several new antidepressants have been launched. These include the Serotonin Noradrenaline Reuptake Inhibitors (SNRIs), reboxetine and bupropion. More recent data is not currently available. A Drug Utilization Review (DUR) of a more recent nature is important as the market and awareness of antidepressants has increased rapidly in the past few years and the effect of newer drugs on prescriptions patterns is not known. Therefore, in order to further understand utilization patterns of antidepressants in South Africa and compare these with international findings and treatment guidelines, a DUR needs to be conducted. DURs have been recognized as important tools in identifying trends and to provide a platform for future planning (Truter, 2001; WHO, 2003).

1.2 CHAPTER LAYOUT

This dissertation will begin with a brief overview of antidepressants and an overview of the disorders which are primarily listed as an indication for the use of an antidepressant (depressive and anxiety-related disorders and pain).

Chapter Four will review literature available on the controversies surrounding antidepressants and will progress on to a review of drug utilisation studies. Chapter Four will round off with an exclusive review of antidepressant utilization reviews.

The methodology of the research will be discussed in Chapter Five. This chapter will begin with the aim and objectives of the study and the research method employed to achieve this.

Chapter Six and Seven consists of the presentation of the results. Chapter Six presents the results of one dataset and Chapter Seven is a presentation of the results from another dataset.

Chapter Eight discusses the results presented in Chapter Six and Seven in relation to international and local findings. This chapter concludes with the limitations of the study

Chapter Nine concludes the dissertation and provides recommendations arising from the research.

Appendices and references follow.

CHAPTER TWO: PHARMACOLOGY OF ANTIDEPRESSANTS

This chapter (Chapter Two) will provide a brief overview of the pharmacology of antidepressants. Background information, the mechanism of action, indications, adverse effects and cautions will be provided on each class of antidepressant. This chapter (Chapter Two) considers antidepressants according to their pharmacological class which includes: tricyclic antidepressants, selective serotonin reuptake inhibitors, selective serotonin noradrenaline reuptake inhibitors and other antidepressants (monoamine oxidase inhibitors, noradrenergic and specific serotonergic agents, serotonin reuptake inhibitors and receptor antagonists, dopamine reuptake inhibitors and selective noradrenaline reuptake inhibitors).

2.1 TRICYCLIC ANTIDEPRESSANTS

The tricyclic group of antidepressants are the oldest class of antidepressants. The drugs in this class of antidepressants include: amitriptyline, imipramine, clomipramine, dothiepin, lofepramine. These drugs were the first line treatment of major depressive disorder (MDD) till the development of selective serotonin reuptake inhibitors (SSRIs) (O'Donnell et al, 2011).

2.1.1 PHARMACOLOGY

Tricyclic antidepressants (TCAs) have a mechanism of action that is not exclusive to a particular transport system or enzyme. These drugs work through a series of different mechanisms. These mechanisms (O'Donnell et al, 2011) are detailed in the Table 2.1 (page 4).

Table 2.1 The mechanism of action of tricyclic antidepressants

ACTION	EFFECT	CONSEQUENCE
Inhibition of Reuptake	Presynaptic re-uptake of serotonin and noradrenaline is inhibited.	Increase neurotransmission of serotonin and noradrenaline postsynaptically
Muscarinic Receptor Antagonist	Prevents acetylcholine from stimulating muscarinic receptors	Parasympathetic response is depressed
Alpha-1 Receptor Antagonist	Prevents noradrenaline from stimulating alpha-1 receptors	Sympathetic response in vascular smooth muscle is depressed
Histamine-1 Receptor Antagonist	Prevents histamine from stimulating histamine receptors	Anti-histamine effects
Sodium Channel Blockade	Inhibits sodium from entering cells	Prolongs action potential by membrane stabilizing effect

(O'Donnell et al, 2011)

2.1.2 INDICATIONS

The South African Medicines Formulary (Rossiter, 2008) list the indications for TCAs as the following:

- Major Depressive Disorder

- Anxiety-related disorders
- Nocturnal enuresis
- Adjunctive pain management.

The Department of Health's Standard Treatment Guidelines also includes TCAs (specifically amitriptyline) in the treatment of the following conditions (Department of Health, 2006):

- Pain in Herpes Zoster,
- Chronic Pain (R62[3]),
- Pain Associated With Irritable Bowel Syndrome (K58),
- Neuropathy (G62),
- Urinary Incontinence (N81),
- Diabetic Neuropathy (E10),
- As Adjunctive Pain Control in Rheumatoid Arthritis (M06),
- Migraine Prophylaxis (G43),
- Tension Headache (G44) and
- Major Depressive Disorder (F32)

[3] This code corresponds to the ICD-10 code

2.1.3 ADVERSE EFFECTS AND CAUTIONS

The adverse effects of TCAs are associated with their antimuscarinic, antihistaminic and alpha-1 receptor blockade actions.

The antimuscarinic adverse effects include dry mouth, constipation, urinary retention, constipation and blurred vision. The antihistaminic adverse effects primarily include sedation and weight gain.

The blockade of alpha-1 receptors by TCAs cause cardiovascular adverse effects by blocking alpha-1 mediated vasoconstriction. The dilation of blood vessels results in a drop in blood pressure, to compensate for this cardiac output is increased. Postural hypotension, tachycardia and palpitations are therefore adverse effects of TCAs (Westfall et al, 2011).

Sodium channel blockade by TCAs also lead to cardiovascular effects such as arrhythmias and AV-nodal block. These drugs are therefore contraindicated for use in patients after a myocardial infarction.

Other adverse effects include: disorientation, change in libido, tremors, anxiety, fatigue and impotence (Rossiter, 2008).

The adverse effects of TCAs require regular monitoring of patients with a cardiovascular condition. The antimuscarinic effects are of concern to patients with glaucoma, prostate enlargement and the elderly. The cardiotoxic nature of these drugs contributes to the fatality if taken in doses exceeding those recommended. Suicidal patients or patients with a history of suicide attempt require diligent monitoring and cautions prescribing.

2.2 SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The adverse effects of the TCAs place a limit in their use, therefore, drug development shifted to drugs that were more selective and considered safer (O'Donnell et al, 2011). The selective serotonin reuptake inhibitors (SSRIs) were introduced in the late 1980s and onwards. These drugs are safer in overdose and thus provide a distinct advantage when compared to TCAs (O'Donnell et al, 2011). In addition, SSRIs do not have the anticholinergic effects of TCAs (Rossiter, 2008). The available SSRIs include: fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine and sertraline.

2.2.1 PHARMACOLOGY

The SSRIs class of antidepressants works by inhibiting the reuptake of serotonin into the presynaptic terminal. This allows for increased serotonergic transmission postsynaptically (O'Donnell et al, 2011).

2.2.2 INDICATIONS

SSRIs are approved for use in the treatment of depressive and anxiety-related disorders (Rossiter, 2008) and in premenstrual dysphoric syndrome (O'Donnell et al, 2011).SSRIs are also used in the prevention of vasovagal symptoms in postmenopausal females (O'Donnell et al, 2011).Sertraline and paroxetine are indicated in the treatment of post-traumatic stress disorder (O'Donnell et al, 2011).

2.1.3 ADVERSE EFFECTS AND CAUTIONS

The SSRIs have the advantage of not possessing anticholinergic effects and are safer in overdose. Nevertheless, their list of adverse effects is also extensive. The common adverse effects include: change in libido, insomnia, gastrointestinal disturbance (nausea, vomiting, diarrhea), weight gain, anxiety, sexual dysfunction, dizziness, confusion, amnesia and emotional lability (O'Donnell et al, 2011; Rossiter, 2008).Other uncommon adverse effects include: hypertension, palpitations, skin disturbances and chest pain (O'Donnell et al, 2011).

SSRIs are contraindicated in patients with severe renal or hepatic impairment. In addition, the risk of serotonin syndrome suggests that these drugs cannot be used with a monoamine oxidase inhibitor (O'Donnell et al, 2011; Rossiter, 2008). Serotonin syndrome occurs when serotonin in the body is elevated. The symptoms include: confusion, agitation, tachycardia, fever, seizures, hypertension, myoclonus and fever. Serotonin syndrome is potentially fatal and use of SSRIs with drugs that increase serotonin levels is contraindicated (O'Donnell et al, 2011; Rossiter, 2008).

2.3 SEROTONIN NORADRENALINE REUPTAKE INHIBITORS

Serotonin Noradrenaline Reuptake Inhibitors (SNRIs) were developed in order to increase serotonergic and noradrenaline transmission. The available SNRIs include venlafaxine, desvenlafaxine, duloxetine and milnacipran (not available in South Africa) (O'Donnell et al, 2011).

2.3.1 PHARMACOLOGY

The SNRIs' mechanism of action includes inhibiting the reuptake of serotonin and noradrenaline into the presynaptic cleft. This allows for increased stimulation of serotonin and adrenergic receptors postsynaptically.

2.3.2 INDICATIONS

The SNRIs are used in the treatment of depressive and anxiety-related disorders and in the management of pain syndromes such as fibromylagia and neuropathic pain (O'Donnell et al, 2011; Rossiter, 2008). Other off-label use includes premenstrual dysphoric syndrome, eating disorders and the vasovagal symptoms of menopause (O'Donnell et al, 2011).

2.3.3 ADVERSE EFFECTS AND CAUTIONS

The list of adverse effects of SNRIs are similar to the adverse effects observed with SSRI treatment. These include: sleep disturbances, anxiety, headache, sexual dysfunction and gastrointestinal disturbance. The SNRIs can potentially increase blood pressure and heart rate and should be used with caution in patients with a cardiac disorder.

Use of SNRIs with other drugs that increase serotonin (MAOIs; SSRIs) can cause serotonin syndrome. SNRIs are contraindicated for use with MAOIs and require precautionary measures, for example a reduction in dose, if used with an SSRI (Rossiter, 2008).

2.4 OTHER ANTIDEPRESSANTS

Antidepressants which do not have the same mechanism of action as TCAs, SSRIs or SNRIs work through either direct activity on receptors, increased synthesis of neurotransmitters or inhibition or neurotransmitter reuptake. These other antidepressants include:

- Monoamine oxidase inhibitors (moclobemide, tranylcypromine)
- Noradrenergic and Specific Serotonergic Agents (mirtazapine)
- Serotonin Reuptake Inhibitors and Receptor Antagonists (trazodone)
- Dopamine Reuptake Inhibitors (bupropion)
- Selective Noradrenaline Reuptake Inhibitors (reboxetine)

The mechanism of action, indications, adverse effects and cautionary use of these drugs (O'Donnell et al, 2011) will be presented in a tabulated format in the sections below. Table 2.2 (page 10 – 12) lists the antidepressants' mechanism of action. Table 2.3 (page 13) has the approved list of indications for these drugs and Table 2.4 (page 14 -15) lists the adverse effects and cautions exercised when using these antidepressants.

2.4.1 PHARMACOLOGY

Table 2.2 The mechanism of action of 'other' antidepressants

DRUG CLASS	DRUGS	MECHANISM OF ACTION
Monoamine Oxidase Inhibitors (Irreversible)	Tranylcypromine	The enzyme monoamine oxidase is irreversibly inhibited. This results in

DRUG CLASS	DRUGS	MECHANISM OF ACTION
		the inhibition of the breakdown of biogenic amines like noradrenaline, serotonin and dopamine. The activity of these neurotransmitters is increased
Monoamine Oxidase Inhibitors (Reversible)	Moclobemide	The subtype, A, monoamine oxidase is reversibly inhibited. Increased serotonin and noradrenaline is a consequence. The breakdown of other biogenic amines, like tyramine, is not affected
Noradrenergic and Specific Serotonergic Agents	Mirtazapine	The inhibitory presynaptic alpha-2 receptor is blocked. This results in increased noradrenaline and serotonin transmission. Several serotonin receptors (2A, 2C, 3) are antagonized. Histamine-1 receptors are also blocked

DRUG CLASS	DRUGS	MECHANISM OF ACTION
Serotonin Reuptake Inhibitors and Receptor Antagonists	Trazodone	Reuptake of serotonin into presynaptic neurons is blocked. Acts as an antagonist at alpha-1, histamine-1 and serotonin (1A, 2A, 2B, 2C)receptors
Dopamine Reuptake Inhibitors	Bupropion	Inhibits the reuptake of dopamine, allowing for increased dopaminergic transmission postsynaptically. Direct noradrenaline and serotonin reuptake inhibition is negligible
Selective Noradrenaline Reuptake Inhibitor	Reboxetine	Inhibits the reuptake of noradrenaline into the presynaptic neuron. Increased noradrenaline transmission postsynpatically

(O'Donnell et al, 2011)

2.4.2 INDICATIONS

Table 2.3 Indications for use of antidepressants

DRUG CLASS	DRUGS	INDICATIONs
Monoamine Oxidase Inhibitors (Irreversible)	Tranylcypromine	Atypical and refractory depression
Monoamine Oxidase Inhibitors (Reversible)	Moclobemide	Depressive disorders
Noradrenergic and Specific Serotonergic Agents	Mirtazapine	Depressive disorders
Serotonin Reuptake Inhibitors and Receptor Antagonists	Trazodone	Depressive disorders Insomnia (off-label)
Dopamine Reuptake Inhibitors	Bupropion	Smoking cessation Depressive disorders
Selective Noradrenaline Reuptake Inhibitor	Reboxetine	Depressive disorders Panic disorder

(O'Donnell et al, 2011)

2.4.3 ADVERSE EFFECTS AND CAUTIONS

Table 2.4 Adverse effects and cautions of 'other' antidepressants

DRUG CLASS	DRUGS	ADVERSE EFFECTS	CAUTIONS
Monoamine Oxidase Inhibitors (Irreversible)	Tranylcypromine	Serotonin Syndrome Hypertensive reaction	Strict avoidance of drugs that increase serotonin and tyramine-containing foods. Regular monitoring of patients is essential
Monoamine Oxidase Inhibitors (Reversible)	Moclobemide	Serotonin Syndrome Sleep disturbances Anxiety Headache, dizziness Gastrointestinal disturbances	Contraindicated with the use of other serotonin increasing drugs.
Noradrenergic and Specific Serotonergic Agents	Mirtazapine	Sedation Increase appetite and weight gain Tremor Blood dyscrasias	Manic patients History of seizures or renal impairment

DRUG CLASS	DRUGS	ADVERSE EFFECTS	CAUTIONS
Serotonin Reuptake Inhibitors and Receptor Antagonists	Trazodone	Sedation Hypotension Headaches, dizziness	Elderly patients Cardiovascular patients
Dopamine Reuptake Inhibitors	Bupropion	Hypersensitivity reactions Seizures Insomnia Headache, dizziness Anxiety Gastrointestinal disturbance	History of seizures or hypersensitivity to the drug
Selective Noradrenaline Reuptake Inhibitor	Reboxetine	Sleep disturbances Dry mouth Dizziness	Elderly patients Patients with urological problems

(O'Donnell et al, 2011)

2.5 ANTIDEPRESSANT DRUG DEVELOPMENT

There is considerable research in developing drugs and using old drugs in novel ways to treat depression. Agomelatine has been recently introduced into the market. It is a melatonergic antidepressant with agonizing effects at melatonin receptors and antagonizing activity at serotonin-2C receptors (Kupfer et al, 2012).

Intravenous ketamine and N-methyl-D-aspartate glutamate-receptor antagonists are under study (Kupfer et al, 2012) for the treatment of depression. As scientific understanding of the process underlying MDD progresses, drug development is sure to follow suit. Antidepressants are a group of drugs that have shown considerable dynamism over the past few decades, the recent introduction of agomelatine proves that this has not halted. A group of drugs that are growing deserve studies conducted on their usage patterns.

The following chapter (Chapter Three) will provide a brief overview of the disorders treated with antidepressants: Major Depressive Disorder (MDD), anxiety-related conditions and pain.

CHAPTER THREE: OVERVIEW OF AFFECTIVE, ANXIETY-RELATED DISORDERS AND PAIN

The previous chapter (Chapter Two) provided a brief overview of antidepressants and their pharmacology. This chapter (Chapter Three) will discuss the disorders which are primarily listed as indications for antidepressants: major depressive, anxiety-related disorders and pain.

A definition, epidemiology of disorder, burden of disease, diagnostic criteria and treatment will be elaborated upon for both disorders. Anxiety-related disorders will be further classified according to the subtypes.

3.1 MAJOR DEPRESSIVE DISORDER

The normal emotions of sadness and grief are common. Most people will experience this set of emotions on occasion. When these feelings persist, a psychiatric diagnosis of major depressive disorder (MDD) may ensue.

3.1.1 DEFINITION AND DIAGNOSIS

The definition of Major Depressive Disorder (MDD) is closely linked to its diagnosis. The Diagnostic and Statistical Manual IV defines Major Depressive Disorder (MDD) as a "clinical course that is characterized by one or more Major Depressive Episodes". A diagnosis of a Major Depressive Episode is made if the patient experiences a period of at least 2 weeks during which there is a close to constant state of depressed mood or a loss of interest or pleasure, accompanied by at least four of the following symptoms: change in appetite or weight; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or guilt; difficulty in thinking, concentrating or

decision-making; recurrent thoughts of death or suicidal ideation, attempts or plans. This change of mood is accompanied with a considerable change in social and occupational functioning (American Psychiatric Association, 2000).

A Major Depressive Episode most commonly recurs. The frequency and spacing between depressive episodes change between patients. Episodes may appear as distinct occurrences between years of normal mood or some symptoms may remain between episodes and never completely diminish. With each successive episode, the likelihood of future episodes increases this lends to the chronic nature of MDD (Finley et al, 2009).

Patients' presentation of MDD also varies to a considerable degree. Some patients' present and express feelings of sadness while others present with an anxious or irritable behavior. Patients may also present with no change in mood but express unclear and chronic somatic symptoms (Finley et al, 2009). A diagnosis of MDD should be considered within a variety of presentations.

The biological process underlying MDD has been an evolving subject. Current understanding of the pathophysiological process behind MDD will be discussed in the next section.

3.1.2 PATHOPHYSIOLOGY

The biological process of MDD is currently linked to a number of theories. The monoamine hypothesis, neuroendocrine abnormalities and genetics are the most widely studied areas thus far.

The rationale behind the monoamine hypothesis stems from the understanding of the mechanism of action of certain drugs. Drugs that increase the concentration of serotonin

and noradrenaline by inhibiting their reuptake or inhibiting their breakdown were observed to have antidepressant effects (Belmaker et al, 2008). Drugs which decrease the concentration of monoamines were found to precipitate symptoms of depression (Finley et al, 2009). The dysregulation of monoamine neurotransmitters and their relationship to depression is based on an observational theory. Studies that have aimed to draw direct links between deficient neurotransmitters and depression have not yet produced an outcome which reliably supports this theory (Belmaker et al, 2008). The strength of this theory lies in its 'predictive power'; newly developed drugs which increase serotonin and noradrenalin concentration in the synaptic cleft have been clinically found to have antidepressant effects (Belmaker et al, 2008). The weakness of the monoamine hypothesis lies in its inability to explain why clinical trials show a two-thirds response to antidepressants (Belmaker et al, 2008). This suggests that other mechanisms may be at play.

Neuroendocrine disruption has also been suggested to be an underlying mechanism of MDD. High levels of cortisol have been observed in the plasma of patients with MDD (Burke et al, 2005) and high levels of corticotrophin releasing hormone have also been seen in patients with MDD (Galard et al, 2002). This theory is not without criticism. Acute doses of corticosteroids have been shown to improve mood (Finley et al, 2009) suggesting that a skewed cortisol response is the body's effort to combat MDD (Finley et al, 2009).

In addition to cortisol, disturbances in thyroid function are also associated with MDD. Hypothyroidism is associated with symptoms of MDD (Hage et al, 2012). Studies observing thyroid hormone functioning in patients with MDD have been mixed (Finley et al, 2009; Hage et al, 2012). The role of thyroid functioning and hormone levels in MDD requires further study before defining a mechanism.

Another area of study has looked at the genetic predisposition of MDD. The heritability of MDD has been suggested to be less profound than the heritability of other psychiatric disorders such as schizophrenia (Belmaker et al, 2008). The relationship between MDD and the genome is complex and is most likely attributed to a combination of genomic

factors. The impact of environmental factors on gene expression has also been suggested as altered in patients with MDD (Belmaker et al, 2008).

Increasing attention is also being placed on the pharmacogenomics of antidepressant drugs. Variations in genes have been proposed to impact on the response rate of antidepressants (Finley et al, 2009). Genetic testing of patients being treated with Selective Serotonin Reuptake Inhibitors (SSRIs) has not yet been recommended and further studies and evidence is required before the use of this approach is accepted (Finley et al, 2009; Laje et al, 2009; Crisafulli et al, 2011).

3.1.3 EPIDEMIOLOGY

Global prevalence of depression is reported as approximately 10% (Finley et al, 2009). The lifetime prevalence of MDD in a study conducted in the United States was found to be 16.2% and the 12-month prevalence was 6.6% (Kessler et al, 2003). A South African study has found the lifetime prevalence of MDD was 9.8% and the 12-month prevalence was 4.9% (Seedat et al, 2009).

It is suggested that MDD is associated with a combination of environmental and genetic factors (Finley et al, 2009). MDD has been suggested to be associated with lower socio-economic class, stressful life events and genetic factors (Finley et al, 2009). The South African Stress and Health (SASH) study found that an increase risk of a mood disorder was associated with females, lower education, negative life events and childhood parental separation (Seedat et al, 2009).

3.1.4 BURDEN OF DISEASE

Disruption of a balanced state of emotions creates a burden to patients and disables their social and economic environment and the health care system. Depressed patients are more likely to experience an increase in morbidity, an impairment of functioning, an increase in mortality in the presence of co-morbid diseases, resulting in an increase in utilization of the health care system (Cassano et al, 2002). The World Health Organization World Health Survey showed that after accounting for socio-economic and health conditions, depression was found to be the leading cause of worsening health status when compared to angina, arthritis, asthma and diabetes (Moussavi et al, 2007). It was also noted that study participants with depression and another chronic disease had an even lower health status than those with no depression and a chronic disease. A study conducted by Carney and his colleagues (2008) showed that depressed patients had a higher mortality rate up to 5 years after an acute myocardial infarction. Patients with HIV and depression have shown enhanced disease progression, non-adherence to treatment regimes, increased utilization of health care services, a poorer quality of life and emotional suffering (Valente, 2003).

The burden of MDD has been suggested to be the third leading cause of disability globally (WHO, 2008). MDD represents a significant challenge to patients and the health care system. Intervention is, therefore, of significant importance. Treatment of MDD will be discussed in the next section 3.1.5.

3.1.5 TREATMENT

The treatment goals of MDD are to achieve remission of symptoms and prevent recurring episodes (Nutt et al, 2010). Treatment should be individualized and prepare the patient for a potentially long-term plan (Davidson, 2010). Individualized response and history of response should be considered before initiating treatment (Finley et al, 2009). Possible treatment approaches can be broken down into three categories:

- Psychotherapy

- Somatic therapy
- Pharmacotherapy

A brief description of each form of therapy will be elucidated below.

3.1.5.1 PSYCHOTHERAPY

Psychotherapy has shown efficacy in various studies (Luty et al, 2007; Bell et al, 2009). It has been suggested that psychotherapy has the advantage of having effects that last longer than pharmacological treatment and therefore has been suggested to prevent further relapses (Finley et al, 2009). Cognitive-behavioral therapy, a form of psychotherapy, centers on recognizing and reversing negative thought patterns. This, in turn, leads to a change of depressed and negative emotions (Finley et al, 2009). Other forms of psychotherapy include: interpersonal therapy, psychoanalytic therapy and psychodynamic therapy.

Studies have shown that combining psychotherapy and pharmacotherapy to be of benefit and better than either alone (Schramm et al, 2007; Schramm et al, 2008). The disadvantage of both these forms of therapy is their response rate, which may take weeks. Somatic therapy, in contrast, is more rapid. The options are discussed in the next section 3.1.5.2.

3.1.5.2 SOMATIC THERAPY

Somatic therapy includes electro-convulsive therapy (ECT), transcranialmagenetic stimulation (TMS), vagal nerve stimulation (VNS) and deep brain stimulation (DBS). ECT is a well-recognized somatic therapy with reportedly good outcomes; a meta-analysis done by the UK ECT Review group (2003) concluded that ECT is effective in treating depression in the short-term and is considered to have a faster effect than pharmacological intervention for this purpose. It is recommended in treating severe and psychotic depression, suicidal patients and treatment-resistant depression (Finley et al, 2009).

TMS has been receiving considerable attention lately. It involves allowing a magnetic field to penetrate the cerebral cortex which in turn causes a biological response (the generation of action potentials). To-date various clinical trials have been conducted with mixed outcomes. More research needs to be done before conclusions can be drawn but this poses a promising alternative if successful (Gershon et al, 2003).

VNS has recently been approved by The USA Food and Drug Administration as treatment for refractory depression. It is an invasive treatment where a pulse-generator is surgically implanted to stimulate the vagus nerve (Nemeroff et al, 2007). The cost-effectiveness of this procedure has not been established (Finley et al, 2009).

DBS is, by contrast, still in its experimental stages. It is an invasive process that involves the placement of electrodes into specific areas of the brain; a pulse is then generated to stimulate the area (Mohr et al, 2011). If approved, this would undoubtedly be a costly treatment that would require the resources necessary for an invasive procedure.

3.1.5.3 PHARMACOTHERAPY

A pharmacotherapeutic intervention is recommended by the American Psychiatric Association (APA) Treatment guideline for the initial treatment of patients with mild to moderate MDD and should definitely be provided to patients with severe MDD. Efficacy between the different classes of antidepressants is comparable and the APA suggests selecting an antidepressant on the following factors:

- Safety and tolerability of adverse effects
- History of response to the drug
- Cost
- Patient preference

- Pharmacological properties (half-life and drug-interactions)

The APA suggests an SSRI, SNRI, mirtazapine or bupropion as optimal. (American Psychiatric Association, 2006).

The South African Department of Health Standard Treatment Guidelines lists the pharmacotherapeutic treatment of MDD with a TCA if no contraindication exists (cardiovascular disease). If a patient has a cardiovascular disease, an SSRI should be used. Elderly patients are advised to be treated with caution in the case of either TCA or SSRI usage with the recommendation of starting with a low dose and gradually increasing to an optimal dose. The guideline advises the use of an antidepressant for six months following remission of symptoms. Patients with recurring MDD (three or more episodes) are advised to be reviewed every 2 years (Department of Health, 2006).

A recent study has found that considering patient preference is an important facet of treatment. Patients who attribute their MDD to a 'chemical imbalance' were found to show a better response to pharmacotherapy. Patients who attributed their MDD to a stressful life experience were likely to respond to a combination of psycho- and pharmacotherapy (Steidtmann et al, 2012). Pharmacotherapeutic treatment is a significant component of the treatment of MDD, an increasing recognized and burdensome disorder. Whether alone or in combination it forms part of international and local guidelines. It is, however, surrounded by a significant amount of controversy with regards to its efficacy, adverse effects and suicidality. This will be discussed in Chapter Four.

3.2 ANXIETY-RELATED DISORDERS

Anxiety is part of the range of emotions experienced by all humans. It is a feeling of indistinct fear, nervousness and uneasiness experienced in response to a physical or psychological threat (Guthrie et al, 2009). This section will briefly discuss the anxiety spectrum of disorders within the context of their definition, classification, prevalence and treatment.

3.2.1 DEFINITION

Anxiety disorders can be defined as the persistent feelings of anxiety that do not abate after the removal of the source of threat or is disproportionate to the threat and impairs normal functioning (Guthrie et al, 2009). When this occurs, anxiety is considered pathological.

3.2.2 CLASSIFICATION

Anxiety consists of a spectrum of disorders. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classifies anxiety-related accordingly:

- Generalized Anxiety Disorder: chronic worry that is uncontrollable and interferes with daily functioning
- Panic Disorder: acute episodic moments of extreme fear associated with increased heart rate and respiration, tremor and gastrointestinal disturbance
- Phobic Disorders: excessive fear that leads to avoidance of the precipitating factor
- Obsessive Compulsive Disorders: disabling obsession or compulsion that impairs normal functioning

- Posttraumatic and Acute Stress Disorder: re-experiencing symptoms of a past traumatic event that is disabling, distressful and accompanied by physical symptoms

  (American Psychiatric Association, 2000)

3.2.3 DIAGNOSIS

The American Psychiatric Association has published diagnostic criteria for each form of anxiety. The diagnostic criteria for generalized anxiety disorder are the presence of unrealistic or extreme anxiety for six months or longer. The anxiety is accompanied with at least three of the following symptoms: restlessness, fatigue, concentration difficulties, irritability, sleep disturbance, muscle tension. The anxiety should not be attributed to substances, medical conditions and impacts on the patient's functioning (American Psychiatric Association, 2000).

The spectrum of other anxiety disorders are diagnosed according to the hallmark features of the respective disorder. But all are related to persistent concern, worry or fear that persists long after the removal of the causative factor and is presently not attributable to substances or other general disease and impairs normal functioning (Guthrie et al, 2009).

3.2.4 EPIDEMIOLOGY

The lifetime prevalence of generalized anxiety disorder is between 3.9% and 6.6% (Guthrie et al, 2009). The lifetime prevalence of anxiety in South Africa is considerably higher and determined to be as high as 15.8% in the SASH study (Seedat et al, 2009); the 12-month prevalence was 8.1% (Seedat et al, 2009).

The SASH study showed that an anxiety disorder showed significant associative factors similar to MDD. Female gender and negative life event were found to be significantly predictors of anxiety. In contrast to MDD, however, childhood parental separation was not a significant factor but urban location and relationship problems were (Seedat et al, 2009).

Patients with an anxiety disorder have also been suggested to likely have another comorbid psychiatric condition such as MDD or substance abuse (Guthrie et al, 2009).

3.2.5 BURDEN OF DISEASE

The burden of anxiety is considered similar to the burden of MDD with significant impact on disability, poor work functioning and increased use of health care resources.

A review article conducted on 34 studies on the burden of anxiety found that anxiety reduced the quality of life of patients (Hoffman et al, 2008). There is a reported impact on general, mental and physical health and impaired social and occupational functioning. The review also suggested that impairment of the quality of life of patients with anxiety was comparable to the impairment seen in patients with chronic physical conditions (Hoffman et al, 2008).

The presence of anxiety with another co-morbid condition impairs quality of life even further (Wittchen, 2002; Hoffman et al, 2008). The economic and health care burden of anxiety is also an area of concern. Patients with anxiety display either poor occupational productivity or absenteeism (Wittchen, 2002; Hoffman et al, 2008). This direct economic cost is exacerbated by the indirect cost of healthcare utilization. Patients with anxiety display use of health care facilities more than the general population (Wittchen, 2002). Patients with anxiety were found to approach primary health care facilities for vague symptoms, pain and sleep disturbance and are also shown to display increased visits to specialist gastroenterologists compared to patients without anxiety (Hoffman et al, 2008).

Anxiety undoubtedly is a major contributor to a deterioration of a patient's quality of life and increases financial burden. To reduce this burden Wittchen (2008) suggests that early recognition and appropriate treatment is essential. The next section 3.2.6 will discuss current treatment recommendations.

3.2.6 TREATMENT

The goals of treatment of anxiety are to: decrease symptom severity and frequency, improve functioning and quality of life and decrease disability (Wittchen, 2008; Guthrie et al, 2009).

Treatment of the different forms of anxiety involves psychotherapy and pharmacotherapy (Guthrie et al, 2009). Psychotherapy includes relaxation and meditation training, dynamic and supportive psychotherapy and commonly cognitive behavioral therapy (Guthrie et al, 2009).

Similar to the treatment of MDD, cognitive behavioral therapy concentrates on identifying negative thoughts and focusing on their conversion to more positive thoughts which precipitates a change in behavior (Guthrie et al, 2009). Psychotherapy is a valuable component of anxiety treatment and produces effect that are long term but they are resource and time intensive (Guthrie et al, 2009). Pharmacotherapy options are an adjuvant or alternate option.

For the short-term pharmacotherapeutic treatment of anxiety, the use of benzodiazepines has been established (Wittchen, 2008). This group of drugs provides quick relief (Guthrie et al, 2009) and are used in acute management of episodic anxiety (O'Donnell et al, 2011). The benzodiazepines do not provide a long-term solution for anxiety because of their

adverse effect profile. Prolonged use of these drugs can lead to dependence and abuse (O'Donnell et al, 2011) and are associated with cognitive impairment, memory difficulties, withdrawal symptoms, sedation and tolerance to anxiolytic effects with chronic treatment (O'Donnell et al, 2011).

Buspirone is an alternate anxiolytic that does not cause sedation, memory or cognitive impairment and has a reduced risk of dependence (O'Donnell et al, 2011). Buspirone and benzodiazepines, however, are limited by the fact that they do not treat the often co-morbid depression in patients with a form of anxiety (Wittchen, 2008).

Antidepressants, in particular SSRIs and SNRIs, are considered the first line treatment of anxiety disorders internationally (American Psychiatric Association, 2006). The South African Department of Health's Standard Treatment Guidelines also suggests SSRIs for the maintenance treatment of anxiety (Department of Health, 2006). Antidepressants are effective in treating anxiety and the co-morbid depression (Wittchen 2008). These drugs, however, are used for the long-term treatment of an anxiety disorder and are not considered for acute attacks, benzodiazepines are used in these situations (Guthrie et al, 2009).

The increasing positive outcomes of studies researching antidepressants for the treatment of anxiety have placed these drugs as the forerunners of pharmocotherapeutic anxiety treatment (Wittchen, 2008). The treatment of anxiety with efficacious agents has the consequence of reducing the economic, social and functional burden of anxiety.

3.3 PAIN

Most people will experience some form of pain in their life. The variations of pain experienced are considerable. This section will briefly discuss pain and pain management.

3.3.1 DEFINITION

Pain is subjective and often defined in the manner explained by the patient (Baumann et al, 2011). It involves an unpleasant sensory and emotional experience usually precipitated by damage (Mersky et al, 2011). Acute pain may be beneficial and alerts an individual to harm or damage. When it persists after recognition of the harm and is severe and unremitting it may require treatment. Chronic pain syndromes occur when the acute pain does not subside and continues for months or longer with adverse effects on functionality, sleep and psychological well being (Baumann et al, 2011).

3.3.2 PATHOPHYSIOLOGY

Nerves play a major role in the pathophysiology of pain. Pain can be nociceptive, neuropathic or functional. The pathophysiological process of nociceptive pain is thought to begin with the stimulation of nociceptors. Stimulation of these nociceptors can be as a result of thermal, mechanical and chemical signals. Chemical signals include the release of histamine, interleukins, serotonin, bradykinins, substance P and others. Activation of the nociceptors results in the generation of an action potential that is transmitted to the spinal cord and then the brain. During this transmission various neurotransmitters are also released. The perception of pain by the patient can be dictated by cognitive processes which limit or enhance the number of pain signals. A depressive or anxious state is thought to worsen the perception of pain while relaxation and distraction is thought to lessen pain (Baumann et al, 2011).

Nociceptive pain is believed to differ from neuropathic pain. Damage to nerves is thought to cause neuropathic pain which is often more chronic in nature. Functional pain is thought to be as a result of the abnormal functioning of the nerve system and is also more chronic in nature (Baumann et al, 2011).

3.3.4 TREATMENT

The options for treatment include a non-pharmacological and a pharmacological approach. Non-pharmacological approaches include relaxation, education and information prior to painful procedures and cognitive behavioral therapy (Baumann et al, 2011).

The pharmacological approach is dependent on the type of pain. Mild to moderate acute pain is managed with paracetamol and nonsteroidal inflammatory drugs (NSAIDs). Chronic and severe pain is managed with opioid agents and central analgesics like tramadol (Baumann et al, 2011).

NSAIDs and paracetamol are considered ineffective for the treatment of neuropathic pain. Opioids and tramadol are second-line treatment and considered if there is a failed response to first-line treatment. First-line treatments of neuropathic pain are anticonvulsant, topical lidocaine and antidepressants (O'Connor et al, 2009). The antidepressants considered are tricyclic antidepressants and serotonin noradrenaline reuptake inhibitors.

Antidepressants are a significant component in the arena of pharmacotherapeutic management of depression, anxiety and pain syndromes. They are, nevertheless, surrounded with a considerable degree of controversy with regards to their efficacy, tolerability and safety. These aspects will be discussed in Chapter Four. Usage of

antidepressants assessed through drug utilization studies will also be discussed in Chapter Four.

CHAPTER FOUR: A LITERATURE REVIEW ON THE CONTROVERSY SURROUNDING ANTIDEPRESSANTS AND A REVIEW ON DRUG UTILISATION

This chapter (Chapter Four) will review the literature on the controversy surrounding antidepressants and why a decision was made to conduct a drug utilization review on antidepressants. A literature review on drug utilization studies in general will follow and drug utilization reviews done on antidepressants will conclude this chapter (Chapter Four). The methodology of the literature search is described in Chapter Five.

4.1 CONTROVERSIES SURROUNDING USE OF ANTIDEPRESSANTS

Chapter Two provided a pharmacological overview of antidepressants. Chapter Three discussed the disorders that are treated with an antidepressant. This chapter (Chapter Four) will highlight the controversies surrounding the use of antidepressants. The controversies covered include the efficacy debate on antidepressants and concerns raised on the safety of antidepressants. This chapter will then progress on to the theory behind drug utilization reviews and conclude with utilization studies done on antidepressants.

4.1.1 EFFICACY DEBATE

A well publicized meta-analysis conducted by Kirsch et al (2008) on published and unpublished antidepressant trials suggested that antidepressant efficacy has been overstated. The article suggests that differences in results between drug and placebo groups may be statistically significant but are not clinically significant. In addition, it was concluded that significant results for participants who were initially classified as severely depressed are not due to an increase in response to the drug but rather to a decrease in response to the placebo. This article brought into question the efficacy of antidepressants and produced a large response amongst scientists, the general media and the public.

In addition, the bias in the publication of antidepressant trials has also been highlighted. Turner et al (2008) suggested that there is a tendency to only publish antidepressant trials that have a positive outcome and trials that have a negative outcome are either not published or published in a manner that portrays a positive outcome. The authors suggested that this selective publication of trials creates a bias and creates a set of consequences that are not optimal for health care professionals, researchers and patients (Turner et al, 2008).

In reply to this controversy, which has brought into question whether antidepressant efficacy has been overstated or not, a study was conducted with the same data used by Kirsch et al (2008) in their meta-analysis. The authors concluded that Kirsch et al (2008) failed to report that venlafaxine and paroxetine had improvements on the Hamilton Depression Scale (HAMD) that are above the threshold set by the United Kingdom's National Institute for Health and Clinical Excellence (NICE) (Fountoulakis et al, 2011). In addition, the authors also questioned the accuracy of Kirsch's calculations when explaining the difference between placebo and the drug. Fountoulakis et al (2011) also suggested that Kirsch et al (2008) selectively reported results and their conclusions were flawed.

Other critiques of Kirsch's conclusions have questioned the clinical trial methodology. The following points have been raised in literature:

- **Length of clinical trials**

The short length of time of the trials (between four and six weeks) included in Kirsch et al's (2008) meta-analysis has been suggested to have produced a negative bias and that longer length trials may report results with better efficacy (Horder et al, 2011).

- **Diagnostic Criteria**

The use of depressive scales has been questioned and a flaw in the variable diagnostic criteria employed in clinical trials has been postulated (Bech, 2010). Some clinical trials employ the $HAMD_6$ scale while others use the $HAMD_{17}$ scale (Bech, 2010). This has resulted in suggestions being made for more standardized scales with better outcomes to be employed by clinical trials (Parker, 2009; Bech, 2010).

- **Study population and recruitment**

Other critiques of Kirsch et al (2008) have also suggested that their conclusions are unfounded and questioned clinical trial methodology with regards to participant recruitment and inclusion (McAllister-Williams, 2008; Moller, 2008; Bech, 2010; Brody et al, 2011; Horder et al, 2011). It has been postulated that the clinical trials conducted on antidepressants were done in the United States where participants are recruited through advertising and may join to receive free health care and medication and, therefore, may be particularly more likely to show a response (McAllister-Williams, 2008). This produces a study population which is potentially biased, especially when studying a condition such as depression where there is no identifiable bio-marker at present (Brody et al, 2011). The recruitment process of antidepressant clinical trials has also increasingly included patients who are 'less depressed' and patients with severe depression; co-morbid anxiety and suicidal ideation are excluded from clinical trials. These patients have been suggested to be more likely to respond to a placebo as they are less severely depressed (Parker, 2009; Brody et al, 2011). These inclusion criteria also create the problem of including patients in trials who show no parallel to patients seen in 'real-world' clinical practice (Parker, 2009).

Patients recruited for clinical trials, in general, have been suggested to be emotionally upset, weakened and may surrender and display compliance to the added care in a clinical trial (Schafer, 1982).

The under-reporting of 'eligibility criteria' in clinical trials has also lead to a potential bias and the lack of information on the recruitment process negatively impacts decision-making (Gross et al, 2002). Clinical trials that are sponsored by pharmaceutical companies have also potentially increased the placebo response because an incentive to enrol subjects may result in an exaggeration of symptoms at the initial visit (Brody et al, 2011). A call for more robust clinical trials that adopt a 'naturalistic approach', are more generalizable to the clinical environment and considers co-morbidities and primary health care settings has been made (Parker et al, 2009; Brody et al. 2011; Horder et al, 2011).

- **'Real world' experience**

Kirsch et al (2008) has suggested that antidepressants may be no better than a placebo. The clinical experience of antidepressants, however, has warranted their use and it has been suggested that the danger of Kirsch's conclusions are that patients who might benefit from an antidepressant may be denied this opportunity (Moller, 2008). Clinicians have also suggested that the goal of treatment is to achieve a positive response in a patient's depressive symptoms and that prescribing a placebo is unethical, hence using an antidepressant should not be discouraged if it elicits a positive response (McAllister-Williams, 2008).

The debate on the efficacy of antidepressants is likely to continue, especially with the introduction of new drugs as time progresses. This debate is a 'hot topic' and there is support for the usage of antidepressants and support for not using an antidepressant. Nevertheless, antidepressants remain a class of drugs that have shown considerable growth in usage patterns globally (Mant et al, 2004; Lader, 2007; Trifiro, 2007; Ufer et al, 2007).

4.1.2 SAFETY

The safety of antidepressants with regards to suicidality, adverse effects and safety in pregnancy has also added to the controversy surrounding antidepressant usage.

In 2005, the United States Food and Drug Administration (FDA) instructed a black-box warning to be placed on SSRIs which emphasized the increased risk of suicidal thoughts and behaviours in children and adolescents. This warning was instituted following a meta-analysis to determine the risk of suicidality amongst young patients in antidepressant trials (Hammad et al, 2006). The meta-analysis did not find a reported suicide but suggested that the risk of suicide or suicidal behaviour in young patients was increased in those on short-term antidepressants. The FDA did not contra-indicate the use of antidepressants amongst the youth but advised caution and careful consideration of the risk-benefit ratio in young patients (Hammad et al, 2006)

Another meta-analysis looked at paediatric trials of antidepressants in major depressive disorder, anxiety and obsessive-compulsive disorders and also found no completed suicides but a small increase in suicidal thoughts or behaviours in users of antidepressants (Bridge et al, 2007).

In contrast to these meta-analyses, a retrospective observational study across over 65 000 patients found the highest risk of suicide to be a month before antidepressant treatment was started (Simon et al, 2006). Suicide may be a manifestation of the major depressive disorder and not necessarily the treatment. It has been postulated that the black-box warnings may, in fact, discourage antidepressant treatment when it is needed (Simon et al, 2006).The risk-benefit analysis of antidepressants in younger patients seems to favour the use antidepressants but with cautionary use, close monitoring and follow-up care (Hammad et al, 2006; Simon et al, 2006; Bridge et al, 2007).

The risk-benefit analysis of antidepressants in pregnancy has also favoured the use of antidepressants in pregnancy. In-utero exposure to antidepressants has produced adverse effects such as neonatal pulmonary hypertension, cardiac malformations and SSRI neonatal behaviour (Jeffries et al, 2011; Koren et al, 2012). SSRI neonatal behaviour is believed to result from neonatal withdrawal of the SSRI, the symptoms include: irritability,

sleep disturbances and respiratory and gastro-intestinal disturbances but are transient (Koren et al, 2009; Jeffries et al, 2011). The adverse effects of neonatal pulmonary hypertension and cardiac malformations have been suggested to be of minimal risk (Koren et a, 2011). In contrast, the risk of not treating depression in pregnancy has been suggested to be evident and places the child at future risk of behavioural problems and a lower intelligence quotient (Nulman et al, 2012). Antidepressant exposure in-utero was found not to adversely affect behaviour or cognition and untreated depression during pregnancy was suggested as more of a risk than antidepressant treatment during pregnancy (Nulman et al, 2012).

The South African Medicines Formulary lists antidepressants as a Category C with the exception of paroxetine. A Category C drug is a drug which has undergone animal studies and adverse effects have been found following in-utero exposure to drugs in the neonate but no sufficient human studies have been conducted or that no animal studies and inadequate human studies have been conducted (Rossiter, 2008). Paroxetine is the only antidepressant with a Category D classification showing that studies have shown a risk of cardiac malformations. Pregnant women or women considering pregnancy who are on paroxetine have been advised to consider changing antidepressants or using alternate treatments (Jeffries et al, 2011).

As with younger patients, pregnant women who are using an antidepressant are not contra-indicated from doing so but rather careful consideration, monitoring and a risk-benefit analysis unique to the patient needs to be conducted.

As mentioned in Chapter Two, the adverse effects of antidepressants, in particular the TCAs need to be considered as part of their safety profile. The SSRIs and SNRIs are generally favourable but the MAOIs incur upon dietary habits and concomitant drug usage.

The TCA group of drugs possess anticholinergic, sedative and cardiovascular adverse effects which necessitate cautious use of these drugs amongst elderly patients and patients

with a cardiovascular disorder. In addition, TCAs can be fatal in overdose. Suicidal patients, therefore, require close monitoring and supervision and the lowest effective dose of a TCA. The safety profile of TCAs create a worrying set of circumstances and their use has, consequently, been discouraged internationally and more a favourable approach is directed towards the newer SSRIs and SNRIs (Mann, 2005). MAOI usage has also been discouraged because of the restrictions placed on patient's diets and the high number of drug interactions (Mann, 2005).

The controversies surrounding the use of antidepressants have not slowed the wide-use of antidepressants. This group of drugs remains a significant part of the global spectrum of prescription. This continued prescribing of antidepressants warrants information on their usage and patterns of usage. In this way problems in prescribing, patterns and preferences of drugs and areas of interest will be highlighted and perhaps encourage a refinement of treatment strategies. A Drug Utilization Review (DUR) provides valuable information on medication utilization which can be evaluated for appropriateness and confer a degree of the quality of care (Schneeweiss et al, 2005).

The next section 4.2 will provide the theory behind DURs and the following section 4.3 will review DURs on antidepressants.

4.2 DRUG UTILIZATION REVIEWS

The World Health Organization Collaborating Centre for Drug Statistics and Methodology (WHOCC) recommends conducting research on drug utilization to describe the extent, nature and determinants of drug use and to identify problems which warrant further study (WHO, 2003). This section will define drug utilization reviews, discuss the application, benefits and methodology.

4.2.1 DEFINITION

In 1977, the WHOCC defined drug utilization research as the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences (WHO, 2003). Presently, drug utilization studies have blurred with pharmacoepidemiological studies. The WHOCC defines pharmacoepidemiology as the study of the clinical use of drugs with the purpose of supporting rational and cost-effective use of drugs in the population and improving health outcomes (WHO, 2003).

4.2.2 APPLICATION

Drug Utilization Reviews (DURs) can be applied through a number of ways. These include: international, national and local studies. International studies involve describing and comparing patterns of specific drug use over geographic regions or time (Sachdeva, 2010). National studies involve assessing use of drugs and comparing this to national drug policies or formularies (WHO, 2003). Local studies are drug utilization studies conducted at hospitals or pharmacies, the aim of drug utilization reviews are to profile drug use and costs at a local level. This allows for budgeting and ordering of drugs and identifying adherence to local formularies and drug policies (WHO, 2003; Sachdeva, 2010).

Drug utilization studies can be further applied to identify the determinants of drug use and the health outcomes of drug use (WHO, 2003). The scope of drug utilization studies is broad and encompasses a range of areas which can be studied (WHO, 2003). Our research will apply drug utilization studies to describe the patterns of antidepressant use, identify the determinants of the type of antidepressant used and identify the determinants of the duration of antidepressant use.

4.2.3 BENEFITS

Drug utilization reviews and studies are a continual process with the ultimate end point being an improvement in the quality of drug use (Sachdeva et al, 2010). It would be difficult to improve the quality of drug use without first identifying the patterns of drug use and highlighting which areas deserve refinement and then encouraging rational use of drugs.

Rational drug use is defined as: the use of a well-documented drug for the required indication at the correct dosage, an affordable price and sufficient information (WHO, 2003). Rational drug use is bolstered by drug utilization studies because a drug utilization study can identify areas of irrational drug use and promote suggestions to improve prescribing practice. Social, economic, geographical and demographic influences on drug use can be studied and hypotheses on divergence from guidelines can be proposed. Amendments to guidelines can also be suggested and the impact of educational and promotional efforts can be studied (WHO. 2003)

The benefit of drug utilization studies is in what happens after the study is completed. Feedback to clinicians on appropriate drug use to improve prescribing and the subsequent development of criteria, standards and policies of rational drug use are aided by drug utilization studies (Sachdeva et al, 2010).

The scope and benefits of drug utilization are wide. The methods employed in drug utilization reviews are also wide and vary depending on the aim of the study. The next section 4.2.4 will discuss the different methods employed in drug utilization studies.

4.2.4 METHODOLOGY

Drug utilization studies can be quantitative or qualitative. Quantitative studies involve measuring drug use. Qualitative studies involve analyzing drug use and link prescribing to the reasoning behind prescriptions (Sachdeva et al, 2010). Our study aimed to combine a quantitative and qualitative approach. The frequency and pattern of antidepressant use was quantitatively assessed and the qualitative component involved explaining the statistical inferences for the type of antidepressant used and the duration of treatment.

Data for a drug utilization study can be sourced from a number of places. Arguably, the most accessible is computerized databases with medical information. Pharmacy records, practitioner medical files and population surveys can de be conducted and obtained on drug use (Sachdeva et al, 2010).

Medical databases contain information on drug use, patient particulars and importantly indications of use. Diagnoses and patient demographic information is informative, valuable and allows the researcher to link drug use with an indication and qualitatively examine the data. All sources of data have limitations; medical databases may suffer from incompleteness, patient surveys have the problem of recall bias and pharmacy records may have insufficient information on diagnoses (Sachdeva et al, 2010).

Once the source of data is identified, the next step involves identifying the drug, drug class or disease state to be studied (Sachdeva et al, 2010). Data on the identified area of study is

then collected, organized and analyzed. This is also a variable area of the methodology of drug utilization studies. Organizing and analyzing the data also depends on the source of data and include:

- Determining utilization rates
- Separating utilization by drug class and determining the frequencies
- Describing the profile of users,
- Determining the reasons for use of drugs
- Commenting on the economical implications
- Comparing the prescribed dose to the recommended dose
- Comparing use of drugs to guidelines (WHO, 2003)

Data that lacks diagnoses cannot comment on the reasoning behind drug use and data that lacks dosages cannot comment on the appropriateness of the drug dosage.

For international comparisons of drug utilization patterns, the WHOCC recommends classifying drugs according to the Anatomical Therapeutic Chemical (ATC) system along with the Defined Daily Dose (DDD) as a measure of drug consumption. The ATC involves dividing drugs according to the anatomical region where they act and their chemical, therapeutic and pharmacological properties (WHO, 2011). The DDD is the assumed average maintenance dose per day for a drug used for its primary indication in adults (WHO, 2003). The ATC/DDD system involves classifying a drug according to its ATC reference and presenting drug consumption as DDDs/1 000 inhabitants/day. The ATC/DDD system is employed in national drug consumption studies to allow for international comparison or comparison over time (WHO, 2011). A limitation of this method is that the DDDs do not represent the actual dose taken by the patient and does not take into account that the drug may not be taken on a regular basis (Smith et al, 2008).

The WHOCC also recommends utilizing the prescribed daily dose (PDD) as a measure to reflect actual prescribed drug dosage in situations where the dosage of drug may vary

according to indication, guidelines or different patient groups (WHO, 2003). The PDD may also be compared to the DDD to give an indication of the difference between actual drug dose and the defined drug dose (WHO, 2003). The limitation of the PDD is that it is the 'prescribed' dose and does not represent the actual dose taken by the patient (Smith et al, 2008).

Drug utilization studies are an evolving area of study and with the increasing availability of computerized data and linked information their scope is sure to grow and a change in the methodology employed will likely pursue. The methodology employed in this study is, to the researcher's knowledge, a novel approach in the South African scene of drug utilization studies. It does not strictly follow the WHOCC's guideline methodology but encompasses a set of statistical techniques that provide inferential information on antidepressant use in two samples. The methodology is discussed in Chapter Five.

The next section will review the literature on drug utilization studies conducted on antidepressants.

4.3 DRUG UTILIZATION REVIEW ON ANTIDEPRESSANTS

As discussed in the previous section 4.2.4 the methodology of drug utilization studies varies, so do the aims and findings. This section will begin with a review of findings in international studies that assessed patterns of antidepressant use with regards to frequency of antidepressant use, the age and gender of users and the frequency of diagnosis. The factors affecting the type of antidepressant used and the duration of treatment will follow. This section will conclude with an exclusive review of the available South African antidepressant drug utilization reviews.

4.3.1 PATTERNS OF USAGE

The patterns of antidepressant usage can be assessed according to frequency of drug use, the age and gender of users and the frequency of diagnoses of antidepressant prescriptions.

4.3.1.1 FREQUENCY OF DRUG USE

The frequency of antidepressant drug use seems to be skewed towards the newer SSRIs in international studies. SSRIs and other newer agents from the bulk of antidepressant prescriptions in most European, American, Asian and Australian studies (Roberts et al, 2001; Mant et al, 2004; Colman et al, 2006; Sim et al, 2006;Trifiro et al, 2007;Bauer et al, 2008; Zullino et al, 2009; Sundell et al, 2011). The exceptions to this were found in a German (Ufer et al, 2007) and a Taiwanese (Wu et al, 2012) study. The reasons for this divergence were proposed as being economically (Ufer et al, 2007) and diagnostically linked (Wu et al, 2012) with TCAs being used for non-psychiatric conditions in Taiwan. German prescribers seem to favour cheaper generic drugs as a result of the country's re-imbursement policy (Ufer et al, 2007).

The international preference towards SSRIs internationally has been explained by the fact that SSRIs have a simpler dosing schedule and a better safety and tolerability profile (Chen et al, 2008; Sonnenberg et al, 2008). Industry marketing of newer agents (De Las Cuevas et al, 2002), consumer advertising (Smith et al, 2008) and depression awareness campaigns (McManus et al, 2000; Colman et al, 2006) have also been suggested to have increased SSRI antidepressant use.

As part of this study's aim, the frequency of antidepressants used was assessed to determine which end of the spectrum our South African samples belong to.

4.3.1.2. AGE

The age of patients using an antidepressant show two distinct patterns. The majority of users of antidepressants have been found to be middle-aged (between 40 and 55 years) in some studies (Lawrenson et al, 2000; Bramesfeld et al, 2007; Larson et al, 2007;) while the majority of users were found to be the elderly population (Over 65 years)in other studies (Carrasco-Garrido et al, 2007; Trifiro et al, 2007; Demyttenaere et al, 2008; Sonnenberg et al, 2008; Sihvo et al, 2008).

The relationship between age and antidepressant use is poorly understood (Bramesfeld et al, 2007). Antidepressant use amongst the elderly has been attributed to the fact that the elderly have a negative perception of their health and well-being and the presence of chronic physical and health problems may predispose them to using antidepressants (Carrasco-Garrido et al, 2007).Elderly patients are also more likely to visit general practitioners for chronic conditions were the practitioner may have the opportunity to prescribe an antidepressant for an underlying psychiatric condition (Sihvo et al, 2008).

The use of antidepressants by middle-aged adults has been explained by the fact that this age group display higher rates of a mood disorder (Rait et al, 2009; Kessler et al, 2003) or

poorer mental health (Sundell et al, 2011). The lack of consensus with regards to the association between age and antidepressant use suggests that other factors may be more closely linked with antidepressant use. Geographic, ethnic, social and co-morbid conditions are believed to influence antidepressant usage patterns more strongly than age (Paulose-Ram et al, 2007; Demyttenaere et al, 2008; Walters et al, 2008).

Gender is another demographic factor studied when describing the profile of antidepressant users. This will be discussed in the next sub-section.

4.3.1.3 GENDER

The prevalence of antidepressant use has been found to be higher amongst females than males in numerous studies (Olfson et al, 2006; Trifiro et al, 2006; Gardarsdottir et al, 2007; Larson et al, 2007; Paulose-Ram et al, 2007; Sihvo et al, 2008; Carta et al, 2010; Sundell et al, 2011). A few studies have suggested that there is no or minimal association between gender and antidepressant use (Alonso et al, 2004).

Reasons for increased use of antidepressant by females could be explained by the increased prevalence of mood disorders in women and social factors which suggest that women are more likely to seek help and express symptoms and less likely to consume alcohol as a coping mechanism (Carrasco-Garrido et al, 2007; Van der Heyden et al, 2009).

There seems to be general consensus that females form the majority of users of antidepressants.

4.3.1.4 FREQUENCY OF DIAGNOSIS

Including a patient's diagnosis is an important aspect of drug utilization studies as it removes 'misclassification bias' (Patten et al, 2007). Antidepressants cannot solely be classified as a measure of depression treatment as these drugs have been approved for many other indications (anxiety, pain and non-psychiatric disorders). Including data on a patient's related diagnosis is an important part of drug utilization studies and provides clinically relevant information on drug use.

Not all antidepressant utilization studies have included information on diagnoses. Studies observing changes in usage patterns of antidepressants over years or between regions may only look at sales patterns of antidepressants and not include an analysis of indications (McManus et al, 2000; Patten et al, 2005; Paulose-Ram et al, 2007; Chen et al, 2008; Smith et al, 2008; Harman et al, 2009; Sundell et al, 2011). This has been mentioned as a limitation in some of the studies (Patten et al, 2005; Paulose-Ram et al, 2007; Chen et al, 2008; Sundell et al, 2011).

Studying the trends in the diagnoses patterns of antidepressant provides an idea of the reasoning behind antidepressant prescriptions. Antidepressants have been used in mood and anxiety disorders and for non-psychiatric purposes such as chronic pain management (Rossiter, 2008). Antidepressant utilization studies that have looked at the linked diagnosis for the antidepressant prescription have found psychiatric and non-psychiatric use of antidepressants. A psychiatric diagnosis accounted for the majority of prescriptions in European and Canadian studies (Gardarsdottir et al, 2007; Patten et al, 2007; Trifiro et al, 2007; Sihvo et al, 2008). Two of these studies, however, did acknowledge a significant proportion of diagnoses attributed to a non-psychiatric diagnosis (Patten et al, 2007; Sihvo et al, 2008) In contrast, a non-psychiatric diagnosis formed the majority of diagnoses in a recent Asian study (Wu et al, 2012).

Assessing diagnostic indications also allows for comparison between usage patterns of different antidepressants. The following section 4.3.2 will elaborate on this further.

4.3.2 FACTORS AFFECTING TYPE OF ANTIDEPRESSANT USED

Various factors such as age, gender and importantly diagnosis can affect the type of antidepressant used. The types of antidepressant used are generally distinguished on their mechanism of action. Most studies have looked at the differences in usage patterns between TCAs and new generation antidepressants such as the SSRIs.

The effect of age on whether a patient receives a TCA or a newer generation antidepressant is inconclusive. Elderly patients are more susceptible to the adverse effects of TCAs and are advised to be monitored when taking a TCA (Rossiter, 2008). Reason would have it that these drugs would account for fewer prescriptions in the elderly patient population and the newer generation drugs would be preferred. Studies have found a contrary result to this. TCA users were older than users of new generation antidepressants in several studies (Sim et al, 2006; Bauer et al, 2008; Zullino et al, 2008; Exeter et al, 2009).

Reasons for higher use of TCA by older patients compared to younger patients have been attributed to increased awareness amongst younger patients and a preference towards better tolerated drugs (Sim et al, 2006). It has also been suggested that older patients may have been stabilized on a TCA for a long period of time and the practitioner may be unwilling to change therapy (Zullino et al, 2008).

Gender, another demographic factor, has shown no association with the type of antidepressant used by a patient in some studies (Lawrenson et al, 2000; Sim et al, 2006; Exeter et al, 2009). Only one international study found that female gender was associated with TCA usage (Trifiro et al, 2007). Studies, which found no association between gender

and antidepressant type included other factors in their research that were found to be more closely linked to the type of antidepressant, used. These other factors include: cost, physician and patient past experience and preference (Bauer et al, 2008); patient education (Bauer et al, 2008); ethnicity (Exeter et al, 2009) and hospitalization (Sim et al, 2006).

Arguably one of the most important clinical factors to consider when prescribing an antidepressant is the diagnosis. TCAs have been shown to be effective in treating chronic pain syndromes while SSRIs show less efficacy (Dharmshaktu et al, 2012). If one considers this, a non-psychiatric diagnosis would be more closely associated with a TCA compared to a new generation antidepressant. Conversely, a newer generation antidepressant would more likely be associated with a psychiatric diagnosis.

This trend of TCA usage being associated with non-psychiatric use has been observed in numerous studies (Gardarsdottir et al, 2007; Patten et al, 2007; Trifiro et al, 2007; Sonnenberg et al, 2008; Wu et al, 2012). The established recognition of TCAs in treating non-psychiatric conditions, like pain syndromes, has contributed to this trend (Trifiro et al, 2007). An Asian study suggested that TCAs are re-imbursed by medical aid funds for an increased number of indications compared to SSRIs and are therefore preferred (Wu et al, 2012). The favourable costing of TCAs would possibly also favour their prescriptions when treating off-label conditions.

A patient's diagnosis was not associated with the type of antidepressant used in a minority of studies. (Sim et al, 2006; Zullino et al, 2008). These studies found no correlation between the indication of use and the antidepressant type. Zullino et al (2008) only looked at antidepressant prescriptions by psychiatrists. Psychiatrists are mental health specialist and are perhaps less likely to see patients with non-psychiatric conditions. Zullino et al (2008) would, therefore, encounter less non-psychiatric indications in their study compared to studies that looked at general databases. In addition, it was suggested that sleep disorders were more likely to be treated with a non-benzodiazepine sedative than a TCA by psychiatrists (Zullino et al, 2008). A psychiatric setting was also evident in Sim et al's (2006) study and would suggest a similar reason for lack of association between

diagnosis and antidepressant type as Zullino et al (2008). In addition, Sim et al, (2006) conducted a cross-national study of five East Asian countries and suggested regional prescribing differences, re-imbursement policies, economic factors and prescriber preferences as other possible factors affecting the type of antidepressant used.

The factors that affect whether a patient receives an older TCA antidepressant or a newer generation antidepressant are numerous and include demographic, clinical, economic and individual preferential factors. These factors may also overlap and studies which research these associations may bring to light other factors, confirm present reasoning or create more questions. But ultimately, will increase our understanding behind the rationale of antidepressant prescriptions.

4.3.3 FACTORS AFFECTING DURATION OF TREATMENT WITH ANTIDEPRESSANTS

International and national guidelines recommend that antidepressants should be continued for a minimum of six months when treating major depressive disorder and the maintenance phase of anxiety disorders (American Psychiatric Association, 2006; Department of Health, 2006). The degree to which this is adhered to is largely disappointing. Studies have found that one in three patients do not return for a repeat prescription of an antidepressant (Hansen et al, 2004) and only one in five patients continue treatment beyond four months (Serna et al, 2010).

Utilization studies on antidepressants have sought to understand and attribute the low duration of treatment to various factors. The significance of demographic, clinical and other factors differ across different study settings. The effects of the type of antidepressant, age, gender, and diagnoses have shown inconsistencies. A review of studies that have examined these factors is considered below.

The newer generation of antidepressants has shown better duration of treatment periods compared to the TCAs in numerous international studies (Lawrenson et al, 2000; Hansen et al, 2004; McManus et al, 2004; Serna et al, 2010). Better tolerance to SSRIs has been largely suggested as the reason for this (Lawrenson et al, 2000; Hansen et al, 2004). One study, however, did find that the antidepressant type did not affect the duration of treatment (McGettigan et al, 2000) and attributed dosage levels to be of more significance when analyzing duration of treatment with an antidepressant.

The effect of age on adherence to the recommended duration of treatment with an antidepressant have found that older patients are associated with using antidepressants for longer periods of time in some studies (McGettigan et al, 2000; McManus et al, 2004; Parabiaghi et al, 2011). Other studies have shown no association between age and duration of treatment (Hansen et al, 2004; Serna et al 2010; Burton et al, 2012). These inconsistencies and lack of international agreement of the effect of age on duration of treatment implies that no clear understanding has been reached. Elderly patients may be more compliant because of previous experience with other chronic conditions and their behaviour patterns display an understanding of chronic medication adherence (McGettigan et al, 2000) or elderly patients may visit a health care practitioner more often and the notion of adherence may be re-inforced. In contrast, elderly patients may suffer from cognitive decline and memory difficulties and display behaviours that result in shorter durations of treatment (Sihvo et al, 2008). The reasoning's on both ends of the spectrums have their merits and suggest the importance of individual differences.

Another demographic factor, gender, also lacks a clear and distinct pattern when considering the duration of treatment with an antidepressant. Gender has largely been found to be a non-significant factor when assessing antidepressant duration of treatment (McGettigan et al, 2000; Hansen et al, 2004; Sihvo et al, 2008; Burton et al, 2012). Personality traits, and not gender-specific differences, are possibly associated with adherence to treatment to a higher degree.

A patient's diagnosis has displayed a more significant role in determining the duration of treatment with an antidepressant. Patients with a psychiatric condition display patterns of use that are suggestive of longer periods of treatment with an antidepressant, compared to patients with a non-psychiatric condition (Sihvo et al, 2008; Burton et al, 2012). A patient's diagnosis was not available for study in a number of studies (McGettigan et al, 2000; McManus et al, 2004; Parabiaghi et al, 2011). The importance of including diagnosis in studies that assess drugs with a wide indication of use should not be ignored. A patient's diagnosis provides key information, especially when assessing the appropriateness of treatment (Parabiaghi et al, 2011). The ability to distinguish between diagnoses is important when commenting on whether duration of treatment with an antidepressant is appropriate or not. A diagnosis related to a pain syndrome may warrant once-off or a short period of treatment. A diagnosis of MMD, however, will not warrant a period of treatment that is less than recommended.

The lack of clinical information, such as diagnosis, in some studies suggest that more studies that look at this relationship will bolster the current understanding of the utilization patterns of antidepressants and their duration of treatment.

4.3.4 SOUTH AFRICAN STUDIES

The researcher has found a few South African studies conducted on utilization patterns of antidepressants these include: a drug utilization review of TCAs (Truter et al, 1997 & 2006) and of SSRIs (Truter et al, 1996) and a review of the usage of TCAs and SSRIs in adolescents (Kairuz et al, 2003).

The findings of each study differ but consistently found that TCAs were the most frequently prescribed antidepressant followed by SSRIs (Truter et al, 1996; Kairuz et al, 2003). The most recent South African has shown a shift towards the SSRIs (Truter et al, 2006) but this study lacked information on diagnoses and was confined to medical aid data.

The prescribed daily dose of TCAs was also found to be below the defined daily dose (Truter et al, 1997; Kairuz et al, 2003;Truter et al, 2006) but that SSRIs are prescribed in doses that are closer to the defined daily dose (Truter et al, 1996; Kairuz et al, 2003).The higher rate of TCA usage was attributed to its lower cost (Kairuz et al 2003).

The gender distribution of users of antidepressants also seems to consistently favour females (Truter et al, 1996 & 1997; Kairuz et al, 2003; Truter et al, 2006) this is a trend seen internationally as well. The duration of treatment was mentioned in one study and found to be inadequate (Kairuz et al, 2003). The published South African studies, however, do not contain information on the indication of use of antidepressants. Linking drug use to indications is also a beneficial aspect of drug utilization reviews and provides reasoning behind prescriptions especially for a group of drugs like antidepressants that have increasing wide indications.

Since these studies have been conducted, there has been an increase in the number of antidepressants available on the market. The effect of the introduction of these newer agents has not been studied. In addition it has been postulated that South African antidepressant prescribing trends may follow international trends with the newer SSRIs overtaking the TCAs in term of usage (Truter et al, 1997). Our research hopes to shed light in this hypothesis by studying usage of antidepressants in the most populated province of South Africa.

CHAPTER FIVE: METHODOLOGY

5.1 AIM

The aim of the study was to conduct a Drug Utilization Review (DUR) on antidepressants and determine current utilization patterns of antidepressants in a rapidly growing area of dispensing. The emergent utilization patterns were assessed against current local and international usage patterns and treatment guidelines.

5.2 OBJECTIVES

5.2.1 DESCRIPTIVE OBJECTIVES

To review the usage of antidepressants available on the South African market by:

1. Determining the frequency of prescriptions for each antidepressant
2. Determining the demographic profile of the users of antidepressants
3. Describing the differences in use between different antidepressant types
4. Describing the diagnosis associated with antidepressant prescriptions
5. Determining the percentage of indicated and off-label use of antidepressants
6. Obtaining the number of repeat prescriptions per patient
7. Determining the number of prescriptions for generic and original-branded antidepressant drugs

5.2.2 STATISTICAL OBJECTIVES

- To determine which demographic and clinical predictors (age, gender, diagnosis, duration of treatment) influenced the type of antidepressant used in the two samples of patients

- To determine which demographic and clinical predictors influenced the duration of treatment with an antidepressant

- To determine which demographic and clinical predictors influenced a patient's diagnosis

5.2.3 QUALITATIVE OBJECTIVES

- To compare similarities and differences in antidepressant prescribing between the two geographical areas

- To compare the similarities and differences in antidepressant use in our samples with other local and international studies

- To compare the data against current treatment guidelines for affective disorders

5.3 METHODOLGY

5.3.1 ETHICAL CONSIDERATIONS

Ethical clearance for the study was obtained from the University of Witwatersrand's Human Research Ethics Committee before research began. Clearance Certificate number: M080615(see Appendix 1A for ethical clearance certificate)

5.3.2 STUDY DESIGN

A literature search was done on PUBMED and Google Scholar with the search terms: DRUG UTILIZATION REVIEW; ANTIDEPRESSSANT USE; UTILIZATION OF ANTIDEPRESSANTS. Articles which discussed utilization of antidepressants that pre-dated 2000 were not reviewed as a decision by the researcher was made that these DURs would no longer be a valid representation of more current use of antidepressants. The exception to this was in relation to DUR conducted in South Africa as these were more scarce than international findings.

A Drug Utilization Review is an observational descriptive study. In wanting to describe antidepressant usage in Gauteng, public health records were excluded because of the incomprehensive and variable nature of public files. A medical aid company was initially proposed as the data source during the proposal and ethical permission stage of the research. It was not possible to retrieve the required data within the time frame of the research. Data was therefore sought from medical data warehousing companies which are a secondary source of claims data. The proposed plan for data management and analysis remained unchanged despite the secondary source and thus no amendments were sought for the Ethical Clearance Certificate. This study acquired databases from medical data warehousing companies from two distinct areas in Greater Johannesburg, East and South Rand.

Medical data warehousing companies serve the medical profession with online software that records patient particulars, documents patients' visits, records diagnoses, procedures and prescriptions and integrates other financial and medical aid information. These databases have information on patients with and without medical aid but serve the private sector of health care. The information was anonymous as the software engineering of these databases allowed for patient coding that could not be traced back to the patient by the researcher.

Two medical data warehousing companies were chosen because on completion of the descriptive analysis of one dataset a vast difference was found in usage patterns compared to international studies. The extensive use of amitriptyline in the first dataset (2009) was considerably different to international trends which favoured the newer SSRIs. This prompted the researcher to acquire another dataset in order to ascertain if the usage patterns were unique to those specific doctors at that particular time period. Statistical comparison of the two databases was **not** an aim of this study. Instead, usage patterns in one dataset were descriptively compared to usage in the other dataset.

5.3.2.1 COMPANY PROFILES

Company A serves doctors in a more economically thriving part of Johannesburg. Company B enlists doctors who serve patients with a more varying economic status, from low to upper middle class. Company A, also has a wider varying degree of physician specialty. Their enlisted practitioners include general practitioners, specialists, dentists and allied health professionals (physiotherapists and audiologists) in central eastern Johannesburg. Company B, stores data for general practitioners serving the southern suburbs of Johannesburg (Lenasia, Lenasia South, Kliptown, and Fordsburg). Both datasets represent drugs which were dispensed by the respective doctor. Details of the dispensing doctor's license could not be obtained from the anonymous nature of the datasets.

5.3.2.2 DATA HANDLING

Company A was approached in early 2009 to supply one years' worth of their medical records. The company approved the use of their data for the purposes of this study. Company A provided one years' (Aug 2008 to Aug 2009) worth of patient records in comma separated value (CSV) format on a CD in September 2009. The CD contained a memory of 3GBs of patient records. The CD was copied, the original was kept by the principal researcher and the duplicate was kept by the supervisor in locked locations. The format of the information was inappropriate for analysis; therefore the CSV data file was converted into Microsoft Excel 2007 format. The data fields in the file contained the following:

- Doctor Number
- Doctor Type
- Unique Anonymous Patient Number
- Gender
- Date of Birth
- Visit Number
- Treatment Date
- ICD-10 Code[4]
- Item Type which included a NAPPI[5] code, consultation code and procedure code.
- Medical Aid Charged
- Patient Charged

The patient population in this dataset will be referred to as Sample A.

The dataset contained 1 048 576 patient records. The researcher followed the steps as per the flow diagram in Figure 5.1 when extracting data.

[4] ICD-10 Codes are the World Health Organization's (WHO) International Classification of Diseases

[5] NAPPI code is the South African National Pharmaceutical Product Index

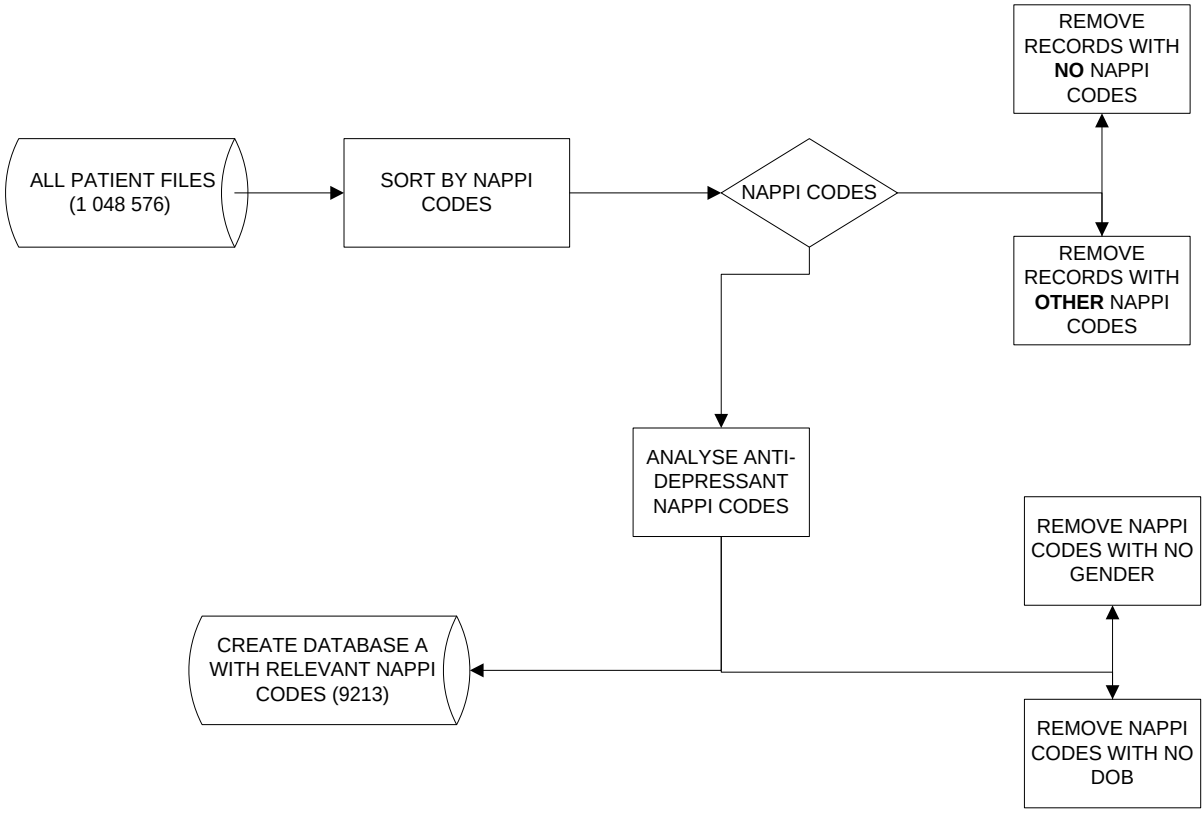


Figure 5.1 Process of extracting data for Dataset A

Refer to Appendix 1B for list of antidepressant NAPPI codes.

Company B was approached in July 2011 with a request to supply one year's patient records. The company had software that allowed for patient records with specific NAPPI codes to be extracted. A list of all antidepressants available in South Africa at the date of request was supplied along with the corresponding NAPPI codes to minimize the time spent in extracting patient records not necessary to this study. In September 2011, Company B ran each antidepressant NAPPI code through its system of patient records. Any patient who was prescribed with the corresponding drug between September 2010 and September 2011 was flagged and their patient record was imported into Microsoft Excel

2007. This process took 3 weeks as Company B ran the searches for NAPPI codes after business hours. The Microsoft Excel files were emailed by Company B to the principal researcher and supervisor. The data fields across all the files were the same and included the following:

- Patient Code
- Date of Birth
- Gender
- Treatment Date
- ICD-10 Code
- NAPPI Code

The patient population in this dataset will be referred to as Sample B.

All the Microsoft Excel 2007 files from Sample B were merged into a single file. This file contained 1236 prescriptions for antidepressants, representing 818 patients. Patients with a blank record for two or more fields were excluded from the dataset. The files were merged into a single file to identify patients who appeared in different files as a result of receiving drugs with differing NAPPI codes. Certain patient records were duplicated as they appeared in the medical aid claim and the cash payment parts of the software system. If a patient made a co-payment and the doctor claimed from their respective medical aid, this entry appeared twice. The researcher looked for duplicates manually, to lessen the chance of deleting repeat visits by patients.

Table 5.1 (page 62) lists the differences between Dataset A and B

Table 5.1 The differences between Dataset A and Dataset B

	DATASET A	**DATASET B**
LOCATION	Eastern suburbs of Johannesburg	Southern suburbs of Johannesburg
ENLISTED USERS	• General practitioners • Medical Specialists • Dentists • Physiotherapists • Occupational Therapists • Speech and Hearing Therapists	• General practitioners
DATA FIELDS	• Doctor Number • Doctor Type • Unique Anonymous Patient Number • Gender • Date of Birth • Visit Number • Treatment Date • ICD-10 Code • Item Type (NAPPI code, consultation code, procedure	• Patient Code • Gender • Date of Birth • Treatment Date • ICD-10 Code • NAPPI Code

	code) • Medical Aid Charged • Patient Charged	

Dataset B did not have details of the Doctor Number, Doctor Type or the Charges claimed from medical aid or paid by the patient. A decision was made not to include doctor type or costing in the data analysis of Sample A and B.

Dataset A and B did not contain details of the prescriber instructions for the antidepressants. The Prescribed Daily Dose (PDD) could not be deduced from the data. A comparison between the PDD and the Defined Daily Dose (DDD), therefore, could not be done.

5.3.3 MANAGEMENT OF DATA

Both datasets were managed in the same way with regards to calculating the age of patients and the creation of categorical variables. Variables were grouped and assigned a category to determine which variables influenced the choice of antidepressant and duration of treatment. The details of these are presented in this section.

5.3.3.1 CALCULATION OF AGE AND NUMBER OF PRESCRIPTIONS

The ages of patients in Datasets A and B were calculated by subtracting the patient's date of birth from the date of treatment in Microsoft Excel 2007. This gave the patient's age at the time of treatment.

The number of times a patient returned for a repeat prescription was determined by sorting the Microsoft Excel 2007 file according to patient number. Patients who returned then appeared consecutively. A new variable was created that recorded the number of prescriptions a single patient had received.

5.3.3.2 CATEGORICAL VARIABLES AND CODING

The following new variables were created:

1.**Antidepressant Type** to classify the antidepressant dispensed as either an older generation (all the TCAs) or a newer generation drug (the SSRIs, MAOIs, SNRIs and others)

Table 5.2 Classification of antidepressant type

CODE	DRUG
0	Older generation (amitriptyline, imipramine, clomipramine, dothiepin)
1	Newer generation (fluoxetine, paroxetine, citalopram, escitalopram, sertraline, tranylcypromine*, moclobemide, duloxetine, venlafaxine, bupropion, trazodone, reboxetine, mianserin)

(*Tranylcypromine is an old drug and no prescriptions appear for it but it was included for completeness)

2. **The "Brand"** of the antidepressant prescribed assigned whether the drug was an original branded drug or a generic. See Appendix 1 for list of drugs and branding. The table which follows details the coding

Table 5.3 Classification of antidepressant branding

CODE	BRAND
0	Generic
1	Original Brand Drug

3. **ICD10-codes** of patients were classified according to categories. The primary use of antidepressants is in the treatment of psychiatric conditions but their off-label use includes treatment of pain disorders. The distribution of the diagnosis made when prescribing an antidepressant was determined from this category. Certain disorders mentioned in the 'other' category could infer towards a diagnosis for pain. For example, a diagnosis for diabetes mellitus or HIV could suggest a diabetic or peripheral neuropathy which would account for a 'pain' diagnosis. The researcher, did not consider these inferences in the categorisation. Refer to Appendix 2 for the table detailing the ICD10 codes and the category they were assigned to.

Table 5.4 Categorisation of ICD-10 codes

CODE	ICD-10 CODE
0	All Psychiatric Diagnoses
1	Pain and Related Diagnoses
2	Other

4. **Psychiatric Diagnosis**. All patients with a psychiatric diagnosis were further categorised. This was done to see the distribution of psychiatric conditions being diagnosed and treated with an antidepressant. Please refer to Appendix 2 for the ICD-10 codes. The table detailing the category and coding is below.

Table 5.5 Categorisation of psychiatric diagnoses

CODE	PSYCHIATRIC DIAGNOSIS
0	Affective Disorders (Bipolar, Recurrent and Episodic Depression)
1	Anxiety-related conditions and Stress (Generalised Anxiety, Panic Disorder, Phobic Anxiety, Obsessive Compulsive Disorders, Reaction to Severe Stress, Neurosis)
2	Sleep disorders
3	Other (Adverse Life Events, Psychiatric Counselling)

5. **Gender** of the patients were represented as either "male" or "female" in the datasets, these were coded as following:

Table 5.6 Gender Coding

CODE	GENDER
0	Male

CODE	GENDER
1	Female

6. **Age** was a continuous variable which was also categorised. An age category was created to group patients according to their age in order to determine if these categories influence antidepressant prescribing. The age category was determined by following the guidelines set out by South African legislation. Children under the age of 12 require a parent/guardian to assist in their medical treatment (s129(2) of Children's Act 38 of 2005). Adolescents (over 12years) can legally obtain medical treatment without consent from their parent/guardian (s129(2) of Children's Act 38 of 2005). South African Law places individuals over 16 years as having full capacity(s17 and s14 of Children's Act 38 of 2005). Adults over 65 years are generally agreed upon as eligible for retirement and constitute our 'elderly' population. The legal categories of age also allowed for clinical distinction of users of antidepressants based on their age. This allowed for a clinical comparison of antidepressant use across different and distinct age categories.

Table 5.7 Classification of age categories

CODE	AGE CATEGORY
0	0 – 12 years
1	13 – 16 years
2	17 – 65 years
3	66 years and older

7. **The number of prescriptions** a patient received was also assigned to a category called 'duration of treatment'. Treatment guidelines suggest that antidepressants should be

continued for a minimum of six months in order for an adequate response to treatment to occur (American Psychiatric Association, 2000). Patients who were dispensed a minimum of six months antidepressant treatments were grouped in one category. Patients who only received one prescription of antidepressant were grouped into another category. Patients who returned for repeats but not for as many as are suggested were also grouped into one category. The table which details this category is presented below.

Table 5.8 Classification of duration of treatment

CODE	DURATION OF TREATMENT
0	Six months or longer
1	Between two and six months
2	One month

5.3.3.3 STATISTICAL TESTS AND REASONING

Pearson's Chi squared tests were conducted to query the relationship between two categorical variables. Contingency tables and graphs were drawn to visually present the relationship between variables (Brink, 2006).

Continuous variables were tested for normality of distribution using the Shapiro-Wilk test (Brink, 2006). Normally distributed data was compared using the student's t-test and non-parametric values were analysed using the Wilcoxon rank-sum test (Mann-Whitney U test).

Logistic regression was conducted to determine which variable were predictors of the type of antidepressant received (old or new generation) and to obtain the odds ratio (OR) and 95% confidence intervals (95% CI).

A p-value was considered significant if less than 0.05. All statistical tests were done using STATA version 10.1. Descriptive statistics were completed using Microsoft Excel 2007 and where necessary STATA v 10.1 (stated).

5.4 LIMITATIONS OF STUDY DESIGN

This study used two pre-existing datasets from private companies. The concerns of reliability and validity of the research is present in many research environments. The reliability of data obtained in the data collection process is a measure of how dependable the data is with regards to its quality. Validity is the degree to which the instrument employed measures what it is meant to measure (Brink, 2006).

The reliability of the datasets in this study was determined on the initial input of raw data, which was captured by the respective private practice enlisted to the company. While, these companies offer a paid-for service to aid medical practices in managing their data, the possibility of entering incorrect data should be acknowledged. If incorrect patient factors (age, gender or ICD-10) were entered on the patient's initial visit, this would carry through to subsequent visits. A breakdown in the chain of information storage could also affect the reliability of the data. For example, if the respective doctor made a manual hand-written note of the patient age or diagnosis and hands it to an assistant to capture into the system, it is possible that in capturing data a mistake could occur. In addition, patients returning for a repeat prescription of an antidepressant with a simultaneous co-diagnosis may have had this co-diagnosis entered into the system but not the diagnosis made for the antidepressant.

The principal tool for data collection in this study were datasets. Datasets are a valid tool in studying retrospective data as they contain a number of valid variables essential to the objectives of this research. The drug prescribed, patient particulars such as gender, age, diagnosis and the number of repeat prescriptions were present in these datasets and allowed for a measure of these factors to be studied.

The datasets, unfortunately, had missing fields which would have been of interest to a DUR. The prescriber's instructions could not be deduced from the data, therefore the PDD and DDD could not be compared in this study. In addition, the WHO Collaborating Centre for Drug Statistics and Methodology classifies drug according to the Anatomical Therapeutic Chemical (ATC) system. This system groups drugs according to the organ or system where they act, their pharmacological, therapeutic and chemical properties. Dataset A and B did not include the ATC code for the drugs prescribed. The WHO recommends linking the ATC and DDD (ATC/DDD) as a method to study drug use. The nature of this data did not allow us to follow the ATC/DDD methodology (WHO, 2003).

The researcher did not take into account the date sequence of prescriptions. Prescriptions for pain or other indications would likely be intermittent but prescriptions for major depressive disorder would be of amore continuous date sequence. This differentiation was not considered in this study.

CHAPTER SIX: RESULTS OF DATASET A

The results for the study are presented in different chapters. This chapter (Chapter Six) will present the findings of Dataset A and Chapter Seven will present the results of Dataset B. The presentation of the results will begin with the descriptive results. The inferential statistical component will follow and the chapter will conclude with a summary of statistical results.

A breakdown of the results chapter is presented in the diagram below:

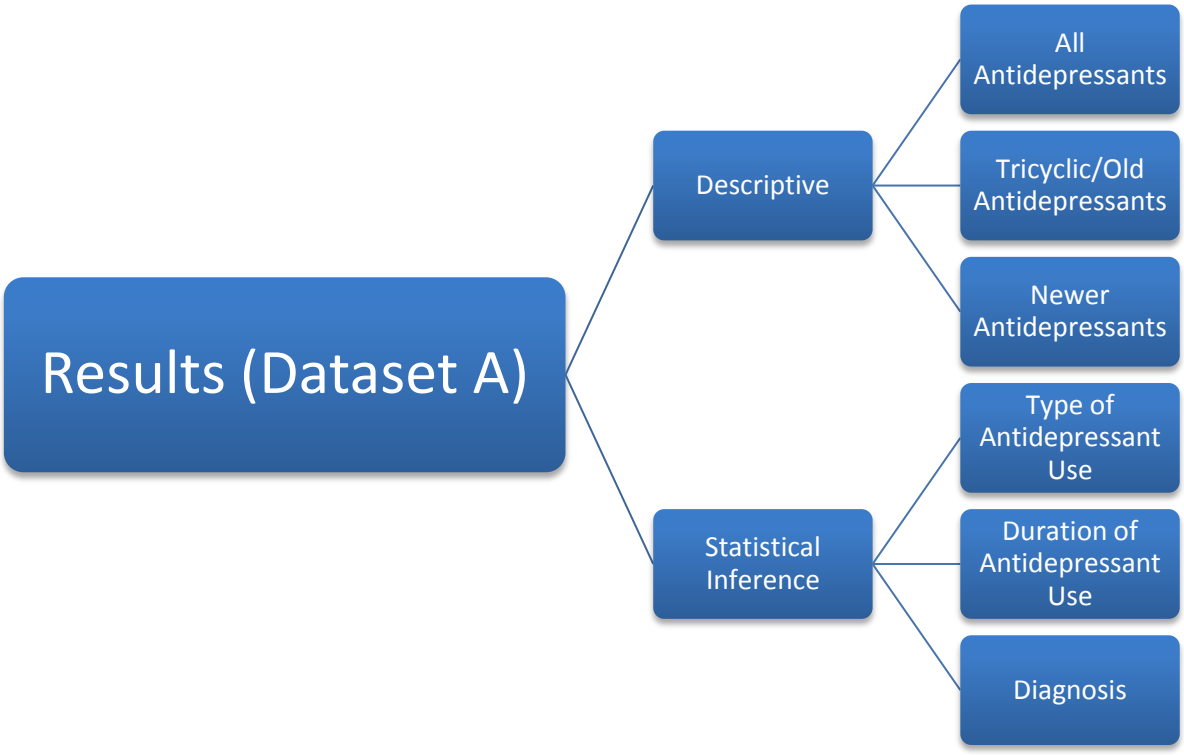


Figure 6.1 Presentation of results

6.1 DESCRIPTIVE RESULTS FROM DATASET A

The descriptive results are considered with regards to the demographic profile of users (age and gender), the frequency of antidepressant prescriptions, the number of repeat and sole prescriptions and the frequency of diagnoses in their raw and categorised form. All these findings from Dataset A are presented in this Section 6.1. Sections 6.2 and 6.3 will provide the descriptive results according to antidepressant groupings.

6.1.1 DEMOGRAPHICS OF SAMPLE

Dataset A contained 9 213 antidepressant prescriptions, representing 6 555 patients. Just over 70%of the sample was female (69.96%;n=6 445) and 30.04% was male (n=2 768). The mean age of the population was 43.86±13.81 (range: 2.19-96.05).

6.1.2 FREQUENCY OF PRESCRIPTIONS

The most frequently dispensed antidepressant was amitriptyline (67.75%, n=6 242) followed by fluoxetine (12.72%, n=1 172), venlafaxine (8.67%, n=799), citalopram (6.70%, n=617), imipramine (1.9%%, n=183), escitalopram (0.68%, n=63). Duloxetine, paroxetine, clomipramine, mirtazapine, trazodone, moclobemide, bupropion, dothiepin and sertraline accounted for the remaining prescriptions (1.48%, n=137). The older generation of antidepressants were more frequently dispensed to this population (69.92%, n=6 442). Newer generation antidepressants accounted for 30.08% of prescriptions (n=2 771). A great majority of the prescriptions were for generic antidepressants (89.99%, n=8 291).

6.1.3 NUMBER OF PRESCRIPTIONS

Antidepressant prescriptions were dispensed to patients at an average/mean of 2.95±3.77 times (range:1-19) per patient. The following table shows the breakdown of the number of antidepressant prescriptions according to a defined category.

Table 6.1 Frequency of the number of antidepressant prescriptions according to a category (Dataset A)

Number of Antidepressant Prescriptions	**Number of Patients (n=9 213)**	**Percentage (%)**
1	4 941	53.63%
2 – 5	3 070	33.32%
6 or more	1 202	13.05%

6.1.4 FREQUENCY OF DIAGNOSES

The most frequent diagnosis was for muscle and joint-related disorders (25.16%, n=2 227), followed by migraine and headache (16.06%, n=1 424) and stress and related conditions (15.38%, n=1 364). Depressive episode accounted for 2.18% (n=196) prescriptions and Recurrent Depression accounted for 3.30% (n=294). Anxiety-related conditions were the

diagnosis for 3.78% (n=337) of antidepressant prescriptions. The breakdown of the remaining 34.14% diagnoses is described in Figure 6.2 (page 75).

When ICD-10 codes were grouped into categories, the results in Table 6.2 were extracted:

Table 6.2 Frequency of ICD-10 categories (Dataset A)

ICD-10 Category	**Number (n=8 859)**	**Percentage (%)**
Psychiatric Conditions (0)	2 302	25.99
Pain (1)	4 429	50.01
Other (2)	2 125	24.00

Note: 356 patients had no record of diagnosis.

Please refer to Appendix 2 for the details of the ICD-10 code categorisation.

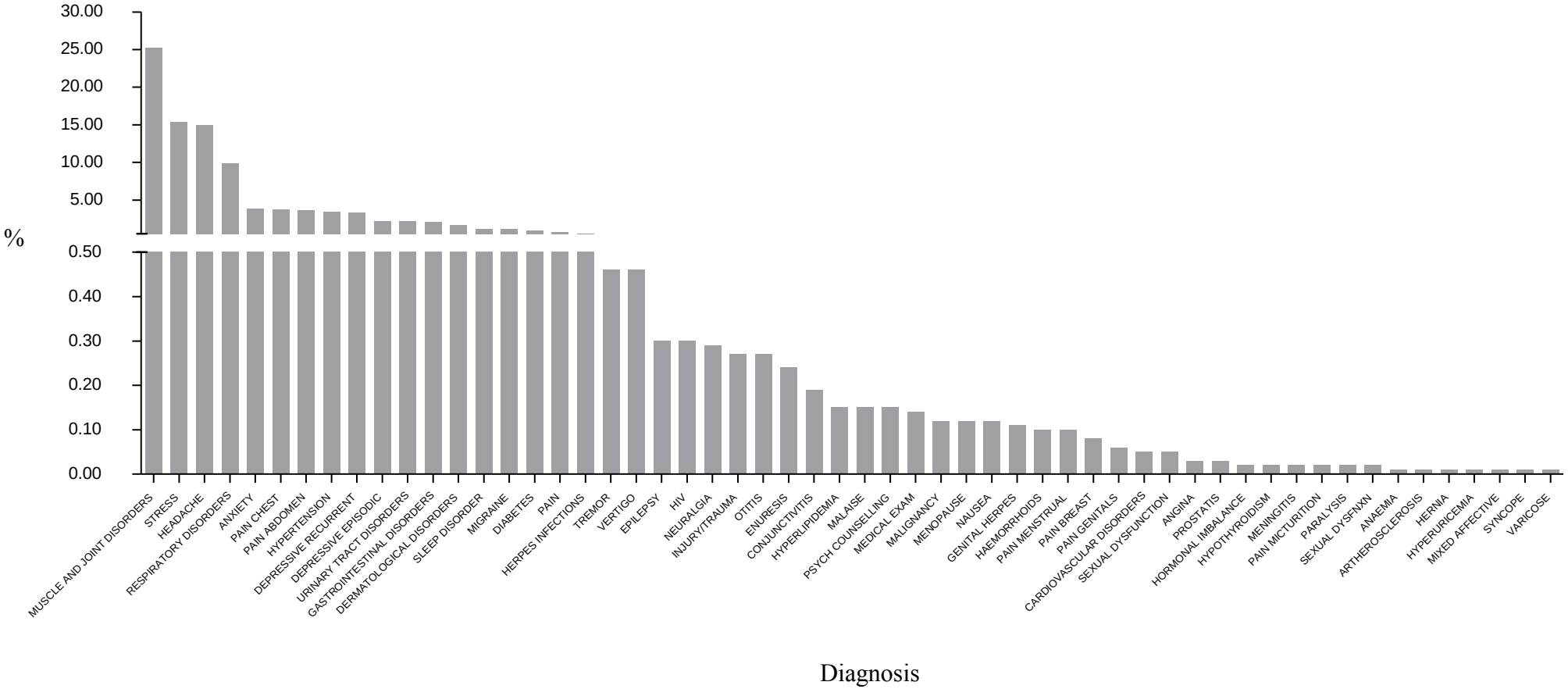


Figure 6.2 Frequency of diagnoses in Dataset A for all antidepressants

Please refer to Appendix 3 for a tabulated format of this graph

The most frequent psychiatric diagnosis was for F43.0: Acute Stress Reaction (56.60%, n=1 303), followed by F33.2: Recurrent Depressive Disorders (12.68%, n=292) and F41.9: Anxiety disorder, unspecified (7.69%, n=177). The breakdown of Psychiatric Conditions is presented in the table below.

Table 6.3 Frequency of psychiatric diagnosis categories (Dataset A)

Psychiatric Diagnosis Category	**Number (n=2 302)**	**Percentage (%)**
Affective Conditions (0)	493	21.24
Anxiety-related conditions and Stress(1)	1 701	73.72
Sleep disorders (2)	102	4.43
Psychiatric Counselling (3)	13	0.56

Please refer to Appendix 2 the details of the ICD-10 code categorisation.

6.2 DESCRIPTIVE RESULTS ACCORDING TO DRUG GROUP

The descriptive results for the two different antidepressant groups are presented in two sections (6.2.1 and 6.2.2). This section will describe the demographics of users and will conclude with a table that summarises all the information with the two drug groups alongside each other for descriptive comparison.

6.2.1 TRICYCLIC ANTIDEPRESSANTS

There were 6 442 prescriptions for tricyclic antidepressants. The mean age of patients was 43 years (±14; 3-93). Females constituted 70.04% (n=4512) of the sample. Amitriptyline accounted for the majority of prescriptions (96.90%, n=6242), imipramine accounted for 2.84% of prescriptions (n=183). Clomipramine and dothiepin formed the remaining 0.26%, n=17).

The majority of prescriptions were given for a diagnosis related to muscle and joint disorders. Depression, neuralgia and stress accounted for more prescriptions than headache and migraine diagnoses. A detailed breakdown of the diagnoses linked to TCA usage is given in Figure 6.3 (pg 78).

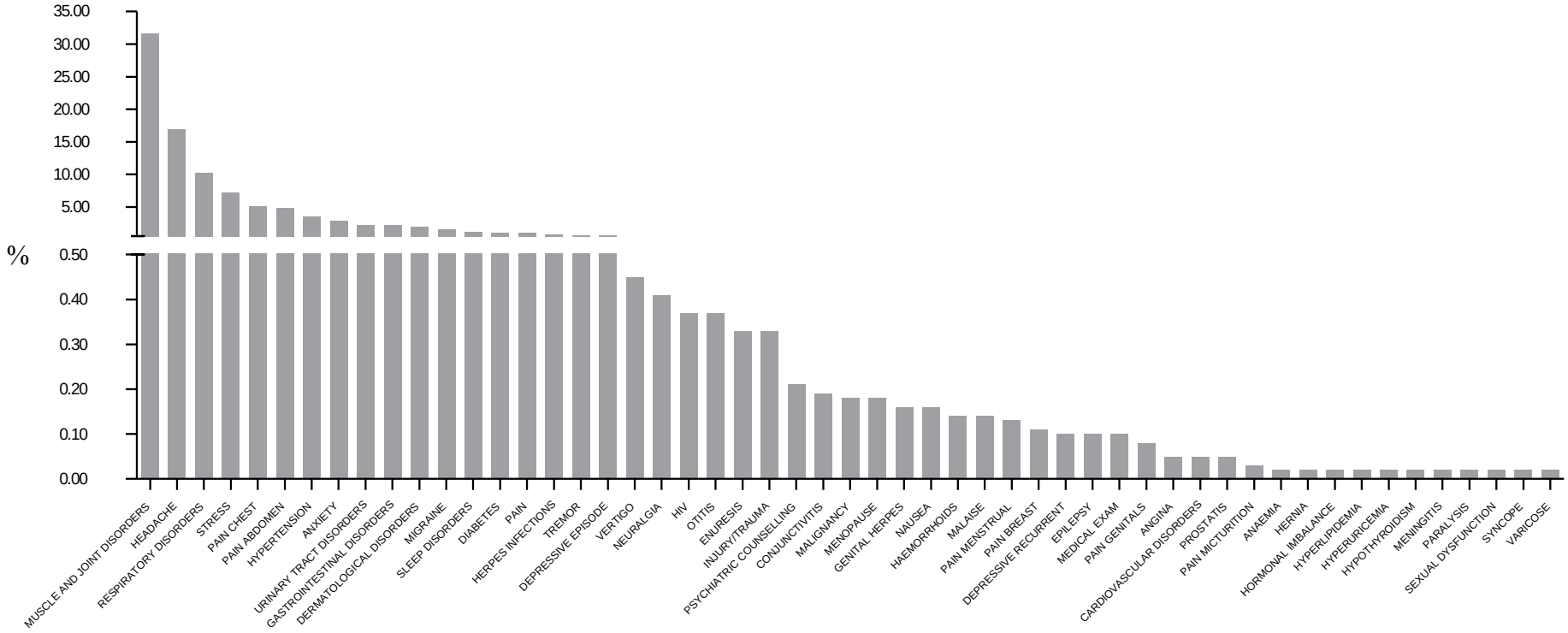


Figure 6.3 Frequency of diagnoses for tricyclic antidepressants (Dataset A)

Please refer to Appendix 4 for the tabulated form of this graph

Patients diagnosed with a pain condition, accounted for 62.07% (n=3901) of TCA prescriptions. A psychiatric condition accounted for 12.11% (n=761), the remaining 25.82% of prescriptions were for non-psychiatric and non-pain use.

For patients with a psychiatric condition, the majority of prescriptions (59.66%, n=454) were for an acute stressful reaction. Affective disorders formed 6.04% (n=46) and anxiety-related disorders accounted for 24.17% (n=184) of the psychiatric use of TCAs.

The majority of TCA prescriptions were on a once-off basis. See graph (figure 6.4) below. The mean number of visits by patients who were prescribed a TCA was 2.4 ±3.01 times (range:1-19).

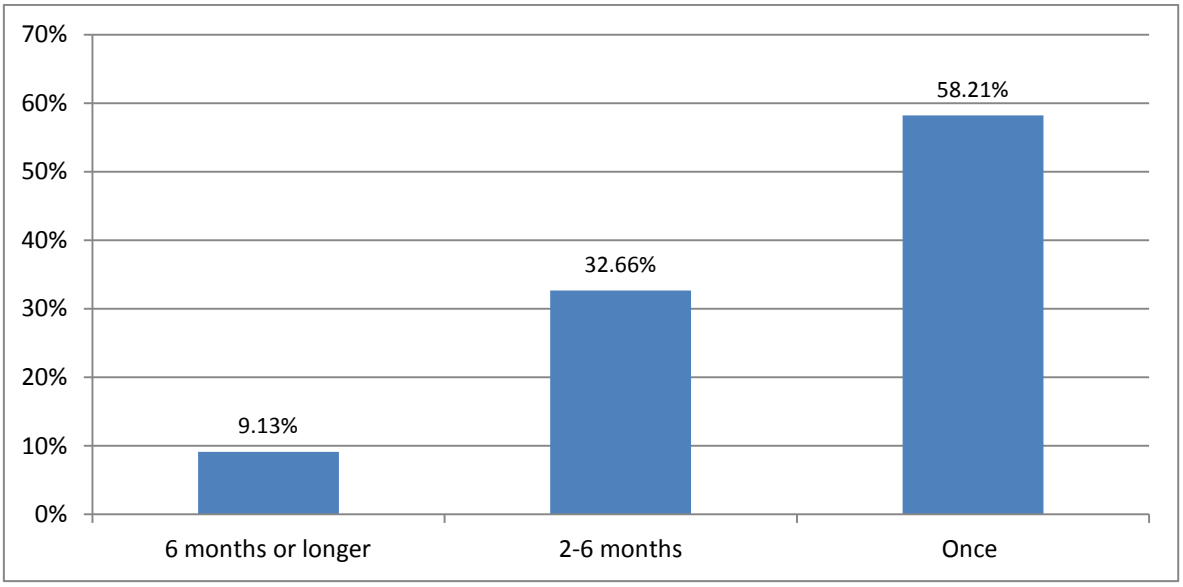


Figure 6.4 Frequency of number of prescriptions according to a category for tricyclic antidepressants (Dataset A)

6.2.2 NEWER GENERATION ANTIDEPRESSANT DRUGS

The use of SSRIs, SNRIs, MAOIs and mirtazapine are described together as new generation antidepressants.

There were 2771 prescriptions for new generation antidepressants. The mean age of patients was 46 (±13; 2-96). Females constituted 69.56% (n=1933) of the sample. Fluoxetine accounted for the majority of prescriptions. The breakdown of the prescriptions according to drug is given in the graph below:

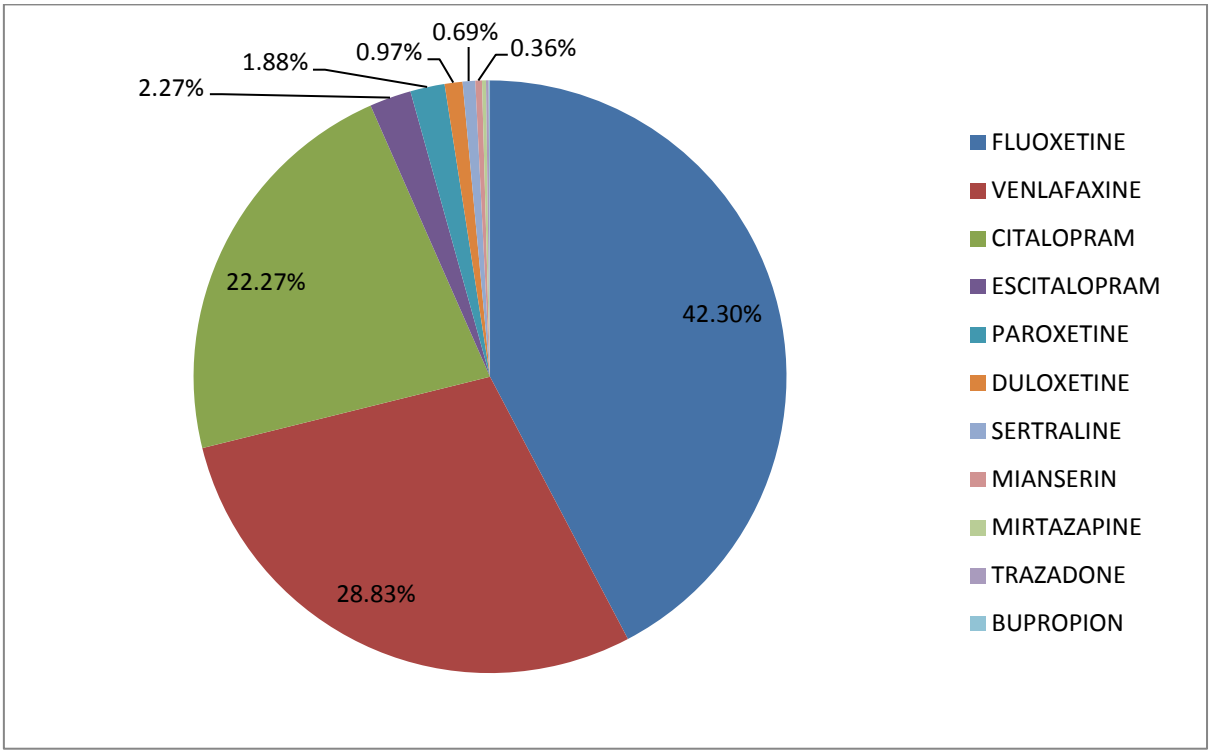


Figure 6.5 Frequency of prescriptions for newer generation antidepressants(Dataset A)

The majority of prescriptions were given for a stress disorder (F43.0: reaction to acute stress or Z63.7: stressful life event). A recurrent depressive disorder accounted for more prescriptions than anxiety or a depressive episode. Respiratory disorders also accounted

for a considerable proportion of prescription. A detailed breakdown of the diagnoses linked to newer generation antidepressant usage is given in the graph (figure 6.7)on page 82.

Patients diagnosed with a psychiatric condition, accounted for 59.82% (n=1541) of new generation antidepressant prescriptions. Pain accounted for 20.54% (n=528) of prescriptions. For patients with a psychiatric condition, a stress-related disorder formed the majority of prescriptions (59.17%, n=910). This was followed by an affective disorder and anxiety. Detailed breakdown of the diagnoses of patients with a psychiatric is given in Figure 6.6 below:

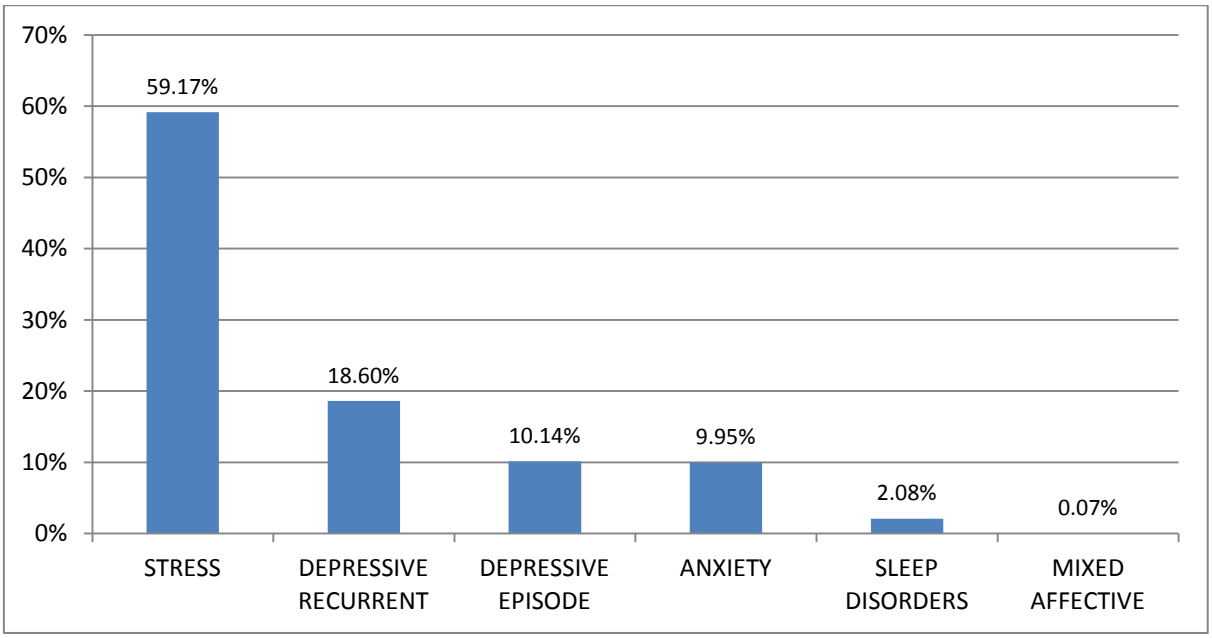


Figure 6.6 Frequency of psychiatric diagnoses for newer generation antidepressants (Dataset A)

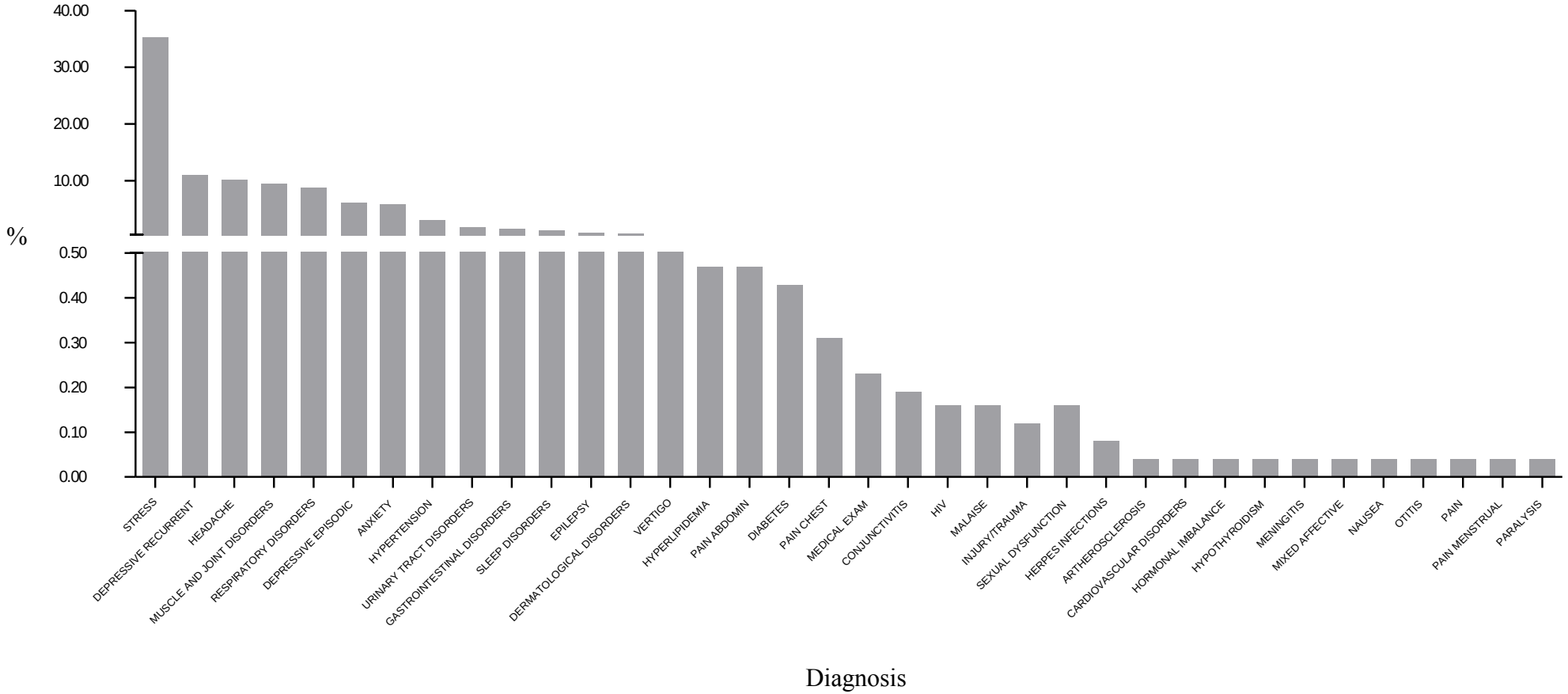


Figure 6.7 Frequency of diagnoses for newer generation antidepressants (Dataset A)

Please refer to Appendix 5 for a tabulated form of this graph

Just over 40% (42.98%; n=1191) of patients taking a new generation antidepressant received the drug once. Patients who received the drug for between two and six months accounted for 34.86% (n=966). The remaining patients (22.16%; n=614) received the drug on a chronic basis for six months or longer. The average number of visits by patients who were prescribed a new generation antidepressant was 4.19 ±4.88 times (range:1-19).

Predictors of whether a patient will receive a TCA or a newer generation drug is given in the next section.

The table below summarises the descriptive differences between the older generation (tricyclic) and the newer generation antidepressants.

Table 6.4 Descriptive differences between older and newer generation antidepressants (Dataset A)

Variable	Category	Old Generation Antidepressant	New Generation Antidepressant
Number		6442	2771
Age		43 (±14; 3-93)	46 (±13; 2-96)
Gender	Female	70.04% (N=4 512)	69.76% (N=1 933)
	Male	29.96% (N=1 930)	30.24% (N=838)
Drug (% Of Total)		Amitriptyline 93.22% (N=6 242)	Fluoxetine 42.30% (N=1 172)
		Imipramine 2.84% (N=183)	Venlafaxine 28.82% (N=799)
		Clomipramine 0.23% (N=15)	Citalopram 22.27% (N=617)
		Dothiepin 0.03% (N=2)	Escitalopram 2.27% (N=63)
			Paroxetine 1.88% (N=52)
			Duloxetine 0.97% (N=27)

Variable	Category	Old Generation Antidepressant	New Generation Antidepressant
			Sertraline 0.69% (N=19)
			Mianserin 0.36% (N=10)
			Mirtazapine 0.22% (N=6)
			Trazodone 0.14% (N=4)
			Bupropion 0.07% (N=2)
Number Of Prescriptions (% Of Total)	One	58.12% (N=3 750)	42.98% (N=1 191)
	Two To Five	32.66% (N=2 104)	34.86% (N=966)
	Six Or More	9.13% (N=588)	22.16% (N=614)
Diagnosis (% Of Total)	Psychiatric	12.11% (N=761)	59.82% (N=1 541)
	Pain	62.07% (N=3 901)	20.54% (N=528)
	Other	25.82% (N=1 623)	19.64% (N=502)
Psychiatric Condition (% Of Total)	Affective	5.99% (N=46)	29.01% (N=447)
	Anxiety and Stress	83.20% (N=639)	68.96% (N=1 062)
	Sleep Disorders	9.11% (N=70)	2.08% (N=32)
	Psychiatric Counselling	1.69% (N=13)	0.00% (N=0)

6.3 INFERENTIAL STATISTICS

Data was entered into STATA (v10.0) to determine the relationship between factors associated with:

- Type of antidepressant prescribed
- Duration of treatment
- Diagnosis

This section will provide the results of the strength of association between variables with regards to these factors. Logistic regression results will follow and a summary will conclude this section.

6.3.1 FACTORS ASSOCIATED WITH TYPE OF ANTIDEPRESSANT USED

Age, gender, ICD-10, psychiatric diagnosis and number of visits were statistically tested to determine if any of these factors are significantly related to the type of antidepressant prescribed. These factors were also tested to determine their predictive qualities in determining if a patient will receive a TCA or a newer generation antidepressant.

6.3.1.1 CONTINUOUS VARIABLES

The variables 'age' and 'number of prescriptions' failed the Shapiro-Wilk test for normality of distribution ($p<0.0001$). See Appendix 6A and 6B for results of these tests. The relationship between 'age' and the type of antidepressant and the relationship between 'number of prescriptions' and the type of antidepressant was tested using the Mann-Whitney U test as these variables displayed a non-parametric distribution. The results of these are presented in this section.

6.3.1.1 (a) AGE

The results from the Mann-Whitney U test (see Appendix 7) produced a probability less than 0.05 ($p<0.0001$). This signifies that age was related to the type of antidepressant prescribed. The mean age of patients taking a TCA was 43.15 and the mean age of patients taking a new generation antidepressant was 45.51

6.3.1.1 (b) NUMBER OF PRESCRIPTIONS

The number of prescriptions a patient received for an antidepressant was significantly associated with the type of drug prescribed ($p<0.0001$). The results of the Mann-Whitney U test is presented in Appendix 8. The mean number of visits by a patient taking an old generation drug was 2.42(±3.01; 95CI 2.34 – 2.48). The mean number of visits by patients taking a new generation drug was 4.19(±4.88; 95CI 4.01 – 4.37). See appendix for results of the Mann-Whitney U test.

6.3.1.2 CATEGORICAL VARIABLES

6.3.1.2 (a) GENDER

The Chi-squared table of the relationship between gender and the type of antidepressant is presented in table 6.5 on the next page.

Table 6.5 Chi-squared table of gender and antidepressant type(Dataset A)

Gender	Old Antidepressant	New Antidepressant	Total
Male (n)	1 930	838	2 768
%	69.73	30.27	100
Female (n)	4 512	1 933	6 445
%	70.01	29.99	100
Total (n)	6 442	2 771	9 213
%	69.92	30.08	100

Pearson Chi^2 = 0.0734

Pr = 0.786

Gender was not significantly related to the type of antidepressant prescribed ($p>0.05$).

6.3.1.2 (b) ICD-10 CATEGORY

The Chi-squared graph (Figure 6.4, page 88) below illustrates that the category of a patient's ICD-10 diagnosis was significantly associated with the type of antidepressant they received. Patients with a psychiatric diagnosis were more likely to be treated with a newer generation antidepressant. Patients with diagnosis related to pain were more likely to be using a TCA. Any other diagnoses were also more likely to be treated with a TCA.

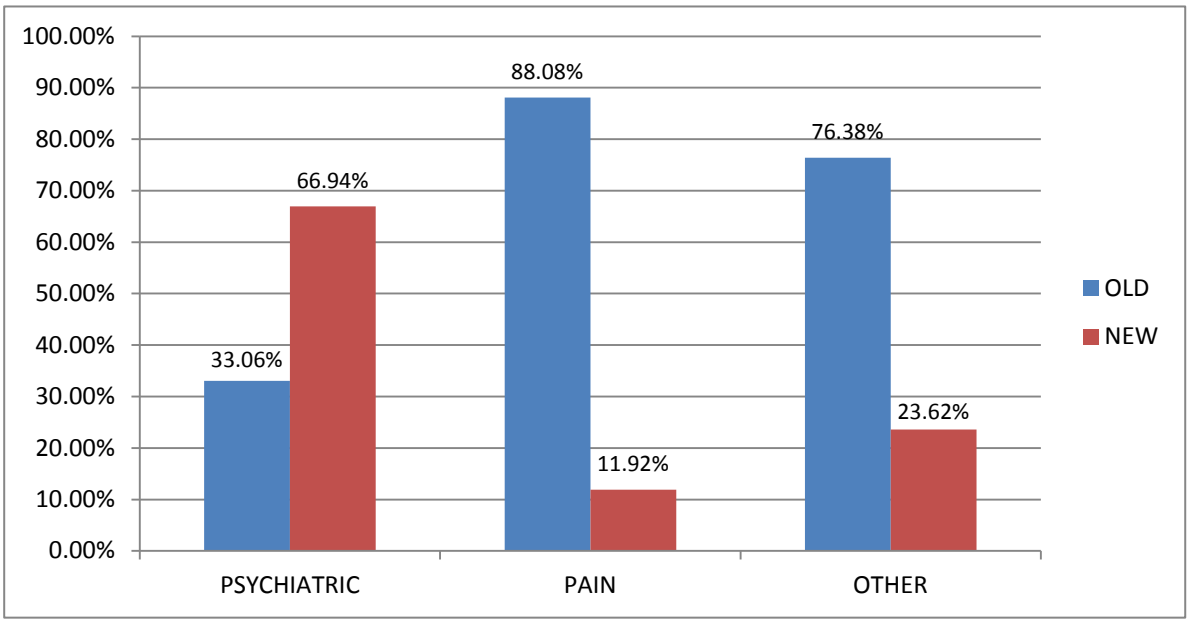


Figure 6.8 Chi-squared graph* for association between ICD-10 category and antidepressant type(Dataset A)

*Pearson Chi^2= 2.3e+03

*P<0.0001

Please refer to Appendix 9 for the Chi-squared table

6.3.1.2 (c) PSYCHIATRIC DIAGNOSIS

An affective disorder was significantly associated with receiving a new generation antidepressant. Anxiety and stress were also more likely to be treated with a new generation antidepressant. Sleep disorders were more likely to be treated with a TCA (p<0.0001), patients coming in for psychiatric counselling, received a TCA. The Chi-squared graph (Figure 6.9, page 89) illustrates this relationship.

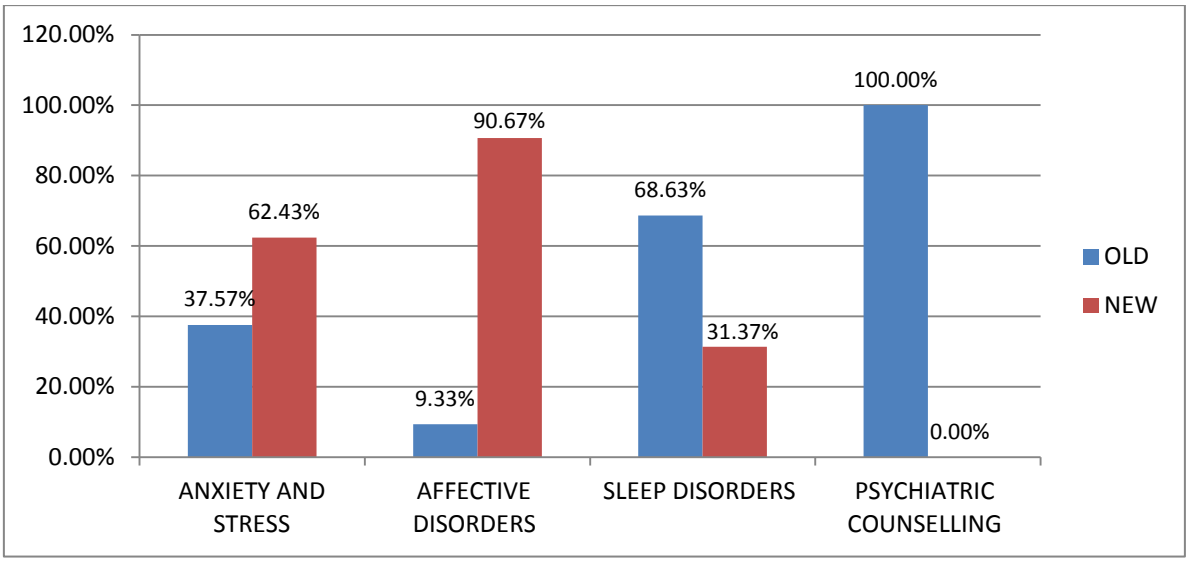


Figure 6.9 Chi-squared graph* for association between psychiatric diagnosis category and antidepressant type(Dataset A)

*Pearson Chi^2= 221.73

*P<0.0001

Please refer to Appendix 10 for tabulated form of this graph

6.3.1.2 (d) NUMBER OF PRESCRIPTIONS CATEGORY

Patients receiving an antidepressant for less than 6 months were significantly associated with taking an older generation antidepressant (p<0.0001). Patients taking an antidepressant for six months or longer were taking newer generation antidepressants to a slight majority. A graphical presentation of this is presented in Figure 6.10 (page 90).

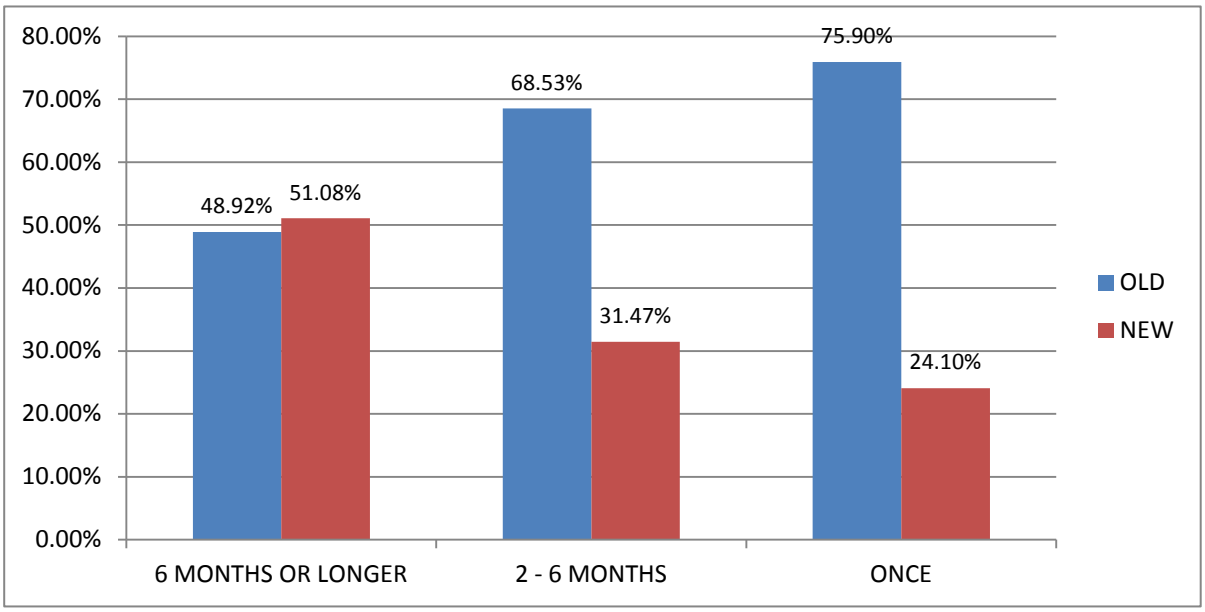


Figure 6.10 Chi-squared graph* for association between number of prescriptions category and antidepressant type(Dataset A)

*Pearson Chi^2= 338.7823

*P<0.0001

Please refer to Appendix 11 for a tabulated form of this graph

6.3.1.2 (e) AGE CATEGORY

All age categories were more likely to receive an older generation drug. But the percentage of elderly patients receiving an older generation (59.81%, n=323) was less than the other age categories. Conversely, the proportion of elderly patients receiving a newer generation drug (40.19%, n=217) was more than the other age groups. The graph in Figure 6.11 (page 91) below details this. Therefore, elderly patients were more likely to receive the newer generation antidepressants compared to other groups.

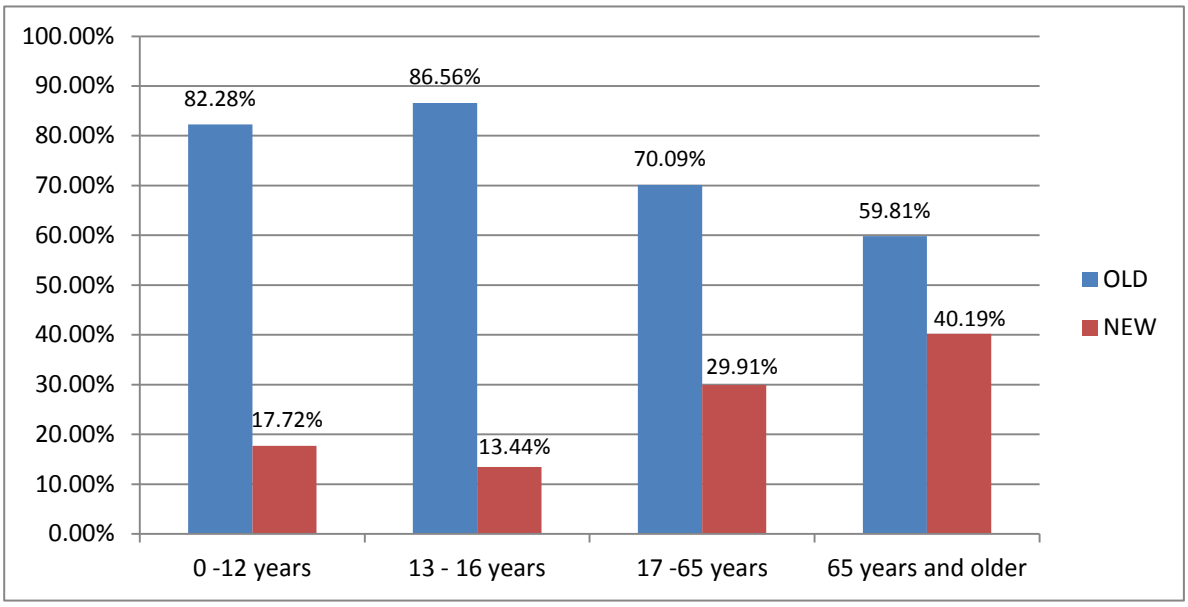


Figure 6.11 Chi-squared graph* for association between age category and antidepressant type(Dataset A)

*Pearson Chi^2= 56.5558

*P<0.0001

Please refer to Appendix 12 for a tabulated form of this graph

SUMMARY OF SIGNIFICANT FACTORS

They type of drug prescribed was significantly associated with the demographic factor of age and clinical factors (ICD-10 category and psychiatric diagnoses). These statistically significant variables were entered into a logistic regression model. The results of this is presented in section 6.3.1.3.

6.3.1.3 LOGISTIC REGRESSION

The significant factors were entered into a logistic regression model. The type of antidepressant (old or new generation) was the dependent variable. A patient's diagnosis had a strong effect on the odds of the type of drug they would receive. Patients with a psychiatric condition were 6.53 times more likely to get a new generation drug compared to another diagnosis. Patients with a pain condition were 2.31 times more likely to get a TCA. Table 6.6 below gives the results. Patients with an affective disorder, older than 65 years and who had been treated for longer than six months also had a higher odds of receiving a new generation drug. Table 6.6 (pg 93) details the odds ratios, 95% confidence intervals and p-values.

Table 6.6 Logistic regression values of factors associated with the type of antidepressant used (Dataset A)

VARIABLE		OLD			NEW		
		OR	p-value	95%CI	OR	p-value	95% CI
Gender	Male	N/S			N/S		
	Female	N/S			N/S		
ICD-10 Category	Psychiatric	0.16	<0.0001	0.14 - 0.18	6.53	<0.0001	5.72 - 7.45
	Pain	2.31	<0.0001	2.02 - 2.64	0.43	<0.0001	0.38 - 0.50
	Other	1.00		~	1.00		~
Psychiatric Category	Affective	0.16	<0.0001	0.12 - 0.23	5.78	<0.0001	4.19 - 7.95
	Anxiety and stress	1.00		~	1.00		~
	Sleep	3.67	<0.0001	2.39 - 5.63	0.28	<0.0001	0.18 - 0.42
	Psychiatric Counselling						
Duration Of Treatment Category (number of prescriptions)	6 months or more	0.30	<0.0001	0.27 - 0.34	3.29	<0.0001	2.88 - 3.74
	2-5 months	0.69	<0.0001	0.62 - 0.76	1.45	<0.0001	1.31 - 1.60
	once	1.00		~	1.00		~
Age Category	0 -12years	1.00		~	1.00		~
	13 – 16years	1.38	0.370	0.68 - 2.83	0.72	0.370	0.35 - 1.47
	17 – 65years	0.50	0.021	0.28 - 0.90	1.98	0.021	1.11 - 3.53
	66+ years	0.32	<0.0001	0.18 - 0.59	3.11	<0.0001	1.71 - 5.70
Age (continuous variable)		0.98	<0.0001	0.98 - 0.99	1.01	<0.0001	1.00 - 1.02
Number Of Visits (continuous variable)		0.89	<0.0001	0.88 - 0.90	1.12	<0.0001	1.11 - 1.13

Note: Cannot calculate OR for Psychiatric Counselling because ALL were given TCA

N/S: Not Significant

OLD: Old generation antidepressant

NEW: New generation antidepressant

6.3.2 FACTORS ASSOCIATED WITH DURATION OF TREATMENT

Age, gender, ICD-10, psychiatric diagnosis were statistically tested to determine which of these factors are significantly related to whether a patient will return for a repeat prescription of the drug or not. These factors were also tested to determine their predictive qualities in determining if a patient will get the drug once off or return.

6.3.2.1 CONTINUOUS VARIABLES

6.3.2.1 (a) AGE

Age was significantly related to whether a patient received the drug once or more than once ($p<0.0001$). Please refer to Appendix 13 for the results of the Mann-Whitney U test. The mean age of patients taking the drug once was 40.46 (±12.95; 95%CI 40.09 – 40.81) the mean age of patients taking the drug more than once was 47.81 (±13.72 95%CI 47.40 – 48.22).

6.3.2.2 CATEGORICAL VARIABLES

6.3.2.2 (a) AGE CATEGORY

The age category which a patient falls into was significantly associated with return visits. Elderly group (65+) were more likely to return for a repeat prescription (>once) compared to all other age groups. The Chi-squared graph in Figure 6.12 (page 95) below illustrates this.

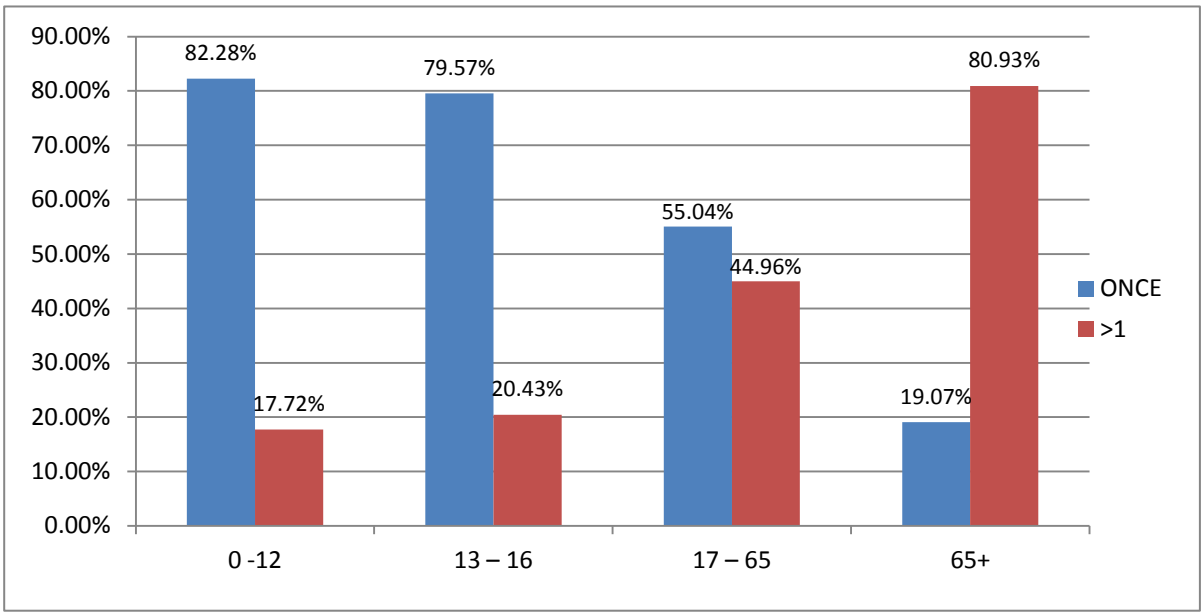


Figure 6.12 Chi-squared graph* for association between age category and duration of treatment(Dataset A)

*Pearson Chi^2= 342.4730

*P<0.0001

Please refer to Appendix 14 for the table of this graph

6.3.2.2 (b) GENDER

Gender was not a significant factor of whether the drug is used once-off or not. The proportion of females returning for a repeat is higher (47.91%) was only slightly higher than that of males (42.67%). Table 6.7 (page 96) below provides the association between these factors.

Table 6.7 Chi-squared table* of gender and duration of treatment (Dataset A)

Gender	ONCE	>1	Total
Male (n)	1 587	1 181	2 768
%	57.33	42.67	100
Female (n)	3 357	3 088	6 445
%	52.09	47.91	100
Total (n)	4 944	4 269	9 213
%	53.66	46.34	100

*Pearson Chi^2= 21.4385

*p>0.05

6.3.2.2 (c) ICD-10 CATEGORY

ICD-10 category was significantly associated with whether a patient returned for a prescription. Patients with a psychiatric diagnosis were significantly associated with returning for a prescription. Patients with a diagnosis of pain or 'other' were more likely to receive the drug once. The graph below (Figure 6.13, page 97) illustrates this.

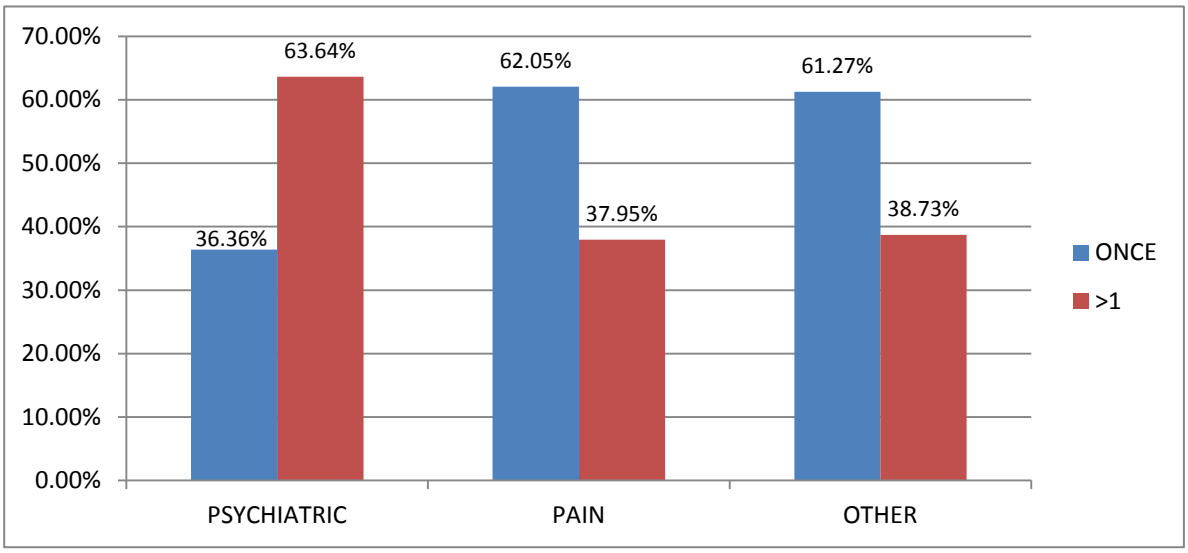


Figure 6.13 Chi-squared graph* for association between ICD-10 category and duration of treatment(Dataset A)

*Pearson Chi^2= 445.9814

*P<0.0001

Please refer to Appendix 15 for the table format of this graph

6.3.2.2 (d) PSYCHIATRIC DIAGNOSIS

Patients with a psychiatric diagnosis of an affective disorder, a psychiatric consult or a sleep disorder were more likely to return for a repeat. Patients with anxiety and stress were less likely to receive repeats. The Chi-squared graph below (Figure 6.14, page 98) details the percentage of users who received the drug once or more than once according to the category of their psychiatric diagnosis.

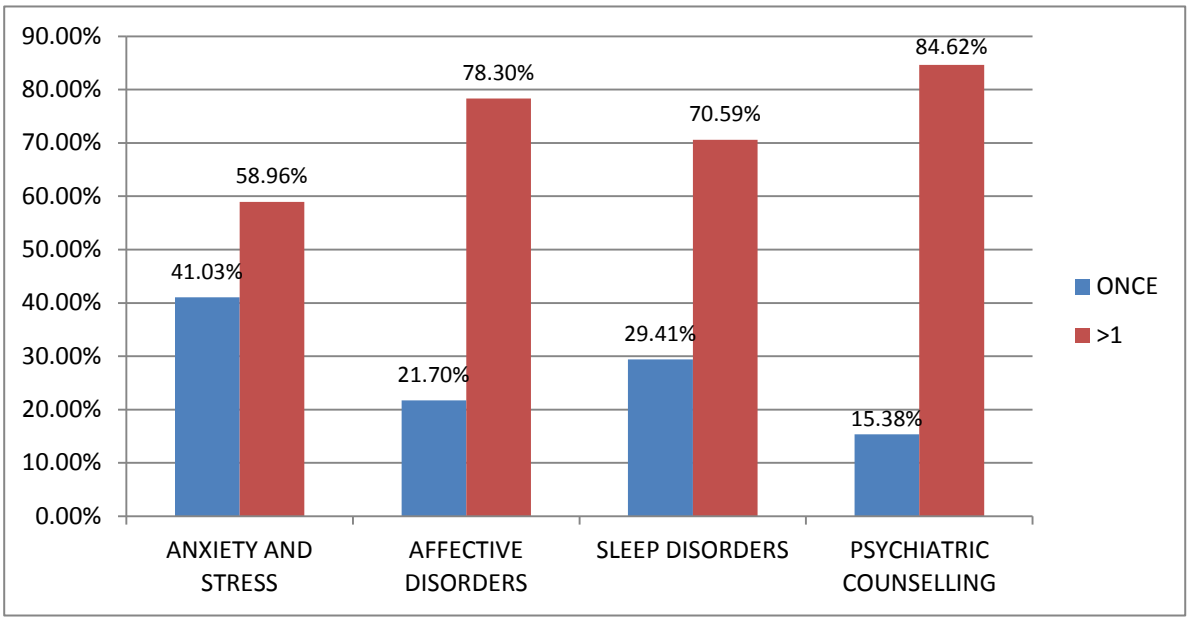


Figure 6.14 Chi-squared graph* for association between ICD-10 category and duration of treatment(Dataset A)

*Pearson Chi^2=67.5921

*P<0.0001

SUMMARY

A patient's age, ICD-10 diagnosis and category of psychiatric condition was related to whether they will return for a repeat prescription. The statistically significant factors were entered into a logistic regression model to determine their predictive qualities.

6.3.2.3 LOGISTIC REGRESSION

The significant factors were entered into a logistic regression model. Whether the patient received the drug once or more than once was the dependent variable. Elderly patients (65 years and older) were 19.70 times more likely to receive a repeat prescription for an antidepressant. Those with a psychiatric condition and those with a psychiatric condition

being an affective disorder were also more likely to receive repeats. The table below gives the odds ratio, 95% CI and p-values for each factor.

Table 6.8 Logistic regression values of factors associated with once-off and repeat prescriptions (Dataset A)

VARIABLE		ONCE			REPEATS		
		OR	p-value	95%CI	OR	p-value	95%CI
Gender	Male	N/S			N/S		
	Female	N/S			N/S		
ICD-10 Category	Psychiatric	0.36	<0.0001	0.32 - 0.41	2.77	<0.0001	2.45 - 3.13
	Pain	1.03	0.557	0.93 - 1.14	0.97	0.557	0.87 - 1.08
	Other	1.00		~	1.00		~
Psychiatric Category	Affective	0.39	<0.0001	0.31 - 0.50	2.55	<0.0001	2.01 - 3.23
	Anxiety and stress	1.00		~	1.00		~
	Sleep disorders	0.60	0.022	0.29 - 0.93	1.67	0.022	1.08 - 2.58
	Psychiatric Counselling	0.26	0.082	0.06 - 1.18	3.82	0.082	0.84 - 17.30
Age Category	0 -12years	1.00		~	1.00		~
	13 – 16years	0.84	0.612	0.43 - 1.65	1.19	0.612	0.60 - 2.34
	17 – 65years	0.26	<0.0001	0.14 - 0.47	3.79	<0.0001	2.13 - 6.77
	66+ years	0.06	<0.0001	0.03 - 0.09	19.70	<0.0001	10.64 - 36.48
Age (continuous variable)		0.96	<0.0001	0.95 - 0.96	1.04	<0.0001	1.04 - 1.05

6.3.3 FACTORS ASSOCIATED WITH DIAGNOSIS

Females constituted a majority of users of antidepressants. Gender was statistically tested against ICD-10 category to determine if there is an association. Both genders were more likely to have a diagnosis related to pain. But the proportion of females with a psychiatric disorder (27.09%) was slightly higher than that of males (23.47%), this was not a statistically significant difference. Please see the chi-squared table (Table 6.9) for the details of this association.

Table 6.9 Chi-squared table* of gender and ICD-10 category (Dataset A)

Gender	Psychiatric	Pain	Other	Total
Male (n)	631	1 389	668	2 688
%	23.47	51.67	24.85	100
Female (n)	1 671	3 040	1 457	6 168
%	27.09	49.29	23.62	100
Total (n)	2 302	4 429	2 125	8 856
%	25.99	50.01	24	100

*Pearson Chi^2=12.7338

*P>0.05

A patient's age group was also statistically tested against their diagnosis. Elderly patients were more likely to have a psychiatric diagnosis compared to all other age groups (OR 2.22; 95%CI 1.29 – 3.80; p = 0.004). Adolescents were more likely to have a diagnosis related to a pain condition (OR 2.38; 95%CI 0.77 – 7.35; p = 0.013). The table that follows (page 101) gives the results of Chi-squared test.

Table 6.10 Chi-squared table* of age category and ICD-10 category (Dataset A)

Age Category	Psychiatric	Pain	Other	Total
0 -12 years (n)	6	39	25	70
%	8.57	55.71	35.71	100
13 - 16 years (n)	7	130	48	185
%	3.78	70.27	25.95	100
17 -65 years (n)	2 026	4 164	1 962	8 152
%	24.85	51.08	24.07	100
66 years and older (n)	263	96	90	449
%	58.57	21.38	20.04	100
Total (n)	2 302	4 429	2 125	8 856
%	25.99	50.01	24	100

*Pearson Chi^2= 329.0523

*P<0.0001

6.4 SUMMARY TABLE OF INFERENTIAL STATISTICS

The table below is a summary of the inferential statistics presented above. The significant and non significant findings are displayed against the relevant dependent variable.

Table 6.11 Summary of inferential statistics (Dataset A)

Factor	**Drug Type (Old vs New generation drug)**	**Repeats (Once-off vs Repeats)**	**Diagnosis (Psychiatric vs Pain vs Other**
Age (continuous variable)	✓	✓	~
Number of visits (continuous variable)	✓	~	~
Age Category	✓	✓	✓
Number of Visits Category	✓	~	~
Gender Category	×	✓	×
ICD-10 Category	✓	✓	~
Psychiatric Category	✓	✓	~

✓ = significant ($p<0.05$)

× = not significant

~ = not applicable/not tested

CHAPTER SEVEN: RESULTS OF DATASET B

The results of Dataset B will be presented in this chapter (Chapter Seven) and will follow the same format as Chapter Six. A breakdown of the results for Dataset B will follow Figure 6.1.

7.1 DESCRIPTIVE RESULTS FROM DATASET B

This section (Section 7.1) will provide the descriptive results for Dataset B. It will begin with the descriptive results of the entire sample and follow with the descriptive results according to drug group.

7.1.1 DEMOGRAPHICS OF SAMPLE

Dataset B contained 1244 antidepressant prescriptions, representing 839 patients. The mean age of the population was 46.27±13.03 (range:4.93-81.57). The majority of the sample was female (61.98%; n= 771). Males constituted 38.02% of the sample (n=38.02).

The frequency of age distribution according to a defined category is given in the Table 7.1 (page 104).

Table 7.1 Frequency of age category (Dataset B)

Age Category	Number of Patients (n=1244)	Percentage (%)
0 – 12 years	6	0.48%
13 – 16 years	4	0.32%
17 – 65 years	1 155	92.85%
66 years an older	79	6.35%

7.1.2 FREQUENCY OF PRESCRIPTIONS

The most frequently dispensed antidepressant was amitriptyline (64.07%, n=797) followed by fluoxetine (13.10%, n=163), citalopram (10.05%, n=125), clomipramine (4.02%, n=50) and escitalopram (3.46%, n=43). Duloxetine, paroxetine, venlafaxine, imipramine, mirtazapine, trazodone, moclobemide and sertraline accounted for the remaining 5.3% (n=66) of prescriptions. The older generation of antidepressants was more frequently dispensed to this population (68.81%, n=856). Newer generation antidepressants accounted for 31.19% of prescriptions (n=388). A great majority of the prescriptions were for generic antidepressants (89.19%, n=1112).

7.1.3 NUMBER OF PRESCRIPTIONS

Antidepressant prescriptions were dispensed to patients at an average of 2.57±2.47 times (range:1-10) per patient. The following table (Table 7.2, page 105) shows the breakdown of the number of antidepressant prescriptions according to a defined category.

Table 7.2 Frequency of the number of antidepressant prescriptions according to a category (Dataset B)

Number of Antidepressant Prescriptions	**Number of Patients (n=1244)**	**Percentage (%)**
1	656	53.73%
2 – 5	427	34.32%
6 or more	161	13.94%

7.1.4 FREQUENCY OF DIAGNOSES

The most frequent diagnosis was for a Depressive Episode (28.94%, n=352), followed by muscle and joint disorders (n=346, 27.81%) and anxiety and related conditions (5.71%, n=76). The breakdown of the remaining 37.54% diagnoses is described in the graph below (Figure 7.1 page 106).

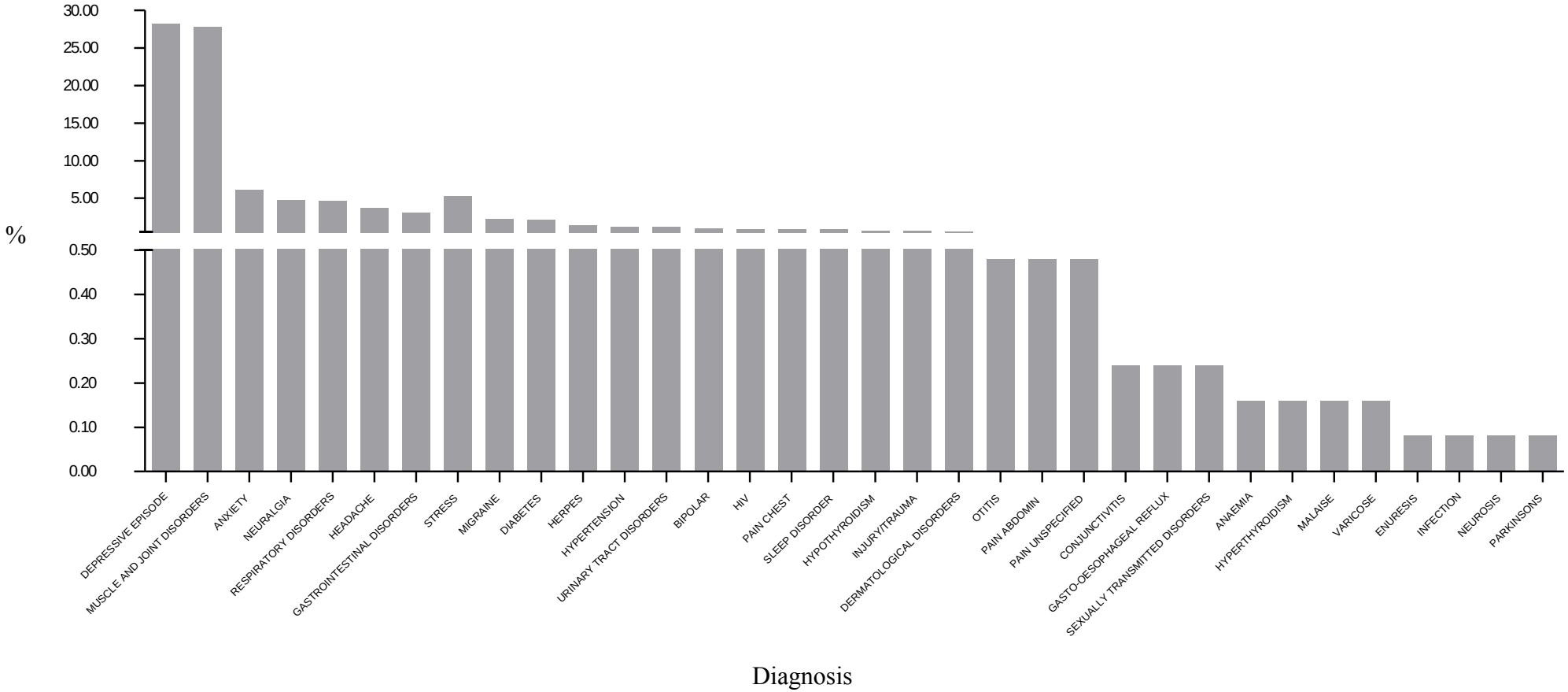


Figure 7.1 Frequency of diagnoses for all antidepressants (Dataset B)

Please refer to Appendix 17 for a tabulated form of this graph.

When ICD-10 codes were grouped into categories, psychiatric and pain conditions formed the bulk of prescription. The results are described in the graph (Figure 7.2) below.

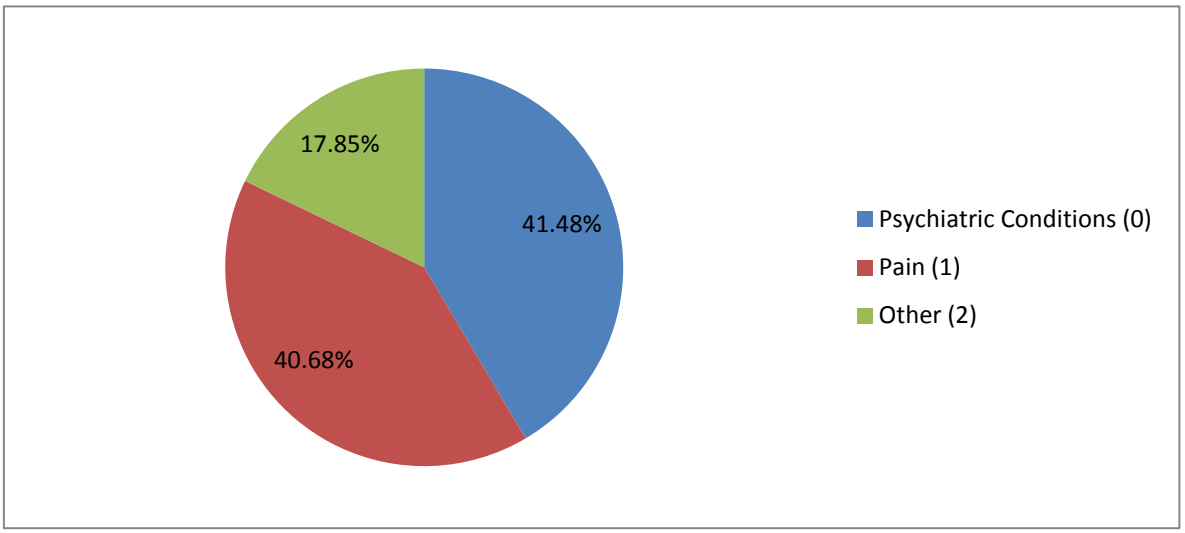


Figure 7.2 Frequency of ICD-10 categories (Dataset B)

Please refer to Appendix 2 the details of the ICD-10 code categorisation.

All patients with a psychiatric diagnosis were grouped into another category. Affective disorders formed the majority. The breakdown of Psychiatric Conditions is presented in the table (Table 7.3) below.

Table 7.3 Frequency of psychiatric diagnosis categories (Dataset B)

Psychiatric Diagnosis Category	**Number (n=516)**	**Percentage (%)**
Affective Conditions	364	72.09
Anxiety-related conditions and Stress	142	25.97
Sleep disorders	10	1.94

The most frequent psychiatric diagnosis was for F32.9: depressive episode (67.52%, n=352) followed by F41.9: anxiety, unspecified (11.63, n=60) and F43.0: acute stress reaction (6.59%, n=34). Please refer to Appendix 2 for the details of the ICD-10 code categorisation.

7.2 DESCRIPTIVE RESULTS ACCORDING TO DRUG GROUP

The descriptive results for the two different antidepressant groups are presented in two sections (7.2.1 and 7.2.2). This section will describe the demographics of users and will conclude with a table that summarises all the information with the two drug groups alongside each other for descriptive comparison.

7.2.1 TRICYCLIC ANTIDEPRESSANTS

There were 856 prescriptions for tricyclic antidepressants. The mean age of patients was 46 (±12; 5-79). Females constituted 59.81% (n=512) of the sample. Amitriptyline accounted for the majority of prescriptions. The breakdown of the prescriptions according to drug is given in the Figure 7.3 (pg 109).

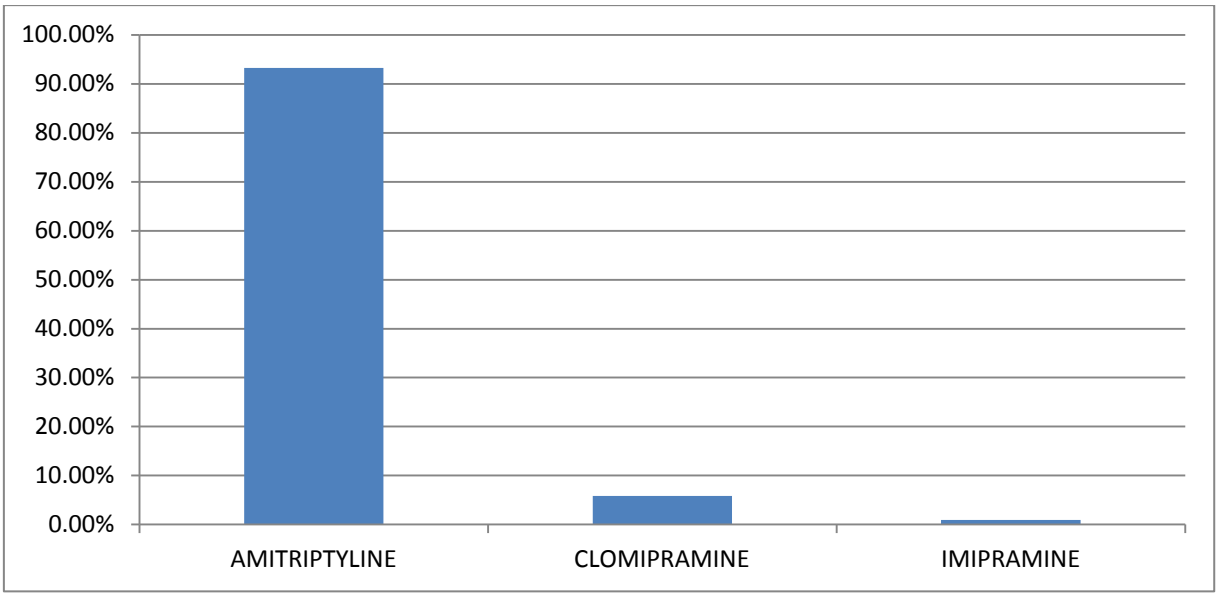


Figure 7.3 Frequency of prescriptions for tricyclic antidepressants (Dataset B)

The majority of prescriptions were given for a diagnosis related to muscle and joint disorders. Depression, neuralgia and stress accounted for more prescriptions than headache and migraine diagnoses. A detailed breakdown of the diagnoses linked with TCA usage is given in the Figure 7.4 (pg 110).

Patients diagnosed with a psychiatric condition, accounted for 20.58% (n=1177). A pain diagnosis formed the majority of diagnoses for TCA prescriptions (58.25%, n=498).

For patients with a psychiatric condition, depressive disorders formed the majority of prescriptions (43.24%, n=72). This was followed by stress (30.27%, n=56) and anxiety and anxiety related conditions (21.08%, n=39). Sleep disorders accounted for the remaining 5.41% (n=10).

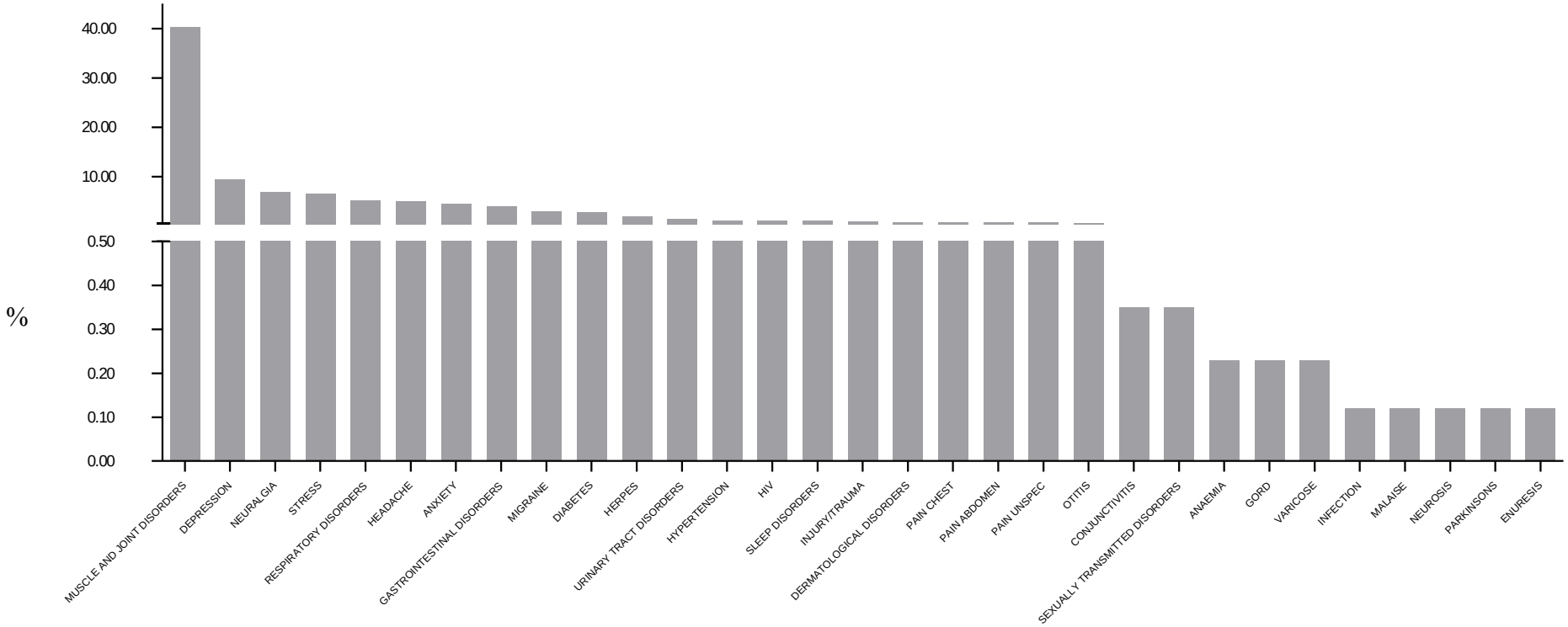


Figure 7.4 Frequency of diagnoses of tricyclic antidepressants (Dataset B)

Please refer to Appendix 18 for the tabulated form of this graph

The majority of patients taking a TCA received the drug once (60.00%; n=513). Just over a third of patients received the TCA for between two and six months (35.20%; n=301). A small minority (4.81%, n=41)received the drug on a chronic basis for six months or longer. The average number of visits by patients who were prescribed a TCA was 1.96 times (range:1-9).

7.2.2 NEWER GENERATION ANTIDEPRESSANT DRUGS

The use of SSRIs, SNRIs, MAOIs and mirtazapine are described together as new generation antidepressants.

There were 388 prescriptions for the new generation antidepressants. The mean age of patients was 46 (±15; 9-82). Females constituted 66.84% (n=259) of the sample. Fluoxetine accounted for the majority of prescriptions. The breakdown of the prescriptions according to drug is given in the graph (Figure 7.5) below:

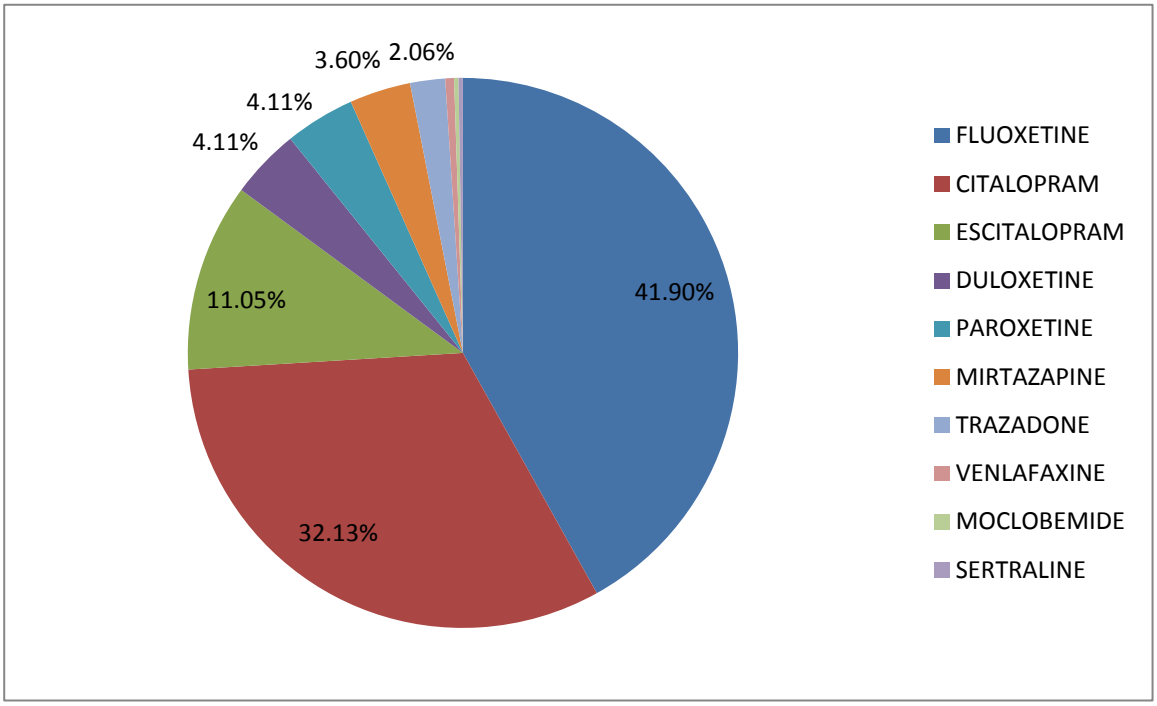


Figure 7.5 Frequency of prescriptions for newer generation antidepressants (Dataset B)

The majority of prescriptions were given for a depressive disorder. Anxiety-related disorders accounted for more prescriptions than stress and bipolar. Respiratory disorders also accounted for a considerable proportion of prescription. A detailed breakdown of the diagnoses linked with newer generation antidepressant usage is given in Figure 7.6 (pg 113).

Patients diagnosed with a psychiatric condition, accounted for 85.09% (n=339) of new generation antidepressant prescriptions. For patients with a psychiatric condition, depressive disorders formed the majority of prescriptions (86.71%, n=287). This was followed by anxiety and anxiety-related conditions (9.97%, n=33). Stress and bi-polar disorder accounted for the remaining. There were no prescriptions for sleep disorders.

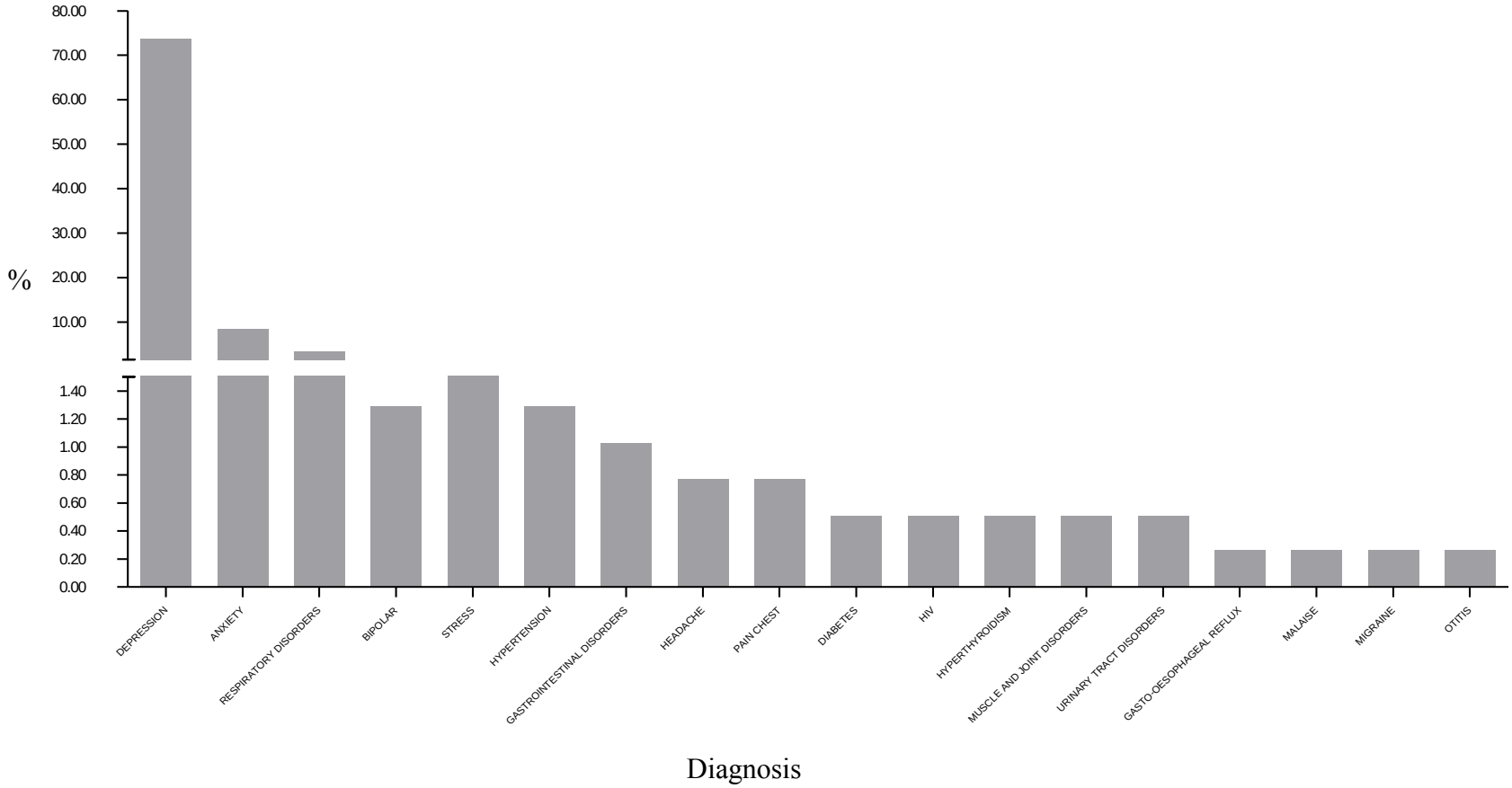


Figure 7.6 Frequency of diagnoses for newer generation antidepressants (Dataset B)

Please refer to Appendix 19 for the tabulated form of this graph.

A slight majority of patients taking a new generation antidepressant received the drug once (36.76%; n=126). Approximately a third of patients received it for between two and six months (32.39%; n=126). The remaining 30.85% (n=120) of patients received the drug on a chronic basis for six months or longer. The average number of visits by patients who were prescribed a new generation antidepressant was 3.92 times (range:1-10).

Table 7.4 below summarises the descriptive differences between the older generation and the newer generation antidepressants.

Table 7.4 Descriptive differences between older and newer generation antidepressants (Dataset B)

Variable	**Category**	**Old Generation Antidepressant**	**New Generation Antidepressant**
Number		856	388
Age		46 (±12; 5-79)	46 (±15; 9-82)
Gender	Female	59.81% (n=512)	66.75% (n=259)
	Male	40.19% (n=344)	33.25% (n=129)
Drug (% of total)		Amitriptyline 93.22% (N=797)	Fluoxetine 41.90% (N=163)
		Clomipramine 5.85% (N=50)	Citalopram 32.12% (N+125)
		Imipramine 0.58% (N=8)	Escitalopram 11.05% (N=43)
			Duloxetine 4.11% (N=16)
			Paroxetine 4.11% (N=16)
			Mirtazapine 3.60% (N=14)
			Venlafaxine

Variable	Category	Old Generation Antidepressant	New Generation Antidepressant
			0.51% (N=2)
			Moclobemide 0.26% (N=1)
			Sertraline 0.26% (N=1)
Number Of Prescriptions(% of total)	One	60.00% (n=513)	36.76% (n=143)
	Two To Five	35.20% (n=301)	32.39% (n=126)
	Six Or More	4.81% (n=41)	30.85% (n=120)
Diagnosis (% of total)	Psychiatric	20.58% (n=177)	87.15% (n=339)
	Pain	58.25% (n=498)	2.31% (n=8)
	Other	21.17% (n=181)	10.54% (n=41)
Psychiatric Condition (% of total psychiatric)	Affective	40.68% (n=72)	86.14% (n=292)
	Anxiety And Stress	53.67% (n=95)	13.86% (n=47)
	Sleep Disorders	5.65% (n=10)	(n=0)

Predictors of whether a patient would receive a TCA or a newer generation drug is given in the next section (Section 7.3).

7.3 INFERENTIAL STATISTICS

Data was entered into STATA (v10.0) to determine the relationship between factors associated with:

- Type of antidepressant prescribed
- Duration of Treatment
- Diagnosis

This section will provide the results of the strength of association between variables with regards to these factors. Logistic regression results will follow and a summary will conclude this section.

7.3.1FACTORS ASSOCIATED WITH TYPE OF ANTIDEPRESSANT USED

Age, gender, ICD-10, psychiatric diagnosis and number of visits were statistically tested to determine which of these factors are significantly related to the type of antidepressant prescribed. These factors were also tested to determine their predictive qualities in determining if a patient will receive a TCA or a newer generation antidepressant.

7.3.1.1 CONTINUOUS VARIABLLES

The variables ‘age’ and ‘number of prescriptions’ failed the Shapiro-Wilk test for normality of distribution ($p<0.0001$). See Appendix 20A and 20B for results of these tests. The relationship between ‘age’ and the type of antidepressant and the relationship between ‘number of prescriptions’ and the type of antidepressant was tested using the Mann-Whitney U test as these variables displayed a non-parametric distribution. The results of these are presented in this section.

7.3.1.1 (a)AGE

Age was not significantly related to the type of antidepressant received ($p>0.05$). The mean age of patients taking a TCA is 46.38 and the mean age of patients taking a new generation antidepressant is 46.03. Results of the Mann-Whitney U test is given in Appendix 21.

7.3.1.1 (b) NUMBER OF PRESCRIPTIONS

A p-value less than 0.05 ($p<0.0001$) shows that the number of prescriptions a patient received for an antidepressant was significantly associated with the type of drug prescribed. Please see Appendix 22 for the results of the Mann-Whitney U test. The mean number of visits by a patient taking an older generation drug was 1.96(±1.69; 95CI 1.84 – 2.07). The mean number of visits by patients taking a new generation drug was 3.93 (±3.24; 95CI 3.60 – 4.25).

7.3.1.2 CATEGORICAL VARIABLES

7.3.1.2 (a) GENDER

The Chi-squared table of the relationship between gender and the type of antidepressant is presented in Table 7.5 (page 118).

Table 7.5 Chi-squared table* of gender and antidepressant type(Dataset B)

Gender	Old Antidepressant	New Antidepressant	Total
Male (n)	344	129	473
%	72.73	27.27	100
Female (n)	512	259	771
%	66.41	33.59	100
Total	856	388	1 244
	68.81	31.19	100

*Pearson Chi^2 = 5.4559

*P<0.05

Gender was related to the type of antidepressant prescribed (p<0.05). Females were significantly associated with receiving a newer generation antidepressant as compared to males.

7.3.1.2 (b) ICD-10 CATEGORY

A patient's diagnosis was significantly related to the type of drug prescribed. Patients with a psychiatric diagnosis were more likely treated with a newer generation antidepressant. Patients with diagnosis related to pain were more likely to be using a TCA. Any other diagnosis was also more likely to be treated with a TCA. This is illustrated in the graph below (Figure 7.7, page 119).

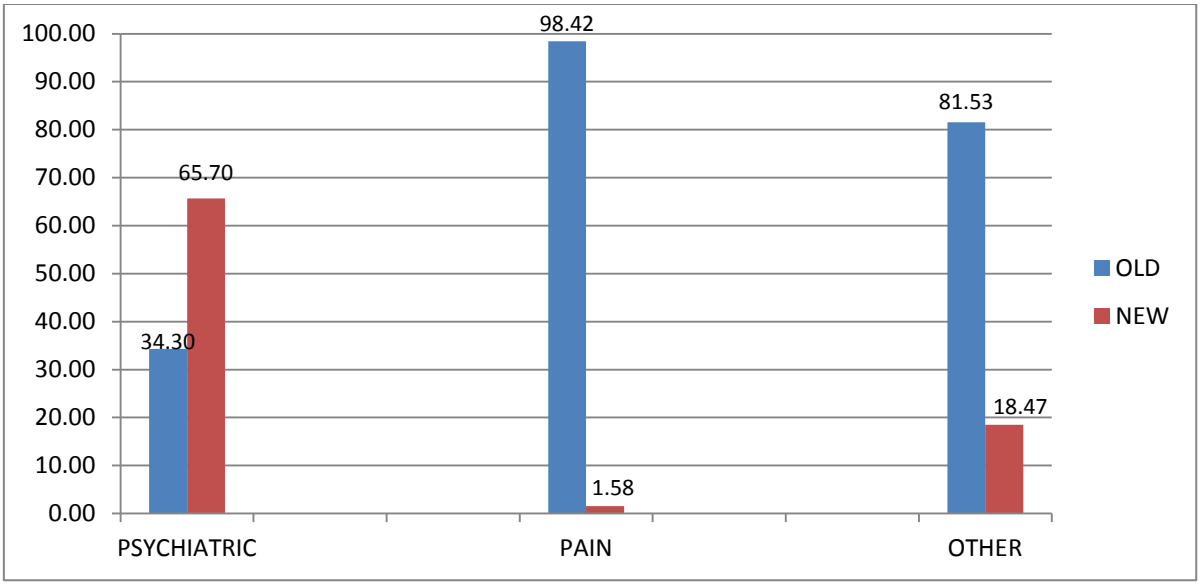


Figure 7.7 Chi-squared graph* for association between ICD-10 category and antidepressant type(Dataset B)

*Pearson Chi^2= 509.7333

*P<0.0001

Please refer to Appendix 23 for the tabulated form of this graph

7.3.1.2 (c) PSYCHIATRIC DIAGNOSIS

An affective disorder was significantly associated with receiving a new generation antidepressant. Anxiety, stress and sleep disorders were more likely to be treated with a TCA (p<0.0001). This is presented in the graph that follows (Figure 7.8, page 120).

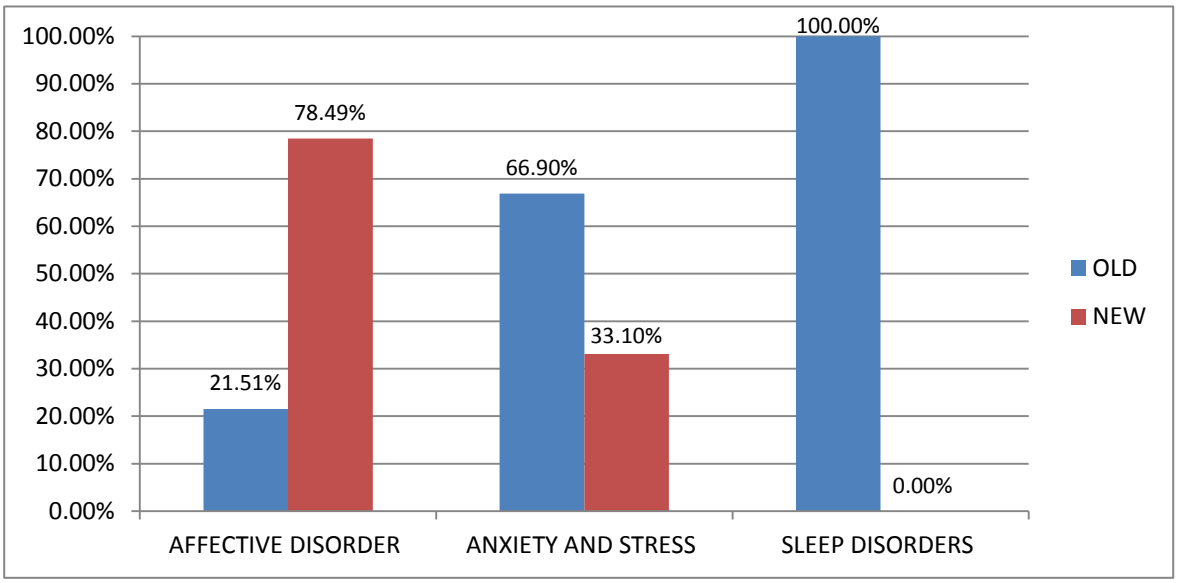


Figure 7.8 Chi-squared graph* for association between psychiatric diagnosis category and antidepressant type(Dataset B)

*Pearson Chi^2= 122.7362

*P<0.0001

Please refer to Appendix 24 for the tabulated form of this graph

7.3.1.2 (d) NUMBER OF PRESCRIPTIONS CATEGORY

Patients receiving an antidepressant for 6 months or longer were significantly associated with taking a newer generation antidepressant (p<0.0001). This is presented in the graph that follows on the next page (Figure 7.9, page 121).

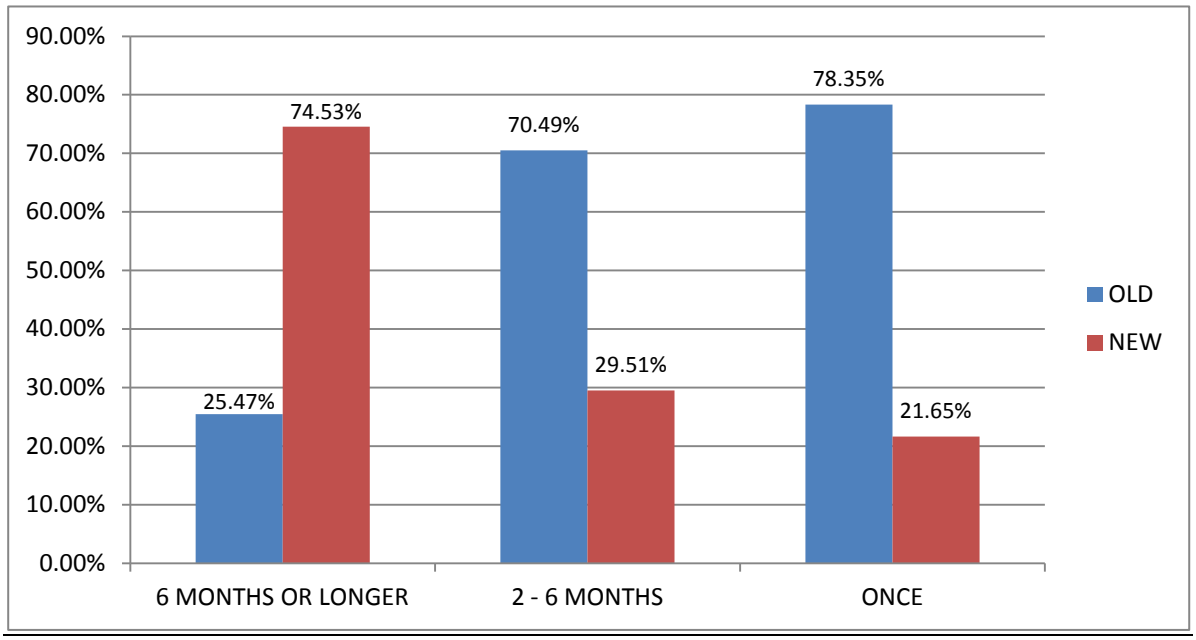


Figure 7.9 Chi-squared graph* for association between number of prescriptions category and antidepressant type(Dataset B)

*Pearson Chi^2= 169.3389

*P<0.0001

Please refer to Appendix 26 for the table form of this graph

7.3.1.2 (e) AGE CATEGORY

Patients between the age of 17 and 65 years were significantly associated with taking an older generation antidepressant (p<0.0001). Patients between 13 and 16 years were significantly associated with taking a newer generation drug. Elderly patients (65 years and older) and patients younger than 12 years showed usage patterns that were similar for both types of antidepressants. A graphical representation of this is in Figure 7.10 (page 122).

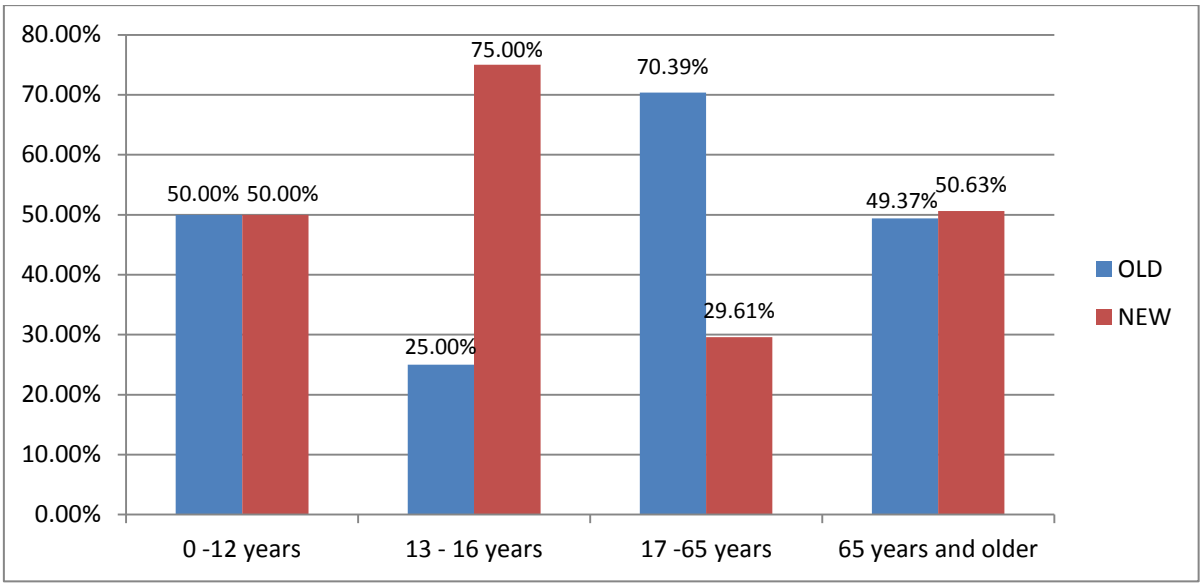


Figure 7.10 Chi-squared graph* for association between age category and antidepressant type(Dataset B)

*Pearson Chi^2= 19.8242

*P<0.0001

Please refer to Appendix 26 for the tabulated form of this graph

SUMMARY OF SIGNIFICANT FACTORS

They type of drug prescribed was significantly associated with demographic factors (gender, age category and number of prescriptions) and clinical factors (ICD-10 category and psychiatric diagnoses).

7.3.1.3 LOGISTIC REGRESSION

The significant factors were entered into a logistic regression model. The type of antidepressant (old or new generation antidepressant) was the dependent variable. Females were 1.35 times more likely to get a new generation drug. A patient's diagnosis had a strong effect on the odds of the type of drug they would receive. Patients with a psychiatric condition were 8.46 times more likely to get a new generation drug compared to another diagnosis. Patients with a pain condition were 14.10 times more likely to get a TCA. The table below gives the results. Patients with an affective disorder, between the ages of 13 and 16 years and those who had been treated for longer than six months also had a higher odds of receiving a new generation drug. Table 7.6 (pg 124) below details the odds ratios, 95% confidence intervals and p-values.

Table 7.6 Logistic regression values of factors associated with the type of antidepressant used (Dataset B)

VARIABLE		OLD			NEW		
		OR	p-value	95%CI	OR	p-value	95% CI
Gender	Male	1.00		~	1.00		~
	Female	0.74	0.020	0.57 - 0.95	1.35	0.020	1.04 - 1.73
ICD-10 Category	Psychiatric	0.11	<0.0001	0.08 - 0.17	8.46	<0.0001	5.76 - 12.42
	Pain	14.10	<0.0001	6.49 - 30.65	0.07	<0.0001	0.03 - 0.15
	Other	1.00		~	1.00		~
Psychiatric Category	Affective	0.11	<0.0001	0.07 - 0.17	8.89	<0.0001	5.68 - 13.90
	Sleep	~		~	~		~
	Anxiety and stress	1.00		~	1.00		~
Duration Of Treatment Category (number of prescriptions)	6 months or more	0.09	<0.0001	0.06 - 0.14	10.59	<0.0001	7.09 - 15.81
	2-5 months	0.66	0.003	0.50 - 0.87	1.51	0.003	1.15 - 2.00
	once	1.00		~	1.00		~
Age Category	0 -12years	1.00		~	1.00		~
	13 – 16years	0.33	0.437	0.02 - 5.32	3.00	0.437	0.18 - 47.96
	17 – 65years	2.38	0.290	0.48 - 11.84	0.42	0.290	0.08 - 2.09
	66+ years	0.98	0.976	0.19 - 5.12	1.02	0.976	0.20 - 5.39
Age (continuous variable)		N/S			N/S		
Number Of Visits (continuous variable)		0.73	<0.0001	0.69 - 0.77	1.37	<0.0001	1.30 - 1.44

Note: Cannot calculate OR for Sleep and Other because ALL were given TCA

OLD: Old generation antidepressant

NEW: New generation antidepressant

7.3.2 FACTORS ASSOCIATED WITH DURATION OF TREATMENT

Age, gender, ICD-10, psychiatric diagnosis were statistically tested to determine which of these factors are significantly related to whether a patient will return for a repeat prescription of the drug. These factors were also tested to determine their predictive qualities in determining if a patient will get the drug once off or return.

7.3.2.1 CONTINUOUS VARIBALES

7.3.2.1 (a) AGE

Age was significantly related to whether a patient receives the drug once or more than once ($p<0.0001$). The mean age of patients taking the drug once was 44.04 (±12.25; 95%CI 43.10 – 44.98). The mean age of patients taking the drug more than once was 48.80 (±13.46; 95%CI 47.71 – 49.89). Results of the Mann-Whitney U test are in Appendix 27.

7.3.2.2 CATEGORICAL VARIBALES

7.3.2.2 (a) AGE CATEGORY

The age category which a patient falls into was significantly associated with return visits. Elderly group (66+) were more likely to return for a repeat prescription compared to all other age groups. The graph that follows illustrates this (Figure 7.11, page 126).

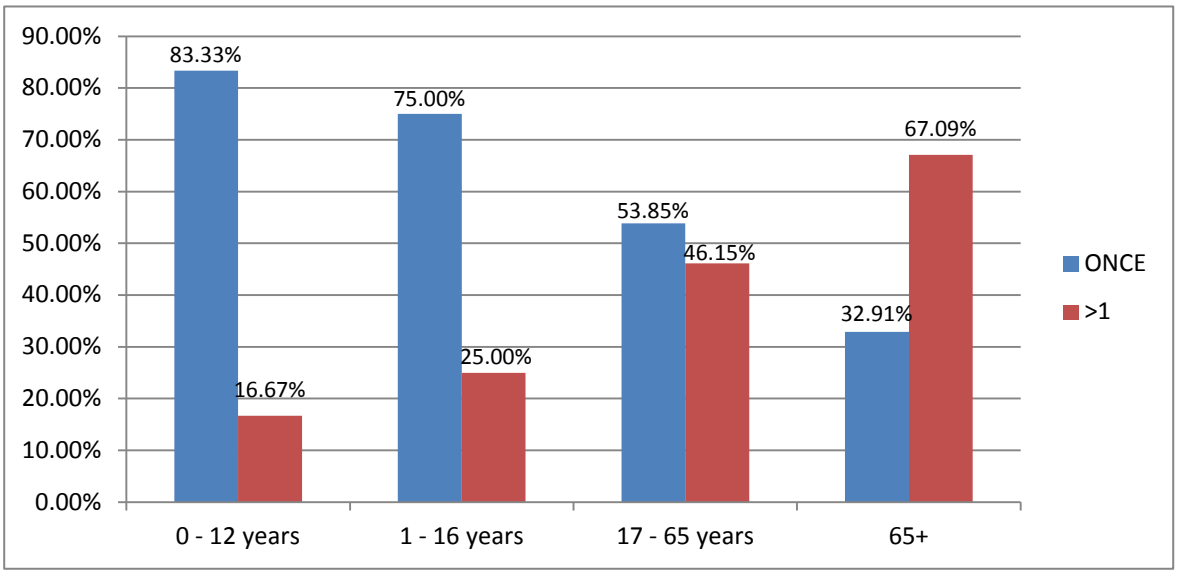


Figure 7.11 Chi-squared graph* for association between age category and duration of treatment(Dataset B)

*Pearson Chi^2= 16.0835

*P<0.05

Please refer to Appendix 28 for the table form of this graph

7.3.2.2 (b) GENDER

The Chi-squared table (Table 7.7) below gives a p-value greater than 0.05. This signifies that a patient's gender was not significantly related to whether a patient will return for a repeat prescription.

Table 7.7 Chi-squared table* of the association between gender and duration of treatment (Dataset B)

Gender	ONCE	>1	Total
Male (n)	239	234	473
%	50.53	49.47	100

Gender	ONCE	>1	Total
FEMALE (n)	417	354	771
%	54.09	45.91	100
Total (n)	656	588	1244
%	52.73	47.27	100

*Pearson Chi^2= 1.4881

*p>0.05

7.3.2.2 (c) ICD-10 CATEGORY

ICD-10 category was significantly associated with whether a patient would return for a prescription. Patients with a psychiatric diagnosis were significantly associated with returning for a prescription. Patients with a diagnosis of pain or 'other' were more likely to receive the drug once. This is illustrated in the graph (Figure 7.12) below.

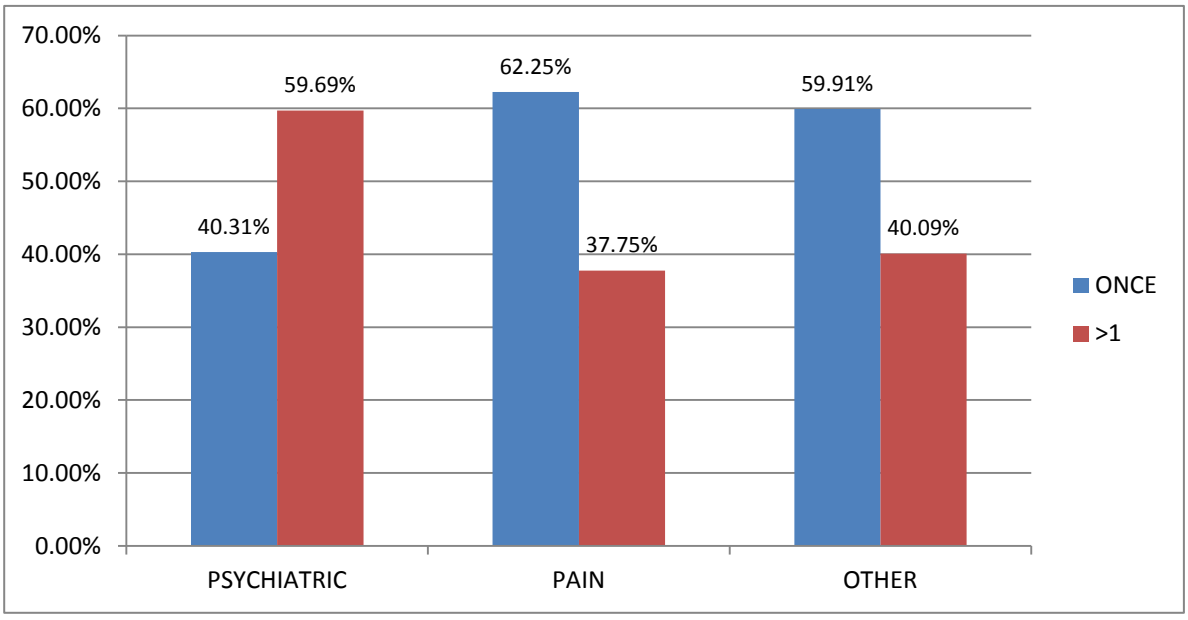


Figure 7.12 Chi-squared graph* for association between ICD-10 category and duration of treatment (Dataset B)

*Pearson Chi^2= 54.9350

*P<0.0001

Appendix 29 has the Chi-squared table form of this graph.

7.3.2.2 (d) PSYCHIATRIC DIAGNOSIS

Patients with a psychiatric diagnosis being an affective disorder were more likely to return for a repeat. Patients with sleep disorders only received the drug once. Patients with an anxiety-related condition or stress showed almost equal usage patterns across the two outcome variables (once or more than once). This is illustrated in Table 7.8 below.

Table 7.8 Chi-squared table* of the association between psychiatric diagnosis category and duration of treatment(Dataset B)

Psychiatric Diagnosis Category	**ONCE**	**>1**	**Total**
Anxiety-related conditions and stress(n)	70	72	142
%	49.25	50.75	100
Affective disorders (n)	130	234	364
%	35.71	64.28	100
Sleep disorders (n)	10	0	10
%	100	0	100
Total (n)	177	339	516
%	35.85	64.17	100

*Pearson Chi^2= 22.8636

*P<0.0001

SUMMARY

A patient's age, ICD-10 diagnosis and category of psychiatric condition was related to whether they would return for a repeat prescription or receive the drug once. A patient's gender was not significantly associated to returning for a repeat prescription. The statistically significant factors were entered into a logistic regression model to determine their predictive qualities.

7.3.2.3 LOGISTIC REGRESSION

The significant factors were entered into a logistic regression model. Whether the patient received the drug once or more than once was the dependent variable. Elderly patients (65 years and older) were 10.19 times more likely to receive a repeat prescription for an antidepressant. Those with a psychiatric condition and those with a psychiatric condition being an affective disorder were also more likely to receive repeats. The table below (Table 7.9, page 130) gives the odds ratio for each factor.

Table 7.9 Logistic regression values of factors associated with once-off and repeat prescriptions (Dataset B)

VARIABLE		ONCE			REPEATS		
		OR	p-value	95%CI	OR	p-value	95%CI
Gender	Male	N/S			N/S		
	Female	N/S			N/S		
ICD-10 Category	Psychiatric	0.45	<0.0001	0.33 - 0.62	2.21	<0.0001	1.60 - 3.05
	Pain	1.10	0.550	0.80 - 1.52	0.91	0.550	0.66 - 1.25
	Other	1.00		~	1.00		~
Psychiatric Category	Affective	0.56	0.005	0.38 - 0.84	1.76	0.005	1.18 - 2.63
	Sleep	~		~	~		~
	Anxiety and stress	1.00		~	1.00		~
Age Category	0 -12years	1.00		~	1.00		~
	13 – 16years	0.60	0.748	0.03 - 13.59	1.67	0.748	0.07 - 37.72
	17 – 65years	0.23	0.185	0.3 - 2.00	4.29	0.185	0.50 - 36.78
	66+ years	0.10	0.038	0.02 - 0.88	10.19	0.038	1.13 - 91.73
Age (continuous variable)		0.97		0.96 - 0.98	1.03		1.02 - 1.04

7.3.4 FACTORS ASSOCIATED WITH DIAGNOSIS

Females constitute a majority of users of antidepressants. Gender was statistically tested against ICD-10 category to determine if there was an association. This is presented in Table 7.10 below. Females were more likely to have a psychiatric diagnosis (OR 1.49; 95%CI 1.11 – 2.00; p=0.008) compared to males.

Table 7.10 Chi-squared table* of gender and ICD-10 category (Dataset B)

Gender	Psychiatric	Pain	Other	Total
Male (n)	147	224	102	473
%	31.08	47.36	21.56	100
Female (n)	369	282	120	771
%	47.86	36.58	15.56	100
Total (n)	516	506	222	1 244
%	41.48	40.68	17.85	100

*Pearson Chi^2= 34.1957

*P<0.0001

A patient's age group was also statistically tested against their diagnosis. Elderly patients (66+) were more likely to have a psychiatric diagnosis compared to all other age groups (OR 10.28; 95%CI 1.73 – 60.90; p = 0.010). The Chi-squared table (Table 7.11) below illustrates the association between a patient's age category and their diagnostic category.

Table 7.11 Chi-squared table* of age category and ICD-10 category (Dataset B)

Age Category	Psychiatric	Pain	Other	Total
0 -12 years (n)	2	1	3	6
%	33.33	16.67	50	100
13 - 16 years (n)	2	0	2	4
%	50	0	50	100
17 -65 years (n)	470	475	210	1 155
%	40.69	41.13	18.18	100
66 years and older (n)	42	30	7	79
%	53.16	37.97	8.86	100
Total (n)	516	506	222	1 244
%	41.48	40.68	17.85	100

*Pearson Chi^2= 15.0559

*P<0.05

7.4 SUMMARY TABLE OF INFERENTIAL STATISTICS

The table below is a summary of the inferential statistics presented in the sections above.

Table 7.12 Summary of inferential statistics (Dataset B)

Factor	**Drug Type (Old vs New Generation drug)**	**Repeats (Once-off vs Repeats)**	**Diagnosis (Psychiatric vs Pain vs Other**
Age (continuous variable)	✗	✓	~
Number of visits (continuous variable)	✓	~	~
Age Category	✓	✓	✓
Number of Visits Category	✓	~	~
Gender Category	✓	✗	✓
ICD-10 Category	✓	✓	~
Psychiatric Category	✓	✓	~

✓ = significant ($p<0.05$)

✗ = not significant

~ = not applicable

CHAPTER 8: DISCUSSION

This study is the most recent Drug Utilization Review (DUR) conducted on antidepressants in South Africa. In the previous two chapters (Chapter 6 and 7) the findings of the study were presented. In this chapter (Chapter Eight), the primary findings of the study will be considered within the context of both national and international reported usage. In addition, the inferences on which clinical and demographic factors affect the choice of antidepressant used (Section 8.2) and the duration of treatment (Section 8.3) will be discussed within the framework of our novel approach and compared to other studies.

8.1 PATTERNS OF USAGE

The aim of the study was not to compare the two datasets. Instead, a second dataset (Dataset B) was acquired to determine if the patterns in Dataset A were isolated to that sample or not. The following sections will elucidate on the congruence, or divergence, of the two samples and their difference or similarity within the global and local context.

The two study samples were congruent with regards to the demographic profiles of users. The majority of the users in both samples were female (A: 69.96%, n=6 445; B: 61.98%, n=771) and the mean age of the patients were in the range of mid-adult (A: 43.86 +- 13.81; B: 46.27+-13.03). The two samples were also similar in terms of the frequency of drug used, where amitriptyline formed the majority in both samples (A: 67.75%, n =6242; B: 64.07%, n=797). The frequency of diagnosis differed to a slight degree. Muscle and joint disorders formed the majority of prescriptions in Sample A (25.16%, n=2227). Sample B differed in that the majority of prescriptions were for a depressive episode (28.94%, n=352), however, muscle and joint disorders contributed towards a large proportion of prescriptions as well (27.81%, n=346).

A detailed presentation of the factors age, gender, frequency of drug usage and frequency of diagnoses will be given in the following sections (Section 8.1.1, 8.1.3, 8.1.4).

8.1.1 AGE

The mean age of users of antidepressants is similar in the two samples (A:43.86±13.81; B:46.27±13.03). When patients were grouped into categories the majority of users fell into the adult category of 17-65 years in both samples (A: 91.26%, n=8 408; B: 92.85%, n= 1 155). The incidence of depression has been reported to be the highest amongst this age group (Rait et al, 2009; Kessler et al, 2003) and therefore this age group represents the majority of users of antidepressants. Patients in this age group are also reported to have the highest incidence related to poor mental health (Sundell et al, 2011). The recent South African Census shows that the majority of the population fall into the 15-64 year age group (Statistics South Africa, 2012) and hence patients in this category may also represent a majority because they are the most populous. The unemployment rate is also shown to decrease from the age of 25 to 64 years (Statistics South Africa, 2012). Patients in this age group are, therefore, representative of the work force. Employed members of the population are more likely to have funds to access private health care. Our datasets represent users of antidepressants in a private health care setting. In addition, employed people earning above a certain threshold may be required by their company to enlist to a medical aid (Department of Labour, 2012), patients with a medical aid may be more inclined to access private health care. The highest use of antidepressants by people of a working age has also been reported in a German study (Bramesfeld et al, 2007).

Other studies have shown the highest use of antidepressants to be amongst elderly population (Demyttenaere et al, 2008; Paulose-Ram et al, 2007; Olfson et al, 2009; Parabiaghi et al, 2011).Elderly patients are the second highest age category to use an antidepressant in our two samples (A: 5.86%, n=540; B: 6.35%, n=79). Reasons for our study differing from these European and American studies could lie in the fact that our study assessed usage in a private health care setting. Usage patterns of antidepressants by the public health care sector were beyond the scope of this study. Future studies into the

pattern of usage of antidepressants in public health care setting could elucidate if elderly patients represent a majority or if usage patterns favour the results seen in our two samples. In addition, the ageing population may require assistance from a third party before attempting medical intervention. Another reason for a divergence of our results from international studies could be explained by the fact that South Africa is considered a developing country. The recent Census showed that 60% of South Africa's population is below the age of 35. The average age of a South African is 25 years (Statistics South Africa, 2012). European countries and America, in contrast, have an ageing population. With the average age in these regions ranging from 37 to 42 years (Central Intelligence Agency, 2009). An ageing population would result in higher use of drugs by the elderly. South Africa, in relation to first world countries, does not have an ageing population and highest antidepressant use is seen in adults (17 – 65 years).

Children (A: 0.86%, n=79; B: 0.48%, n=6) and adolescents (A: 2.02% , n=186; B: 0.32%, n=4) form the minority of users as they are, possibly, the least likely age group to seek medical intervention independently. In addition, diagnosis and treatment of childhood and adolescent depression is a subject of controversy. The black-box warnings of suicide on antidepressants have been reported to have lead to a decrease in antidepressant usage amongst children and adolescents (Tournier et al, 2010; Kurian et al, 2007). In addition, the warnings have also been suggested to have lead to a decrease in the number of visits for depressive-related visits (Chen et al, 2011). Low use amongst younger patients have been reported elsewhere (Bramesfeld et al, 2007).

Findings in our study are in accordance with some literature, with adults being the majority of users of antidepressants. Other studies, have differed from this study, showing higher usage amongst the elderly. Children and adolescents usage patterns are in accordance with international trends.

8.1.2 GENDER

Females formed the majority of users of antidepressants in both samples. This skewness in the weighting of gender has been observed in many international studies (Paulose-Ram et al, 2007; Carrasco-Garrido et al, 2007; Barbui et al, 2006; Sihvo et al, 2008; Sundell et al, 2011; Gardarsdottir et al, 2007; Exeter et al, 2009; van der Heydan et al, 2009). In a South African setting, this gender bias has been observed in other studies as well (Truter et al, 1996 1997; Truter et al, 2006). A cross- European study, ESEMED study, found only a slight difference in antidepressant use between genders, with females forming a slight majority. A greater gender bias was seen in this study with when assessing the differences in anxiolytic use, another class of psychotropic drugs (Alonso et al, 2004). The suggested reasons for the favourable use of antidepressants by females have ranged from differences in socioeconomic determinants to differences in frequency of disorders between genders. Prevalence of lifetime major depressive episode in South Africa is 1.75 times more likely to occur in females compared to males and the odds of 12-month depression is even higher for females, 2.17, (Tomlinson et al, 2009). The higher prevalence of depression in women is coupled with the fact that women are also more likely to display health-seeking behaviours (Payne et al, 2004; Carrasco-Garrido et al,2007; Exeter et al, 2009). The presence of mental or mood disorders has also been deemed more socially acceptable in women than men (van der Heydan et al, 2009). It has also been proposed that women are more likely to medicalize social problems and seek pharmocotherapeutic intervention and men are more likely to utilize social outlets, like alcohol and nicotine (Pettinati et al, 2007; Tait et al, 2012).

8.1.3 FREQUENCY OF DRUG USE

A vast majority, almost 90%, of prescriptions in both datasets were for generic drugs. This high generic use in practice could be a reflection of South Africa's National Drug Policy which promotes and encourages the use of generics. Generic drugs are economically more favourable and would be considered an acceptable alternative for dispensing doctors

(which are presented in the Dataset A and B) who may need to treat patients without medical drug re-imbursement schemes.

The most frequently prescribed antidepressant in both study samples was amitriptyline. This differs from most international findings, which have documented that the newer SSRI's are preferred. SSRIs are considered to have over-taken the TCAs, in terms of usage, in the mid 90s internationally (Roberts et al, 2001; Colman et al, 2006; Sim et al, 2006). A South African study on antidepressant use conducted in 1995, found TCAs to be the most commonly used antidepressant but proposed that South Africa would follow international trends with SSRIs over-taking TCAs (Truter et al, 1997). The two samples presented in this research showed that sectors of South African prescribing markets have not followed this trend, even 17 years later. TCAs remain the most commonly prescribed antidepressant in these study samples (A: 69.93%, n=6 442; B: 68.81%, n=856) with amitriptyline accounting for the majority of these. The previously mentioned South African study showed a 40.9% usage of TCAs by patients. Our figure is considerably higher as it was not confined to members of a private medical aid scheme but users of private health care who may not be re-imbursed by a medical aid. In addition, patients in Truter et al's (1997) study were exclusively treated on a chronic basis. Truter et al (2006) documented that antidepressant use was shifting towards the SSRIs in their more recent study. This study also used data from medical aid schemes where payment for drugs may be re-imbursed and patients may be less resistant to use the more expensive SSRI as compared to TCAs.

The other possible reasons for the preferential use of TCAs in the two datasets presented here could be also be due to the fact that these drugs are economically favourable, widely available in generic form and have a wide indication of use. The two datasets in this study represent the prescribing practice of dispensing doctors. These doctors may favour the use of cheaper alternatives when treating patients who have no medical aid and hence no re-imbursement for drugs. In addition, TCAs have wide indications of use. The South African Department of Health (Department of Health, 2006) lists amitriptyline in the Standard Treatment Guideline (STG) as being used in the treatment of many conditions, a list of these conditions is provided in Chapter Two (Section 2.1.2, page 5). The wide indications

of use of the TCA may be linked to the increased frequency of prescriptions for these drugs.

Usage patterns in Taiwan (Wu et al, 2012) and Germany (Ufer et al, 2007) have also shown a preference to TCA's. The Taiwanese study found that even though TCAs were the most commonly prescribed antidepressant in their study, only 6.1% of prescriptions were related to a mood disorder. This study also displays growing recognition of these drugs in treating chronic pain syndromes and other non-psychiatric disorders (Wu et al, 2012). The German study, however, linked the high-use of TCAs in their study to economic reasons and not off-label use. The medical system in Germany has set a limit on annual prescribing costs by primary care physicians. This has the consequence of physicians favouring cheaper and generically available drugs (Ufer et al, 2007).

The high use of amitriptyline, an older antidepressant, in our study is most likely due to a combination of factors. The wide indications of use of these drugs and their availability in generic and reasonably cheap form are, possibly, the main contributing factors. Patient and physician preference and past history may also be considered to be contributing factors.

There is no evidence to support the efficacy of one class of antidepressant over another (Mann, 2005), therefore, this study also sought to discover which factors are significant when prescribing one type of antidepressant over another. This is discussed in Section 8.2.

8.1.4 FREQUENCY OF DIAGNOSES

The most frequent diagnosis of users of antidepressants was for a pain related condition in Sample A (50,01%, n=4 429). A pain related condition included muscle and joint disorders, headache and migraine and general pain localized to specific regions. Sample B differed in that the majority of diagnoses were split almost evenly, between psychiatric (41.48%, n=516) and pain conditions (40.68%, n=506). The high number of prescriptions

related to pain in both samples could be attributed to increasing awareness and acceptance of the use of antidepressants in the treatment of pain or as adjunctive pain treatment. TCAs have long been accepted for their efficacy in migraine prophylaxis, treatment of neuropathic pain and other chronic pain disorders (Rossiter, 2008). Studies done on their efficacy in treating inflammatory rheumatoid arthritis and lower back pain have been inconclusive (McCleane, 2008; Richards et al, 2012); their usage in treating arthritis and muscle and joint pain, nevertheless, is high in our study. This usage pattern may not be substantiated by the literature. TCAs are listed in the South African Standard Treatment Guidelines for the management of different pain syndromes (see Section 2.1.2, page 5), physicians may be extrapolating this to the treatment of muscle and joint disorders as a consequence of successful treatment of other pain syndromes.

The use of SSRIs in treating pain is considered less effective than TCAs (McCleane, 2008). There is, however, growing evidence that the newer SNRIs are effective in treating peripheral diabetic neuropathy, fibromyalgia and in migraine prophylaxis (Dharmshaktu et al, 2012). The higher rate of pain diagnoses in Sample A could be a possible reasoning for the increased frequency in venlafaxine prescriptions in this sample. Venlafaxine was the third most highly prescribed antidepressant (8.67%, n=799) in Sample A. Sample B, however, had fewer prescriptions for venlafaxine (0.16%, n=2) and approximately 10% less diagnoses related to pain than Sample A.

The use of antidepressants in treating psychiatric disorders is clinically and regulatory approved for a number of disorders. Our samples showed differences in psychiatric use of antidepressants. The majority of psychiatric diagnoses in Sample A were for anxiety-related conditions and life stress (A: 73.72%, n=1 701), this was followed by affective disorders (21.24%, n=493) Antidepressants are approved for use in both categories. Sleep disorders accounted to 4.43% (n=102) of psychiatric use. Sedation is an adverse effect of TCAs (Westfall et al, 2012) and seems to be used clinically to treat sleep disorders as they are less addictive than benzodiazepines and relatively cheaper compared to non-benzodiazepine sedatives (zolpidem, zopiclone). In addition, they may be used to treat a symptom (insomnia) of depression or a stress disorder. Sample B's pattern of psychiatric

did not confirm this. The majority of psychiatric diagnoses were for an affective disorder (72.09%; n=364) in Sample B.

The high number of psychiatric diagnoses related to anxiety and stress in Sample A could be as a result of the high burden of these conditions in South Africa. The South African Stress and Health (SASH) study found anxiety disorders to be the most prevalent mental disorder. This was especially seen in more urbanized provinces. Data from our samples come from urbanized regions of Johannesburg, South Africa. Johannesburg is in the province with the fifth highest prevalence of anxiety in SASH study (Herman et al, 2009; Seedat et al, 2009).

Just under a quarter of prescriptions in both samples were for a condition not related to a psychiatric or a pain condition (A: 24.00%, n=2 125; B: 17.85%, n=222). Some of the diagnoses in this category, for example: enuresis is recognized as being appropriately treated with antidepressants, particularly TCAs. Indications such as herpes infections are also associated with TCA use for treating the associated herpetic neuralgia. Similarly, diabetic patients may also use TCAs to treat diabetic neuropathy. Other indications such as respiratory, gastric, dermatological and cardiovascular disorders are not recognized as appropriate indications for the use of antidepressants. These disorders may not have necessarily been treated by an antidepressant; instead, these disorders were most likely co-morbid with an affective or anxiety disorder. Other reasons for the high number of other indications could be a falsely entered ICD-10 code, an ICD-10 code from a patient's previous visit to the physician may have been carried to through to subsequent visits. This is a limitation of the nature of the studied data and is discussed in Section 8.4 below.

The prevalence of depression as a co-morbid disease is reported to be high in a South African study (Muller et al, 2008) and internationally (Moussavi et al, 2007; Gabilondo et al, 2012). The two study samples analysed displayed a high number of diagnoses not related to an identifiable indication for an antidepressant. The possibility that these disorders were co-morbid with an affective or anxiety disorder needs to be considered.

This study displays a high number of diagnoses related to a respiratory disorder (A: 9.80%, n=868; B: 4.66%, n=58). A recent Spanish study showed the highest association between a respiratory disorder and depression (Gabilondo et al, 2012). The association between respiratory disorders and major depressive disorder is not clear, it has been hypothesized that the treatment of some respiratory disorders with corticosteroids may influence mood, behaviour and brain excitability (Barnes, 2011, Schimmer et al, 2011). Corticosteroids have central nervous system adverse effects which include psychosis, mania, insomnia, restlessness, suicidal ideation and to a small extent depression or anxiety (Schimmer et al, 2011). The abrupt termination of treatment may result in adrenal insufficiency with depression and apathy as symptoms (Schimmer et al, 2011). The role of tobacco smoking has also been suggested to influence this relationship. Patients who are addicted to tobacco have been shown to display an increase occurrence of mood disorders (Adams et al, 2012; Grover et al, 2012). Tobacco use is a major risk factor for the development of respiratory disorders such as emphysema and chronic obstructive pulmonary disorder. The scope of our data did not allow for an association to be made between major depressive disorder and other chronic physical illness. But the high number of respiratory disorders in users of antidepressants suggest that there might be a relationship. Further investigation would clarify this.

Not all DUR conducted have access to patient particulars, such as ICD-10 codes. The two datasets presented in this study were acquired from companies that included this valuable information. The patterns in both are similar with regards to the frequency of diagnoses, even though these are two separate and stand-alone datasets. This indicates that the strength of the trends and patterns drawn are corroborated. In a South African setting, the use of antidepressants in the management of pain seems to supercede the management of psychiatric disorders. In international studies, psychiatric disorders such as Major Depressive Disorder (MDD) and anxiety contribute towards a substantial amount of indications but the influence of other indications is a considerable factor as well. A British study found 70% of antidepressant prescriptions linked with a depression diagnosis (Lawrenson et al, 2000), this study also displayed a high number of diagnoses related to chronic diseases. A Dutch study found 45% of antidepressant prescriptions related to a

diagnosis of depression (Gardarsdottir et al, 2007). This trend is similar to Sample B (B: 41.48%, n=516). The study also concurs with our results in finding that a large percentage (35.8%) of antidepressant prescriptions were for an indication not approved. The strength of comparison is bolstered by this study's classification of diagnosis. The authors listed indications which were clinically accepted but still considered off-label (eg: sleeping disorders, pain syndromes and enuresis) as approved indications. The grouping of our diagnoses also considered this. Reasons for the high proportion of diagnoses related to 'other' in their study were proposed as the diagnosis being co-morbid with depression; patients visiting the physician for an unrelated condition but receiving a repeat antidepressant prescription and the physician may have still been evaluating the patient and a diagnostic code for depression was not yet entered (Gardarsdottir et al, 2007). The nature of this Dutch study is similar to ours and the reasons proposed above as to why a high proportion of prescriptions are not linked to a psychiatric or pain condition; may extend to our study as well. A Finnish study also displayed a high proportion of non-psychiatric use of antidepressants. In this study, the authors found a third of antidepressant use was related to non-psychiatric use and 59% of prescriptions were for depression or anxiety or a history of depression and anxiety. The study did not breakdown non-psychiatric use further and considered approved indications (eg: fibromylagia pain and eating disorders) as a reason for this percentage (Sihvo et al, 2008). Canadian studies have mirrored this trend as well (Beck et al, 2004; Patten et al, 2005; Patten et al, 2007).

Our two samples show high usage of antidepressants for non-psychiatric purposes. Some of these indications are clinically approved while others are not. The use of antidepressants for non-psychiatric purposes is a trend observed internationally and in accordance with our results.

8.2 FACTORS AFFECTING TYPE OF DRUG USED

Our study has provided patterns of usage, which are different to international trends. This is especially observed with regards to the frequency of the type of antidepressants used. Our two study samples showed that the older generation of antidepressants, the TCAs, formed the bulk of prescriptions. Only two other countries, Taiwan and Germany, were found to follow this trend. The researcher proceeded to undertake a novel approach in determining which factors affect the type of antidepressant used. No other South African studies, to the researcher's knowledge, have answered this question. Patient factors such as age, gender, diagnosis, psychiatric diagnosis and duration of treatment were statistically entered into logistic regression models to determine if they predicted whether a patient would receive an older TCA or a newer generation antidepressant. Newer generation antidepressants predominantly include the Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Noradrenaline Reuptake Inhibitors (SNRIs), Monoamine Oxidase Inhibitors (MAOIs) and other drugs (trazodone) which are, not necessarily, new were included in this group but accounted for minimal to no prescriptions.

8.2.1 AGE

TCA usage is associated with an adverse effect profile which is particularly concerning in elderly patients (Rossiter, 2008). TCAs have anticholinegic, hypotensive and cardiac effects, which necessitates regular monitoring in elderly patients. In addition, TCAs can be fatal in overdose and careful dosing is required for all age groups. The adverse effects of TCAs may limit their usage in older patients. To provide more insight into this statement, the variable, age, was statistically tested in two ways: as a continuous and categorical variable. The reason for statistically testing age in two distinct ways is that results from age as a continuous variable yielded a significant outcome in Sample A ($p<0.0001$) and a non-significant outcome in Sample B ($p>0.05$). This difference prompted further investigation and a patient's age was grouped into categories according to their age. Please refer to Section 5.3.3.2 for a detailed breakdown of the age categories.

AGE AS A CONTINUOUS VARIABLE

Sample A showed a statistical association between age and the type of antidepressant used. With increasing age, patients had a higher probability of receiving a newer antidepressant(OR 1.01 95% CI 1.00-1.0). The difference in the mean age of users is small (43.15years for TCA and 45.31years for new generation antidepressant) but is statistically significant ($p<0.0001$) and shows a tendency to prescribe newer drugs to older patients. The clinical significance of this statistical outcome is not strongly apparent. The mean ages of the users of two groups of antidepressants are numerically but not clinically distinguishable. A clinical trend of prescribing newer antidepressants to older patients, therefore, cannot be made.

Sample B showed no statistical association between age and drug type ($p>0.05$). Advancement in age did not increase the odds of receiving a newer or older generation drug. TCA's remain the most frequently prescribed antidepressants in adults in both samples, a finding not consistent with international trends. This is most likely as a result of the high use of TCAs in treating non-psychiatric disorders, it is economically more viable and has a wide indication of usage.

Age, as a continuous variable, yielded opposing results in our two samples. In addition the statistical association may not, necessarily, be clinically important. Because the two samples were not congruent in describing the influence of age on prescribing either a TCA or a newer generation antidepressant, the analysis was performed again using more clinically relevant age categories as clarified in Section 5.3.3.2. The statistical association between the type of antidepressant used and a patient's age category was statistically significant in both samples but as discussed below, variations between age categories occurred.

AGE AS A CATEGORICAL VARIABLE

Sample A's logistic regression model of age category and the type of antidepressant used showed that adults (17-65 years) and elderly (66+) had a higher odds of getting a newer generation antidepressant compared to children (0-12). Adults were 1.98 (95%CI 1.11 - 3.53; $p<0.05$) times more likely to get a new antidepressant. Elderly patients were 3.11 (95% CI 1.71 -5.70; $p<0.0001$) times more likely to get a newer generation antidepressant.

Sample B differed from Sample A and statistically showed that adolescents had a higher use of newer generation antidepressants (75%; n=3). The results from the logistic regression model, however, provided non-significant results. Because of the small number of patients belonging to this age group (n=4) and infants and children (n=6) trends from these age groups will not be considered further. With regards to adults and the elderly, TCA usage dominated. But elderly patients had a lower rate of TCA use (49.37%, n= 39) than adults (70.39%, n=813). The results of the chi-squared test show that this was significant ($p<0.0001$). This is consistent with Sample A which showed a preferential use of newer drugs by the elderly. Just under 60%(59.81%, n=323) of patients older than 65 were taking a TCA while 70.09% (n=5 893) of adult patients (17-65years) were taking a TCA. This association was statistically significant ($p<0.0001$). The rate of TCA use by the elderly, nevertheless, is still high.

Both samples display that elderly patients are more likely to receive a newer generation drug compared to adults. The chi-squared tests in both samples show this was significant ($p<0.0001$ for Sample A and B). There are international studies which have agreed with this finding (Trifiro et al, 2006) while others have not (Sim et al, 2006; Zullino et al, 2008). South African studies have shown increased usage of TCAs by older patients compared to younger patients (Truter et al, 1996; Truter et al, 1996). This is a result in conflict with our finding. This study, however, is 17 years old and a change in prescribing patterns seems to have occurred over the past decade and a half. Increased awareness, education and the availability of newer antidepressants in generic form may be influencing this. This is an encouraging trend but further emphasis needs to be applied on cautionary

use of TCA in elderly patients. Even though TCA usage is declining in this age group, usage still remains high with approximately half of elderly patients receiving a TCA.

Studies observing the differences between TCAs and other antidepressants are not as abundant as DURs on antidepressants. Results on both ends of the spectrum have been found with regards to the influence of age on the type of antidepressant prescribed. Trifiro et al (2006) have shown that users on non-TCA/other antidepressants were older than users of TCA drugs. Their result was clinically significant but contrary to our study their classification of non-TCA antidepressants found a higher use of trazodone in elderly. Trazodone accounted for a minimal number of antidepressant prescriptions in both our samples possibly as a result of its high cost. Swiss, Australian, European and East Asian studies, however, found that users of the newer generation of antidepressants are younger (Sim et al, 2006; Bauer et al, 2008; Zullino et al, 2008; Exeter et al, 2009). Older patients were found to be statistically more likely to receive a TCA. Reasons for this included that older patients may have been stabilized on TCAs for long periods of time and physicians may display an unwillingness to change treatment (Zullino et al, 2008). Conversely, it has been suggested that younger patients display a preference for drugs with a more accepted adverse effect profile and there has been a growth in the acceptance and preference of newer generation antidepressants (Sim et al, 2006).

The association between age and diagnosis could explain reasons for increased use of newer antidepressants by the elderly compared to younger patients in Sample A. Younger patients were more likely to have a diagnosis related to a pain condition (55.71%, n= 39 for 0-12 years; 70.27%, n=130 for adolescents). As mentioned earlier, the use of TCAs in treating pain is well established in the South African context. The Department of Health's Standard Treatment Guideline's lists amitriptyline in the management of many different pain conditions (Department of Health, 2006). Treatment of pain in younger members of the sample seems to follow these guidelines in Sample A. There may be a resistance by prescribers to utilize other pain-management drugs in younger patients. Non-Steroidal Inflammatory Drugs (NSAIDs) and opioids have an adverse effect profile that may dictate less usage in this age population. Prescriptions listed for other diagnoses (non-psychiatric and non-pain) were also high in these age groups (35.71%, n=25 for 0-12 years; 25.95%,

n=48 for 13-16years). Urinary incontinence and nocturnal enuresis are approved indications for the use of TCAs (Rossiter, 2008), usage of TCAs in these age groups could be accounted for by these indications as well.

In contrast, a psychiatric diagnosis was found to be more likely in the elderly patient group (OR 2.22; 95%CI 0.77 – 7.35; $p<0.05$). This finding prompts the reasoning of why this patient group displayed higher use of newer generation antidepressants.

Despite the statistical association of prescribing newer antidepressants to older patients, the usage of TCAs in the elderly age category is still high. Both samples showed a high usage of these drugs in elderly patients. Over 50% of patients older than 66years were taking a TCA in Samples A and B. The adverse effect profile in this age group needs to be considered before prescribing a TCA. A recommendation of this study would be to alert prescribers, particularly general practitioners, on the high use of TCA in the elderly and highlight the concern surrounding the adverse effect profile before dispensing these drugs.

8.2.2 GENDER

The effect of gender on the type of antidepressant prescribed is another demographic factor demonstrating inconsistencies. Females form the majority in both samples, (A: 69.96%, n=6 445; B: 61.98%, n= 771). Sample A showed no statistical association between the type of drug used and gender ($p>0.05$) while Sample B showed a statistical preference of females using newer generation drugs ($p<0.05$). Females were 1.35 times (95%CI 1.04-1.73; $p<0.05$) more likely to receive a new generation antidepressant compared to males in Sample B.

The divergence between the two samples could be accounted for by the fact that in Sample B the statistical association between gender and diagnoses ($p<0.0001$) was far greater and

significant than that of Sample A ($p>0.05$). A psychiatric diagnosis was evident in 47.86% (n=369) of females in Sample B compared to 31.08% (n=147) of males in Sample B. In Sample A, a psychiatric diagnosis was seen in 27.09% (n=1 671) of females and 23.47% (n=631) of males. Therefore, females in Sample B showed a higher proportion of psychiatric diagnosis for a psychiatric condition and consequently a higher proportion of females taking a newer generation antidepressant. The higher incidence of psychiatric disorders in females is discussed in Section 8.1.2.

South African studies that have looked at the relationship between gender and antidepressant usage and have shown that TCA usage is higher amongst females (Truter et al, 1996; Kairuz et al, 2003). Other international studies have also found similar trends to Sample A where gender was not significantly related to the type of antidepressant used in British, East Asian and Australian studies (Lawrenson et al, 2000; Sim et al, 2006; Exeter et al, 2009).

Sample A's findings are not supported by Sample B or other South African studies but are supported by international trends. The effect on gender on the type of antidepressant used seems to differ under different study parameters. This suggests that the role of gender is not clearly defined and may, in fact, play no part in whether a patient receives a TCA or a newer generation antidepressant. Other factors are likely to play a more significant role. The effect of diagnosis shows the strongest effect on the type of antidepressant dispensed. This will be dealt with in Section 8.2.3.

8.2.3 DIAGNOSIS

The TCA antidepressant class is associated with a wide indication of use and is not limited to psychiatric disorders. It is often used in treating many pain syndromes and other disorders (urinary incontinence). In contrast to this, SSRIs and other antidepressants are primarily recommended for use in psychiatric disorders such as mood and anxiety-related disorders. Statistical tests were conducted to determine if a patient's diagnosis had an

effect on whether they would receive an older TCA or a newer generation antidepressant. A patient's diagnosis was found to be a significant predictor of whether they would receive an older TCA or a newer generation antidepressant in both samples. Furthermore, all patients with a psychiatric diagnosis were further broken down into the type of psychiatric disorder diagnosed. This also had an effect on the type of antidepressant used. This section (Section 8.2.3) will detail these relationships in Sample A and B.

Sample A showed that 66.94% (n=1 541) of patients with a psychiatric disorder were taking a newer generation drug. The majority of patients with a diagnosis related to pain or 'other' were observed to be taking an older TCA (Pain: 88.08%, n=3 901; Other: 76.38%, n=1 623). This difference was statistically significant ($p<0.0001$). On logistic regression it was shown that patients with a psychiatric disorder were 6.53 times (95% CI 5.72 - 7.45; $p<0.0001$) more likely to receive a new generation antidepressant. Patients with a diagnosis of pain were 2.31 times (95% CI 2.02 -2.64; $p<0.0001$) more likely to get a TCA.

Sample B displayed a similar trend with regards to the differences in the type of antidepressant used and a patient's diagnosis. 65.70% (n=339) of psychiatric diagnoses were treated with a new generation antidepressant. Only 1.58% (n=8) of patients with a diagnosis for pain with treated with a new antidepressant. The majority of users with 'other' diagnoses were also receiving a TCA (81.53%, n=181). The differences were statistically significant ($p<0.0001$). On logistic regression, it was observed that patients with a psychiatric diagnosis were 8.46 times (95% CI 5.76 - 12.42; $p<0.0001$) more likely to receive a new antidepressant. And patients with a pain diagnosis were 14.10 times (95% CI 6.49 - 30.65; $p<0.0001$) more likely to receive a TCA. The two samples displayed a similar pattern with regards to the association between diagnosis and the type of antidepressant used. Patients with a psychiatric diagnosis were statistically more likely to receive a new generation antidepressant and patients with pain were more likely to receive a TCA.

When distinguishing between psychiatric disorders, the two samples differed. Sample A showed that affective (90.67%, n=447) and anxiety and stress related conditions (62.43%, n=1 062) were treated with new generation antidepressants. In contrast, 68.63% (n=70) of sleep disorders were treated with a TCA. Sample B differed in that only affective disorders were primarily treated with a new generation antidepressant (78.49%, n=292). Anxiety and stress (66.90%, n=95) and sleep disorders (100.00%, n=10) were treated with a TCA. These associations were statistically significant ($p<0.0001$).

On logistic regression, patients from Sample A with a psychiatric diagnosis being an affective condition were 5.78 times (95% CI 4.19 – 7.95; $p<0.0001$) times more likely to receive a new generation antidepressant. Those with a sleep disorder were 3.67 times (95% CI 2.39 – 5.63) more likely to receive a TCA. Sample B's results showed that patients with an affective disorder were 8.89 times (95%CI 5.68 - 13.90) likely to receive an new generation antidepressant compared to patients with an anxiety or stress related condition.

A patient's diagnosis and psychiatric diagnosis was a significant factor in determining whether they received a TCA or a new generation antidepressant in both the study samples. Other available South African studies have not studied this association. A DUR conducted on antidepressants in adolescents did not include diagnoses (Kairuz et al, 2003) while others only studied patients with a diagnosis of depression (Truter et al, 1996; Truter et al, 1997). The novelty of this study lies in the nature of the data acquired. The presence of a high number of diagnoses related to non-depressive diagnoses suggests that future studies should include diagnostic information on patients prescribed the drug in question. This will ensure that a more complete picture of drug utilization will be achieved. Patten et al (2007) has suggested that selecting information on drug use that is limited to a specific diagnoses renders the study sensitive to 'misclassification bias'.

Some international studies that have looked at the relationship between diagnosis and the type of antidepressant used have agreed with our findings. European, Canadian and a Taiwanese study have also found that TCAs were associated with non-psychiatric use (Trifiro et al, 2006; Gardarsdottir et al, 2007; Patten et al, 2007; Sonnenberg et al, 2008;

Wu et al, 2012). Reasons provided for this included that the use of TCAs in treating pain conditions is an approved indication and that the evidence for this is recognized (Wu et al, 2012). In addition, the use of new antidepressants in treating a condition for which it is not currently approved may not be re-imbursed by medical aids (Wu et al, 2012) and therefore TCAs would be preferred in this instance. A Dutch study suggested that the presence of non-psychiatric use was particularly high with TCAs but approximately half of these diagnoses were for an indication not registered. This was accounted for by the fact that the physician had not entered the indication into the dataset, a patient was visiting the physician for an unrelated condition and requesting a repeat prescription and that the majority of off-label users were for elderly patients with a general poorer health state and visited the physician more often with co-morbid complaints (Gardarsdottir et al, 2007).

Samples A and B displayed a high use of TCAs in treating sleep disorders; this was observed in one of these studies (Gardarsdottir et al, 2007). Sedation is an adverse effect of TCAs (Rossiter, 2008). This adverse effect seems to have therapeutic benefit for patients who are not considered for treatment with a benzodiazepine, another sedative drug. Treatment of sleep disorders, however, was not strongly associated with TCA use in two other studies. Both these studies found usage of trazodone to be associated with sleep disorders (Trifiro et al, 2007; Wu et al, 2012). Usage patterns in our two study samples showed minimal to no use of trazodone. Trazodone is not listed on the Department of Health's Standard Treatment Guidelines or Essential Drug List (Department of Health, 2006). Physicians in private practice seem to adhere to the EDL with regards to trazodone. In addition, TCAs may be preferred in treating sleep disorders which are co-morbid with a chronic pain condition or a psychiatric disorder.

Studies which do not agree with our findings have suggested that a patient's diagnosis was not a significant factor related to the type of antidepressant used (Zullino et al, 2008). An East Asian study found that the new generation antidepressants were associated with diagnoses related to 'other' and less likely associated with a diagnosis for an affective disorder (Sim et al, 2006). This study looked at antidepressant usage in five East Asian countries (Japan, Korea, China, Singapore and Taiwan). A suggested reason proposed for this association may be found in the differing physician practices and patient factors across

the countries. In addition, conditions that were co-morbid with an affective disorder or the treatment of addictive conditions could account for the higher use of new generation antidepressants in treating 'other' diagnoses (Sim et al, 2006).

The association between diagnosis and the type of antidepressant used is an encouraging finding of Sample A and B. This association is statistically confirmed and suggests some diagnostic thought behind the choice of antidepressant. The duration of treatment with an antidepressant is, however, an area of concern. This will be discussed in Section 8.2.4.

8.2.4 DURATION OF TREATMENT

The average duration of treatment with an antidepressant was below the recommended guidelines of 6 months. The average number of antidepressant prescriptions in Sample A was 2.95 (± 3.77). This was similar in Sample B (2.57 ± 2.47). Patients received half the recommended number of antidepressant prescriptions. In addition, patients who received treatment for the recommended duration of six months formed approximately 13% in both samples. International studies have found that less than 50% of patients receive an antidepressant for six months (McCombs et al, 1999; Demyttenaere et al, 2001; McManus et al, 2004). To determine if the type of drug prescribed affected this, statistical tests were employed. The results of this will be detailed in this section (Section 8.2.4).

To answer the question of whether the type of drug used did affect the duration of treatment with an antidepressant two statistical methods were used. Statistical testing was initially completed with the duration of treatment as a continuous variable. Thereafter the duration of treatment was categorized according to clinical criteria as detailed in Section 5.3.3.2.

The results of the duration of treatment as a continuous variable yielded a significant outcome in both samples ($p<0.0001$). For Sample A, the mean duration of treatment by

patients taking an old TCA was 2.42 (±3.01) and the mean duration of treatment for patients taking a newer generation antidepressant was 4.19 (±4.88). Sample B showed a similar trend (old generation: 1.96 ±1.69; new generation: 3.93±3.24). Patients taking a new generation antidepressant received the drug on an average of four times. Patients taking an older TCA received the drug twice. Patients taking a new generation antidepressant were likely to receive it for almost twice as longer than a patient taking a TCA.

To determine if users of old TCAs or users of newer generation antidepressant are more likely to receive antidepressants according to the recommended guideline of 6 months we conducted chi-squared and logistic regression tests. Sample A showed that amongst patients who received treatment for six months or longer only a marginal majority were receiving a new generation antidepressant (51.08%, n=614). In contrast, patients who received an antidepressant for between two and six months and those who only received it once were predominantly taking an older TCA ($p<0.0001$). This was statistically significant. Patients on treatment for six or months or longer were 3.29 times (95% CI 2.88 - 3.74)more likely than those patients who received the drug once-off to be receiving a new generation antidepressant($p<0.0001$).

Sample B displayed a slightly different trend. A large majority of patients who received treatment for six months or longer were receiving a new generation antidepressant (74.53%, n=120). This was a considerably larger majority than Sample A. Patients who received treatment for between two and five months or once-off, however, displayed a parallel pattern to Sample A. The majority of these patients were taking an older TCA. These differences were statistically significant ($p<0.0001$).Patients on treatment for six or months or longer were 10.59 times (95% CI 7.09 – 15.81) more likely to be receiving a new generation antidepressant ($p<0.0001$).

The relationship between duration of treatment and the type of antidepressant has been assessed in other studies. Comparable trends seem to emerge across international borders. The newer generation antidepressants, in particular SSRIs, seem to be used for longer

periods of time than the older TCAs. This has been observed in Australian, British, European and American studies (McCombs et al, 1999; Lawrenson et al, 2000; Hansen et al, 2004; McManus et al, 2004). The available South African studies also showed that older TCAs were more likely to be prescribed once-off compared to fluoxetine (Kairuz et al, 2003). Reasons proposed for this include that the newer generation antidepressants have a better adverse effect profile than the older TCAs and therefore result in better compliance (Lawrenson et al, 2000; Hansen et al, 2004). In addition, patient knowledge and education offered on their disease state was suggested to improve compliance (McCombs et al, 1999). The factors affecting patient compliance could not be ascertained from the nature of our study. In addition, the prescriber influences on the duration of treatment could also not be attained from the nature of this data. A future study examining patient and prescriber factors affecting adherence, duration and compliance of antidepressant therapy would elicit a deeper understanding of why duration of treatment with an antidepressant remains low.

The components of our data did allow us to study the patient's demographic and clinical factors affecting the duration of treatment. This will be discussed in the next section (Section 8.3).

8.3 FACTORS AFFECTING DURATION OF TREATMENT

The previous section (Section 8.2.4) discussed the short rate of duration of treatment with an antidepressant and its relation to the type of antidepressant used. This section (Section 8.3) will comment on whether a patient's age, gender or diagnosis affected whether they receive the drug once or more than once. The reasons for looking at this aspect in a binary manner (once or more than once) lies in the fact that that the number of patients who received an adequate duration of treatment (six months or longer) was small (approximately 13% in both samples). The researcher, therefore, undertook to examine if

once-off or repeat treatment was affected by certain demographic and clinical factors and not distinguish between adequate and non-adequate duration of treatment.

The limitations of this study need to be considered in the light of the findings presented below. Please refer to Section 8.4 for a discussion on the limitations.

8.3.1 AGE

Elderly patients who visit their health care practitioner more often have shown better adherence to medication regimens (Mansur et al, 2008). This would suggest that increased visits to a physician would have the implication of re-filling prescriptions and an opportunity for the dispenser to provide more information regarding adherence and returning for a repeat prescription. Our study sought to determine if an increase in age had this implication for antidepressants usage.

In Section 8.2.1 an explanation was given for why the variable, age, was handled in two distinct manners. In this section (Section 8.3.1), age, was statistically tested in two ways as well: as a continuous and categorical variable. When age was tested as a continuous variable, a significant outcome was observed in Sample A and B ($p<0.0001$). The clinically meaningfulness of the results was brought into question again. The mean age of users of antidepressants once-off and repeat users were numerically discernible and ranged between 40 and 49. This difference, however, has little clinical meaning. The age of a patient was, therefore categorized as explained in the methodology (Section 5.3.3.2).

Sample A produced a significant outcome ($p<0.0001$) and showed that elderly patients (65 years and older) accounted for the age category with the most number or repeat visits (80.93%, n=437). Other patient age groups' repeat rate ranged from as little as 17% of children (0-12 years) to 45% of adults (17 – 65 years). The difference in the number of return visits across the age categories was statistically significant. Elderly patients were

19.70 times (95%CI 10.64 - 36.48; p<0.0001)) more likely to return for a repeat prescription of an antidepressant compared to children. Adults were 3.79 times (95%CI 2.13 - 6.77; p<0.0001) more likely to return for a repeat prescription compared to children.

Sample B, however, showed that children, adolescents and the elderly were more likely to return for a repeat prescription of an antidepressant. Because children (n=6) and adolescents (n=4) accounted formed a small proportion of the total sample. Their results, therefore, cannot be considered as a more generalized trend. Elderly patients, however, displayed increased return visits (67.09%, n=53) compared to adults (46.15%, n=533). This difference was statistically significant (p<0.05).

International studies have mirrored this pattern. Elderly patients were observed to have received more prescriptions for antidepressants in European and Australian studies (McGettigan et al, 2000; McManus et al, 2004;Parabiaghi et al, 2011). Reasons for increased duration of treatment amongst the elderly have been suggested to be associated with more likeliness of receiving ongoing treatment for other chronic disorders. This has the effect of building habitual patterns of taking medicines and returning for repeats (McGettigan et al, 2000). Patients with other chronic illnesses were also associated with longer duration of antidepressant treatment in another study (Serna et al, 2010).

A Finnish study found conflicting results to our study. It was observed that older patients were associated with using antidepressants on a short-term basis (this was defined as one or two months). This study, however, used a survey method to determine patterns of antidepressant utilization and sited under-reporting and lack of awareness by the elderly as a reason for the outcome (Sihvo et al, 2008). In addition, elderly patients have been regarded as less compliant when taking medications due to the larger number of concomitant medications, cognitive impairment and physical decline (Gellad et al, 2011; Campbell et al, 2012).

The results of this study show that elderly age is associated with returning for a repeat prescription for an antidepressant. The reasons for this may include increased visits to the physician and better adherence patterns drawn from previous experience with other chronic illnesses. Adherence and following recommended guidelines on usage of drugs is a complex and multi-faceted subject. It is likely that age combined with many other factors is likely to influence a patient's return for further prescriptions.

8.3.2 GENDER

Gender plays a role in determining health-seeking behaviour. Females have been suggested to display increased health-seeking tendencies (Fleury et al, 2012). Health-seeking behaviour may have the implication of displaying increased tendencies to follow recommended directions of drug use. Our study sought to elicit an association between gender and repeat prescriptions for an antidepressant. The findings will be discussed in this section (Section 8.3.2).

Sample A and B found a non-significant relationship between gender and whether patients receive a prescription for an antidepressant once or more than once ($p>0.05$). This is a finding contrary to many other studies. An Australian study researched antidepressant use in the 'continuation phase' of treatment and found that females represented a majority of patients on 'continuation phase' of antidepressant therapy (McManus et al, 2004). A Spanish study found that males displayed shorter treatment periods (Serna et al, 2010). This study noted that efficacy of antidepressants is equal in both genders and that lower efficacy could not account for discontinuation in males. Other factors such as: personality, stigma, collapse of the therapeutic partnership and negative attitude concerning the value of treatment could account for the higher rate of antidepressant discontinuation amongst males (Serna et al, 2010).

There have been studies which have concurred with our findings and found no association between gender and whether a patient continues with antidepressant therapy or not

(McGettigan et al, 2000; Hansen et al, 2004; Sihvo et al, 2008; Burton et al, 2012). These studies listed other reasons for discontinuation of antidepressant treatment. Factors such as: socio-economic status, prescriber work load and practice, patient's age, diagnosis, dosage level and medical history were listed as reasons significantly associated with duration of treatment with an antidepressant (McGettigan et al, 2000; Hansen et al, 2004; Sihvo et al, 2008; Burton et al, 2012). Our study did not include information on some of the factors mentioned above. Our data did not assess socio-economic status of the patient, prescriber factors and antidepressant dosage. Information on a patient's age and diagnosis was available for comparison. Section 8.3.1 detailed the relation between age and duration of treatment with an antidepressant. The next section (Section 8.3.3) will discuss whether a patient's diagnosis affected their duration of therapy.

8.3.3 DIAGNOSIS

When treating a psychiatric condition, in particular an affective disorder, recommended guidelines suggest continuing antidepressant therapy for a minimum of six months (American Psychiatric Association, 2006). When treating anxiety, the South African Department of Health directs physicians to treat patients with a chronic form of anxiety on the maintenance phase of therapy for a minimum of six months (Department of Health, 2006). Acute anxiety is treated for six weeks (Department of Health, 2006). If a patient has a psychiatric disorder, in particular an affective disorder, treatment with an antidepressant should be for a minimum of six months. The different indications of an antidepressant dictate different instructions of use.

The indications for the older generation of antidepressants, TCAs, are wide. These indications are discussed in 2.1.2. Usage of TCAs in treating non-psychiatric disorders follows different directions of use. When treating pain, in particular, their usage may be limited to the presence of the condition. In which case, once-off treatment may be adequate. In addition, certain newer drugs like venlafaxine are increasingly being recognized (Dharmshaktu et al, 2012) for their efficacy in treating neuropathic pain.

A patient's diagnosis may therefore affect the pattern of duration of antidepressant use. To determine if a patient's diagnosis had an effect on whether they returned for a repeat or not will be further elaborated upon in this section (Section 8.3.3).

Sample A showed that a diagnosis does affect whether a patient will return for a repeat prescription or not. Over 60% of patients with a psychiatric diagnosis returned for a repeat prescription of an antidepressant. This number is contrasted with patients who had a pain-related diagnosis or 'other'. Patients in these two categories showed a return rate of approximately 38%. This difference was statistically significant ($p<0.0001$). On logistic regression model, patients with a psychiatric diagnosis were 2.77 times (95% CI 2.45 - 3.13; $p<0.0001$) more likely to receive a repeat prescription for an antidepressant.

Patients in Sample A with a diagnosis for a psychiatric condition were included in another category and grouped according to their psychiatric diagnosis as explained in Section 5.3.3.2 Patients with an affective, sleep disorder and those receiving psychiatric counselling accounted for users with the highest number of repeat prescriptions (78.3%, n=386 for affective disorders; 70.59%, n=72 for sleep disorders; 84.62%, n=11 for psychiatric counselling). Patients with an anxiety-related condition or stress displayed the lowest rate of return for a repeat (58.96%, n=1 003). Patients with an affective disorder were 2.55 times (95%CI 2.01 - 3.23; $p<0.0001$) more likely to return for a repeat prescription.

Sample B displayed a similar trend, approximately 60% of patients with a psychiatric disorder returned for a repeat prescription. This is compared to around 40% of patients with a pain-related disorder or 'other'. The logistic regression model showed that patients with a psychiatric disorder were 2.21 times (95%CI 1.60 - 3.05, $p<0.0001$) more likely to receive more than once prescription for an antidepressant.

When observing the trends amongst patients with a psychiatric disorder. Patients in Sample B with an affective were only slightly more likely (OR1.76; 95% CI 1.18 - 2.63; $p<0.05$) to return for a repeat prescription compared to those with an anxiety-related condition or stress. All patients with a sleep disorder received the drug once. The glaring difference between samples, with regards to this category, seems to be the prescriptions for a sleep disorder. Patients in Sample A with a sleep disorder showed high return rates for a repeat prescription (70.59%, n=72). These patients may be having a sleep disorder related to an affective disorder as well but the diagnosis for an affective disorder may still be under consideration by the prescriber. Alternatively, the diagnosis from a patient's initial visit may have been carried through to subsequent visits.

The relationship between a patient's diagnosis and their duration of treatment with an antidepressant has been studied in international papers. Patient's with a psychiatric disorder or a history of a psychiatric disorders have been found to continue antidepressant treatment for longer of periods of time than those with a diagnosis for another disorder (Sihvo et al, 2008; Burton et al, 2012). Sample A and B displayed a trend that suggested that a patient's diagnosis did affect the duration of treatment with an antidepressant. Patient's with a psychiatric diagnosis were more likely to return for a repeat prescription. The distribution of diagnoses can also account for the low duration of treatment patterns seen in Sample A and B. Pain and 'other' diagnoses represented a majority of diagnoses in these samples and use of antidepressants in these situations on a once-off or self-limited basis may be warranted.

Patient's with a psychiatric diagnosis being an affective disorder displayed a high return rate of just under 80% in Sample A and approximately 64% in Sample B. These are proportions which are seen in other studies. Reported continuation of antidepressant in MDD has been noted to range from 50 to 75% (McGettigan et al, 2000; Hansen et al, 2004; Hansen et al, 2007; Burton et al, 2012). One study suggested that this proportion may be substantiated as general physicians see patients who are less severely depressed and that the recommended guidelines of continuing treatment for a minimum of six months may not be essential in general practice (McManus et al, 2004). But a consistent theme emerges of continuing prescriber education on the duration of treatment with an

antidepressant when treating an affective disorder and emphasizing upon patient education on compliance (McGettigan et al, 2000; Hansen et al, 2004; Serna et al, 2010; Burton et al, 2012).

When looking at the factors that influence duration of treatment with an antidepressant, Sihvo et al (2008) suggests looking at the 'whole picture' and not restricting data to patients with only a diagnosis of depression or utilizing data which omits the diagnostic factor. The analyses of Sample A and B sought to provide reasons attached to the duration of treatment of antidepressants. Although the capacity of the data and study design did not permit the study of certain key areas such as prescriber factors and patient's attitudes and socio-economic factors related to duration of treatment, this study was able to highlight the importance of diagnosis (further limitations of the study are discussed in Section 8.4). A patient's diagnosis provides a wealth of information and should not be ignored when assessing the utilization of drugs or the utilization patterns of drugs.

8.4 LIMITATIONS

The findings of this study need to be considered within the light of the limitations of the study design and the nature of the data.

- **Variability between two data warehousing companies**

The study consisted of the retrospective review of the utilization pattern of antidepressants in two distinct samples. The two samples were acquired from different medical data warehousing companies over different time periods. Acquiring data from different companies has the potential of increasing the variability of data fields. The positivity of the two datasets acquired lies in the fact that both samples included data fields that were comparable. The only identifiable difference was that Dataset B did not include costing fields (charges to the patient and charges to the medical aid) or information on the type of doctor utilizing the software. The researcher therefore did not consider these factors in the study. The economics of antidepressant utilization is an interesting research topic. The role of medical aid formularies and their effect on prescribing drugs, which are re-imbursable is a valuable frontier in the study of drug utilization patterns. This study did not comment on this.

- **Existing databases**

When utilizing existing databases in research a limit is placed upon the number of factors available for comment. The nature of database information does not include socio-demographic or socio-economic factors. In the study of drugs used in treating psychiatric disorders these factors may be of particular interest.

- **Broad trends**

In addition, databases provide no insight into the thoughts and motivations of prescribers. Instances where diversions from recommended guidelines occur cannot be considered

warranted on the basis of this format of study. Instead, drug utilization reviews identify broad trends and not individualized or specific appropriateness of use.

- **Reliability of existing databases**

Existing databases also have the limitation placed upon the reliability of the data. Data captured in a database is not put under any process control by researchers and therefore data may be missing from certain fields or pose the danger of being incorrect. There is no measure in controlling this limitation. Even though, medical data software is a product paid for by professionals to aid in record keeping and administration, the possibility of falsely entered or missing information occurs. In addition, information from patients' previous visits may carry through to subsequent visits and patient visits to other health care facilities will not be captured.

- **Prescribing instruction**

The most unfortunate limitation of this study is that the data did not include prescriber instructions on antidepressant use. The researcher could not deduce the dosage and directions of use. This made the task of comparing the Prescribed Daily Dose (PDD) against the Defined Daily Dose (DDD) impossible. The World Health Organization Collaborating Centre for Drug Statistics (WHOCC) also recommends using the Anatomical Therapeutic Chemical (ATC) and DDD methodology when conducting a DUR. The aim of the ATC/DDD methodology is to allow for comparisons of utilization studies across countries and settings over different time periods. This study provides a limitation in that the utilization patterns in our samples may not be available for statistical comparison against other utilization studies. As valuable as this exercise is, it was not the initial aim of this study. The aim of the study was in providing an understanding of why South African patterns of antidepressant usage favours the older generation of antidepressants, the TCAs. This pattern of usage is vastly different from international trends which favour SSRI usage. This study is only available for descriptive comparison and not statistical comparison.

- **Treatment compliance**

In addition, this study aimed to consider the factors associated with the duration of treatment with an antidepressant. Again, this component did not include personalized perceptions of patients and prescribers. When considering treatment compliance and adherence to recommended guidelines a more thematic and individualized approach may prove beneficial. The unwanted adverse effects, stigma, value of treatment, self-limited symptoms and the economic burden of antidepressant use are just some of the themes which may emerge when considering antidepressant discontinuation.

When considering the duration of treatment with antidepressants, information on repeat prescriptions that were have been obtained elsewhere was not available. Prescriptions filled in a pharmacy or at another dispensing doctor were not represented in the data.

- **Prescribing factors**

This study looked at data from dispensing doctors. The drugs prescribed were most likely an indication of the medicine stock of the medical practice. A limitation of this study is that it did not look at the factors which regulate what stock is kept (economic factors, formularies and demand).In addition, this study could not account for all the factors affecting the type of antidepressant used or the duration of treatment. It is difficult for any study to account for all the factors as prescribing is a dynamic process and influenced by factors that are continuously changing and emerging. However, the possibility of continuing this study and determining what other factors may influence the choice of antidepressant prescribed and the duration of treatment with an antidepressant within the framework of a different study design would provide more insight into these multi-faceted subjects. This will be discussed in the next Section 9.1.

The marvellous richness of human experience would lose something of rewarding joy if there were no limitations to overcome

-Helen Keller

CHAPTER 9: CONCLUSION

This study has shown that the older generation of antidepressants, the tricyclics (TCAs), accounted for the majority of antidepressant prescriptions in sectors of the South African prescribing market. Females formed the majority of users and a large proportion of prescriptions were related to a pain condition.

The type of antidepressant prescribed was affected by a patient's diagnosis, psychiatric condition and age. Gender had no effect on the type of antidepressant prescribed. These findings suggest that diagnostic thought plays a key role in determining the type of antidepressant prescribed. This is a promising factor and commendable on the part of prescribers.

Duration of treatment with an antidepressant according to local and international guidelines, however, falls short in our study samples. The number of repeat prescriptions is far below recommended guidelines and is affected by the type of antidepressant prescribed, age and diagnosis. The categories of patients identified as once-off users of antidepressants are: patients less than 65 years and with a psychiatric condition being an anxiety-related disorder deserve special and added intervention in continuing treatment as recommended. Further recommendations of the study are elaborated upon in the next section.

9.1 RECOMMENDATIONS

Future studies that also look at antidepressant utilization patterns should consider adopting a qualitative component which interviews and surveys prescribers and patients on what factors affect their choice of antidepressant and the duration of treatment with an antidepressant.

When considering utilization of drugs, it is always of importance to include information on a patient's diagnosis. This is especially of interest when studying drugs with a broad indication of use or attached stigma, such as antidepressants. Considering only patients with a diagnosis of depression does not provide an accurate representation of antidepressant use. This reasoning would extend to other drug utilization studies such as anti-retrovirals, psychotropics and anti-infectives. Future DURs should ideally always consider clinical information such as a patient's diagnosis.

A future DUR on antidepressants would also benefit from a more holistic approach and include co-prescriptions, co-morbidities and a component that looks at whether co-morbidities are related to the pharmacological adverse effects of the antidepressants. For example do drugs which cause dry mouth result in dental problems in the patient? Are drugs which cause weight gain showing an increased in Type II diabetes?

In light of the findings of this study, recommendations on continued education on the appropriate use of antidepressants needs to be emphasized. Utilizing antidepressants for the appropriate length of treatment needs to be stressed. Patients and prescribers need to be aware of the importance of continuing treatment according to recommended guidelines.

In addition, the continued use of TCA amongst the elderly requires a degree of caution. The potentially dangerous adverse effects of these drugs need to be considered before

prescribing them. Education and information addressed at prescribers in identifying high-risk patients (elderly and suicidal) needs to be encouraged.

Drug utilization is an evolving process and it is recommended that studies assessing utilization patterns of drugs should be a continual process. Changes over time are expected and what influences this change is a valuable tool in our understanding of drug usage. It is easy to assume that utilization patterns of antidepressants in South Africa will eventually follow international trends but only continual studies will highlight the truth in this or identify the distinctive and unique nature of our drug usage patterns.

APPENDICES

APPENDIX 1A – ETHICAL CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Laher

CLEARANCE CERTIFICATE **PROTOCOL NUMBER M080615**

PROJECT A Drug Utilisation Review of Antidepressants in a South African Medical Aid Population

INVESTIGATORS Miss S Laher

DEPARTMENT Pharmacy & Pharmacology

DATE CONSIDERED 08.06.27

DECISION OF THE COMMITTEE* Approved subject obtaining and submitting written permission from the Medical Aid Company to access client records

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08.06.30 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Mrs S Moch

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 1B

Table A1b Listing of antidepressant drugs with South African National Pharmaceutical Product Index(NAPPI) codes and branding according to the Monthly Index of Medical Specialities (MIMS) February 2011

NAPPI code	Drug	Dosage	Dosage form	Brand
703419-006	Clomipramine	10mg	Tabs	Original
703427-009	Clomipramine	25mg	Tabs	Original
781193-001	Clomipramine	75mg	SR Tabs	Original
703400-002	Clomipramine	25mg	Inj	Generic
703381-001	Clomipramine	25mg	Tabs	Generic
723002-002	Lofepramine	70mg	Tabs	Original
723002-010	Lofepramine	70mg	Tabs	Original
847410-005	Clomipramine	10mg	Tabs	Generic
847429-008	Clomipramine	25mg	Tabs	Generic
724661-107	Imipramine	10mg	Tabs	Generic
724661-115	Imipramine	10mg	Tabs	Generic
724688-102	Imipramine	25mg	Tabs	Generic
724688-110	Imipramine	25mg	Tabs	Generic
757888-003	Dothiepin	25mg	Caps	Original
784230-005	Amitriptyline	25mg	Tabs	Generic
784230-013	Amitriptyline	25mg	Tabs	Generic
816515-018	Dothiepin	75mg	Tabs	Generic
820660-019	Dothiepin	25mg	Caps	Generic
800198-018	Dothiepin	25mg	Caps	Generic
800201-019	Dothiepin	75mg	Tabs	Generic
771120-001	Imipramine	10mg	Tabs	Original
771139-004	Imipramine	25mg	Tabs	Original
772003-009	Amitriptyline	10mg	Tabs	Generic
772003-017	Amitriptyline	10mg	Tabs	Generic
771996-004	Amitriptyline	25mg	Tabs	Generic
771996-012	Amitriptyline	25mg	Tabs	Generic
772860-009	Amitriptyline	25mg	Tabs	Generic

NAPPI code	Drug	Dosage	Dosage form	Brand
772364-001	Trimipramine	25mg	Tabs	Generic
772356-009	Trimipramine	50mg	Caps	Generic
735795-002	Mianserin	10mg	Tabs	Generic
735795-010	Mianserin	10mg	Tabs	Generic
735795-029	Mianserin	10mg	Tabs	Generic
735817-022	Mianserin	30mg	Tabs	Generic
735817-014	Mianserin	30mg	Tabs	Generic
752975-013	Tranylcypromine	10mg	Tabs	Generic
897213-009	Moclobemide	150mg	Tabs	Generic
702008-001	Moclobemide	300mg	Tabs	Generic
703391-001	Fluoxetine	20mg	Caps	Generic
704904-001	Paroxetine	20mg	Tabs	Generic
702796-001	Citalopram	20mg	Tabs	Generic
707606-011	Sertraline	50mg	Tabs	Generic
791571-009	Paroxetine	20mg	Tabs	Original
703219-001	Paroxetine	30mg	Tabs	Original
704647-001	Paroxetine	12.5mg	Tabs	Original
704646-001	Paroxetine	25mg	Tabs	Original
713583-001	Citalopram	20mg	Tabs	Generic
713548-001	Citalopram	40mg	Tabs	Generic
712093-001	Sertraline	50mg	Tabs	Generic
712092-001	Sertraline	100mg	Tabs	Generic
712959-001	Escitalopram	10mg	Tabs	Generic
707396-001	Citalopram	10mg	Tabs	Generic
707398-001	Citalopram	20mg	Tabs	Generic
707397-001	Citalopram	40mg	Tabs	Generic
707399-001	Paroxetine	20mg	Tabs	Generic
707400-001	Paroxetine	30mg	Tabs	Generic
707294-001	Sertraline	50mg	Tabs	Generic
707293-001	Sertraline	100mg	Tabs	Generic
707888-001	Citalopram	20mg	Tabs	Generic
700157-001	Citalopram	20mg	Tabs	Generic

NAPPI code	Drug	Dosage	Dosage form	Brand
703232-001	Escitalopram	10mg	Tabs	Original
709647-001	Escitalopram	20mg	Tabs	Original
810622-009	Citalopram	20mg	Tabs	Original
704331-001	Citalopram	20mg	Tabs	Generic
709407-001	Citalopram	20mg	Tabs	Generic
709644-001	Citalopram	40mg	Tabs	Generic
711214-001	Escitalopram	10mg	Tabs	Generic
711215-001	Escitalopram	20mg	Tabs	Generic
704792-001	Paroxetine	20mg	Tabs	Generic
704328-001	Citalopram	20mg	Tabs	Generic
705252-001	Citalopram	40mg	Tabs	Generic
894303-007	Fluoxetine	20mg	Tabs	Generic
713445-001	Citalopram	20mg	Tabs	Generic
713757-001	Citalopram	40mg	Tabs	Generic
706443-001	Fluvoxamine	100mg	Tabs	Generic
704840-001	Fluvoxamine	100mg	Tabs	Generic
710374-001	Escitalopram	5mg	Tabs	Generic
710303-001	Escitalopram	10mg	Tabs	Generic
710304-001	Escitalopram	20mg	Tabs	Generic
820016-004	Fluoxetine	20mg	Caps	Generic
821063-006	Fluoxetine	20mg	Caps	Generic
700877-003	Fluoxetine	20mg	Tabs	Generic
805203-028	Fluvoxamine	100mg	Tabs	Original
714012-001	Escitalopram	10mg	Tabs	Generic
714013-001	Escitalopram	20mg	Tabs	Generic
840653-018	Fluoxetine	20mg	Caps	Generic
705186-001	Paroxetine	20mg	Tabs	Generic
704794-001	Paroxetine	20mg	Tabs	Generic
879282-010	Fluoxetine	20mg	Tabs	Generic
894243-001	Fluoxetine	20mg	Dispers.Tabs	Generic
894249-002	Fluoxetine	40mg	Dispers.Tabs	Generic
757969-011	Fluoxetine	20mg	Caps	Original

NAPPI code	Drug	Dosage	Dosage form	Brand
822981-017	Fluoxetine	40mg	Tabs	Original
700686-001	Fluoxetine	20mg	Caps	Generic
707426-001	Fluoxetine	20mg	Caps	Generic
704590-001	Citalopram	20mg	Tabs	Generic
838713-009	Fluoxetine	20mg	Caps	Generic
838713-017	Fluoxetine	20mg	Caps	Generic
705420-001	Sertraline	50mg	Tabs	Generic
703132-001	Sertraline	50mg	Tabs	Generic
703999-001	Sertraline	100mg	Tabs	Generic
705122-001	Paroxetine	20mg	Tabs	Generic
705123-001	Paroxetine	30mg	Tabs	Generic
709904-001	Sertraline	50mg	Tabs	Generic
703992-001	Sertraline	50mg	Tabs	Generic
703993-001	Sertraline	100mg	Tabs	Generic
707304-001	Citalopram	20mg	Tabs	Generic
705174-001	Fluoxetine	20mg	Caps	Generic
705633-001	Paroxetine	20mg	Tabs	Generic
868833-002	Sertraline	50mg	Tabs	Original
705064-001	Fluoxetine	20mg	Caps	Generic
703911-002	Duloxetine	30mg	Caps	Original
703910-002	Duloxetine	60mg	Caps	Original
713705-001	Duloxetine	30mg	Caps	Generic
712786-001	Duloxetine	60mg	Caps	Generic
852937-008	Venlafaxine	75mg	Caps	Original
853945-019	Venlafaxine	150mg	Caps	Original
713648-001	Venlafaxine	37.5mg	Tabs	Generic
713649-001	Venlafaxine	75mg	Tabs	Generic
713650-001	Venlafaxine	150mg	Tabs	Generic
710972-001	Venlafaxine	37.5mg	Tabs	Generic
710973-001	Venlafaxine	75mg	Tabs	Generic
710742-001	Venlafaxine	75mg	Caps	Generic
710743-001	Venlafaxine	150mg	Caps	Generic

NAPPI code	Drug	Dosage	Dosage form	Brand
706399-001	Venlafaxine	37.5mg	Caps	Generic
706402-001	Venlafaxine	75mg	Caps	Generic
706404-001	Venlafaxine	150mg	Caps	Generic
708239-001	Mirtazapine	15mg	Tabs	Generic
708242-001	Mirtazapine	30mg	Tabs	Generic
709692-001	Mirtazapine	15mg	Tabs	Generic
709693-001	Mirtazapine	30mg	Tabs	Generic
714596-001	Trazodone	50mg	Caps	Generic
714597-001	Trazodone	100mg	Caps	Generic
710528-001	Mirtazapine	15mg	Tabs	Generic
710529-001	Mirtazapine	30mg	Tabs	Generic
864420-005	Reboxetine	4mg	Tabs	Original
726656-003	Flupenthixol	0.5mg	Tabs	Generic
726664-006	Flupenthixol	1mg	Tabs	Generic
744417-007	Trazodone	50mg	Caps	Generic
744425-018	Trazodone	100mg	Caps	Generic
710802-001	Mirtazapine	15mg	Tabs	Generic
710803-001	Mirtazapine	30mg	Tabs	Generic
897760-018	Mirtazapine	15mg	Tabs	Generic
842958-002	Mirtazapine	30mg	Tabs	Generic
707189-001	Mirtazapine	15mg	Tabs	Generic
707190-001	Mirtazapine	30mg	Tabs	Generic
704070-001	Buproprion	150mg	SR Tabs	Original
711008-001	Buproprion	150mg	XL Tabs	Original
711009-001	Buproprion	300mg	XL Tabs	Original
703419-006	Clomipramine	10mg	Tabs	Original
703427-009	Clomipramine	25mg	Tabs	Original
781193-001	Clomipramine	75mg	SR Tabs	Original
703400-002	Clomipramine	25mg	Inj	Generic
703381-001	Clomipramine	25mg	Tabs	Generic
723002-002	Lofepramine	70mg	Tabs	Original
723002-010	Lofepramine	70mg	Tabs	Original

NAPPI code	Drug	Dosage	Dosage form	Brand
847410-005	Clomipramine	10mg	Tabs	Generic
847429-008	Clomipramine	25mg	Tabs	Generic
724661-107	Imipramine	10mg	Tabs	Generic
724661-115	Imipramine	10mg	Tabs	Generic
724688-102	Imipramine	25mg	Tabs	Generic
724688-110	Imipramine	25mg	Tabs	Generic
757888-003	Dothiepin	25mg	Caps	Original
784230-005	Amitriptyline	25mg	Tabs	Generic
784230-013	Amitriptyline	25mg	Tabs	Generic
816515-018	Dothiepin	75mg	Tabs	Generic
820660-019	Dothiepin	25mg	Caps	Generic
800198-018	Dothiepin	25mg	Caps	Generic
800201-019	Dothiepin	75mg	Tabs	Generic
771120-001	Imipramine	10mg	Tabs	Original
771139-004	Imipramine	25mg	Tabs	Original
772003-009	Amitriptyline	10mg	Tabs	Generic
772003-017	Amitriptyline	10mg	Tabs	Generic
771996-004	Amitriptyline	25mg	Tabs	Generic
771996-012	Amitriptyline	25mg	Tabs	Generic
772860-009	Amitriptyline	25mg	Tabs	Generic
772364-001	Trimipramine	25mg	Tabs	Generic
772356-009	Trimipramine	50mg	Caps	Generic
735795-002	Mianserin	10mg	Tabs	Generic
735795-010	Mianserin	10mg	Tabs	Generic
735795-029	Mianserin	10mg	Tabs	Generic
735817-022	Mianserin	30mg	Tabs	Generic
735817-014	Mianserin	30mg	Tabs	Generic
752975-013	Tranylcypromine	10mg	Tabs	Generic
897213-009	Moclobemide	150mg	Tabs	Generic
702008-001	Moclobemide	300mg	Tabs	Generic
703391-001	Fluoxetine	20mg	Caps	Generic
704904-001	Paroxetine	20mg	Tabs	Generic

NAPPI code	Drug	Dosage	Dosage form	Brand
702796-001	Citalopram	20mg	Tabs	Generic
707606-011	Sertraline	50mg	Tabs	Generic
791571-009	Paroxetine	20mg	Tabs	Original
703219-001	Paroxetine	30mg	Tabs	Original
704647-001	Paroxetine	12.5mg	Tabs	Original
704646-001	Paroxetine	25mg	Tabs	Original
713583-001	Citalopram	20mg	Tabs	Generic
713548-001	Citalopram	40mg	Tabs	Generic
712093-001	Sertraline	50mg	Tabs	Generic
712092-001	Sertraline	100mg	Tabs	Generic
712959-001	Escitalopram	10mg	Tabs	Generic
707396-001	Citalopram	10mg	Tabs	Generic
707398-001	Citalopram	20mg	Tabs	Generic
707397-001	Citalopram	40mg	Tabs	Generic
707399-001	Paroxetine	20mg	Tabs	Generic
707400-001	Paroxetine	30mg	Tabs	Generic
707294-001	Sertraline	50mg	Tabs	Generic
707293-001	Sertraline	100mg	Tabs	Generic
707888-001	Citalopram	20mg	Tabs	Generic
700157-001	Citalopram	20mg	Tabs	Generic
703232-001	Escitalopram	10mg	Tabs	Original
709647-001	Escitalopram	20mg	Tabs	Original
810622-009	Citalopram	20mg	Tabs	Original
704331-001	Citalopram	20mg	Tabs	Generic
709407-001	Citalopram	20mg	Tabs	Generic
709644-001	Citalopram	40mg	Tabs	Generic
711214-001	Escitalopram	10mg	Tabs	Generic
711215-001	Escitalopram	20mg	Tabs	Generic
704792-001	Paroxetine	20mg	Tabs	Generic
704328-001	Citalopram	20mg	Tabs	Generic
705252-001	Citalopram	40mg	Tabs	Generic
894303-007	Fluoxetine	20mg	Tabs	Generic

NAPPI code	Drug	Dosage	Dosage form	Brand
713445-001	Citalopram	20mg	Tabs	Generic
713757-001	Citalopram	40mg	Tabs	Generic
706443-001	Fluvoxamine	100mg	Tabs	Generic
704840-001	Fluvoxamine	100mg	Tabs	Generic
710374-001	Escitalopram	5mg	Tabs	Generic
710303-001	Escitalopram	10mg	Tabs	Generic
710304-001	Escitalopram	20mg	Tabs	Generic
820016-004	Fluoxetine	20mg	Caps	Generic
821063-006	Fluoxetine	20mg	Caps	Generic
700877-003	Fluoxetine	20mg	Tabs	Generic
805203-028	Fluvoxamine	100mg	Tabs	Original
714012-001	Escitalopram	10mg	Tabs	Generic
714013-001	Escitalopram	20mg	Tabs	Generic
840653-018	Fluoxetine	20mg	Caps	Generic
705186-001	Paroxetine	20mg	Tabs	Generic
704794-001	Paroxetine	20mg	Tabs	Generic
879282-010	Fluoxetine	20mg	Tabs	Generic
894243-001	Fluoxetine	20mg	Dispers.Tabs	Generic
894249-002	Fluoxetine	40mg	Dispers.Tabs	Generic
757969-011	Fluoxetine	20mg	Caps	Original
822981-017	Fluoxetine	40mg	Tabs	Original
700686-001	Fluoxetine	20mg	Caps	Generic
707426-001	Fluoxetine	20mg	Caps	Generic
704590-001	Citalopram	20mg	Tabs	Generic
838713-009	Fluoxetine	20mg	Caps	Generic
838713-017	Fluoxetine	20mg	Caps	Generic
705420-001	Sertraline	50mg	Tabs	Generic
703132-001	Sertraline	50mg	Tabs	Generic
703999-001	Sertraline	100mg	Tabs	Generic
705122-001	Paroxetine	20mg	Tabs	Generic
705123-001	Paroxetine	30mg	Tabs	Generic
709904-001	Sertraline	50mg	Tabs	Generic

NAPPI code	Drug	Dosage	Dosage form	Brand
703992-001	Sertraline	50mg	Tabs	Generic
703993-001	Sertraline	100mg	Tabs	Generic
707304-001	Citalopram	20mg	Tabs	Generic
705174-001	Fluoxetine	20mg	Caps	Generic
705633-001	Paroxetine	20mg	Tabs	Generic
868833-002	Sertraline	50mg	Tabs	Original
705064-001	Fluoxetine	20mg	Caps	Generic
703911-002	Duloxetine	30mg	Caps	Original
703910-002	Duloxetine	60mg	Caps	Original
713705-001	Duloxetine	30mg	Caps	Generic
712786-001	Duloxetine	60mg	Caps	Generic
852937-008	Venlafaxine	75mg	Caps	Original
853945-019	Venlafaxine	150mg	Caps	Original
713648-001	Venlafaxine	37.5mg	Tabs	Generic
713649-001	Venlafaxine	75mg	Tabs	Generic
713650-001	Venlafaxine	150mg	Tabs	Generic
710972-001	Venlafaxine	37.5mg	Tabs	Generic
710973-001	Venlafaxine	75mg	Tabs	Generic
710742-001	Venlafaxine	75mg	Caps	Generic
710743-001	Venlafaxine	150mg	Caps	Generic
706399-001	Venlafaxine	37.5mg	Caps	Generic
706402-001	Venlafaxine	75mg	Caps	Generic
706404-001	Venlafaxine	150mg	Caps	Generic
708239-001	Mirtazapine	15mg	Tabs	Generic
708242-001	Mirtazapine	30mg	Tabs	Generic
709692-001	Mirtazapine	15mg	Tabs	Generic
709693-001	Mirtazapine	30mg	Tabs	Generic
714596-001	Trazodone	50mg	Caps	Generic
714597-001	Trazodone	100mg	Caps	Generic
710528-001	Mirtazapine	15mg	Tabs	Generic
710529-001	Mirtazapine	30mg	Tabs	Generic
864420-005	Reboxetine	4mg	Tabs	Original

NAPPI code	Drug	Dosage	Dosage form	Brand
726656-003	Flupenthixol	0.5mg	Tabs	Generic
726664-006	Flupenthixol	1mg	Tabs	Generic
744417-007	Trazodone	50mg	Caps	Generic
744425-018	Trazodone	100mg	Caps	Generic
710802-001	Mirtazapine	15mg	Tabs	Generic
710803-001	Mirtazapine	30mg	Tabs	Generic
897760-018	Mirtazapine	15mg	Tabs	Generic
842958-002	Mirtazapine	30mg	Tabs	Generic
707189-001	Mirtazapine	15mg	Tabs	Generic
707190-001	Mirtazapine	30mg	Tabs	Generic
704070-001	Buproprion	150mg	SR Tabs	Original
711008-001	Buproprion	150mg	XL Tabs	Original
711009-001	Buproprion	300mg	XL Tabs	Original

Tabs = Tablet

SR Tabs = Slow Release Tablets

Inj = Injection

Caps = Capsules

XL tabs = Prolonged Release Tablets

APPENDIX 2

Table A2 Listing of ICD-10 codes with assigned category

Category	ICD-10 Code	Description
0 (Psychiatric)	F31.0 – F31.9	Bipolar Affective Disorder
	F32.0 – F32.9	Major Depressive Episode
	F33.0 – F33.9	Recurrent Depressive Episode
	F41.0 – F41.1	Anxiety Disorders
	F43.0 –F43.2	Reaction to severe stress and Adjustment Disorders
	F48.0 – F48.9	Neurotic Disorders
	F51.0 – F51.9	Nonorganic Sleep Disorders
	F92.0 – F92.9	Mixed Disorder of Conduct and Emotion
	G47.0 – G47.4	Sleep Disorders
	Z56.0 – Z56.9	Problems related to employment or unemployment
	Z63.0 – Z63.9	Problems Relating to Primary Support Group
	Z71.0 – Z71.9	Persons Encountering Health Services for Counselling
	Z73.0 – Z73.9	Problems Related to Life Management Difficulty
1 (Pain)	G43.0 – G43.9	Migraine
	G44.0 – G44.9	Other Headache Syndromes
	G50.0 – G50.9	Trigeminal Nerve Disorders
	G51.0 – G51.9	Facial Nerve Disorders
	G54.0 – G54.9	Nerve Root and Plexus Disorders

Category	ICD-10 Code	Description
1 (Pain)	G56.0 – G56.9	Mononeuropathies of Upper Limb
	G58.0 – G58.9	Other Mononeuropathies
	G62.0 – G62.9	Other Polyneuropathies
	H47.0	Other Disorders of Optic Nerve
	M06.0	Other Rheumatoid Arthritis
	M10.0	Gout
	M13.0	Other Arthritis
	M15.0	Polyarthrosis
	M17.0	Gonarthrosis
	M19.0	Other Arthrosis
	M25.0	Joint Disorders, not specified elsewhere
	M30.0	Polyarteritis nodosa and related conditions
	M43.0	Other deforming dorsopathies
	M47.0	Spondylosis
	M50.0	Cervical Disc Disorders
	M51.0	Other intervertebral disc disorders
	M54.0	Dorsalgia
	M60.0	Myositis
	M62.0	Other disorders of muscle
	M65.0	Synovitis
	M67.0	Other disorders of synovium and tendon
	M71.0	Other bursopathies
	M75.0	Shoulder lesions
	M76.0	Enthesopathies of lower limb, excluding foot

Category	ICD-10 Code	Description
1 (Pain)	M79.0	Other soft tissue disorders, not elsewhere specified
	M94.0	Other disorders of cartilage
	N61.0	Inflammation of breast
	N76.0	Inflammation of vagina
	N94.0	Pain associated with female genital organs and menstruation
	R07.0 – R07.9	Pain in throat and chest
	R10.0	Abdominal and pelvic pain
	R20.0	Paraesthesia of skin
	R30.0	Pain associated with micturition
	R51.0	Headache
	R52.0	Pain, not elsewhere specified
	S13.0	Dislocation, sprain or strain of joints and ligaments at neck level
	S32.0	Fracture of lumbar spine and pelvis
	T00.0	Superficial Injuries Involving multiple body regions
	T09.0	Other injuries of spine and trunk, level unspecified
	T14.0	Injury of unspecified body region
	T30.0	Burn and corrosion of unspecified body region
	W19.0 – W19.9	Unspecified fall
2 (Other)	A03.0 - A03.9	Shigellosis

Category	ICD-10 Code	Description
2 (Other)	A06.0 - A06.9	Amoebiasis
	A08.0 - A08.5	Viral and other specified intestinal infections
	A09.0 - A09.9	Other gastroenteritis and colitis of infectious and unspecified origin
	A25.0 - A25.9	Rat-bite fevers
	A54.0 - A54.9	Gonococcal infection
	A60.0 - A60.9	Anogenital herpesviral [herpes simplex] infection
	B00.0 - B00.9	Herpesviral [herpes simplex] infections
	B01.0 - B01.9	Varicella [chickenpox]
	B02.0 - B02.9	Zoster [herpes zoster]
	B20.0 - B20.9	Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases
	B23.0 - B23.8	Human immunodeficiency virus [HIV] disease resulting in other conditions
	B24.0	Unspecified human immunodeficiency virus [HIV] disease
	B34.0 - B34.9	Viral infection of unspecified site
	C41.0 - C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
	C49.0 - C49.9	Malignant neoplasm of other connective and soft tissue

Category	ICD-10 Code	Description
2 (Other)	C76.0 - C76.8	Malignant neoplasm of other and ill-defined sites
	D64.0 - D64.9	Other anaemias
	D50.0 - D50.9	Iron deficiency anaemia
	E03.0 - E03.9	Other hypothyroidism
	E05.0 - E05.9	Thyrotoxicosis [hyperthyroidism]
	E10.0	Insulin-dependent diabetes mellitus
	E11.0	Non-insulin-dependent diabetes mellitus
	E13.0	Other specified diabetes mellitus
	E14.0	Unspecified diabetes mellitus
	E23.0 - E23.7	Hypofunction and other disorders of pituitary gland
	E28.0 - E28.9	Ovarian dysfunction
	E78.0 - E78.9	Disorders of lipoprotein metabolism and other lipidaemias
	F52.0 – F52.9	Sexual dysfunction, not caused by organic disorder or disease
	G03.0 - G03.9	Meningitis due to other and unspecified causes
	G20.0	Parkinson's disease
	G25.0 - G25.9	Other extrapyramidal and movement disorders
	G40.0 - G40.9	Epilepsy
	G58.0 - G58.9	Other mononeuropathies
	G82.0 - G82.5	Paraplegia and tetraplegia

Category	ICD-10 Code	Description
2 (Other)	G83.0 - G83.9	Other paralytic syndromes
	H10.0 - H10.9	Conjunctivitis
	H11.0 - H11.9	Other disorders of conjunctiva
	H60.0 - H60.9	Otitis externa
	H65.0 - H65.9	Nonsuppurative otitis media
	H66.0 - H66.9	Suppurative and unspecified otitis media
	H81.0 - H81.9	Disorders of vestibular function
	I10.0	Essential (primary) hypertension
	I15.0 - I15.9	Secondary hypertension
	I20.0 - I20.9	Angina pectoris
	I25.0 - I25.9	Chronic ischaemic heart disease
	I84.0 - I84.9	Haemorrhoids
	J00.0	Acute nasopharyngitis [common cold]
	J01.0 - J01.9	Acute sinusitis
	J02.0 - J02.9	Acute pharyngitis
	J03.0 - J03.9	Acute tonsillitis
	J06.0 - J06.9	Acute upper respiratory infections of multiple and unspecified sites
	J10.0 - J10.8	Influenza due to other identified influenza virus
	J11.0 - J11.8	Influenza, virus not identified
	J18.0 - J18.9	Pneumonia, organism unspecified

Category	ICD-10 Code	Description
2 (Other)	J20.0 - J20.9	Acute bronchitis
	J21.0 – J21.9	Acute bronchiolitis
	J22.0	Unspecified acute lower respiratory infection
	J32.0 - J32.9	Chronic sinusitis
	J38.0 - J38.7	Diseases of vocal cords and larynx, not elsewhere classified
	J40.0	Bronchitis, not specified as acute or chronic
	J43.0 - J43.9	Emphysema
	J45.0 - J45.9	Asthma
	J47.0	Bronchiectasis
	J92.0 - J92.9	Pleural plaque
	J94.0 - J94.9	Other pleural conditions
	K12.0 - K12.3	Stomatitis and related lesions
	K13.0 - K13.7	Other diseases of lip and oral mucosa
	K21.0 - K21.9	Gastro-oesophageal reflux disease
	K25.0	Gastric ulcer
	K26.0	Duodenal ulcer
	K27.0	Peptic ulcer, site unspecified
	K29.0 - K29.9	Gastritis and duodenitis
	K30.0	Dyspepsia
	K40.0 - K40.9	Inguinal hernia
	K52.0 - K52.9	Other noninfective gastroenteritis and colitis
	K56.0 - K56.7	Paralytic ileus and intestinal obstruction without hernia

Category	ICD-10 Code	Description
2 (Other)	K58.0 - K58.9	Irritable bowel syndrome
	K59.0 - K59.9	Other functional intestinal disorders
	K63.0 - K63.9	Other diseases of intestine
	L01.0 - L01.1	Impetigo
	L02.0 - L02.9	Cutaneous abscess, furuncle and carbuncle
	L05.0 - L05.9	Pilonidal cyst
	L23.0 - L23.9	Allergic contact dermatitis
	L30.0 - L30.9	Other dermatitis
	L50.0 - L50.9	Urticaria
	L70.0 - L70.9	Acne
	L93.0 - L93.2	Lupus erythematosus
	N05.0	Unspecified nephritic syndrome
	N12.0	Tubulo-interstitial nephritis, not specified as acute or chronic
	N30.0 - N30.9	Cystitis
	N34.0 - N34.3	Urethritis and urethral syndrome
	N39.0 - N39.9	Other disorders of urinary system
	N41.0 - N41.9	Inflammatory diseases of prostate
	N48.0 - N48.9	Other disorders of penis
	N64.0 - N64.9	Other disorders of breast
	N73.0 - N73.9	Other female pelvic inflammatory diseases
	N76.0 - N76.8	Other inflammation of vagina and vulva

Category	ICD-10 Code	Description
2 (Other)	N91.0 - N91.5	Absent, scanty and rare menstruation
	N92.0 - N92.6	Excessive, frequent and irregular menstruation
	N93.0 - N93.9	Other abnormal uterine and vaginal bleeding
	N95.0 - N95.9	Menopausal and other perimenopausal disorders
	O16.0	Unspecified maternal hypertension
	R09.0 - R09.8	Other symptoms and signs involving the circulatory and respiratory systems
	R11.0	Nausea and vomiting
	R12.0	Heartburn
	R19.0 - R19.8	Other symptoms and signs involving the digestive system and abdomen
	R21.0	Rash and other nonspecific skin eruption
	R23.0 - R23.8	Other skin changes
	R25.0 - R25.8	Abnormal involuntary movements
	R29.0 - R29.8	Other symptoms and signs involving the nervous and musculoskeletal systems
	R32.0	Unspecified urinary incontinence / Enuresis
	R42.0	Dizziness and giddiness
	R53.0	Malaise and fatigue
	R55.0	Syncope and collapse

Category	ICD-10 Code	Description
2 (Other)	T78.0 - T78.9	Adverse effects, not elsewhere classified
	Z00.0 - Z00.8	General examination and investigation of persons without complaint and reported diagnosis
	Z01.0 - Z01.9	Other special examinations and investigations of persons without complaint or reported diagnosis
	Z32.0	Pregnant state, incidental

APPENDIX 3

Table A3 Frequency of diagnoses for all antidepressants in Dataset A

Diagnosis	**Number**	**%**
Muscle And Joint Disorders	2227	25.16%
Stress	1364	15.38%
Headache	1324	14.96%
Respiratory Disorders	868	9.80%
Anxiety	337	3.78%
Pain Chest	325	3.67%
Pain Abdomen	320	3.61%
Hypertension	300	3.39%
Depressive Recurrent	294	3.30%
Depressive Episodic	196	2.18%
Urinary Tract Disorders	188	2.12%
Gastric Disorders	180	2.03%
Dermatological Disorders	143	1.62%
Sleep Disorder	102	1.15%
Migraine	100	1.13%
Diabetes	78	0.88%
Pain	61	0.69%
Hepres	50	0.56%
Tremor	41	0.46%
Vertigo	41	0.46%
Epilepsy	27	0.30%
Hiv	27	0.30%
Neuralgia	26	0.29%
Injury/Trauma	24	0.27%
Otitis	24	0.27%
Enuresis	21	0.24%
Conjunctivitis	17	0.19%
Hyperlipidemia	13	0.15%
Malaise	13	0.15%
Psychiatric Counselling	13	0.15%

Diagnosis	Number	%
Medical Exam	12	0.14%
Malignancy	11	0.12%
Menopause	11	0.12%
Nausea	11	0.12%
Genital Herpes	10	0.11%
Haemorrhoids	9	0.10%
Pain Menstrual	9	0.10%
Pain Breast	7	0.08%
Sexual Dysfunction	6	0.07%
Pain Genital	5	0.06%
Cardiovascular Disorders	4	0.05%
Angina	3	0.03%
Prostatis	3	0.03%
Hormonal Imbalance	2	0.02%
Hypothyroidism	2	0.02%
Meningitis	2	0.02%
Pain Micturition	2	0.02%
Paralysis	2	0.02%
Anaemia	1	0.01%
Artherosclerosis	1	0.01%
Hernia	1	0.01%
Hyperuricemia	1	0.01%
Mixed Affective	1	0.01%
Syncope	1	0.01%
Varicose Veins	1	0.01%

APPENDIX 4

Table A4 Frequency of diagnoses for tricyclic antidepressants in Dataset A

Diagnosis	**Number**	**%**
Muscle And Joint Disorders	1984	31.58%
Headache	1064	16.94%
Respiratory Disorders	641	10.20%
Stress	455	7.20%
Pain Chest	317	5.05%
Pain Abdomen	308	4.90%
Hypertension	222	3.53%
Anxiety	184	2.90%
Urinary Tract Disorders	140	2.23%
Gastrointestinal Disorders	138	2.20%
Dermatological Disorders	123	1.96%
Migraine	100	1.59%
Sleep Disorders	70	1.11%
Diabetes	67	1.07%
Pain	60	0.96%
Herpes Infections	48	0.76%
Tremor	41	0.65%
Depressive Episode	37	0.59%
Vertigo	28	0.45%
Neuralgia	26	0.41%
Hiv	23	0.37%
Otitis	23	0.37%
Enuresis	21	0.33%
Injury/Trauma	21	0.33%
Psychiatric Counselling	13	0.21%
Conjunctivitis	12	0.19%
Malignancy	11	0.18%
Menopause	11	0.18%
Genital Herpes	10	0.16%
Nausea	10	0.16%

Diagnosis	Number	%
Haemorrhoids	9	0.14%
Malaise	9	0.14%
Pain Menstrual	8	0.13%
Pain Breast	7	0.11%
Depressive Recurrent	6	0.10%
Epilepsy	6	0.10%
Medical Exam	6	0.10%
Pain Genitals	5	0.08%
Angina	3	0.05%
Cardiovascular Disorders	3	0.05%
Prostatis	3	0.05%
Pain Micturition	2	0.03%
Anaemia	1	0.02%
Hernia	1	0.02%
Hormonal Imbalance	1	0.02%
Hyperlipidemia	1	0.02%
Hyperuricemia	1	0.02%
Hypothyroidism	1	0.02%
Meningitis	1	0.02%
Paralysis	1	0.02%
Sexual Dysfunction	1	0.02%
Syncope	1	0.02%
Varicose Veins	1	0.02%

APPENDIX 5

Table A5 Frequency of diagnoses for newer generation antidepressants in Dataset A

Diagnosis	**Number**	**%**
Stress	910	35.39%
Depressive Recurrent	288	11.12%
Headache	260	10.11%
Muscle And Joint Disorders	243	9.45%
Respiratory Disorders	227	8.83%
Depressive Episodic	158	6.07%
Anxiety	153	5.95%
Hypertension	78	3.03%
Urinary Tract Disorders	48	1.87%
Gastrointestinal Disorders	42	1.63%
Sleep Disorders	32	1.24%
Epilepsy	21	0.82%
Dermatological Disorders	20	0.78%
Vertigo	13	0.51%
Hyperlipidemia	12	0.47%
Pain Abdomin	12	0.47%
Diabetes	11	0.43%
Pain Chest	8	0.31%
Medical Exam	6	0.23%
Conjunctivitis	5	0.19%
Hiv	4	0.16%
Malaise	4	0.16%
Injury/Trauma	3	0.12%
Sexual Dysfunction	4	0.16%
Herpes Infections	2	0.08%
Artherosclerosis	1	0.04%
Cardiovascular Disorders	1	0.04%
Hormonal Imbalance	1	0.04%
Hypothyroidism	1	0.04%
Meningitis	1	0.04%

Diagnosis	Number	%
Mixed Affective	1	0.04%
Nausea	1	0.04%
Otitis	1	0.04%
Pain	1	0.04%
Pain Menstrual	1	0.04%
Paralysis	1	0.04%

APPENDIX 6A

Results from the Shapiro-Wilk test for normality of distribution of the continuous variable 'age' in Dataset A

Table A6a Shapiro-Wilk test for normality of distribution:

Variable	Observations	W	V	Z	Prob>z
AGE	9213	0.99	45.52	10.19	0.0000

The variable age fails the test for normality.

APPENDIX 6B

Results from the Shapiro-Wilk test for normality of distribution of the continuous variable 'number of prescriptions' in Dataset A.

Table A6b Shapiro-Wilk test for normality of distribution:

Variable	Observations	W	V	Z	Prob>z
NUMBER OF VISITS	9212	0.75	1155.57	18.38	0.000

The variable number of prescriptions failed the test for normality of distribution

APPENDIX 7

Results from the Two-sample Wilcoxon Rank-sum (Mann-Whitney U) test for 'age' and 'drug type' in Dataset A is presented below:

DRUGTYPE	obs	rank sum	expected
0	6442	28994284	29678294
1	2771	13450008	12765997
Combined	9213	42444291	42444291

Unadjusted variance 1.371e+10

Adjustment for ties -2089.0025

---

adjusted variance 1.371e+10

z = -5.843

Prob> |z| = >0.00001

APPENDIX 8

Two-sample Wilcoxon rank-sum (Mann-Whitney U) test for 'number of prescriptions' and 'drug type' in Dataset A is presented below:

DRUGTYPE	obs	rank sum	expected
0	6442	27709991	29675073
1	2770	14725088	12760005
combined	9212	42435078	42435078

unadjusted variance 1.370e+10

adjustment for ties -2.212e+09

---

adjusted variance 1.149e+10

z = -18.334

Prob> |z| = > 0.00001

APPENDIX 9

Table A9 Chi-squared table for association between ICD-10 category and antidepressant type (Dataset A)

ICD-10 Category	Old Generation	New Generation	Total
Psychiatric (n)	761	1 541	2 302
%	33.06	66.94	100
Pain (n)	3 901	528	4 429
%	88.08	11.92	100
Other (n)	1 623	502	2 125
%	76.38	23.62	100
Total (n)	6 285	2 571	8 856
%	70.97	29.03	100

APPENDIX 10

Table A10 Chi-squared table for association between psychiatric diagnosis category and antidepressant type (Dataset A)

Psychiatric Diagnosis Category	**Old Generation**	**New Generation**	**Total**
Anxiety-related conditions and stress(n)	639	1 062	1 701
%	37.57	62.43	100
Affective disorders (n)	46	447	493
%	9.33	90.67	100
Sleep disorders (n)	70	32	102
%	68.63	31.37	100
Psychiatric Counselling (n)	13	0	13
%	100	0	100
Total (n)	768	1 530	2 302
%	33.42	66.58	100

APPENDIX 11

Table A11 Chi-squared table for association between number of prescriptions category and antidepressant type (Dataset A)

Number of Prescriptions Category	Old Generation	New Generation	Total
6 Months or longer (n)	588	614	1 202
%	48.92	51.08	100
2 – 5 Months (n)	2 104	966	3 070
%	68.53	31.47	100
Once(n)	3 750	1 191	4 941
%	75.9	24.1	100
Total (n)	6 442	2 771	9 213
%	69.92	30.08	100

APPENDIX 12

Table A12 Chi-squared table for association between age category and antidepressant type (Dataset A)

Age Category	Old Generation	New Generation	Total
0 -12 years (n)	65	14	79
%	82.28	17.72	100
13 - 16 years (n)	161	25	186
%	86.56	13.44	100
17 -65 years (n)	5 893	2 515	8 408
%	70.09	29.91	100
66 years and older (n)	323	217	540
%	59.81	40.19	100
Total (n)	6 442	2 771	9 213

APPENDIX 13

Two-sample Wilcoxon rank-sum (Mann-Whitney U) test for 'age' and 'duration of treatment' in Dataset A is presented below:

var20	obs	rank sum	expected
0	4944	19764164	22777008
1	4269	22680128	19667283
combined	9213	42444291	42444291

unadjusted variance 1.621e+10

adjustment for ties -2469.9396

---

adjusted variance 1.621e+10

z = -23.667

Prob > |z| = <0.00001

APPENDIX 14

Table A14 Chi-squared table for association between age category and duration of treatment (Dataset A)

Age Category	ONCE	>1	Total
0 -12 years (n)	65	14	79
%	82.28	17.72	100
13 - 16 years (n)	148	38	186
%	79.57	20.43	100
17 -65 years (n)	4 628	3 780	8 408
%	55.04	44.96	100
66 years and older (n)	103	437	540
%	19.07	80.93	100
Total (n)	4 944	4 269	9 213
%	53.66	46.34	100

APPENDIX 15

Table A15 Chi-squared table for association between ICD-10 category and duration of treatment (Dataset A)

ICD10 Category	ONCE	>1	Total
Psychiatric (n)	837	1 465	2 302
%	36.36	63.64	100
Pain (n)	2 748	1 681	4 429
%	62.05	37.95	100
Other (n)	1 302	823	2 125
%	61.27	38.73	100
Total (n)	4 887	3 969	8 856
%	55.18	44.82	100

APPENDIX 16

Table A16 Chi-squared table for association between psychiatric diagnosis category and duration of treatment (Dataset A)

Psychiatric Diagnosis Category	ONCE	>1	Total
Anxiety-related conditions and stress(n)	698	1 003	1 701
%	41.03	58.96	100
Affective disorders (n)	107	386	493
%	21.7	78.3	100
Sleep disorders (n)	30	72	102
%	29.41	70.59	100
Psychiatric Counselling (n)	2	11	13
%	15.38	84.62	100
Total (n)	832	1 466	2 302
%	36.21	63.79	100

APPENDIX 17

Table A17 Frequency of diagnoses for all antidepressants in Dataset B

Diagnosis	**Number**	**%**
Depressive Episode	352	28.94%
Muscle And Joint Disorders	346	27.81%
Anxiety	76	5.71%
Stress	66	4.98%
Respiratory Disorders	58	4.66%
Headache	46	3.70%
Gastric Disorders	38	3.05%
Migraine	27	2.17%
Diabetes	26	2.09%
Herpes	17	1.37%
Hypertension	15	1.21%
Urinary	15	1.21%
Bipolar	12	0.96%
H**IV**	11	0.88%
Pain Chest	10	0.80%
Sleep Disorder	10	0.72%
Hypothyroidism	8	0.64%
Injury/Trauma	8	0.64%
Dermatological Disorders	7	0.56%
Otitis	6	0.48%
Pain Abdomen	6	0.48%
Pain Unspecified	6	0.48%
Conjunctivitis	3	0.24%
Gastro-Oesophageal Reflux Disorder	3	0.24%

Diagnosis	**Number**	**%**
Sexually Transmitted Disorders	3	0.24%
Anaemia	2	0.16%
Hyperthyroidism	2	0.16%
Malaise	2	0.16%
Varicose	2	0.16%
Enuresis	1	0.08%
Infection	1	0.08%
Neurosis	1	0.08%
Parkinson’s	1	0.08%

APPENDIX 18

Table A18 Frequency of diagnoses for tricyclic antidepressants in Dataset B

Diagnosis	**Number**	**%**
Muscle And Joint Disorders	344	40.23%
Depression	80	9.36%
Neuralgia	59	6.90%
Stress	56	6.55%
Respiratory Disorders	45	5.26%
Headache	43	5.03%
Anxiety	39	4.56%
Gastrointestinal Disorders	34	3.98%
Migraine	26	3.04%
Diabetes	24	2.81%
Herpes	17	1.99%
Urinary Tract Disorders	13	1.52%
Hypertension	10	1.17%
HIV	9	1.05%
Sleep Disorders	10	1.17%
Injury/Trauma	8	0.94%
Dermatological Disorders	7	0.82%
Pain Chest	7	0.82%
Pain Abdomen	6	0.70%
Pain Unspec	6	0.70%
Otitis	5	0.58%
Conjunctivitis	3	0.35%
Sexually Transmitted Disorders	3	0.35%
Anaemia	2	0.23%
Gastro-Oesophageal Reflux Disorder	2	0.23%
Varicose	2	0.23%
Infection	1	0.12%
Malaise	1	0.12%
Neurosis	1	0.12%
Parkinson’s	1	0.12%
Enuresis	1	0.12%

APPENDIX 19

Table A19 Frequency of diagnoses for newer generation antidepressants (Dataset B)

Diagnosis	**Number**	**%**
Depression	287	73.78%
Anxiety	33	8.48%
Respiratory Disorders	13	3.34%
Bipolar	5	1.29%
Stress	6	1.54%
Hypertension	5	1.29%
Gastrointestinal Disorders	4	1.03%
Headache	3	0.77%
Pain Chest	3	0.77%
Diabetes	2	0.51%
HIV	2	0.51%
Hyperthyroidism	2	0.51%
Muscle And Joint Disorders	2	0.51%
Urinary Tract Disorders	2	0.51%
Gastro-Oesophageal Reflux Disorder	1	0.26%
Malaise	1	0.26%
Migraine	1	0.26%
Otitis	1	0.26%

APPENDIX 20A

Results from the Shapiro-Wilk test for normality of distribution of the continuous variable 'age' in Dataset B.

Table A20a Shapiro-Wilk test for normality of distribution:

Variable	Observations	W	V	Z	Prob>z
AGE	1244	0.97	2.9	2.67	0.00381

The variable age fails the test for normality.

APPENDIX 20B

Results from the Shapiro-Wilk test for normality of distribution of the continuous variable 'number of prescriptions' in Dataset B.

Table A20b Shapiro-Wilk test for normality of distribution:

Variable	Observations	W	V	Z	Prob>z
NUMBER OF VISITS	1244	0.86	106.01	11.65	0.000

Number of visits failed the test for normality of distribution

APPENDIX 21

Results from the Two-sample Wilcoxon Rank-sum (Mann-Whitney U) test for 'age' and 'drug type' in Dataset B is presented below:

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

DRUGTYPE	obs	rank sum	expected
0	856	536222.5	532860
1	388	238167.5	241530
Combined	1244	774390	774390

Unadjusted variance 34458280

Adjustment for ties -8.6989935

Adjusted variance 34458271

z = 0.573

Prob > |z| = 0.5668

APPENDIX 22

Two-sample Wilcoxon rank-sum (Mann-Whitney U) test for 'number of prescriptions' and 'drug type' in Dataset B is presented below:

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

DRUGTYPE	obs	rank sum	expected
0	856	476184.5	532860
1	388	298205.5	241530
combined	1244	774390	774390

unadjusted variance 34458280

adjustment for ties -5278622.6

---

adjusted variance 29179657

z = -10.492

Prob > |z| = <0.00001

APPENDIX 23

Table A23 Chi-squared table for association between ICD-10 category and drug type (Dataset B)

ICD-10 Category	Old Generation	New Generation	Total
Psychiatric (n)	177	339	516
%	34.30	65.70	100
Pain (n)	498	8	506
%	98.42	1.58	100
Other (n)	181	41	222
%	81.53	18.47	100
Total (n)	856	388	n=1 244
%	68.81	31.19	100

APPENDIX 24

Table A24 Chi-squared table for association between psychiatric diagnosis and drug type (Dataset B)

Psychiatric Diagnosis Category	**Old Generation**	**New Generation**	**Total**
Anxiety-related conditions and stress(n)	72	292	364
%	21.51	78.49	100
Affective disorders (n)	95	47	142
%	66.90	33.10	100
Sleep disorders (n)	10	0	10
%	100.00	0	100
Total (n)	177	339	516
%	35.85	64.17	100

APPENDIX 25

Table A25 Chi-squared table for association between number of prescriptions and antidepressant type (Dataset B)

Number of Prescriptions Category	**Old Generation**	**New Generation**	**Total**
6 Months or longer (n)	41	120	161
%	25.47	74.53	100
2 – 5 Months (n)	301	126	427
%	70.49	29.51	100
Once(n)	514	142	656
%	78.35	21.65	100
Total (n)	856	388	1 244
%	68.81	31.19	100

APPENDIX 26

Table A26 Chi-squared table for association between age category and antidepressant type (Dataset B)

Age Category	Old Generation	New Generation	Total
0 -12 years (n)	3	3	6
%	50	50	100
13 – 16 years (n)	1	3	4
%	25	75	100
17 -65 years (n)	813	342	1 155
%	70.39	29.61	100
66 years and older (n)	39	40	79
%	49.37	50.63	100
Total (n)	856	388	1 244
%	68.81	31.19	100

APEENDIX 27

Two-sample Wilcoxon rank-sum (Mann-Whitney) test for 'age' and 'duration of treatment' in Dataset B is presented below:

var27binar~n	obs	rank sum	expected
0	656	366704	408360
1	588	407686	366030
combined	1244	774390	774390

unadjusted variance 40019280

adjustment for ties -10.102868

---

adjusted variance 40019270

z = -6.585

Prob > |z| = < 0.00001

APPENDIX 28

Table A28 Chi-squared table for association between age category and duration of treatment (Dataset B)

Age Category	ONCE	>1	Total
0 -12 years (n)	5	1	6
%	83.33	16.67	100
13 - 16 years (n)	3	1	4
%	75	25	100
17 -65 years (n)	622	533	1 155
%	53.85	46.15	100
66 years and older (n)	26	53	79
%	32.91	67.09	100
Total (n)	656	588	1244
%	52.73	47.27	100

APPENDIX 29

Table A29 Chi-squared table for association between ICD-10 category and duration of treatment (Dataset B)

ICD-10 Category	ONCE	>1	Total
Psychiatric (n)	208	308	516
%	40.31	59.69	100
Pain (n)	315	191	506
%	62.25	37.75	100
Other (n)	133	89	222
%	59.91	40.09	100
Total (n)	656	588	1 244
%	52.73	47.27	100

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The Harvard form of referencing was followed in this dissertation. The list of journal, book and online references are presented. Legal references are listed in a separate section below.

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