Prescribing patterns of antidepressants with known off-label indications among adults

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Abstract

Title: Prescribing patterns of antidepressants with known off-label indications among adults

Keywords: off-label, antidepressant, drug utilisation review, prevalence, prescribed daily dose (PDD), number of defined daily dosages (DDDs)

"Off-label use" is defined as the use of medicine for indications other than recommended or registered for, e.g. the prescribing of a particular active substance for a patient younger than the substance is recommended or indicated for, or different formulations or dosages of a substance (Ekins-Daukes *et al.*, 2004:349; Stedman's medical dictionary, 2006). Off-label prescribing is common, and fluctuates by physician, patient and drug (Eguale *et al.,* 2012:781). Drug classes most commonly prescribed off-label include anti-asthmatic, cardiovascular drugs and antidepressants. Lee *et al.* (2012:140) found that 9 out of 10 antidepressants prescribed were associated with unapproved usage of antidepressants. An antidepressant can be defined as a substance that prevents or relieves depression or depressive episodes (Mosby, 2009:115).

There is paucity of information on the off-label prescribing practices of antidepressants in the South African private health sector. According to Eguale *et al.* (2012:781), the paucity of information on off-label prescribing practices may be, in part, ascribed to the difficulty in the establishment of reasons for treatment.

The objective of this study was to determine the prescribing patterns of antidepressants as well as to identify off-label prescribing of antidepressants among adults in a section of the private health sector of South Africa by using a medicine claims database. A quantitative and observational, descriptive cross-sectional design was followed in this study. Data for a period of a year, from January to December 2010 were obtained for analysis. The data set consisted of medicine claims for a total number of 1 220 289 patients, containing a total of 8 515 428 prescriptions and 20 527 777 medicine items.

The study population (patients receiving antidepressants 18 years and older) accounted for 14.8% (n = 1 220 289) of the total data set. The average age of patients receiving antidepressants was 56.1 ± 16.6 (median = 56.2) (Inter quartile range = 43.3–68.1). Results of the study showed that antidepressant prescriptions accounted for 8.3% (n = 8 515 428) of all prescriptions claimed during 2010.

A total 3.5 % (n = 20 527 777) of antidepressants were claimed during the study period. Using the DU90% method it was established that the majority of antidepressant medicine items were

prescribed by general practitioners (i.e. 75.7%, n = 702 285) and psychiatrists (14.9%, n = 702 285). Almost 72% (n = 702 885) of antidepressant medicine items claimed for the study population were for women.

The most prescribed antidepressants (based on the DU90%) were amitriptyline (20.6%, n = 702 885), citalopram (19.2%), escitalopram (14.6%), fluoxetine (11.7%), venlafaxine (5.7%), paroxetine (5.2%), duloxetine (4.4%), sertraline (3.8%), bupropion (3.1%) and mirtazapine (2.6%).

Amitriptyline accounted for 82.4% of off-label prescriptions (n = 2 635), whereas escitalopram and fluoxetine accounted for 4.2% and 3.8%, respectively. The tricyclic antidepressants (TCAs) were mostly prescribed off-label for migraine, headache and sleep disorders. The off-label prescribing of selective serotonin re-uptake inhibitors (SSRIs) included menopause, schizophrenia and headache. The off-label indicated prescriptions of the serotonin and noradrenaline re-uptake inhibitors (SNRIs) were mostly for schizophrenia and other anxiety disorders. Mirtazapine, a serotonin modulator/tetracyclic antidepressant, was mostly prescribed off-label for anxiety disorders. Off-label prescriptions for bupropion, a noradrenaline and dopamine re-uptake inhibitor mainly included other anxiety disorders and attention deficit hyperactivity disorder (ADHD). Furthermore, the prescribed daily dose (PDD) of each active antidepressant for all off-label indications was determined.

In conclusion: This study investigated the off-label prescribing patterns of antidepressants among adults a section of the private health sector of a South Africa, using a large medicine claims database. Recommendations for future research were made.

Opsomming

Titel: Voorskryfpatrone van antidepressante met bekende nie-geregistreerde indikasies onder volwassenes

Sleutelwoorde: antidepressante, nie-geregistreerde, medisyneverbruiksevaluering, voorkoms, voorgeskrewe daaglikse dosis (VDD), aantal gedefinieerde daaglikse dosisse (GDDs)

“Nie-geregistreerde gebruik” word gedefinieer as die gebruik van medisyne vir indikasies anders as waarvoor dit aanbeveel word of geregistreer is, bv. die voorskryf van ‘n spesifieke aktiewe bestanddeel vir ‘n pasiënt wat jonger is as waarvoor die bestanddeel aanbeveel of aangedui word, of verskillende formulerings of dosisse van die bestanddeel (Ekins-Daukes *et al.*, 2004:349; Stedman’s medical dictionary, 2006). Nie-geregistreerdevoorskrywing kom algemeen voor en wissel van dokter, pasiënt en geneesmiddel (Eguale *et al.*, 2012:781). Geneesmiddelgroepe wat meestal vir nie-geregistreerdeindikasies voorgeskryf word, sluit anti-asmatiese middels, kardiovaskulêremiddels en antidepressante in. Lee *et al.* (2012:140) het bevind dat 9 uit 10 anti-depressante wat voorgeskryf word, geassosieer word met nie-goedgekeurde gebruik van antidepressante. ‘n Antidepressant kan gedefinieer word as ‘n stof wat depressie of depressiewe episodes kan verhoed of verlig (Mosby, 2009:115).

Daar is ‘n gebrek aan inligting in verband met nie-geregistreerde voorskryfpraktyke van antidepressante in die Suid-Afrikaanse private-gesondheidsektor. Volgens Eguale *et al.* (2012:781), mag hierdie gebrek aan inligting oor nie-geregistreerdevoorskryfpraktyke deels toegeskryf word aan die probleem om te bepaal wat die redes vir behandeling is. Die doel van hierdie studie was om die voorskryfpatrone van antidepressante te bepaal, asook om die nie-geregistreerdevoorskrywing van antidepressante onder volwassenes in 'n segment van die private-gesondheidsektor van Suid-Afrika te identifiseer, deur van 'n databasis van medisyne-eise gebruik te maak.

‘n Kwantitatiewe, deur-waarneming-bepaalde, beskrywende, deursnee-ontwerp is tydens die studie gevolg. Data vir ‘n tydperk van een jaar, begin Januarie tot Desember 2010, is verkry vir ontleding. Die datastel het bestaan uit medisyne-eise vir 1 220 289 pasiënte, insluitend ‘n totaal van 8 515 428 voorskrifte en 20 527 777 medisyne-items.

Die totale datastel sluit 14.8% (n = 1 220 289) van die studiepopulasie (pasiënte 18 jaar en ouer, wat antidepressante ontvang het) in. Die gemiddelde ouderdom van pasiënte wat antidepressante ontvang het, was 56.1 ± 16.6 (mediaan = 56.2) (interkwartielvariasiewydte = 43.3–68.1). Die resultate van die studie het getoon dat antidepressante, 8.3% (n = 8 515 428)

van alle voorskrifeise van 2010 insluit.

‘n Totaal van 3.4% (n = 20 527 777) van antidepressante is in die studietydperk geëis. Met behulp van die DU - 90% metode, is vasgestel dat die meerderheid van die antidepressant medisyne-items deur algemene praktisyns (d.w.s. 75.7%, n = 702 285) en psigiaters (14.9%, n = 702 285) voorgeskryf is. Byna 72% (n = 702 885) van antidepressant medisyne-items wat vir die studiepopulasie geëis is, was vir vrouens.

Met behulp van die DU - 90% metode is bevind die meeste voorgeskrewe antidepressante was amitriptilien (20.6%, n = 702 885), sitalopram (19.2%), essitalopram (14.6%), fluoksetien (11.7%), venlafaksien (5.7%), paroksetien (5.2%), duloksetien (4.4%), sertralien (3.8%), bupropioon (3.1%) en mirtasepien (2.6%).

Amitriptilien was verantwoordelik vir 82.4% van nie-geregistreerdevoorskrifte, terwyl escitalopram en fluoksetien onderskeidelik 4.2% en 3.8% verteenwoordig het. Die trisikliese antidepressante (TCAs) is meestal voorgeskryf vir migraine, hoofpyn en slaapversteurings. Die nie-geregistreerde indikasies vir die voorskryf van die selektiewe serotonienheropname-inhibeerders (SSRIs), sluit menopouse, skisofrenie en hoofpyn in. Die nie-geregistreerdevoorskrifte van die serotonien- en noradrenalienheropname-inhibeerders (SNRI’s) was meestal vir skisofrenie en ander angsversteurings. Mirtasepien, ‘n serotonienmoduleerder tetrasikliese antidepressant, is meestal vir nie-geregistreerdeangsversteurings voorgeskryf. Bupropioon, ‘n noradrenalien- en dopamienheropname-inhibeerder, is hoofsaaklik vir nie-geregistreerde ander angsversteurings en aandagafleibaarheid en hiperaktiwiteitsindroom (AAHS) voorgeskryf. Verder is die voorgeskrewe daaglikse dosis (VDD) van elke aktiewe bestanddeel vir alle nie-geregistreerde indikasies bepaal.

Samevattend: Hierdie studie het die nie-geregistreerdevoorskryfpatrone van antidepressante onder volwassenes in ‘n segment van die privaatsektor van Suid-Afrika ondersoek, deur van ‘n groot databasis medisyne-eise gebruik te maak. Aanbevelings vir toekomstige navorsing is gemaak.

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List of abbreviations

$5HT_2$	Seretonin type 2 receptor
ADHD	Attention deficit hyperactivity disorder
AMD	Age-related macular degeneration
ATC	The Anatomical Therapeutic Chemical (Classification system)
CI	Confidence interval
CNS	Central nervous system
DDD	Defined daily dose
DUR	Drug utilisation review
EUS	External urethral sphincter
FDA	Food and Drug Administration
GAD	General anxiety disorder
GABA	Gamma-aminobutyric acid
GPs	General practitioners
HCAs	Heterocyclic antidepressants
IBS	Irritable bowel syndrome
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MAOIs	Monoamine oxidase inhibitors
MIMS	Monthly Index of Medical Specialities
MS	Multiple sclerosis
NSWTAG	New South Wales Therapeutic Advisory Group
OCD	Obsessive compulsive disorder
PBM	Pharmaceutical Benefit Management
PDD	Prescribed daily dose
PTSD	Post-traumatic stress disorder
REM	Rapid eye movement
SAMF	South African Medicines Formulary
SNRIs	Selective-norepinephrine reuptake inhibitor
SSRIs	Selective serotonin reuptake inhibitors
TCAs	Tricyclic antidepressants
WHO	World Health Organization

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CHAPTER 1

Introduction and Study overview

1.1 Introduction

This chapter presents the introduction and overview of the study. It contains an overview of the background and the rationale of the study, research questions and objectives and the research method. The chapter concludes with a division of chapters.

1.2 Background and rationale for the study

Good medical practice toward the welfare of patients requires that prescribers use legally available medicines and devices, according to their best knowledge and judgment (U.S. Food and Drug Administration, 1998). This includes the prescribing or administration of any legally marketed product for an off-label use. In such cases, the prescriber has the responsibility to be well informed about the product and to base his/her prescribing practices on firm scientific rationale and sound medical evidence (Everett, 2002:216).

Off-label use is defined as the use of medicine for indications other than recommended or registered for, e.g. the prescribing of a particular active substance for a patient younger than the substance is recommended for, or different formulations or dosages of a substance (Ekins-Daukes *et al.,* 2004:349; Stedman's medical dictionary, 2006). Off-label prescribing also includes the prescribing of a class of medication for a class of disorders – such as prescribing a sodium-channel blocker for neuropathic pain (rather than a specific sodium-channel blocker for a specific cause of neuropathic pain).

Off-label prescribing is common, and fluctuates with physician, patient and drug (Eguale *et al.,* 2012:781). Although there is some evidence of legitimate off-label practices, there is not enough scientific evidence to support the approval of these off-label indications (Clouse, 2003:599). For example, findings from a study by Radley *et al.* (2006:71) indicated that approximately 21% of medicine prescribed was used for unlicensed indications, of which 15% was not therapeutically safe and still needed more scientific evidence. Off-label use is general practice, in particular with the central nervous system drugs, such as the anticonvulsants, antipsychotics and antidepressants (Eguale *et al.,* 2012:781; Emmerich *et al.*, 2012:1279).

An antidepressant can be defined as a substance that prevents or relieves depression or

depressive episodes (Mosby, 2009:115). A number of antidepressants are used off-label, *inter alia*; paroxetine and buspirone have been used for general anxiety disorder (GAD). Paroxetine has also been used for the treatment of premature ejaculation because of the delay or inhibition of ejaculation caused by the selective serotonin reuptake inhibitors (SSRIs) (Stone *et al.,* 2003:502), whereas amitriptyline has been found effective for the treatment of chronic tension-type headaches by reducing the number of days a patient has chronic pain (Oguzhanoglu *et al.,* 1999:532). Antidepressants are also effective in the use of irritable bowel syndrome, in particular, the tricyclic antidepressants (TCAs) (Clouse, 2003:599).

According to Eguale *et al.* (2012:781), little is known about factors that contribute to off-label prescribing. Croghan (2001:133) is of the opinion that an increase in antidepressant utilasation may be ascribed to an increase in the number of prescribers of antidepressants (i.e. both psychiatrists and general practitioners are allowed to prescribe antidepressants). The discovery of new indications for the use of antidepressants may also be the reason for the increase in the use thereof (Pirraglia *et al.,* 2003:156). According to Truter *et al.* (1996:675) there is a need to know why medicine usage increases in daily society; decision-makers need to be alert, and must be prepared to manage this increase.

In general, the use of antidepressants in developed countries has increased over the past 6 years, from a prescribing volume of 231 million in 2006 to 253 million in 2010. Antidepressants were also the second most prescribed therapeutic drug class in the United States from 2006 to 2010 (IMS Institute for Healthcare Informatics, 2011). The number of different active substances increased from 4 in the top 200 drugs dispensed in the United States during 2005 (i.e. paroxetine, fluoxetine, trazadone and amitriptyline), to 6 in 2010, with the addition of sertraline and citalopram to those identified in 2005 (IMS Institute for Healthcare Informatics, 2011). In the 2005 annual review of Mediscor (a South African PBM) antidepressant utilisation represented 10.9% of all medicine used during 2005 (Bester *et al.*, 2006:8). Use of this drug class had increased to 12% in 2010 (Badenhorst *et al.*, 2011:13).

There is a paucity of information on the off-label prescribing practices of antidepressants in the South African private health sector. According to Eguale *et al.* (2012:781), the paucity of information on off-label prescribing practices may be, in part, ascribed to the difficulty in establishing the reasons for treatment. The International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD–10) coding system was furthermore only implemented in the private health care sector of South Africa in July 2005 (Matshidze & Hanmer, 2007:95).

Using drug utilisation reviews, in particular the DU90% method (DU90%), the defined daily

dosage (DDD) and prescribed daily dosage (PDD) methodology provide a useful mechanism to calculate the quantity of medicine being used and prescribed. The use of these methods also provides for the transnational comparison of research findings. Information on the PDDs of antidepressants with known off-label indications might further add to the scientific rationale and evidence for prescribing practices in South Africa.

1.3 Research questions

Based on the above mentioned discussion, the following research questions were formulated:

- What is the off-label use and why is it important?
- What are the identified off-label indications for selected antidepressants?
- How can drug utilisation research (DUR) (in particular the DDD and PDD methodology) add to the quantification of medicine usage and off-label antidepressant use?

1.4 Research aim and objectives

This study was conducted in two phases (refer to paragraph 1.5).

1.4.1 General aim

In accordance with the research questions, the general aim of this study was to determine the prevalence and prescribing patterns of antidepressants with identified off-label indications in adults older than 18 years, by using South African medicine claims data.

1.4.2 Specific objectives

The specific objectives to be addressed in the literature review:

- To conceptualise the meaning of off-label medicine usage.
- To determine the need for off-label prescribing.
- To establish the difficulties that may arise from off-label prescribing.
- To determine off-label prescribing practices in general.
- To identify antidepressants with known off-label indications.

The specific objectives that pertain to the empirical investigation phase of the study include:

- To determine the prevalence of antidepressants with identified off-label indications on the Pharmaceutical Benefit Management (PBM) Company's database, stratified by age, gender, and prescriber.

- To determine the prescribed daily dosage of antidepressants with prescribed off-label indications.

1.5 Research method

The first phase was a literature review, followed by the second phase, consisting of an empirical investigation.

1.5.1 Phase 1: Literature review

The aim of the literature review was to conceptualise off-label medicine use, with emphasis on antidepressants. A detailed on-line literature search was performed to identify all antidepressant active substances with known off-label indications, searching Medline, the Cochrane Library, PubMed, Scopus, Science direct, EbscoHost, and Google Scholar, for publications in the period 2000 to 2013. Appropriate dosages for each of the identified active substances were determined and described, using the World Health Organization (WHO) reference guide for DDDs (WHO, 2011) and relevant articles.

1.5.2 Phase 2: Empirical investigation

A retrospective drug utilisation review was conducted using medicine claims data obtained from a South African pharmaceutical benefit management (PBM) company for the period, 1st January 2010 to 31st December 2010. Antidepressants with off-label indications that were identified in phase one of the study, were further examined in chapter 4.

1.6 Division of chapters

The dissertation consists of 5 chapters. Chapter 1 contains the introduction of the study, chapter 2 the literature study, chapter 3 the empirical investigation, chapter 4 the results and discussion and chapter 5 the conclusion and recommendations.

1.7 Chapter summary

In this chapter a general overview of the study was given, together with the problem statement and research questions. The chapter further described the general and specific research objectives, a brief description of the research methodology and a division of chapters. Chapter 2 entails a discussion of off-label prescribing, presents the process followed in identifying antidepressants with off-label uses and gives an overview of these antidepressants.

CHAPTER 2

Literature review

2.1 Introduction

This chapter presents the literature review phase of the study (refer to paragraph 1.5.1). The specific objectives of this review were to determine the need for off-label prescribing, to review the regulations for off-label prescribing and to determine the off-label indications for antidepressants.

2.2 Terminology and definitions

Off-label use refers to the use of medicine for indications other than what it is recommended or registered for in a specific country, e.g. the prescribing of a particular active substance for a patient younger than which the substance is recommended for, or a different formulation or dosage of a substance (Ekins-Daukes *et al.,* 2004:350; Robberts *et al.*, 2003:905; Stedman's Medical Dictionary, 2006). Off-label prescribing also includes the prescribing of a class of medication for a group of disorders – such as prescribing a sodium-channel blocker for neuropathic pain (rather than a specific sodium-channel blocker for a specific cause of neuropathic pain) (Robberts *et al.*, 2003:905). Hill (2005:17) furthermore describes off-label use as the use of licensed medication outside the conditions of the licence (whereas the term unlicensed is used to describe medicines that never had a licence). The terms off-label use and unlicensed medicine use have also been used interchangeable, for example:

- When medicines were given in a different way than it is licensed for, e.g. when an oral medication was given *via* injection (Collier, 1999:6; Neubert *et al.*, 2004:1060).
- When prohibited dosages of medicine were prescribed to patients; e.g. if there is a lack of data on usage of these medication in the case of children (Collier, 1999:6; Neubert *et al.*, 2004:1060).
- When unlicensed drugs are given to patients, e.g. when medicines are prescribed for a common condition it may be that the product is not licensed or may have been withdrawn for its intended indication (Collier, 1999:6; Neubert *et al.*, 2004:1060).
- When medicines are prescribed for patients in controlled clinical trials, and thus have not yet been given a licence, e.g. the prescribing of these medicines after the trial has been completed, prior to the medicines receiving a licence (Collier, 1999:6; Neubert *et al.*, 2004:1060).

For the purpose of this study the term off-label will be used to describe all active ingredients that

are not used for the indications that they are registered for.

2.3 Need for off-label drug prescribing

According to Radley *et al.* (2006), off-label prescribing allows for a number of advantages, e.g. clinical innovation, treatment of rare conditions, increased return on investment for pharmaceutical firms, options to prescribe in children or adolescents and when the licensed administration route has not been approved.

The most frequent reasons for off-label prescribing are medicines prescribed at a different dose, different formulation, when used in an alternative route of administration or in age groups for which the drug is not licensed, as well as prescribing drugs for different indications (Conroy *et al.*, 2000:79; Neubert *et al.*, 2004:1060). The advice given by hospital, consultants together with the lack of licensed alternatives, is some of the most important reasons for general practitioners to prescribe medicines off-label (Ekins-Daukes *et al.*, 2005:146).

Off-label prescribing is also often indicated in cases where every other option has been exhausted, as in the case of uncommon diseases like cancer (Neubert *et al.*, 2004:1060). Chemotherapeutic drugs are often used off-label due to the fact that these agents are sometimes approved for targeting one type of tumour, but in fact may be effective for other tumours as well. According to Stacy (2009), cardiologists also frequently prescribe beta-blockers for heart failure, although it is not indicated for use in these patients.

Clinical trials are not performed on children, and many products are therefore not licensed for their use. It is, however, inevitable that these medicines are sometimes prescribed for children, because it is often the last line of treatment available (Greener, 2008:506; Ekins-Daukes *et al.*, 2005:148).

2.4 Difficulties that may arise from off-label prescribing

Although off-label prescribing is not an illegal practice, there may be clinical and ethical barriers to overcome when such practices do take place (Collier, 1999:6; Gazarian, 2003:122). In many cases the use of off-label medication is crucial e.g. serious life-threatening diseases such as cancer.

There sometimes is no scientific evidence to prove that these drugs will work for the specific condition (Stacy, 2009; Conroy *et al.*, 2000:79). The biggest concern with regard to off-label prescribing is that there is a huge lack in labelled evidence on the dosages given to paediatric

patients (Ekins-Daukes *et al.*, 2005:146). The bioavailability of these drugs can make the effectiveness of the drugs unpredictable (Schreiner, 2003:950). If a drug is licensed for administration in adults, it does not necessarily mean that the drug will automatically be suitable for the same indication in children, due to the variance in the biological systems of adults and children at different ages (Gazarian, 2003:122). The safety of the drugs for specific indications is furthermore not always established. For example, the frequent publications about combination therapy and the beneficial effects of fen-phen (fenfluramine hydrochloride and phentermine hydrochloride) for the treatment of obesity instigated the co-prescription of these drugs (Stacy, 2009). The outcome was catastrophic, with a number of the patient'sdeveloping severe heart valve damage.

2.5 Off-label prescribing regulations

Medication is required to be registered before it may be legally prescribed, or administrated to patients (Douglas-Hall *et al.*, 2001:890). Information on the direct label of a medicinal product forms part of the manufacturer's advertisement and is indicative of what the product is registered for. This does not mean that it may not be used for other conditions as well (Blum, 2002:1777).

According to Ward *et al.* (2002:181) it is the prescriber's responsibility to prescribe a drug for a specific indication — either being label or off-label. Off-label use is based on the prescribers' own experience, published literature and scientific evidence.

2.5.1 Prescribing regulations in United States of America (USA)

The Food and Drug Administration (FDA) in the USA scrutinizes drugs for off-label use to a lesser extent than for the labelled indications (Radley *et al.*, 2006:1025). According to Kuntz (1998:520), physicians are free to prescribe off-label, subject to liability for medical malpractice suits. However, if prescribing off-label fails to meet a required standard of care, the United States government may intervene and stop such prescribing. Standards applied in these circumstances are the FDA's approval of the indication and dosage but this does not offer convincing proof that a drug is properly prescribed. It still hangs in the balance whether manufacturers will promote such indications with use of requisite studies (Kuntz, 1998:520). Although there is significant evidence that can justify the use of off-label prescribing, there still is a lack of FDA approval and this leads to less scientific inspection of the approved indications (Radley *et al.*, 2006:1023).

According to Radley *et al.* (2006:68) documented scientific evidence of off-label uses of

antidepressants with known off-label indications in practice almost always falls short of what is required by the manufacturer to get FDA approval for a specific indication. The FDA does not promote the use of medication for unapproved uses and restricts physicians from such malpractice.

2.5.2 Prescribing regulations in European countries

Physicians are free to prescribe any drug available on the market for any indication (approved or unapproved) which they consider medically appropriate. The patient must give informed consent that he is aware of the off-label use of the medication (European Union, 2004).

Italian and European regulations will allow prescribing prescription drugs for paediatric indications or indications not licensed for children. Several of these medicines are regularly prescribed to children without the proper knowledge of the medicine peak level dose, pharmacokinetic and pharmacodynamics characteristics and potential side effects (Pandolfini *et al.*, 2002:340).

2.5.3 Prescribing regulations in Australia

New South Wales Therapeutic Advisory Group (NSWTAG) is an independent government group that provides sufficient information to medical personnel to provide safe and effective medicine usage. Before medication is used off-label, the Australian Medicines Handbook, Therapeutic guidelines or international resources such as the British National Formulary should be consulted (Gazarian *et al.*, 2006:545).

Off-label use may be justified by routine high quality supporting evidence, either by cohort or case-studies, randomised controlled trial and meta-analysis that may support the usage of such off-label medications. These studies may improve the safety profile of off-label medication prescribing. This may minimise the prescribing of off-label medication based on “experience” and “opinion” (NHMRC, 2000).

Before a clinician may prescribe off-label, three categories must be approved:

- Justified by high-quality evidence.
- Use within a formal research proposal.
- Individual clinical circumstances has been justified.

Discussing and documentation should be described, in relation to possible alternatives,

potential side effects and the reason for the use of the medication off-label (Gazarian *et al.*, 2006:546).

2.5.4 Prescribing regulations in South Africa

According to Jansen (2009:438), in comparison with the United States of America, there is currently little or no attention given to issues surrounding the use of off-label medication in South Africa. South African studies have shown that it is the physicians' privilege to use his/her expert medical opinion (Jansen & Gouws, 2009:447).

If negligence was found in prescribing medication to a patient and there were adverse drug reactions, patients may sue prescribers. The prescriber must therefore have conclusive evidence that the medication may be used off-label (Jansen & Gouws, 2009:447). When a physician is sued, it is the defending physician's responsibility to provide scientific evidence which approve the off-label use of the specific drug and that this drug is relevant, acceptable and does not have harmful effects for the patient (Jansen & Gouws, 2009:447). In South Africa, package inserts and other relevant documentation such as the South African Medical Formulary (SAMF) are taken into considerations when determining the safety and effective usage of drugs (Jansen & Gouws, 2009:448).

In South Africa there is no case law on a patient giving informed consent when receiving a prescription of off-label medication. Therefore, the court may order that if there is a deficiency in respect of such informed consent, it cannot be based solely on the off-label status of the medication not being revealed (Jansen & Gouws, 2009:447). Circumstances may also play a deciding role: if a medication is prescribed at a higher than approved dose, and it is standard practice to do so, it will be difficult to convince the court that this decision was based on material information. However, this will differ when medication is used for a different condition and in a different manner to which it was approved, even if it is regarded as standard practice to do so, e.g. the intravitreal injection of a medication to treat age-related macular degeneration (AMD) that was approved to be given intravenously for the treatment of metastatic cancer of the colon (Jansen & Gouws, 2009:447).

2.6 Off-label prescribing practices

Literature of the last ten years was evaluated to determine the prevalence of off-label prescribing in different countries, using the criteria, inception year and study period, number of prescriptions, gender and age, percentage off-label use and other noteworthy findings. Table 2.1 summarises these studies.

Table 2.1 Off-label prescribing practices in different countries

Country	Inception year & Study Period	Number of prescriptions	Gender/Age (N)	% off-label use	Other noteworthy findings	Author
Croatia	12 months; May 2010 – Apr 2011	1643	Gender not specified; <20 (neonates:0-28 days, preschool children 3-6 years, school children 7-11 years, adolescents 12-19 years) N = 531	46%	– Most commonly prescribed drug: Proton pump inhibitors	Palcevski *et al.* (2012:1073-1077)
Finland	2 weeks; 16 April 2001 – 25 May 2001	629	Gender not specified; <18 (New-born infants 0 - 27 days, infants and toddlers 28 days – 23 months, children 2 -11 years and adolescents 12 – 17 years) N = 108	49%	– Most prescribed drugs: Oxycodone, thiopental and ketamine	Lindell-Osuagwu *et al.* (2009:277-287)
France	6 months; January 2002 – June 2002	295	M = 235 F = 101 3 – 15 years N = 336	48%	– Main drug classes prescribed: Antipsychotics, stimulants and antidepressants – 61 Patients received antidepressants: Fluoxetine in 11 (18%) patients with depression and 9 (14.75%) with OCD. Sertraline is registered in patients older than 6 when used in OCD	Serreau *et al.* (2004:14-19)

Legend: M = Male; F= Female; Max = Maximum

Table 2.1: Off-label prescribing practices in different countries *continued*

Country	Inception year & Study Period	Number of prescriptions	Gender/Age (N)	% off-label use	Other noteworthy findings	Author
Italy	12 weeks; December 1998 - February 1999	4 265	M = 818 F = 643 3.7 years (1 month – 14 years) N = 1 461	60.0% (range 44% - 71%)	– Most common off-label indication: Respiratory disease – Main drug classes: Antibacterial, anti-asthmatics and analgesics	Pandolfini *et al.* (2002:339-347)
Italy	2 months; July 2004 – August 2004	176	Gender not specified 19 patients (26 – 36 weeks) 15 patients (37 - 39 weeks) N = 34	50.5% (22.7% no information on paediatric use, 27.8% was licensed in paediatric use, but off-label regard to age, dose, route of administration and duration of treatment)	– Main drugs prescribed: Parental nutrition infusions, amikacin, ranitidine, tobramycin, ofloxacin, calcium levofolinate, caffeine and sodium ferric gluconate complex	Dell'Aera *et al.* (2007:361-370)

Legend: M = Male; F= Female; Max = Maximum

Table 2.1: Off-label prescribing practices in different countries *continued*

Country	Inception year & Study Period	Number of prescriptions	Gender/Age (N)	% off-label use	Other noteworthy findings	Author
Nigeria	12 months; April 2003 – March 2004	2 190	Gender not specified Patients (aged 0 – 5 years) N =531	41.9%	– The crushing of tablets to make a suspension was the main cause of off-label usage and using dosages other than it was used registered for	Okechukwu (2009:63)
Serbia	2 years; January 2001 – February 2003	2 037	M = 282 (52%) F= 262 (48%) 4 hours – 18 years (Neonates 0 -27 days, infants and 28 days – 23 months, children 2 - 11 years and adolescents 12 – 17 years) N = 544	58% (Mostly by age and dosage)	– Most common drug prescribed off-label was: Cardiovascular drugs	Bajectic *et al.* (2005:775-779)
Switzerland	6 months; October 2001 – March 2002	483	M = 31 F = 29 3 days – 14 years (range 0.0 - 13.7 years; New-born infants 0 – 27 days, infants and toddlers 28 days – 23 months, children 2 – 11 years and adolescents 12 – 18 years) N = 60	49%	– Most common off-label uses were medicines that were manufactured in the pharmacy, and also not enough paediatric evidence on the off-label use	Di Paolo *et al.* (2006:218-222)

Legend: M = Male; F= Female; Max = Maximum

Table 2.1: Off-label prescribing practices in different countries *continued*

Country	Inception year & Study Period	Number of prescriptions	Gender/Age (N)	% off-label use	Other noteworthy findings	Author
United Kingdom	6 months; January 2002 – June 2002	777	Gender not specified; <18 years (20 days – 17 years) N = 308	49% (54% different indication, 22% paediatric age and 24% had no licence)	– "Medication for children" is the only formulary that had dosage information of more than half of the off-label prescribed drugs in paediatric gastroenterology	Dick *et al.* (2003:571-575)
United States	6 months; January 2004 – June 2004	1 383	Gender not specified; 4.7 years (range, 3 days – 18 years) N = 403	31%	– Most prescribed drug: Ondansteron, albeterol and ranitidine – Ketorolac was prescribed the most for pain when a patient suffered from sickle cell anaemia in vaso-oclusive crisis	Eiland and Knight (2006:1062-1065)
United States	12 months; January 2001 − December 2001	725 million drugs	Gender and age not specified	21%	– 15% of drugs prescribed lacked scientific evidence – 73.0% that lacked scientific evidence also lacked clinical effectiveness – 11% had strong scientific evidence for what it was used for	Radley *et al.* (2006:1023)

Legend: M = Male; F= Female; Max = Maximum

Table 2.1 shows evidence of off-label prescribing practices in several countries. These studies, however, were mostly performed between 2001 and 2004 and thus the prevalence may have changed considerably over the last 10 years. The most common reasons for drugs being used off-label was manufacturing in the pharmacy itself or drugs being used in an age group for which it was not registered. Furthermore, the drug classes most commonly prescribed were anti-asthmatic, cardiovascular drugs and antidepressants. Most studies identified, anaylysed medicine usage patterns in children; if therefore seems that there is a gap with regard to studies anaylysing off-label prescribing practises among adult patients.

2.7. Identification of antidepressants with known off-label indications

A detailed on-line literature search was performed to identify all antidepressant active substances listed as such based on the (Monthly index of medical specialities (MIMS) pharmacological classification system with off-label indications, searching Medline, the Cochrane Library, Pubmed, Scopus, Science direct, EbscoHost, and Google Scholar, for publications between the period 2000 and 2012, in any language. The following entry MeSH terms and boolean operators was used: “antidepressant*” OR “sertraline”, OR “citalopram”, OR “paroxetine”, “fluoxetine”, OR “fluvoxamine”, OR “escitalopram”, OR “duloxetine”, OR “venlafaxine”, OR “nefazodone”, OR “trazodone”, OR “reboxetine”, OR “amitriptyline”, OR “clomipramine”, OR “dosulepin”, OR “doxepin”, OR “imipramine”, OR “lofepramine”, OR “trimipramine”, OR “maprotiline”, OR “mianserin”, OR “mirtazapine”, OR “moclobemide”, OR “tranylcypromine”, OR “buspirone”, OR “agomelatine”, OR “carbamazepine”, OR “amantadine”, OR “diazepam”, OR “gabapentin”, OR “melatonin”, OR “pimozide”, OR “pregabalin”, OR “selegeline”, OR “topiramate”, OR “lithium”, OR “bupropion”, OR “maprotiline”, OR , “AND ”dose“ ”OR “off-label” OR “treatment” OR “effect” OR “outcome” OR “use”.

In this section, antidepressants (bupropion, citalopram, clomipramine, doxepin, escitalopram, fluoxetine, fluvoxamine, imipramine, lofepramine, paroxetine, reboxetine, sertraline, mianserin, mirtazapine, moclobemide, nefazadone, trazodone, trimipramine and venlafaxine) with known off-label indications as summarised in Table 2.2 will be discussed in terms of pharmacological classification, mechanism of action and use.

Table 2.2 Identified antidepressants with known off-label indications

Active ingredient	Dosage (Daily or otherwise stated)	Age (Years)	Indication(s)	Author and Year
Amitriptyline	10 mg titrated with 10 mg or 25 mg increase weekly to with a maximum of 150 mg	18 - 60	Migraine with or without aura	Keskinbora and Aydinli (2008:981)
Amitriptyline	25 mg daily	> 60	Postherpetic neuralgia in acute herpes zoster	Bowsher (1997:329)
Amitriptyline	10 mg daily	18 -75	Irritable bowel syndrome	Sohn *et al.* (2012:863)
Amitriptyline	0 µg/ml – 200 µg/ml	Study not done on patients (bacteria strains)	Antimicrobial and antifungal properties	Mandal *et al.* (2010:641)
Amitriptyline	75 mg daily	18 – 65	Pericranial myofacial pressure (Chronic tension-type headache)	Bendtsen and Jensen (2000:607)
Amitriptyline	Single and multiple doses	In rats	Inflammation	Vismari *et al.*(2010:237)
Agomelatine	25 mg or 50 mg	Not stated	Sleep wake cycles	Quera-Salva *et al.* (2010:226)
Bupropion	150 mg twice daily	Mean age 36 (18 - 50)	Sexual dysfunction in men on SSRIs	Safarinejad (2010:844)
Bupropion	150 mg – 300 mg daily	18 -64	General anxiety disorder	Bystritsky *et al.* (2008:49)
Citalopram	20 mg - 60 mg	24 - 46	Premature ejaculation	Atmaca *et al.* (2002:504)
Citalopram	10 mg	Not stated	Hot flushes	Barton *et al.* (2010:3278)
Cloimipramine	20 mg - 30 mg	44 - 72	Premature ejaculation	Rowland *et al.* (2001:358)
Doxepin	25 mg - 50 mg	Not stated	Insomnia	Wiegand (2008:2413)
Duloxetine	40 mg twice daily	Mean Age 65.8 (range: 47 - 78)	Stress incontinence after radical prostatectomy or cystectomy	Schlenker *et al.* (2006:1076)
Duloxetine	60 mg daily	Not stated	Treatment resistant schizophrenia receiving clozapine	Mico' *et al.* (2011:308)

Table 2.2 Identified antidepressants with known off-label indications*continued*

Active ingredient	Dosage (Daily or otherwise stated)	Age (Years)	Indication(s)	Author and Year
Escitalopram	10 mg - 20 mg	40 - 62	Pain and vasomotor symptoms in hot flushes	LaCroix *et al.* (2012)
Escitalopram	20 mg	Not stated	Migraine prophylaxis	Tarlaci (2009:257)
Espitalopram	10 mg	18 - 65	Reduce pain in opioid dependant patients receiving buprenorphine/naloxone	Tsui *et al.* (2011:2643)
Escitalopram	10 mg – 20 mg	Not stated	Hot flushes and other menopausal symptoms	DeFronzo Dobkin *et al.* (2009:74)
Escitalopram	10 mg - 20 mg	21 - 61	Obsessive-compulsive disorder in schizophrenic patients	Stryjer *et al.* (2013:97)
Fluoxetine	20 mg	Mean age 34.9 ± 10	Pain and constipation which is predominant in irritable bowel syndrome	Vahedi *et al.* (2005:383)
Fluoxetine	20 mg	Not stated	Pre- menstrual syndrome	Nazari *et al.* (2012)
Fluoxetine	20 mg – 40 mg daily	Not stated	Chronic headache	Saper*et al.* (1994:501)
Fluoxetine liquid	9.9 mg ± 4.35 mg	5 - 17	Repetitive behaviours in childhood autism	Hollander *et al.* (2005:588)
Fluvoxamine	Mean dosage of 260 mg	18 - 60	Binge eating disorder	Hudson *et al.* (1998:1759)
Fluvoxamine	200 mg	21 - 34	Bulimia nervosa	Milano *et al.* (2005:280)
Fluvoxamine	100 mg - 300 mg	18 - 65	Panic disorders	Asnis *et al.* (2001:5)
Imipramine	25 mg daily before bedtime	>18	Irritable bowel syndrome	Abdul-Baki *et al.* (2009:3637)
Lofepramine	70 mg twice daily	Not stated	Multiple sclerosis	Loder *et al.* (2002:600)
Mianserin	15 - 30 mg	Mean age 79.1 ± 7.4	Improved sleep in patients with dementia and sleep disorders	Camargos *et al.* (2012:577)
Mirtazapine	30 mg	≥ 18	Social phobia	Muehlbacher *et al.* (2005:582)
Mirtazapine	15 mg to 30 mg at night	18 - 60	Reduction in methamphetamine use	Colfax *et al.* (2011:3)
Mirtazapine	30 mg daily	Not stated	Generalized anxiety disorder	Gambi *et al.* (2005:486)
Moclobemide	300 mg	33.9 ± 2	Multiple sclerosis for the normalization of of the hypothalamus-pituitary-adrenal axis dysregulation	Then Bergh *et al.* (2001:1613)

Table 2.2 Identified antidepressants with known off-label indications *continued*

Active ingredient	Dosage (Daily or otherwise stated)	Age (Years)	Indication(s)	Author and Year
Nefazodone	Mean dosage of 332.4 mg (Range: 200 mg - 400 mg)	Mean age 46.1	Post traumatic stress disorder	Arafa and Shamloul (2006:535)
Paroxetine	10 mg for three days then 20 mg daily	Mean age 52	Treatment of hot flushes after chemotherapy of breast cancer	Weitner *et al.* (2002:342)
Paroxetine	20 mg	Mean age 37.5 (28 - 47)	Premature ejaculation	Sunay *et al.* (2011:765-771)
Paroxetine	5 mg/kg	Study done on mice	Acute pain	Duman *et al.* (2004:163)
Reboxetine/olanzapine	2 mg twice daily	Mean age 30.3 (19 - 48)	Less increase in appetite	Poyurovsky *et al.* (2007:444)
Sertraline	Mean dosage of 68.33 mg (50 mg - 100 mg)	Mean age 37.7	Post dramatic stress disorder	Saygin *et al.* (2002:2)
Sertraline	50 mg	18 - 65	Post traumatic stress disorder	Arafa and Shamloul (2006:535)
Sertraline	100 mg - 200 mg	18 - 65	Binge eating disorder	Leombruni *et al.* (2008:1604)
Sertraline	50 mg daily	40 - 65	Hot flushes	Gordon *et al.* (2006:573)
Trazodone	50 mg	Not stated	Insomnia	Stahl (2009:538)
Trimipramine	100 mg	Not stated	Insomnia improving polysomnographic sleep efficiency and rested feeling	Wiegand (2008:2413)
Venlafaxine	75 mg	Mean age 37.7 ± 7.8	Fibromyalgia	Sayar *et al.* (2003:1563)
Venlafaxine	37.5 mg daily for one week and 75 mg daily for 11 weeks	Not stated	Hot flushes	Evans *et al.* (2005:162)
Venlafaxine	50 mg - 75 mg	6 - 13	Attention deficit hyperactivity disorder	Zarinara *et al.* (2010:533)
Venlafaxine	75 mg daily	Not stated	Migraine prophylaxis	Tarlaci (2009:257)

Table 2.2 shows the identified active ingredients that have an identified off-label use, either by clinical trials and/or pilot studies. It is clear that most of the identified substances were given to patients with an age ranging between from 18 to 65 years. The antidepressant was used off-label for many different indications. The most common usage being for pain, premature ejaculation, eating disorders and post traumatic stress disorders.

The mechanism of action of all antidepressants with known off-label indications, as identified by the indication and dosage that it is registered for and the off-label indication is discussed in the following subsections. Appropriate dosages for each of the identified active substances will be described using the World Health Organization (WHO) reference guide for DDDs (WHO, 2011) and relevant articles.

2.7.3.1 Doxepin

2.7.3.1.1 Pharmacological classification

Doxepin is classified as a tricyclic antidepressant (Wiegand, 2008:2413).

2.7.3.1.2 Mechanism of action

Clinical effects are due to the deactivation of noradrenaline by re-uptake into nerve terminals (Phizer Roerig, 2005:11).

2.7.3.1.3 Indication and dosage

Doxepin is indicated for the treatment of depression in psychoneurotic patients, for anxiety and depression in alcoholics, depression in patients that havean organic disease and also in manic-depressive disorders (Phizer Roerig, 2005:11). The initial dosage is 75 mg daily for mild and moderate cases. Optimal dosages vary between 75 mg and 150 mg daily (Phizer Roerig, 2005:11). In more severe cases the dosage can be increased to a maximum of 300 mg daily (Phizer Roerig, 2005:11). The defined daily dosage (DDD) for doxepin is 100 mg (WHO, 2012).

2.7.3.1.4 Off-label use

According to Hajek *et al.* (2001:455), doxepin, administrated in dosages of 25 mg and 50 mg daily over a four week period has been shown to increase polysomnographical sleep efficiency. **Short-term insomnia** can, therefore, be treated with doxepin if there is some extent of related depressive symptomatology or some sort of history of depression (Hayek *et al.*, 2001:455).

Doxepin is not available in South Africa.

2.7.3.2 Trazodone

2.7.3.2.1. Pharmacological classification

Trazodone is classified by the SAMF as a serotonin reuptake inhibitor and receptor antagonist (Rossiter *et al.*, 2012:493).

2.7.3.2.2 Mechanism of action

Trazodone has hypnotic actions at low dosages by blocking serotonin 2A, histamine 1 and alpha-1 receptors. At high dosages, trazodone blocks the serotonin receptor rendering an antidepressive effect (Stahl, 2009:536; Yamadera *et al.*, 1998:442).

2.7.3.2.3 Indication and dosage

Trazodone is used for the treatment of mixed anxiety, acute depression and management of depression in initial dosages of 100 mg to 150 mg per day. This dose may be increased to 200 mg - 300 mg daily (Rossiter *et al.*, 2012:493). Treatment can be given as a single dose at night or in three to four divided dosages during the day. Hospitalised patients that are being monitored closely can receive up to 600 mg daily (Rossiter *et al.*, 2012:493). According to Rossiter *et al.* (2012:493) the initial dosage for the elderly is 50 mg daily. The DDD for trazodone is 300 mg (WHO, 2012). At the time of the study trazodone was available in South Africa as Molipaxin® and Aspen Trazodone®.

2.7.3.2.4 Off-label use

According to Stahl (2009:539), trazodone may be used off-label as a **hypnotic agent** in dosages of 25 mg to 100 mg daily. By increasing the dosage of trazodone to the extent that saturation of serotonin 2A receptors is exceeded this leads to stimulation of receptors other than serotonin 2A, where these receptors are responsible for other pharmacological reactions. In the dosage range between 25 mg to 150 mg, saturation of the serotonin transporter is lost, leading to a loss of antidepressant effect, while multifunction antagonist action at serotonin 2A, histamine 1 and alpha 1 receptors is retained, causing a hypnotic effect (Stahl, 2009:538).

2.7.3.3 Trimipramine

2.7.3.3.1 Pharmacological classification

Trimipramine is classified by the SAMF as a tricyclic antidepressant (TCA) (Rossiter *et al.*, 2012:487).

2.7.3.3.2 Mechanism of action

The mechanism of action of trimipramine is by the blockade of the amine transport system of the membrane at the adrenergic nerve terminal (SAEPI, 2012a).

2.7.3.3.3 Indication and dosage

Trimipramine is indicated for the treatment of depression, childhood enuresis and severe obsessive-compulsive neurosis in dosages 25 mg to 125 mg daily (SAEPI, 2012a). The DDD for trimipramine is 150 mg (WHO, 2012). Trimipramine is available in South Africa as Tydamine®.

2.7.3.3.4 Off-label use

According to Riemann *et al.* (2002:173) trimipramine increases **polysomnographical sleep efficiency** and the feeling of being rested in the morning when administered in dosages of 100 mg daily with a dosage range of 25 mg to 200 mg.

2.7.3.4 Amitriptyline

2.7.3.4.1 Pharmacological classification

Amitriptyline is classified by the SAMF as a TCA (Rossiter *et al.*, 2012:485).

2.7.3.4.2 Mechanism of action

Amitriptyline inhibits the reuptake of noradrenaline from the pump mechanism into adrenergic neurons (SAEPI, 2012c).

2.7.3.4.3 Indication and dosage

Amitriptyline is most commonly used for the treatment of endogenous depression. The agent

also has some sedative and calming effects which are useful in the treatment of anxiety that is normally present in depressed patients (SAEPI, 2012b). The initial dosage is normally 75 mg to 150 mg, followed by a maintenance dosage of 50 mg to 100 mg in divided dosages (SAEPI, 2012b). The DDD for amitriptyline is 75 mg (WHO, 2012). At the time of the study amitriptyline is available in South Africa as Limbitrol®, Sandoz Amitriptyline® and Trepiline®.

2.7.3.4.4 Off-label use

According to Ashkenazi and Silberstein (2003:342), modulating neurotransmitter systems are a new way of trying to prevent migraine rather than changing intracranial vascular tone. Thus, antidepressants and anti-epileptic drugs represent useful treatment options for **migraine prophylaxis**. Keskinbora and Aydinli (2008:980) found significant improvement in **migraine control** when amitriptyline was used for 8 and 12 weeks compared to the baseline, patients with migraine with or without aura, aged between 18 and 60 years were given 10 mg amitriptyline daily. The dose was increased weekly by increments of 10 mg to 25 mg daily. Dosages of up to 150 mg of amitriptyline were allowed. The study conducted over 12 weeks had an 8 week titration period and then a four week maintenance period (Keskinbora & Aydinli, 2008:980). Chronic tension-type headache tenderness can be reduced by amitriptyline 75 mg daily for 8 weeks; amitriptyline also reduces the grade of **pericranial myofacial pressure** (Bendtsen & Jensen, 2000:607).

Amitriptyline given in 25 mg daily for 90 days can reduce **postherpetic neuralgia** in older patients with acute herpes zoster (Bowsher, 1997:329).

According to Sohn *et al.* (2012:863) patients reported a significant relief in **irritable bowel syndrome** when given amitriptyline 10 mg daily for four weeks.

In a study done by Vismari *et al.* (2010:237), **anti-inflammatory effects** were found when amitriptyline was given in single and multiple doses to rats. There was also significant decrease in leukocyte behaviour. Amitriptyline has **antimicrobial activity both *in vitro and in vivo* and antifungal activity** (Mandal *et al.,* 2010:641).

2.7.3.5 Fluvoxamine

2.7.3.5.1 Pharmacological classification

Fluvoxamine is classified by the SAMF as a selective serotonin reuptake inhibitor (SSRI) (Rossiter *et al.*, 2012:489).

2.7.3.5.2 Mechanism of action

Fluvoxamine has precise serotonin reuptake inhibition in certain neurons in the brain, but only if there is little interference with noradrenergic processes. After oral administration of fluvoxamine the drug is absorbed rapidly and then transformed into inactive metabolites in the liver and excreted by the kidneys (SAEPI, 2012d).

2.7.3.5.3 Indication and dosage

Fluvoxamine is approved for use in obsessive compulsive disorder and for major depressive disorder (Kuntz, 1998:520; SAEPI, 2012d). When used for the treatment of obsessive compulsive disorder, the initial dosage is 50 mg for 3 to 4 days. There after the dosage can be titrated to 100 mg to 200 mg and can then be increased to 300 mg if the patient does not respond to the initial dosage. The DDD for fluvoxamine is 100 mg (WHO, 2012). At the time of the study, fluvoxamine was available in South Africa as Luvox®, Faverin 100® and Fluvoxamine-Hexal®.

2.7.3.5.4 Off-label use

Hudson *et al.* (1998:1759) found that fluvoxamine showed potential in the treatment of **binge eating disorder**, in patients aged 18 to 60 years. The authors established that a mean dosage of 260 mg in a 9 week period resulted in weight loss of 1.2272 kg compared to 0.1365 kg in the placebo group. The fluvoxamine group also had less binge eating episodes than the placebo group (Hudson *et al.*, 1998:1759). This effect of fluvoxamine may be ascribed to potential appetite suppressive characteristics. According to Hudson and colleagues, the effect on appetite may also be caused by nausea (being the most common side effect of fluvoxamine).

Milano *et al.* (2005:280) found that fluvoxamine in dosages of 200 mg daily for 12 weeks could be used to treat **bulimia nervosa** in patients between the ages of 21 to 34 years. Milano *et al.* (2005:278) suggest that the mood disturbances that are related to bulimia nervosa can be a result of the reduction in serotonin levels.

A study conducted by Asnis *et al.* (2001:5) found that fluvoxamine in the dosage range of 100 mg to 300 mg daily for 8 weeks couldbe used to treat **panic disorders** in patients aged 18 to 65 years.

2.7.3.6 Fluoxetine

2.7.3.6.1 Pharmacological classification

Fluoxetine is classified by the SAMF as a SSRI (Rossiter *et al.*, 2012:488).

2.7.3.6.2 Mechanism of action

Fluoxetine is a serotonin reuptake inhibitor and thus blocks the inhibition of serotonin reuptake, thereby increasing the levels of serotonin in the brain (SAEPI, 2012e).

2.7.3.6.3 Indications and dosage

Fluoxetine is used for the treatment of major depressive episodes. It can be a single episode of depression or several episodes that are associated with anxiety (SAEPI, 2012e). According to the South African electronic package inserts (2012e), fluoxetine may also be used for the treatment of obsessive compulsive disorder. Fluoxetine is furthermore indicated for the treatment of bulimia nervosa and binge eating disorder (SAEPI, 2012e). When used in major depressive disorders the dosage is 20 mg in the morning, but can be given in divided dosages of up to 80 mg when needed (SAEPI, 2012e). In obsessive compulsive disorders a dosage of 20 mg to 60 mg is given and 60 mg daily in bulimia nervosa (SAEPI, 2012e). The DDD for fluoxetine is 20 mg (WHO, 2012). At the time of the study fluoxetine was available in South Africa as Prozac®, Lorien®, Lilly-Fluoxetine®, Nuzak®, Rezak®, Ranflocs®, Sandoz Fluoxetine 20®, Zydus-Fluoxetine®, ProHexal®, A-Lennon Fluoxetine®, Fluoxetine Actor 20®, Deprozan® and Trizac®.

2.7.3.6.4 Off-label use

Fluoxetine (20 mg), co-prescribed with buspirone (10 mg), has shown potential in the treatment of **premenstrual syndrome** in female patients (mean age 23 years) (Nazari *et al.,* 2012).

A study conducted by Vahedi *et al.* (2005:383) showed that fluoxetine given 20 mg daily for 12 weeks could be used to treat **pain and constipation, which are predominant in irritable bowel syndrome**.

According to Hollander *et al.* (2005:588) fluoxetine in liquid for administration in a mean dosage of 9.9 mg ± 4.35 mg daily was an effective treatment in **repetitive behaviours in childhood autism** in children of 5 -17 years of age.

Fluoxetine 20 mg to 40 mg showed significant improvement in chronic daily **headache** in the third month of a double-blind trial (Saper *et al.*, 1994:501).

2.7.3.7 Sertraline

2.7.3.7.1 Pharmacological classification

Sertraline is classified by the SAMF as a SSRI (Rossiter *et al.*, 2012:490).

2.7.3.7.2 Mechanism of action

Sertraline is believed to inhibit neuronal uptake of serotonin (SAEPI, 2012f).

2.7.3.7.3 Indication and dosage

Sertraline is indicated for the treatment of major depressive episodes and repeating episodes of obsessive compulsive disorder. It is sometimes used for panic attacks either with or without agoraphobia (SAEPI, 2012f). When used in major depressive disorder the dosage is 50 mg daily, but this can be increased every two weeks by 50 mg to a maximum dosage of 150 mg to 200 mg (SAEPI, 2012f). Obsessive compulsive disorder is treated with 50 mg daily; 100 mg has no additional benefit. Effects are usually seen after 2 to 4 weeks, but results can be seen after just 7 days (SAEPI, 2012f). In panic attacks a dosage of 25 mg daily is usually enough, but can be increased to 50 mg daily after one week (SAEPI, 2012f). The DDD for sertraline is 50 mg (WHO,2012). At the time of the study sertraline was available in South Africa as Zoloft®, Serdep 50®, Serdep 100®, Sertraline Winthrop®, Arrow Sertraline®, Austell-Sertraline®, Serlife®, Zolid®, Sertra®, Sertzol® and Zylin®.

2.7.3.7.4 Off-label use

Sertraline is effective for the treatment of **premature ejaculation** in dosages of 50 mg daily (Arafa & Shamloul, 2006:535). The delay in ejaculation and anorgasmia can be related to high levels of serotonin neurotransmission (Arafa & Shamloul, 2006:535). Activation of serotonin 2C receptor will delay ejaculation whereas activation of serotonin 1A will contribute to ejaculation inactivity (Waldinger, 2005:106).

In a study involving 30 patients with an average age of 37.7 years, sertraline was administered in a dosage range varying between 50 mg to 100 mg, with an average dosage of 68.4 mg. A statistically significant improvement of **post-traumatic stress disorder** was found (Saygin *et*

al., 2002:2).

Sertraline, given 25 mg for 3 days and increased to between 100 mg to 200 mg in increments of 25 mg every third day can be used to treat **binge eating disorder, in** patients aged 18 to 65 years (Leombruni *et al,.* 2008:1604).

A study conducted by Gordon *et al.* (2006:573), found that sertraline given in 50 mg daily could significantly lower the count of **hot flushes** per week.

2.7.3.8 Citalopram

2.7.3.8.1 Pharmacological classification

Citalopram is classified by the SAMF as a SSRI (Rossiter *et al.*, 2012:487) and a bicyclic phthalate derivative (SAEPI, 2012g).

2.7.3.8.2. Mechanism of action

Citalopram is a selective inhibitor of seretonin reuptake (SAEPI, 2012g).

2.7.3.8.3 Indication and dosage

Citalopram is indicated for the treatment of depression and panic disorder with or without agoraphobia (SAEPI, 2012g). When used for depression in adults citalopram is taken in single dosages of 20 mg - 60 mg daily. The maximum dosage for the elderly is 30 mg daily (SAEPI, 2012g). When used in panic disorder 10 mg is usually enough, but can be titrated to 20 mg after one week with a maximum dosage of 60 mg daily (SAEPI, 2012g). The DDD for citalopram is 20 mg (WHO, 2012). At the time of the study citalopram was available in South Africa as Cipramil®, Adco-Talomil®, Cilate®, Cilift®, CitaloHexal®, DRL-Citalopram®, Sandoz-Citalopram®, Austell-Citalopram-Winthrop®, Arrow-Citalopram®, Bio-Citalopram®, Citalopram Actor 20®, Ciloram®, and Depramil®.

2.7.3.8.4 Off-label use

A statistically significant improvement was noted in **hot flushes** in all patients taking citalopram in dosages of 10 mg, 20 mg and 30 mg, when compared to placebo, but no difference was found between patients on different strengths of the drug, which leads to the conclusion that a 10 mg dosage is significant (Barton *et al.*, 2010:3278).

Citalopram, in dosages of 20 mg to 60 mg for 8 weeks, is also effective in the treatment of **premature ejaculation** in men aged 24 to 46 years (Atmaca *et al.*, 2002:504).

2.7.3.9 Nefazodone

2.7.3.9.1 Pharmacological classification

Nefazodone is classified by Brunton *et al.* (2006:435) as an atypical antidepressant.

2.7.3.9.2 Mechanism of action

Nefazodone, a phenylpiperazine antidepressant, blocks the serotonin type 2 receptor ($5HT_2$) (SAEPI, 2012).

2.7.3.9.3 Indication and dosage

Nefazodone should be administered in divided dosages up to 200 mg per day for depression. Dosages may be increased to 100 to 200 mg intervals every second week (Bristol-Myers Squibb Company, 2003). The DDD for nefazodone is 400 mg (WHO, 2012). Nefazodone is not available in South Africa.

2.7.3.9.4 Off-label use

A mean dosage of 332.4 mg per day or 200 to 400 mg daily was given to men and women with post-traumatic stress disorder with a mean age of 46.13 years. A statistically significant improvement was seen in **post-traumatic stress disorder** (Saygin *et al.*, 2002:2).

2.7.3.10 Escitalopram

2.7.3.10.1 Pharmacological classification

Escitalopram is classified by the SAMF as a SSRI (Rossiter *et al.*, 2012:490).

2.7.3.10.2 Mechanism of action

Escitalopram is a SSRI that inhibits the uptake of serotonin in the brain (SAEPI, 2012h).

2.7.3.10.3 Indication and dosage

Escitalopram's registered indication is major depressive episodes (SAEPI, 2012h). It is also used for panic disorder (SAEPI, 2012h). The normal dosage when used in major depressive disorder is 10 mg daily, but this may be increased to 20 mg daily if necessary, depending on the patient's response to the medication (SAEPI, 2012h). In panic disorder an initial dosage of 5 mg is given for one week and thereafter increased to 10 mg per day. The dosage also may be increased to 20 mg daily if the response was not well enough (SAEPI, 2012h). The DDD for escitalopram is 10 mg (WHO, 2012). At the time of the study escitalopram was available in South Africa as Citraz®, Mylan-Escitalopram®, Zytomil®, Cipralex®, Aspen Escitalopram® and Lexamil®.

2.7.3.10.4 Off-label use

Escitalopram causes a statistically significant increase in the quality of life in women with hot flushes (LaCroix *et al.*, 2012). This improvement was also seen in vasomotor symptoms and reduction of pain. Escitalopram furthermore shows a superior effect on **pain in woman with hot flushes** which previously had depression and anxiety (LaCroix *et al.*, 2012). Defronzo Dobkin *et al.* (2009:74), found that escitalopram was effective in reducing hot flushes and other menopausal symptoms in healthy women that would not normally consider antidepressant treatment.

Migraine can be prevented by using escitalopram 20 mg daily for a 3 month period in patients that do not have depression or anxiety (Tarlaci, 2009:257).

Escitalopram in dosages of 10 to 20 mg daily can be used to improve **obsessive-compulsive disorders in schizophrenic patients** (Stryjer *et al.*, 2013:97).

Tsui *et al.* (2011:2643) found that escitalopram 10 mg daily can significantly **reduce pain in opioid dependant patients receiving buprenorphine/naloxone**.

2.7.3.11 Paroxetine

2.7.3.11.1 Pharmacological classification

Paroxetine is classified by the SAMF as a SSRI (Rossiter *et al.*, 2012:489).

2.7.3.11.2 Mechanism of action

Paroxetine is a selective inhibitor of serotonin (SAEPI, 2013a).

2.7.3.11.3 Indication and dosage

Paroxetine is mostly used for the treatment of major recurrent depressive episodes, and can also be used in single depressive episodes. A low dosage is often prescribed later to prevent relapse and more depressive episodes (SAEPI, 2013a). Paroxetine is also used in panic disorder, but mostly in combination with cognitive therapy. Paroxetine is sometimes used for obsessive compulsive disorder, but this is only when social functioning is at risk or the disorder may be time consuming (SAEPI, 2013a). The DDD for paroxetine is 20 mg (WHO, 2012). At the time of the study paroxetine was available in South Africa as Adco-Paroxetine®, Deparoc®, Paxil®, Xet 20®, Austell-Paroxetine®, Aropax®, Paroxetine Unicorn 20®, Serrapress® and Parax 20®.

2.7.3.11.4 Off-label use

In a pilot study, a dose of paroxetine was given to women with hot flushes and other symptoms associated with breast cancer. The dose given was 10 mg at night for 3 days and then increased to 20 mg per day at night (Weitner *et al.*, 2002:341). The administration of these doses showed three definite results: a definite decreasing effect of **hot flushes** in woman that had previously received chemotherapy for breast cancer, a positive effect on mental and emotional fatigue with a substantial progression in vigour and finally, a definite sleep improvement was found in these patients. When estrogen levels decreases in the brain either as a result of menopause or chemotherapy induced menopause, a reduction of serotonin levels as released from the neurons is observed (Bäckström, 1995:181). These abnormal levels have a negative effect leading to depression and irritation, as well as other symptoms that often occur in menopause (Bäckström, 1995:181). The end result being increased fatigue and sleepiness (Weitner *et al.*, 2002:341). Paroxetine can be used for women who have chemotherapy induced hot flushes in addition to natural occurring hot flushes (Weitner *et al.*, 2002:341).

According to Sunay *et al.* (2011:770), paroxetine given in dosages of 20 mg daily significantly improved **premature ejaculation** when given to male patients with a mean age of 37.5 years (range: 28 to 47 years).

A study done by Duman *et al.* (2004:163) found that paroxetine has definite antinoceptive properties in acute pain, when administered in mice. Duman and colleagues found that

paroxetine had similar antinoceptive effects as morphine in magnitude.

2.7.3.12 Reboxetine

2.7.3.12.1 Pharmacological classification

Reboxetine is classified by the SAMF as a noradrenaline reuptake inhibitor (NARI) (Rossiter *et al.*, 2012:495).

2.7.3.12.2 Mechanism of action

Reboxetine has little to no affinity for muscarinic receptors and blocks noradrenaline reuptake. Reboxetine also has a weak inhibitory effect on serotonin reuptake (Rossiter *et al.*, 2012:495; SAEPI, 2013b).

2.7.3.12.3 Indication and dosage

Reboxetine is indicated for the treatment of depressive illness and major depression in dosages of 8 mg daily. The dosage may be increased to 10 mg per day if no clinical response is seen (SAEPI, 2013b). The DDD for reboxetine is 8 mg (WHO, 2012). At the time of the study reboxetine was available in South Africa as Edronax®.

2.7.3.12.4 Off-label use and dosage

Reboxetine acts as a noradrenalin reuptake inhibitor and is regarded as safe and well tolerated in schizophrenic patients who are taking olanzapine. It is believed to have an attenuating effect on the weight gain induced by olanzapine (Poyurovsky *et al.*, 2007:445).

2.7.3.13 Venlafaxine

2.7.3.13.1 Pharmacological classification

Venlafaxine is classified by the SAMF as a SNRI (Rossiter *et al.*, 2012:495).

2.7.3.13.2 Mechanism of action

Venlafaxine inhibits serotonin and noradrenaline reuptake (Rossiter *et al.*, 2012:495).

2.7.3.13.3 Indication and dosage

Venlafaxine is indicated for the treatment of major depressive disorder, generalised anxiety disorder and social anxiety disorder in an initial dosage of 75 mg. Doses can be increased to 150 mg daily after two weeks to a maximum of 225 mg per day. In exceptional cases, the dosage can be increased to 375 mg daily (Rossiter *et al.*, 2012:495). The DDD for venlafaxine is 100 mg (WHO, 2012). At the time of the study venlafaxine was available in South Africa as Efexor XR®, Efegen XR®, Sandoz-Venlafaxine XL®, Illovex SR®, Venlor XR® and Odiven®.

2.7.3.13.4 Off-label use

According to Evans *et al.* (2005:162), venlafaxine is effective in the control of **hot flushes,** given in dosages of 37.5 mg daily for one week and then 75 mg daily for 11 weeks. Venlafaxine has also been shown to be effective for the treatment of **fibromyalgia** in dosages of 75 mg given for 12 weeks (Sayar *et al.*, 2003:1562). Zarinara *et al.* (2010:533) furthermore showed that venlafaxine could be used to treat **attention deficit hyperactivity disorder** in patients aged 6 to 13 years in dosages of 50 mg to 75 mg daily for 6 weeks. Tarlaci (2009:257) found that migraine could be prevented with venlafaxine 75 mg daily for 3 months in patients without depression or anxiety.

2.7.3.14 Bupropion

2.7.3.14.1 Pharmacological classification

Bupropion is classified by the SAMF as a dopamine reuptake inhibitor (Rossiter *et al.*, 2012:495).

2.7.3.14.2 Mechanism of action

Bupropion inhibits dopamine reuptake (Rossiter *et al.*, 2012:495).

2.7.3.14.3 Indication and dosage

Bupropion is used in depressive disorders and nicotine addiction (Zyban®) at a starting dosage of 150 mg daily that can be increased to 300 mg in divided dosages with a maximum dosage of 150 mg every eight hours (Rossiter *et al.*, 2012:495). The DDD for bupropion is 300 mg (WHO, 2012)**.** At the time of the study bupropion was available in South Africa as Wellbutrin SR® and Wellbutrin XL®.

2.7.3.14.4 Off-label use

Men with major depressive disorder treated with SSRIs sometimes have sexual dysfunctions (Williams *et al.*, 2006:209). A study conducted by Safarinejad (2010:844) showed that bupropion slow release tablets (dosages of 150 mg twice daily) had significantly improved the negative effect on **sexual dysfunction** in men with a mean age of 36 years that previously had sexual dysfunction when using a SSRI. There was also a significant increase in the patient's sexual intercourse frequencies per week (Safarinejad, 2010:844).

A study done by Bystritsky *et al.* (2008:49) found that bupropion in dosages of 150 mg to 300 mg daily might be useful to treat general anxiety disorder in patients aged 18 to 64 years.

2.7.3.15 Mirtazapine

2.7.3.15.1 Pharmacological classification

Mirtazapine is classified by the SAMF as a tetracyclic antidepressant and is further sub-classified into the piperazino-azapine group (Rossiter *et al.*, 2012:492).

2.7.3.15.2 Mechanism of action

Mirtazapine acts as a pre-synaptic alpha 2–antagonist. The drug therefore increases serotonin and noradrenaline neurotransmission in the central nervous system (SAEPI, 2013c). Post-synaptic serotonin receptors (serotonin 2A, serotonin 2C and serotonin 3) are also blocked and causes serotonin down-regulation, probably causing the anti-depressive effect (SAEPI, 2013c).

2.7.3.15.3 Indication and dosage

Mirtazapine is used in major depressive illness (SAEPI, 2013c). The starting dose for mirtazapine is 15 mg daily, but may be increased to an effective clinical dosage of 15 mg to 45 mg (SAEPI, 2013c). Doses should be increased by 15 mg intervals over a period of one to two weeks. In the case of acute depressive episodes, mirtazapine should be administered for a period of at least six months. Withdrawal from mirtazapine should be conducted by titrating the dose slowly (SAEPI, 2013c). The DDD for mirtazapine is 30 mg (WHO, 2012). At the time of the study mirtazapine was available in South Africa as Adco-Mirteron®, Aspen Mirtazapine®, Mylan-Mirtazapine®, Mytra®, Sandoz-Mirtazapine® and Remeron®.

2.7.3.15.4 Off-label use

Muehlbacher *et al.* (2005:581) found that women aged 18 years or older given 30 mg of mirtazapine for **social phobia** experienced a significant improvement in social anxiety between one and seven weeks, compared to those on placebo (Muehlbacher *et al.*, 2005:582). Patients also felt a definite decrease in emotional problems when on mirtazapine (Muehlbacher *et al.,* 2005:583). In a study conducted by Colfax *et al.* (2011:8), mirtazapine was given in a dose of 15 mg at night for a week and then 30 mg a night for 12 weeks, which showed a significant **decrease in methamphetamine use** in patients ranging from 18 to 60 years of age (Colfax *et al.*, 2011:3).

Generalized anxiety disorder can be treated with mirtazapine 30 mg with definite improvement from the first week (Gambi *et al.,* 2005:486).

2.7.3.16 Imipramine

2.7.3.16.1 Pharmacological classification

Imipramine is classified by the SAMF as a TCA (Rossiter *et al.*, 2012:485).

2.7.3.16.2 Mechanism of action

Imipramine is a tricyclic antidepressant which has weak anticholinergic and antihistaminic actions (SAEPI, 2013d). According to Harvey (2013), these actions are relative only to other TCAs.

2.7.3.16.3 Indication and dosage

Imipramine is indicated for the treatment of Parkinson's disease, chronic alcoholism, endogenous depression and several behavioural disorders in children (SAEPI, 2013d). The initial dosage is normally 75 mg to 150 mg in adults, 10 mg to 30 mg in the elderly, 50 mg for children over 12 years of age and 25 mg for children aged 6 to 12 years (SAEPI, 2013d). The DDD for imipramine is 100 mg (WHO, 2012). At the time of the study imipramine was available in South Africa as Tofranil® and Ethipramine®.

2.7.3.16.4 Off-label use

A study conducted by Abdul-Baki *et al.* (2009:3637) reported that imipramine might be effective in the use of **irritable bowel syndrome** in dosages of 25 mg before bedtime in patients 18 years and older. The average age range of patients in the study was 42.6 to 45.3 years. Abdul-Baki *et al.* (2009:3637) suggest that this positive effect on irritable bowel syndrome may be due to a modulation of the brain-gut neurologic axis.

2.7.3.17 Clomipramine

2.7.3.17.1 Pharmacological classification

Clomipramine is classified by the SAMF as a TCA (Rossiter *et al.*, 2012:485).

2.7.3.17.2 Mechanism of action

Clomipramine, a tricyclic antidepressant, has antimuscarinic and sedative properties that prevent the uptake of noradrenalin and serotonin at nerve terminals, thus causing an antidepressive effect (SAEPI, 2013e).

2.7.3.17.3 Indication and dosage

Clomipramine can be used to treat mainly major depression, reactive depression and secondary depression and obsessive compulsive disorder (OCD) (SAEPI, 2013e). Dosages must be initiated at a 25 mg dose and can be titrated in increments of 25 mg every 3 to 4 days, to a total of 150 mg daily. Maintenance dosages are normally in the range of 50 mg to 100 mg daily, up to a maximum of 250 mg per day (SAEPI, 2013e). The DDD for clomipramine is 100 mg (WHO, 2012). At the time of the study clomipramine was available in South Africa as Anafranil®, Clomidep® and Equinorm®.

2.7.3.17.4 Off-label use

Rowland *et al.* (2001:358-359) found that clomipramine 20 mg and 30 mg daily significantly improved ejaculation latency times in men that did not respond to 25 mg clomipramine as needed for **premature ejaculation**. The average age range of men in the study was 44 to 72 years (Rowland *et al.*, 2001:358).

2.7.3.18 Lofepramine

2.7.3.18.1 Pharmacological classification

Lofepramine is classified by the SAMF as a TCA (Rossiter *et al.*, 2012:486).

2.7.3.18.2 Mechanism of action

Possible mechanism of lofepramine inhibits uptake of tyramine and noradrenaline into peripheral adrenergic nerves (SAEPI, 2013f).

2.7.3.18.3 Indication and dosage

Lofepramine is used in depressive illnesses at initial dosages of 70 mg to 140 mg in divided daily dosages (SAIPI, 2013f). The dosage may be increased in the first week of treatment from 140 mg to 210 mg daily in divided dosages according to the patient's individual needs, but the dosage should be reduced to a maintenance dosage of 70 mg twice daily after the desired relief has been obtained (SAIPI, 2013f). The DDD for lofepramine is 105 mg (WHO, 2012). Lofepramine is available in South Africa as Emdalen®.

2.7.3.18.4 Off-label use

A study conducted by Loder *et al.* (2002:600) showed that lofepramine in combination with L-phenylalanine and vitamin B12 had a significant effect in reducing **multiple sclerosis** in dosages of 70 mg two times a day. By improving the functioning of the locus *coeruleus/lateral tegmentum* system lofepramine improves all types of multiple sclerosis (Loder *et al.*, 2002:601). The mechanism may involve the regulation of central noradrenergic systems (Loder *et al.*, 2002:601).

2.7.3.19 Agomelatine

2.7.3.19.1 Pharmacological classification

Agomelatine is classified by the SAMF as a melatonergic agonist (Rossiter *et al.*, 2012:495).

2.7.3.19.2 Mechanism of action

Agomelatine acts as an agonist on the melatonin 1 and melatonin 2 receptors and antagonises the serotonin 2c receptor, thus having an antidepressive effect (Rossiter *et al.*, 2012:495).

2.7.3.19.3 Indication and dosage

Agomelatine is used in major depressive disorder in dosages of 25 mg at bedtime and may be increased to 50 mg at bedtime after two weeks (Rossiter *et al.*, 2012:495). The DDD for agomelatine is 25 mg (WHO, 2012). Agomelatine is available in South Africa as Valdoxane®.

2.7.3.19.4 Off-label use

In a study conducted by Quera-Salva *et al.* (2010:226), a significant **increase of sleep-wake** cycles at night was shown in depressed patients. Agomelatine was given in either 25 mg or 50 mg dosages daily for six weeks and the effect of agomelatine on sleep-wake cycles may be ascribed to the serotonin 2C antagonism (Quera-Salva *et al.*, 2010:228). There was a significant increase in the daytime functioning seen from the first weeks as the patients started taking agomelatine (Quera-Salva *et al.*, 2010:228).

2.7.3.20 Moclobemide

2.7.3.20.1 Pharmacological classification

Moclobemide is classified by the SAMF as a monoamine oxidase inhibitor (MAOI) (Rossiter *et al.*, 2012:490).

2.7.3.20.2 Mechanism of action

Moclobemide shows reversible inhibition of monoamine oxidase type A enzyme, and by doing this also decreases the metabolism of serotonin, dopamine and noradrenaline, but increases the extracellular concentrations of these neurotransmitters to have the needed antidepressive effect (SAIPI, 2013g).

2.7.3.20.3 Indication and dosage

Moclobemide is indicated for the treatment of major depression with an initial dose of 300 mg daily in divided dosages after meals for the first week and then increased to 600 mg daily after

week one if needed, due to bioavailability increasing in the first week (SAIPI, 2013f).

In social phobia the dosage is 300 mg in divided dosages for the first 3 days, but must be increased to 600 mg in divided dosages after day 3 for 6 to 8 weeks. Moclobemide should be continued if the patient responds well to treatment (SAEPI, 2013g). The DDD for moclobemide is 300 mg (WHO, 2012). At the time of the study moclobemide is available in South Africa as Depnil®.

2.7.3.20.4 Off-label use

Moclobemide in dosages of 300 mg for 75 days can be used off-label as co-treatment with corticosteroids (flucortolone) for the treatment of **multiple sclerosis, in order to normalise the dysregulation of the hypothalamus-pituitary-adrenal axis** (Then Bergh *et al.*, 2001:1611). Dexametazone helps to down regulate the hypothalamus-pituitary-adrenal axis that is mediated by the glucocorticoid (flucortolone), and thus reflects a negative feedback on the hypothalamus (Then Bergh *et al.*, 2001:1614).

2.7.3.21 Mianserin

2.7.3.21.1 Pharmacological classification

Mianserin is classified by the SAMF as a tetracyclic antidepressant (Rossiter *et al.*, 2012:492).

2.7.3.21.2 Mechanism of action

Mianserin blocks alpha-2 presynaptic receptors, thus increasing noradrenaline in the brain (Rossiter *et al.,* 2012:492).

2.7.3.21.3 Indication and dosage

Mianserin is indicated in depressive illnesses in an initial dosage of 30 mg to 40 mg daily with a maintenance dosage of 30 mg to 90 mg daily, adjusted to the patient's needs (SAIPI, 2013h). The DDD for mianserin is 60 mg (WHO, 2012). Mianserin is available in South Africa as Lantanon®.

2.7.3.21.4 Off-label use

A study conducted by Camargos *et al.* (2012:577) showed that mianserin in dosages of 15 mg

at bedtime and increased to 30 mg after one week significantly **improved sleep in** patients **with dementia and sleep disorders** at a mean age of 79.1 ± 7.4 years**.**

2.7.3.22 Duloxetine

2.7.3.22.1 Pharmacological classification

Duloxetine is classified by the SAMF as a SNRI (Rossiter *et al.*, 2012:494).

2.7.3.22.2 Mechanism of action

Duloxetine is an inhibitor of the reuptake of both serotonin and noradrenaline specifically (Rossiter *et al.*, 2012:494).

2.7.3.22.3 Indication and dosage

Duloxetine is indicated in the treatment of depression, diabetic peripheral neuropathic pain and is registered in other countries for fibromyalgia, generalised anxiety disorder and chronic musculosketal pain in doses of 60 mg daily. For patients with renal impairment, doses should be decreased to 30 mg daily (Rossiter *et al.,* 2012:495). The DDD for duloxetine is 60 mg (WHO, 2012). At the time of the study duloxetine was available in South Africa as Cymbalta® and Cymgen®.

2.7.3.22.4 Off-label use

Duloxetine can be used to treat **stress incontinence after radical prostatectomy or cystectomy** in doses of 40 mg twice daily in patients with a mean age of 65.8 years (range: 47 to 78 years) for a mean duration of 9.4 weeks of treatment (range: 1 to 35 weeks) (Schlenker *et al.,* 2006:1076).Mico *et al.* (2011:308), found that duloxetine can be used in **treatment-resistant schizophrenia** in dosages of 60 mg daily when a patient is resistant to clozapine alone.

2.8 Chapter summary

This chapter gave an overview of what off-label prescribing is, the need for and difficulties that arise when prescribing off-label, the prevalence of off-label prescribing in several countries, the different regulations that have to be met in different countries when prescribing off-label, and central nervous system drugs that are also used for off-label indications. Antidepressants with

identified off-label indications were identified in different journal articles. Hereby the specific objectives set for the literature study, were achieved. Chapter 3 focuses on the empirical investigation phase of the study.

CHAPTER 3

Empirical Investigation

3.1 Introduction

This study consisted of two phases (refer to paragraph 1.5). Phase one was documented in Chapter 2 (literature review) and focused on the identification of antidepressants with documented off-label indications. Specifics of phase two (empirical investigation), are documented in this chapter.

3.2 Study design

A quantitative and observational, descriptive cross-sectional design was followed in this study. **Quantitative studies** give trends in drug use over a period of time. It gives information on which drugs are used by whom in the specific time period (Wettermark *et al.*, 2008:162). According to Ott and Longnecker (2010:18) an **observational study** is described as a study where "*the researcher records information concerning the subjects under study without any interference with the process that is generating the information".* A **cross-sectional study** is described by Banergee (2003:72) as *"a defined population that will be studied in a single time interval, these types of studies is used to determine the prevalence of disease and its characteristics".*

3.3. Research method

In this study, a retrospective drug utilisation review (DUR) was performed on medicine claims data. Diseases were identified using ICD-10 codes.

The World Health Organization Expert Committee (1977) defined **drug utilisation** as "*The marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences".* Wettermark *et al.* (2008:159) gave a more recent definition and described **drug utilisation** studies as "*an eclectic collection of descriptive and analytical methods for the quantification, understanding and evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes*." This definition clearly states that drug utilisation studies define all social-economic principles in the medical world and the safe use of medication as a whole for individuals and the population. In addition, drug utilisation studies are there to optimise drug use and safety for the patient.

In **retrospective drug utilisation** studies drug therapy is reviewed after the medication has been prescribed and dispensed to the patient (Fulda *et al.,* 2004:433). This type of review is used to detect prescribing patterns of medications (WHO, 2003:9). The review is further used to prevent the repetition of medication which is used incorrectly, to decrease medication abuse and improve prescribing by practitioners (Radloff & Jones, 2007:34; WHO, 2003:9). Retrospective DUR may help prescribers to fulfil their patients' needs through rationalising the use of drugs by their patients (WHO, 2003:9).

3.4 Data source

The pharmaceutical data examined in the study was obtained from a medicine claims database of a South African Pharmaceutical Benefit Management (PBM) company . According to Ferver *et al.* (2009:11), claims databases contain information on transactions submitted to an electronic database that have taken place between patients and health care providers. These may include medical aid scheme transactions, claims in hospitals, clinics, nursing homes, pharmacies and individual providers. According to Matshidze and Hanmer (2007:92) claims data within the South African context refer to data that are being collected through the submission or access to benefits by health care providers, usually in the form of clinical, financial and administrative information. The transmission of this data happens to take place on a daily basis by reimbursement processes and paper claims (Matshidze & Hanmer, 2007:92).

The PBM is a privately owned South African managed care organisation that has been doing business for the past 25 years. The PBM Company provides real time electronic pharmaceutical claims processing services to approximately 35 medical schemes in South Africa, which include an estimated 1.5 million beneficiaries. Data for over a period of a year, beginning January to December 2010 were obtained for analysis. The data set consisted of medicine claims for a total number of 1 220 289 patients, containing a total of 8 515 428 prescriptions and 20 527 777 medicine items (refer to Table 4.1).

3.5 Study population

The study population is described by Ott and Longnecker (2010:24), as "*the complete collection of being selected in the sample*".

All patients that received antidepressants were identified using the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD–10) to identify the antidepressants received in South Africa for the year of 2010. The study population was selected from these patients consisting of all patients, 18 years and older (refer to Figure 3.1).

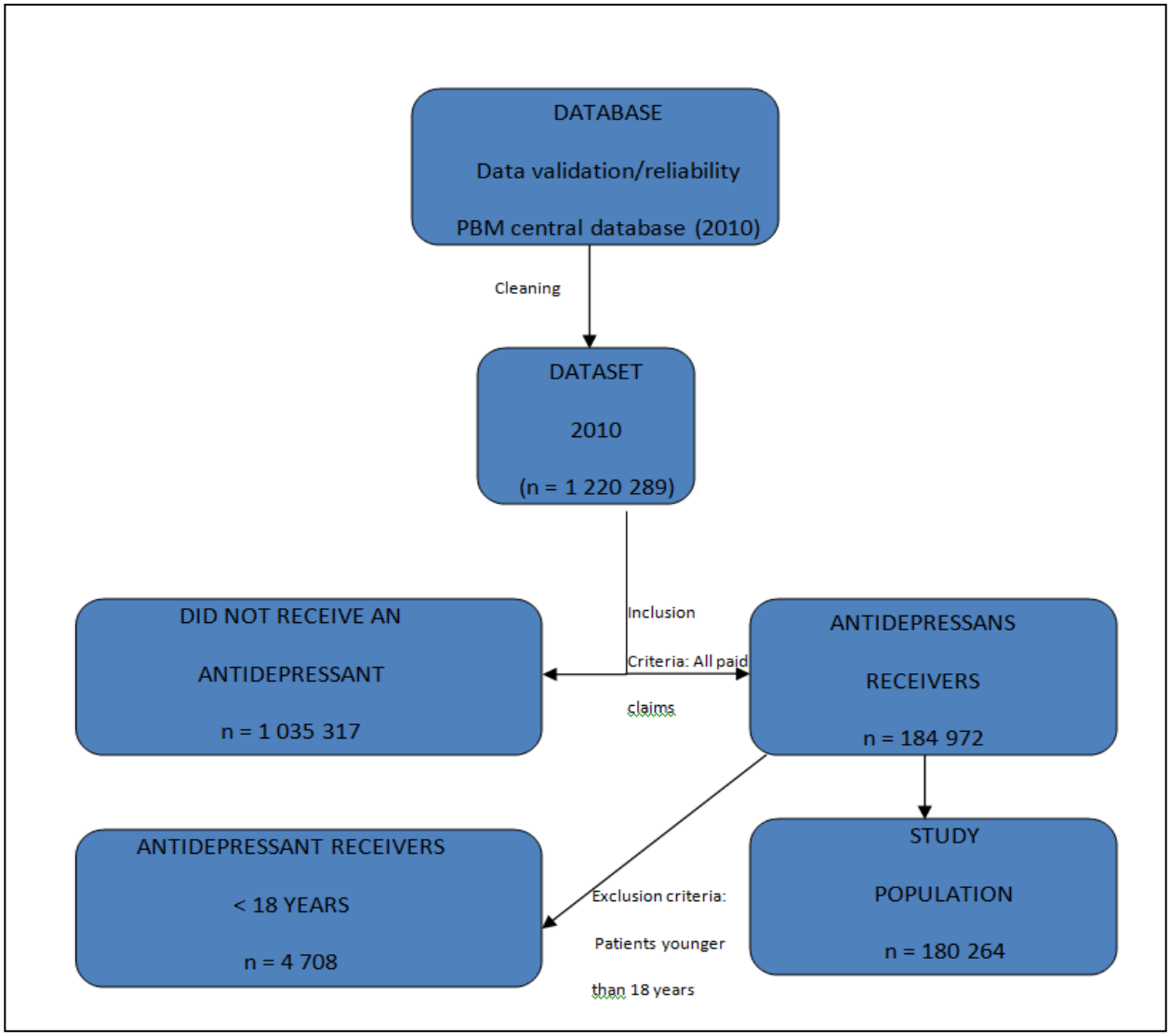

Figure 3.1: Selection of the study population

Cleaning of data was done by deleting duplicate scripts and all scripts containing only non-medicine items. The MIMS® classification code for each active ingredient on the specific data set was inserted (refer to Table 3.1). All paid claims were used and the antidepressant receivers were obtained. The study population was achieved by excluding all patients younger than 18 years of age.

Table 3.1 consists of the PMBs central database data elements available for research.

Table 3.1 Data elements included in the PBMs database selected for research

Type of data	Selected data element
Membership	Date of birth Gender Anonymous membership identifier Anonymous member dependant identifier
Medicine claims	Anonymous prescriber type identifier Anonymous provider identifier National Pharmaceutical Product Interface(NAPPI®)-code Active ingredient Drug trade name Quantity dispensed ICD-10 codes

3.6 Study variables

In this section, all the study variables that were used in this study will be discussed (Table 3.1).

3.6.1 Age

The age of the patients in this study was calculated according to the prescription date in relation to the patient's date of birth. The age of patients were then divided into 4 groups:

- ≤ 43 years
- > 43, ≤ 56 years
- > 56, ≤ 68 years
- > 68 years

Figure 3.2 shows the age distribution of all patients on the data set, all patients on antidepressants and the study population.

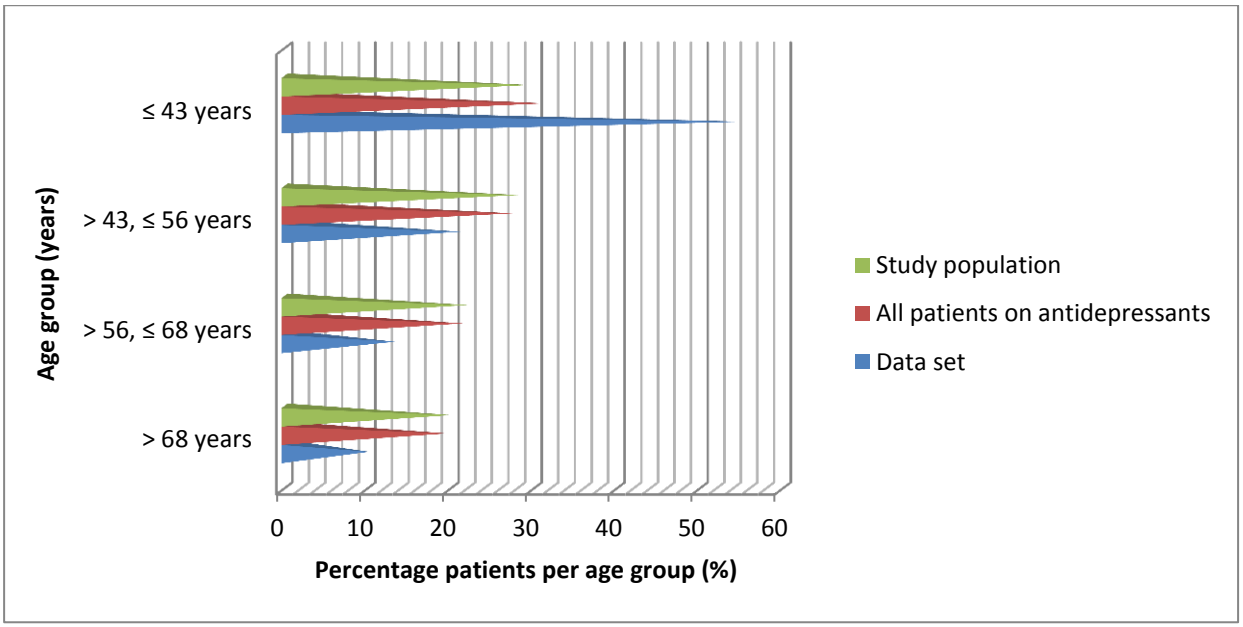

Figure 3.2 Distribution of percentage of patients per age group

Most of the patients on the data set are 43 years and younger. In the study population there is an almost equal number of patients in each age group. The average age of patients receiving antidepressants was 56.1 ± 16.6 (median = 56.2) (IQR = 43.3–68.1) This was much higher than the average age of 29.3 years and 32.9 years for restricted and open medical schemes, respectively, for the year of 2010 (CMS, 2010).

3.6.2 Gender

For the purpose of this study the term gender was used to signify male or female.

3.6.3 Prescriptions and medicine items

The Collins Concise Dictionary (2004) defines a prescription as *"written instructions from a physician to a pharmacist stating the form, dosage, strength, etc., of drug to be issued to a specific patient".* Medicine is defined as "*Any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in the diagnoses, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man"* in terms of the Medicines and Related Substances Control Act (Act 101/1965) as amended. For the purpose of this study the term "medicine" was used to describe any product, substance or active ingredient claimed for a patient included in the database.

3.6.4. Identification of patients and prescriber

Refer to Table 3.1 for codes that are used by the PMB to identify the patient or prescriber.

3.7 Classification systems

Two classification systems were used to select the medicine being referred toin the study.

3.7.1 National Pharmaceutical Product Interface (NAPPI®)-code

Monthly Index of Medical Specialities (MIMS®) classification system and the NAPPI®codes (refer to Table 3.1) of each active ingredient were linked for the purpose of the study.

3.7.2 International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10)

For the purpose of this study the ICD-10 classification system was used to identify the off-label and labelled usage of antidepressants in the study population.

The WHO (2010) explains the ICD as to be a *"standard diagnostic tool for epidemiology, health management and clinical purposes".* This may either be *via* analysis of general health in the population, monitoring of incidence and prevalence of disease, classification of diseases for medical aids, used for mortality and morbidity statistics, and decision making on medicine in some countries. The ICD-10 classification system was introduced in May 1990 and came into use in 1994 in the WHO Member States (WHO, 2010). This classification system was only introduced in the private health care sector of South Africa in July 2005 (Matshidze & Hanmer, 2007:95).

- Claim codes (ICD-10 codes) for antidepressants were categorised as follows: off-label, none, indication, other and mixed, where off-label signifies all claims associated with the ICD-10 codes registered for the off-label use of antidepressants (refer to Tables 2.2 and A.3, Annexure A). The category none was used to signify claims where no ICD-10 code was indicated. The category indication was used to signify all registered ICD-10 codes for the specific antidepressant as determined from the MIMS classification 1.4. The category other was used where the ICD-10 claim code was neither for a registered indication nor an off-label indication. Mixed refers to claims where more than one ICD-10 code where captured per claim (refer to Annexure A, Table A.3).

3.7.3 Classification of antidepressants

Antidepressants can be classified into groups for this study by using the South African Medicines Formulary (SAMF) and the Monthly Index of Medical Specialities (MIMS®) (refer to Table A.1). Table A.1 summarises the classification of antidepressants available in South Africa. This table also includes doxepin and nefazodone that are not available in South Africa.

3.8 Data analysis

The data were analysed using the Statistical Analysis System® SAS 9.3® (SAS Institute Inc., 2002-2010).

3.9 Measures of utilisation

The general measures of utilisation volume in this study were frequency and prevalence (refer to paragraph 3.10.1), and certain drug utilisation measurement-instruments such as defined daily dose (DDD), prescribed daily dose (PDD), DU90% methodology and odds ratio. The following section contains all the measures of utilisation and their application that were used in the study.

3.9.1 Defined daily dose (DDD) and prescribed daily dose (PDD)

The World Health Organization (2011:22) describes the defined daily dose (DDD) as "*the supposed average maintenance dose per day for a drug used for its main indication in adults*." According to Teng *et al.* (2012:1119), the DDD may also represent the ''recommended dosage'' referred to in some literature as the *Pharmacopoeia* or a calculated appropriate dose from clinical reference books.

Limitations of DDDs can essentially be overcome by the prescribed daily dose (PDD) system that gives the actual average dosage prescribed by practitioners calculated *via* a medicine claims database (Serradell*et al.*, 1987:995). The WHO (2003:14) defined the PPD as the *"average dose prescribed according to a representative sample of prescriptions."* The PDD can be determined using prescription studies and pharmacy records. The PDD should relate to the diagnoses of the medication received. The PDD will only present the medication that was dispensed and not the consumption of the medication. The number of DDDs were calculated as follows (refer to paragraph 4.9):

$$\text{Number of DDDs} = \frac{\bar{x} * p}{WHO\ DDD}$$

where:

$\bar{x}$ = mean of what

p = number of prescriptions

WHO DDD = DDD for the specific active ingredient, as assigned by the WHO (WHO, 2011).

3.9.2 DU90% methodology

The DU90% method is an easy way to assess the quality of everyday prescribing practices (Bergman *et al.*, 1998:113; Wettermark *et al.*, 2003:500). The DU90% represents all drugs that account for 90% of claims (Bergman *et al.*, 1998:115).

The DU90% method was used in this study to determine the prevalence of antidepressant prescriptions by prescriber, gender and age groups.

3.9.3 Odds ratio (OR)

The Odds ratio is described by Pelham (2013:114) as *"A ratio between the odds for two potentially related but distinct events".* The odds ratio was calculated as follows (Ott & Longnecker, 2010:531):

$$Odds\ of\ an\ event\ A = \frac{\mathrm{P(A)}}{1 - \mathrm{P(A)}}$$

where:

Odds of an event A= Odds of the event happening

P*(A)* = Probability of event A

1 – P*(A)* = Probability of event A not happening

For the purpose of the study the odds ratios was used to determine the probability of males and females receiving an antidepressant *vs.* not receiving an antidepressant.

3.10 Statistical analysis

In this section, all the statistics used in this study will be discussed.

3.10.1 Frequency and prevalence

The Collins Concise Dictionary (2004) defines frequency as "*the number of individuals in a class"* and prevalence rate is described as the total of patients with a condition divided by the

total patients at risk (Mckenzie *et al.,* 2011:67). Frequency and prevalence included all patients on the dataset in relation to age and gender.

3.10.2 Average (arithmetic mean)

Banergee (2003:3) describes the arithmetic mean as "*the sum of all values making up the set of observations divided by the total number of observations in the set".* The arithmetic mean was calculated as follows (Anderson *et al.,* 2009:83):

$$\bar{x} = \frac{\sum x}{n}$$

Where:

$\bar{x}$ = average

x = value of the data set

$\sum x$ = the sum

n = number of observations

The arithmetic mean was used to determine the average of the number of prescriptions and medicine items received, ages of patients, gender and prescribed daily dosage (PDD) of the study population.

3.10.3 Weighted average

Weighted average is comparable to the mean except some values contribute more interest than other to the final value, whereas the mean all the data points contribute equally to the final value (Petrie and Sabin, 2005:16). Microsoft® Office Excel 2010 was used to calculate the weighted average using the following formula:

$$Weighted\ average = SUMPRODUCT(Xi{:}Xn, Yi{:}Yn)/SUM(Yi{:}Yn)$$

where:

X_i = average of first observation

X_n = average of the last observation

Y_i = frequency of the first observation

Y_n = frequency of the last observation

The weighted average was used to determine the average of the group of herpes neuralgic pain (refer to Table 4.5).

3.10.4 Standard deviation

The standard deviation is described by Pelham (2013:35), as "*an average measure of how*

much each of the scores in the sample differs from the sample mean". The standard deviation was calculated as follows (Pelham, 2013:29):

$$S = \sqrt{\frac{\sum(x-m)^2}{n}}$$

where:

s = standard deviation

x=individual score in our study population

m = mean

n = number of observations

This equation was used to determine the spread of the age of patients receiving antidepressants and spread of number of prescriptions in both gender groups.

3.10.5 Median

Banergee (2003:3) describes the median as the central value or also known as the 50th percentile of a set of observations ranked in order of their magnitude; thus the median divides the observations in two halves. The median was used in conjunction with arithmetic means and standard deviations to present the number of prescriptions received by half of the patients in the data set along with the average (refer to paragraph 3.10.2).

3.10.6 Range and interquartile range

Range is the difference between the highest and lowest values in an entire set of scores (Pelham, 2013:6). Banergee (2003:5) describes the interquartile range as the central or 50% of a distribution. The range rank the data in four even quartiles: the second quartile is the same as the median were the first and third quartile gives the centre of the lower and upper data. In the study the range and interquartile range were used to illustrate the age range of the patients receiving antidepressants.

3.10.7 Effect sizes *(d*-values)

Pelham (2013:29), describes the *d*-value *as "how different two means are in standard deviation units".* The effect sizes were calculated as follows (Steyn, 2009):

$$d = \frac{mean\ 1 - mean\ 2}{\mathit{Smax}}$$

where:

d = effect size

mean 1= average 1

mean 2= average 2

$\delta_{\max}$ = maximum standard deviation between mean 1 and mean 2

The *d*-value can be interpreted as follows (Cohen, 1988:25):

d = 0.2 Small effect

d = 0.5 Medium effect which is observable.

d = 0.8 Large effect

Effect sizes of ≥ 0.8 were deemed practically significant (Steyn, 2009). In this study the effect size (*d*-value) was used to determine practical significance in difference between averages (refer to paragraph 4.4.2).

3.11 Reliability and validity

The research was conducted as if the data were correct and accurate. Results were obtained from only one database and thus interpretation can only be generalised in accordance with this database. The PMB providing the data have a validation process in place to ensure the validity and reliability of the data: eligibility services, gate-keeping services, utilisation management services, clinical management services and real time benefit management (refer to Table A.1, Annexure A and Table 3.2).

To ensure reliable results, the study was conducted following the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)–checklist for retrospective database studies (refer to Table 3.2).

Table 3.2 Checklist of the application of retrospective database studies (Motheral *et al.,* 2003:90-96)

Considerations	Aspect	Checklist item	Approach followed/Cross-reference
Data source	**Relevance**	Have the data attributes been described in sufficient detail for decision makers to determine whether there was a good rationale for using the data source? Has the generalisability of the data source been described?	Refer to paragraph 3.11
	Reliability and validity	Was the reliability and validity of the data described? Was there any quality checks performed? Were there any data cleaning procedures?	Random checks were performed to ensure the validity of the data being used. Data cleaning to place by deleting non-paid claims and non-medicine items. A validation process is done by the PMB providing the data to ensure the validity and reliability of the data (refer to Table A.2, Annexure A)
	Data linkages	Have the necessary linkages among data sources and/or different and/or care sites been carried out appropriately?	Complex data programming was used to obtain the data and was imported into the SAS® for Windows 9.3 analytical programme. Further, random checks on the data set were performed to validity after transposing.
	Eligibility	Was the type of data used to determine member eligibility been described?	In accordance with the confidentiality agreement patients' and health plans were not available for research. Eligibility could therefore not be assessed. This is seen as a study limitation.
Methods	**Research design**	Was a data analysis plan, including study hypothesis developed *a priori?*	The study followed a quantitative and observational, cross-sectional design (refer to paragraph 3.2).
	Design selection	Was a rationale for the particular research design provided?	Refer to paragraph 3.2
	Research design limitations	Has design as potential limitation of the study been identified and addressed?	
	Treatment effect	Were a comparison group specified for studies that were trying to make inferences about the effects of interventions?	Not applicable.
Study population and variable definitions	**Sample selection**	Were the inclusion and exclusion criteria described? Were the steps used to derive the final sample from the initial population described?	Refer to paragraphs 3.4.1 and 3.4.2. Retrospective database studies refer to paragraph 3.3
	Eligibility	Are subjects eligible for the time period over which measurement is occurring?	In accordance with the confidentiality agreement patients' on health plans were not available for research. Eligibility could therefore not be assessed. A validation process is done by the PMB providing the data to ensure the validity and reliability of the data (refer to Table A.2, Annexure A)
	Censoring	Were inclusion/exclusion or eligibility criteria used to address censoring and was the impact on study findings discussed?	

Table 3.2 Checklist of the application of retrospective database studies *(continued)*

Considerations	Aspect	Checklist item	Approach followed/Cross-reference
Study Population and variable definitions *(continued)*	**Definition validity**	Were a rationale and/or supporting literature for the definitions and criteria used? Was sensitivity analysis performed for definitions or criteria that are controversial, uncertain, or novel?	Not applicable
	Timing of outcome	Is there a clear temporal (sequential) relationship between the exposure and outcome?	This was a cross-sectional (refer to paragraph 3.2)
	Event capture	Are the data, as collected, able to identify the intervention and outcomes if they actually occurred?	The database only includes data for medicine items claimed. Out-of-pocket expenditure could therefore not be assessed.
	Disease history	Is there a link between the natural history of the disease being studied and the period for analysis?	This was a cross-sectional (refer to paragraph 3.2)
	Resource valuation	Was an exhaustive list of resources affected by the intervention defined and measured? Were resource prices adjusted to yield a consistent valuation that reflected the opportunity cost of the resource?	Not applicable
Statistics	**Influential cases**	Was the sensitivity of the results to influential cases examined?	Yes
	Relevant variables	Were all variables identified hypothesized to influence the outcome of interest? Were all available variables included in the model?	Yes (refer to paragraph 3.6)
	Statistical models	Was the rationale for the model/statistical method used, explained?	Yes (refer to paragraph 3.9 and 3.10)
	Statistical assumptions	Was the validity of the statistical assumptions underlying analysis, investigated?	Not applicable.
	Multiple tests	If analysis of multiple groups is carried out, are the statistical tests adjusted to reflect this?	Not applicable
	Model prediction	If multivariate statistical techniques are used, discuss how well the model predicts what it is intended to predict?	Practical/statistical analysis performed for all variables refer to paragraph 3.10 and chapter 4
	Control variables	Was a method employed to control for other variables that may affect outcome in studies that examine treatment effects?	Not applicable
Discussions and Conclusions	**Theoretical basis**	Was a theory provided for the findings and have they ruled out other plausible alternative explanations for the findings?	Refer to chapter 4.
	Practical *vs*. statistical significance:	Have the statistical findings been interpreted in terms of their clinical or economic relevance?	Refer to chapter 4
	Generalizability	Have populations and settings to which the results can be generalised, been discussed?	Yes (refer to paragraph 3.11)

3.12 Ethical considerations

Patients, medical schemes, medical practice, pharmacies could not be identified. There was thus no confidentially breach in this study. This study was authorised by the Ethics committee of the North-West University (NWU-00005-07-A5) and the board of directors of the PBM. Data privacy and confidentiality were maintained at all times. Thus, no patient data, medical scheme could be traced and it is not possible to determine which prescriber or provider where involved in the prescribing and dispensing of these medicine items.

3.13 Chapter summary

This chapter consisted of the research methodology followed during the empirical investigation of the study. This included the introduction, study design, data source, study population, the study variable, data analysis and study measures. The validity and reliability of the data were explained and ended with the ethical considerations of the study.

CHAPTER 4

Results and discussion

4.1 Introduction

This chapter will focus on the results and discussion of the empirical investigation phase of the study consisting of a quantitative, observational, descriptive cross-sectional drug utilisation review, described in chapter 3.

4.2 Annotations regarding the data analysis/reporting of results

The subsequent definitions and notes pertain to the data analysis and results in this chapter:

- Data set refers to the 2010 set of data obtained from the pharmaceutical benefit management (PBM) company.
- Beneficiaries are principal members and dependants who were registered as medical aid schemes members in South Africa in terms of the Medical Schemes Act (Act 131/1998) for the period of Jan. 1, 2010 to Dec. 31, 2010.
- Patient refers to any beneficiary who received a prescription/medicine item(s) during the study period, recorded as a “paid claim”.
- Numerical values were rounded up and will thus not necessarily count up to 100%.
- Off-label included all patients with ICD-10 codes in the off-label indication column (refer to paragraph 3.7.2; and Table A.3, Annexure A).
- Indicated included all patients with ICD-10 codes in the indication column (refer to paragraph 3.7.2 and Table A.3, Annexure A).
- Other included all patients without an ICD-10 code in Table A.3 (refer to Annexure A, Table A.3).
- None included all patients where there was no ICD-10 code captured on the claims database for a claim.
- Mixed refers to claims where more than one ICD-10 code were captured per claim (refer to Annexure A, Table A.3).

4.3 Outline for the presentation of results

Section 4.4 gives a general overview of the data set. The study population was selected by the application of exclusion and inclusion criteria (refer to Figure 3.1), which further entailed the demographic overview in terms of beneficiaries in accordance with the Medical Schemes Act, (Act 131/1998) in South Africa, as well as the general prescribing patterns on the data set.

Section 4.5 provides a discussion of the general prescribing patterns of patients receiving antidepressants during the study period. The discussions focus on prevalence of antidepressant usage, stratified by age group and gender.Section 4.6 is a section summary of the total data set and all patients receiving antidepressants for the study period.

The third section, section 4.7, focuses on the study population (patients aged ≥ 18 years and older who received an antidepressant during the study period). It provides an overview of prescribers of antidepressants summarised by the DU90% method, and gives an overview of antidepressants prescribed most in both gender and age group analysis.

The fourth section 4.8 contains the analysis, results and discussion of the utilisation of the antidepressant active ingredients in relation to gender and age.

Results of an analysis of off-label antidepressant prescribing are given in section 4.9. Different claim categories were viewed. Further, all antidepressant in the off-label claim category that had a claim in accordance with the data set and literature from chapter 2 were included in this section.

4.4 General overview of the data set

This section gives an overview of the complete data set that was obtained from the central database from the PBM for the period of 1 January, 2010 to December 31, 2010, based on this specific analysis:

- Review of demographic analysis of study population on the respective data set.
- Review of the prescribing patterns of medicine items from the data set, stratified by age and gender.

The findings discussed in the next section are based on the frequency values in Table 4.1.

Table 4.1: General characteristics of the total data set, and study population

	Total data set	Antidepressants (%)	Study population (%)
Total Number of patients(n)	**1 220 289**	**184 972 (15.2)**	**180 264 (14.8)**
Women	661 007	130 590 (19.8)	128 148 (19.4)
Men	559 282	54 382 (9.7)	52 116 (9.3)
Age group 1 (≤43 years)	675 519	58 050 (8.6)	53 342 (7.9)
Women	360 406	40 710 (11.3)	38 268 (10.6)
Men	315 113	17 340 (5.5)	15 074 (4.8)
Age group 2 (> 43, ≤56 years)	258 219	50 950 (19.7)	50 950 (19.7)

Table 4.1: General characteristics of the total data set, and study population *continued*

	Total data set	Antidepressants (%)	Study population (%)
Women	138 289	35 907 (26.0)	35 907 (26.0)
Men	119 930	15 043 (12.5)	15 043 (12.5)
Age group 3 (> 56, ≤68 years)	161 751	39 694 (24.5)	39 694 (24.5)
Women	86 707	27 498 (32.2)	27 498 (32.2)
Men	75 044	12 196 (16.3)	12 196 (16.3)
Age group 4 (> 68 years)	124 800	36 278 (29.1)	36 278 (29.1)
Women	75 605	26 475 (35.0)	26 475 (35.0)
Men	49 195	9 803 (19.9)	9 803 (19.9)
Total number of prescriptions(n)	**8 515 428**	**704 443 (8.3)**	**692 325 (8.1)**
Women	5 032 177	512 000 (10.2)	505 952 (10.1)
Men	3 483 251	192 443 (5.5)	186 373 (5.4)
Age group 1 (≤43 years)	3 075 771	168 876 (5.5)	156 758 (5.1)
Women	1 799 468	121 043 (6.7)	114 995 (6.4)
Men	1 276 303	47 833 (3.7)	41 763 (3.3)
Age group 2 (> 43, ≤56 years)	1 982 988	186 009 (9.4)	186 009 (9.4)
Women	1 145 821	135 471 (11.8)	135 471 (11.8)
Men	837 167	50 538 (6.3)	50 538 (6.3)
Age group 3 (> 56, ≤68 years)	1 708 914	175 063 (10.2)	175063 (10.2)
Women	984 130	124 421 (11.6)	124 421 (11.6)
Men	724 784	50 642 (7.0)	50 642 (12.6)
Age group 4 (> 68 years)	1 747 755	174 495 (10.0)	174 495 (10.0)
Women	1 102758	131 065 (11.9)	131 065 (11.9)
Men	644 997	43 430 (6.7)	43 430 (6.7)
Total number of medicine items(n)	**20 527 777**	**715 157 (3.5)**	**702 885 (3.4)**
Women	12 103038	519 587 (4.3)	513 461 (4.2)
Men	8 424 739	195 570 (2.3)	189 424 (2.2)
Age group 1 (≤43 years)	6 837 506	172 336 (2.5)	160 064 (2.3)
Women	3 928 694	123 397 (3.1)	117 271 (3.0)
Men	2 908 812	48 939 (1.7)	42 793 (1.5)
Age group 2 (> 43, ≤56 years)	4 709 676	189 132 (4.0)	189 132 (4.0)
Women	2 705 175	137 739 (5.1)	137 739 (5.1)
Men	2 004 501	51 393 (2.6)	51 393 (2.6)
Age group 3 (> 56, ≤68 years)	4 331 680	177 598 (4.1)	177 598 (4.1)
Women	2 495 270	126 183 (5.1)	126 183 (5.1)
Men	1 836 410	51 415 (2.8)	51 415 (2.8)
Age group 4 (> 68 years)	4 648 915	176 091 (3.8)	176 091 (3.8)
Women	2 973 889	132 268 (4.4)	132 268 (4.4)
Men	1 675 016	43 823 (2.6)	43 823 (2.6)

4.4.1 Demographic overview of the data set

The data set for 2010 consisted of information of approximately 1.2 million patients. These

patients represented 14.7% of all medical aid schemes beneficiaries (N = 8 315 718) registered in terms of the Medical Schemes Act (Act 131/1998) during 2010, in South Africa (CMS, 2011:159).

There were fewer men than women in the total data set for 2010 (female: male ratio 1.8), in accordance with the total number of beneficiaries registered in terms of the Medical Schemes Act (Act 131/1998) for 2010 (female: male ratio 1.1) (CMS, 2011:159).

4.4.2 General prescribing patterns on the data set

Approximately 8.5 million prescriptions and 20.5 million medicine items were claimed during the study period.

According to Achat *et al.* (2010:135), women, in general, tend to have a higher prescription claim rate than men. In accordance, more than half of all prescriptions (59.1%, n = 8 515 428) (Table 4.1) claimed during the study period were for women. Most of the medicine items claimed were subsequently for women, representing 59.0% (n = 20 527 777) (Table 4.1).

Patients received an average of 7.0 ± 7.9 (median = 4) prescriptions during the study period. Although not of practical significance (*d*-value = 0.2), the average number of prescriptions claimed per patient was marginally higher for women (7.6 ± 8.4 for women) compared to that for men (average number of prescriptions per patient per year 6.2 ± 7.2).

Using the DU90% method (refer to paragraph 3.9.2), the prescriber categories responsible for 90% of prescriptions during the study period were determined. The DU90% for prescribers was achieved with prescriptions by general practitioners (76.6%) and psychiatrists (19.6%, n = 1 220 289).

4.5 General overview of all patients receiving antidepressants for the study period

In this section, a demographic overview is given, and general prescribing patterns for patients who received antidepressants on the data set, is discussed in relation to the demographic overview and general prescribing patterns of all patients on the database.

4.5.1 Demographic overview of all patients on the data set receiving antidepressants

A total of 184 972 (15.2%) patients received antidepressants during the study period. Women tend to have more psychological barriers to overcome and are more vulnerable to adverse life

events; these are factors that contribute to the prevalence of depression in men and women (Beck *et al.*, 2005:802; Piccinelli & Wilkinson, 2000:490), with subsequent higher drug use. In accordance, men receiving antidepressants were about half that of women. The present study showed that 14.8% (n = 1 220 289) of all patients and 9.3% of men *vs.* 19.4% of women received antidepressants.

The average age of patients receiving antidepressants was 56.1 ± 16.6 years (median = 56.2) (IQR = 43.3–68.1).

4.5.2 General prescribing patterns of patients receiving antidepressants

The 2010 annual review of Mediscor showed that antidepressant utilisation represented 12% of all medicine items prescribed during 2010 (Badenhorst *et al.*, 2011:12-14). This was a higher percentage than in 2005 where antidepressant utilisation represented a total of 10.9% of all medicines received in 2005 (Bester *et al.*, 2006:8). According to Croghan (2001:129-135), an increase in antidepressant prescribing may be ascribed to an increase in the number of prescribers of antidepressants (e.g. both psychiatrists and general practitioners are allowed to prescribe antidepressants). The prescribing of newer antidepressants also increases rapidly after introduction and then level off after a while; this may also be a cause for this increase (Pirraglia *et al.,* 2003:153-157). The discovery of new indications for the use of antidepressants may also be a reason for the increase in the use thereof (Pirraglia *et al.,* 2003:153-157).

The average number of antidepressant prescriptions claimed per patient was 5.3 ± 4.6 (median = 3) for the study period. About 8.3% (n = 8 515 428) of prescriptions and 3.5 % (n = 20 527 777) of all medicine items claimed during the study period were for antidepressants. Antidepressant claimed for women represented 72.6% (n = 715 157) of all antidepressant medicine items claimed. Compared to men, the odds for women receiving antidepressants were also higher in all age groups, e.g. women from age groups one (≤ 43 years) and two (aged > 43, ≤ 56 years) had an odds ratio of 2.1, compared to women aged > 56, ≤ 68 (age group 3) that had an odds ratio of 2.0 and women aged > 68 years (age group 4) that had an odds ratio of 2.1.

Figure 4.1 gives the prevalence percentage (%) of all antidepressant prescriptions (n = 704 443) and medicine items (n = 715 157) claimed during the study period, by age and gender.

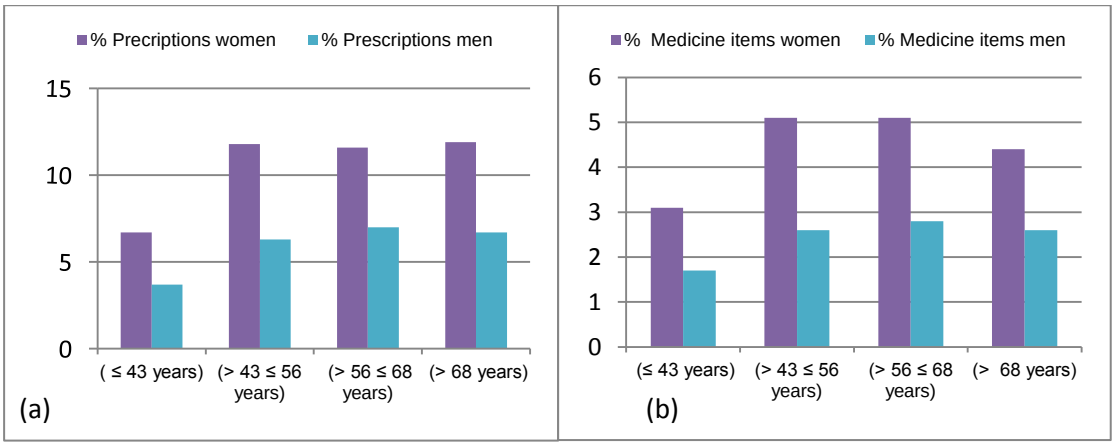

Figure 4.1 Overall antidepressant prescription and medicine item claims for the study period

Antidepressant prescription claims for women (Figure 4.1a) increased with age from 6.7% (n = 1 799 468) on the data set for patients in age group one (≤ 43 years) to 11.9% (n = 1 102 758) in age group 4 (< 68 years). This trend, although to a lesser degree, was also observed in men where there was an increase from 3.7% (n = 1 276 303) in age group one to 6.7% (n = 644 997) in age group four (Figure 4.1a).

The number of antidepressant medicine claims for women (Figure 4.1b) increased from 3.1% (n = 3 928 694) in age group one (≤ 43 years) to 4.4% (n = 2 973 889) in age group four (> 68 years). Similar trends were observed in men where the number of antidepressant medicine claims increased from 1.7% (n = 2 908 812) in age group one to 2.6% (n = 1 675 016) in age group four.

4.5.3 DU90% for prescribers of antidepressants

The DU90% for prescribers of all antidepressants was achieved with general medical practitioners and psychiatrists, prescribing 75.6% and 15.1% of all antidepressant prescriptions (n = 715 157) during the study period.

4.6 Section summary

Antidepressants prescribing account for a vast number of prescriptions in the study period. Burger *et al.* (2009:72) found that women tend to use more antidepressants than men; the findings of the present study are similar to the study by Burger and colleagues, showing that 10% of patients who received medicine paid claims on the data set received an antidepressant.

Woman received more antidepressants than men, but there were also more women on the data

set. General practitioners (GPs) were responsible for most prescriptions. The average age of all patients receiving antidepressants was similar to that of beneficiaries in South Africa during 2010, where the average age was 32.9 years.

4.7. Study population

4.7.1 Demographic overview of the study population

The study population consisted of 180 264 (14.7%) patients ≥18 years, who received an antidepressant during the study period (Table 4.1). The male: female ratio was 2:3. In the study population the average age of patients was 52.46 ± 17.15 years (range: 18.01–103.53) for women and 51.92 ± 16.47 years (range 18.02–99.44) for men (*d*-value = 0.03).

4.7.2 General prescribing patterns for the study population

The majority of patients receiving antidepressants during the study period (98.3%, n = 692 325) were older than 18 years (Table 4.1). A total of 8.3% (n = 8 515 428) of prescriptions and 3.4% (n = 20 527 777) of medicine items were claimed for this study population.
An average of 1.1 ± 0.3 (median = 1) medicine items were claimed per prescription during the study period.

4.7.2.1 General prescribing patterns for the study population, in relation to gender

The study population consisted of 14.8% (n = 1 220 289) of patients on the total data set (women 19.4%, n = 661 007 and men 9.3%, n = 559 282). Antidepressant prescription claims for women accounted for 73.1% (n = 692 325) of antidepressant prescriptions. Almost 72% (n = 702 885) of antidepressant medicine items claimed for the study population were for women.

4.7.2.2 General prescribing patterns for the study population, in relation to age

The study population was divided into four age groups, with age group one consisting of 7.9% (n = 675 519) of patients, age group two 19.7% (n = 258 219), age group three 24.5% (n = 161 751) and age group four 29.1% (n = 124 800). Prescriptions based on age group, accounted for 5.1% (n = 3 075 771), 9.4% (n = 1 982 988), 10.2% (n = 1 708 914) and 10% (n = 1 747 755) of all prescriptions, respectively. Patients aged 18 to 43 years received an average number of 2.94 ± 2.88 prescriptions, compared to 3.65 ± 3.47 during the study period by patients aged 44–56 years; patients aged 57–68 years received 4.41 ± 3.83, and patients

aged older than 68 years, 4.81 ± 3.99.

The number of prescription claimed during the study period increased by age group. This increase was moderately significant (*d* = 0.4) (refer to Table A.4, Annexure A).

4.7.3 Prescription patterns based on prescribers

Using the DU90% method (refer to paragraph 3.9.2), the prescriber categories responsible for 90% of prescriptions for antidepressants during the study period were determined. Figure 4.2 portrays the prescribers' percentage contribution for antidepressant prescriptions for the study population.

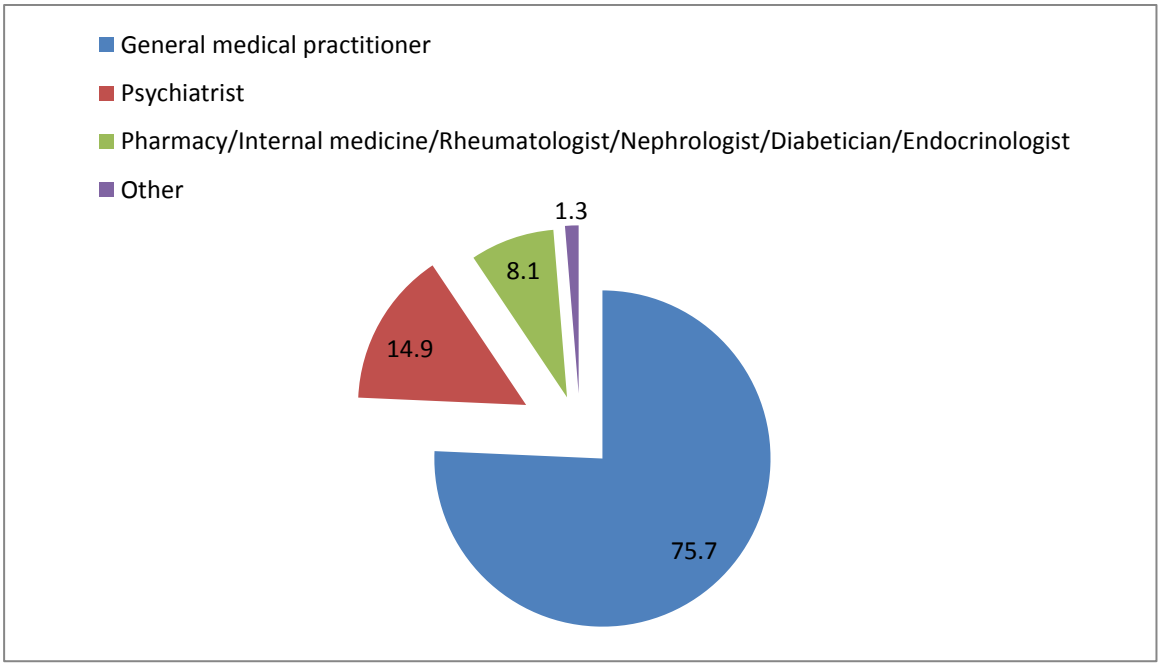

Figure 4.2 DU90% for antidepressant prescribers for the study population

Based on Figure 4.2, the majority of prescriptions (75.7%) were from general practitioners, followed by psychiatrists (14.9%). Similar results werefound by Fairman *et al.* (1998:1182), where an analysis of prescriber speciality in claims for antidepressants showed that 13.0% of antidepressants were prescribed by psychiatrists, 32.0% by non-psychiatrist specialists and 44.0% by non-specialist.

4.8. Utilisation by active ingredient for the study population

In this section the active ingredients of antidepressants will be discussed in accordance with the study population.

4.8.1 Utilisation by active ingredient, in relation to gender and age

Table 4.2 gives a summary of the DU90% frequency and percentage of antidepressants prescribed for the study period, in relation to gender. Active ingredients were listed according to overall prevalence (ranked from one to ten).

Table 4.2 The DU90% list for off-label prescribed antidepressants in relation to gender

Active ingredient	Total [n, (%)] [N = 702 885]	Male [n, (%)] [N = 189 424]	Female [n, (%)] [N = 513 461]
Amitriptyline	144 814 (20.6) [1]	36 130 (5.1) [1]	108 684 (15.5) [1]
Bupropion	21 778 (3.1) [9]	7 088 (1.0) [8]	14 690 (2.1) [9]
Citalopram	134 659 (19.2) [2]	35 584 (5.1) [2]	99 075 (14.1) [2]
Duloxetine	30 642 (4.4) [7]	7 060 (1.0) [9]	23 582 (3.3) [7]
Escitalopram	102 716 (14.6) [3]	29 143 (4.1) [3]	73 573 (10.5) [3]
Fluoxetine	82 056 (11.7) [4]	18 471 (2.6) [4]	63 585 (9.0) [4]
Mirtazapine	18 214 (2.6) [10]	7 010 (1.0) [10]	
Paroxetine	36 207 (5.2) [6]	10 788 (1.5) [6]	25 419 (3.6) [6]
Sertraline	26 821 (3.8) [8]	8 398 (1.2) [7]	18 423 (2.6) [8]
Trazodone			13 610 (1.9) [10]
Venlafaxine	40 233 (5.7) [5]	11 471 (1.6) [5]	28 762 (4.1) [5]
Total	638 140 (90.8)	171 143 (90.4)	469 403 (91.4)

The DU90% for antidepressant prescriptions was achieved with amitriptyline (20.6%, n = 144 814), citalopram (19.2%, n = 134 659), escitalopram (14.6%, n = 107 716), fluoxetine (11.7%, n = 82 056) and venlafaxine (5.7%, n = 40 233). Based on pharmacological drug class, the majority of prescription claims were for the SSRIs (54.9%, n = 385 681), followed by the TCAs (24.4%, n = 171 840) and SNRIs (10.1%, n = 70 875). In a study by Grover *et al.* (2013), the most prescribed drug was escitalopram (40%) followed by sertraline 17.6% and fluoxetine (16.3%). Grower and colleagues showed that in total the SSRIs were prescribed 79.2% of all antidepressants, whereas TCAs represented 15.2% and the SNRIs 11.3%; trends observed in the present study compared with that found by Grover *et al.* (2013). Similar trends were also found in South Africa, using earlier data from 2004 (Burger *et al.*, 2009:72), although the percentage of TCAs prescribed, nearly halved.

The medicine items most prescribed overall in relation to gender were in accordance with the DU90% method for the study population, except for bupropion that changed to the 8th position and duloxetine that changed to the 9th position for males. Trazodone was in the 10th position for females (Table 4.2). The top three active ingredients in both gender groups were amitriptyline, citalopram and escitalopram.

Active ingredients received during the study period are summarised in Table 4.3.

Table 4.3 DU90% list for off-label prescribed antidepressants in relation to age group

Active ingredient	Age group 1 (≤ 43 years) [n, (%)] [N = 160 064]	Age group 2 (> 43, ≤ 56 years) [n, (%)] [N = 189 132]	Age group 3 (> 56, ≤ 68 years) [n, (%)] [N = 177 598]	Age group 4 (> 68 years) [n, (%)] [N = 176 091]
Amitriptyline	23 195 (14.5) [3]	37 687 (19.9) [1]	38 831 (21.9) [1]	45 101 (25.6) [1]
Bupropion	8 572 (5.4) [6]	7 901 (4.2) [8]	4 105 (2.3) [10]	
Citalopram	27 257 (17.0) [2]	33 323 (17.6) [2]	34 235 (19.3) [2]	39 844 (22.6) [2]
Duloxetine	7 608 (4.8) [9]	9 399 (5.0) [6]	8 119 (4.6) [7]	5 516 (3.1) [9]
Escitalopram	30 015 (18.8) [1]	28 285 (15.0) [3]	23 295 (13.1) [3]	21 121 (12.0) [3]
Fluoxetine	20 448 (12.8) [4]	23 446 (12.4) [4]	21 801 (12.3) [4]	16 361 (9.3) [4]
Mirtazapine			4 505 (2.5) [9]	7 528 (4.3) [6]
Paroxetine	7 837 (4.9) [8]	9 300 (4.9) [7]	10 302 (5.8) [5]	8 768 (5.0) [5]
Sertraline	8 217 (5.1) [7]	6 827 (3.6) [9]	6 018 (3.4) [8]	5 759 (3.3) [8]
Trazodone	4 877 (3.0) [10]	5 802 (3.1) [10]		2 673 (1.5) [10]
Venlafaxine	10941 (6.8) [5]	13470 (7.1) [5]	9972 (5.6) [6]	5 850 (3.3) [7]
Total	148 967 (93.1%)	175 440 (92.7%)	161 183 (90.8%)	158 521 (90.0%)

Using the DU90% method, patients aged ≤ 43 years received mainly escitalopram and citalopram, followed by amitriptyline, fluoxetine and venlafaxine. Patients aged > 43 years, ≤ 56 years received mainly amitriptyline, citalopram and escitalopram, followed by fluoxetine and venlafaxine. Patients aged > 56 years, ≤ 68 years and > 68 years had similar trends than patients aged > 43, ≤ 56 years with the exception of paroxetine replacing venlafaxine

4.9 Analyses of off-label antidepressant prescribing for the study population

Patients were categorised, based on the presence of ICD-10 codes on claims for antidepressants. There were five categories, *viz*: “indicated”, “off-label”, “none”, “other” and” “mixed” (refer to paragraph 4.2).

Figure 4.3 illustrates the percentage contribution for antidepressant claim categories in relation to diagnosis (ICD 10 – code) for the study period (refer to paragraph 3.7.2; Table A.3, Annexure A).

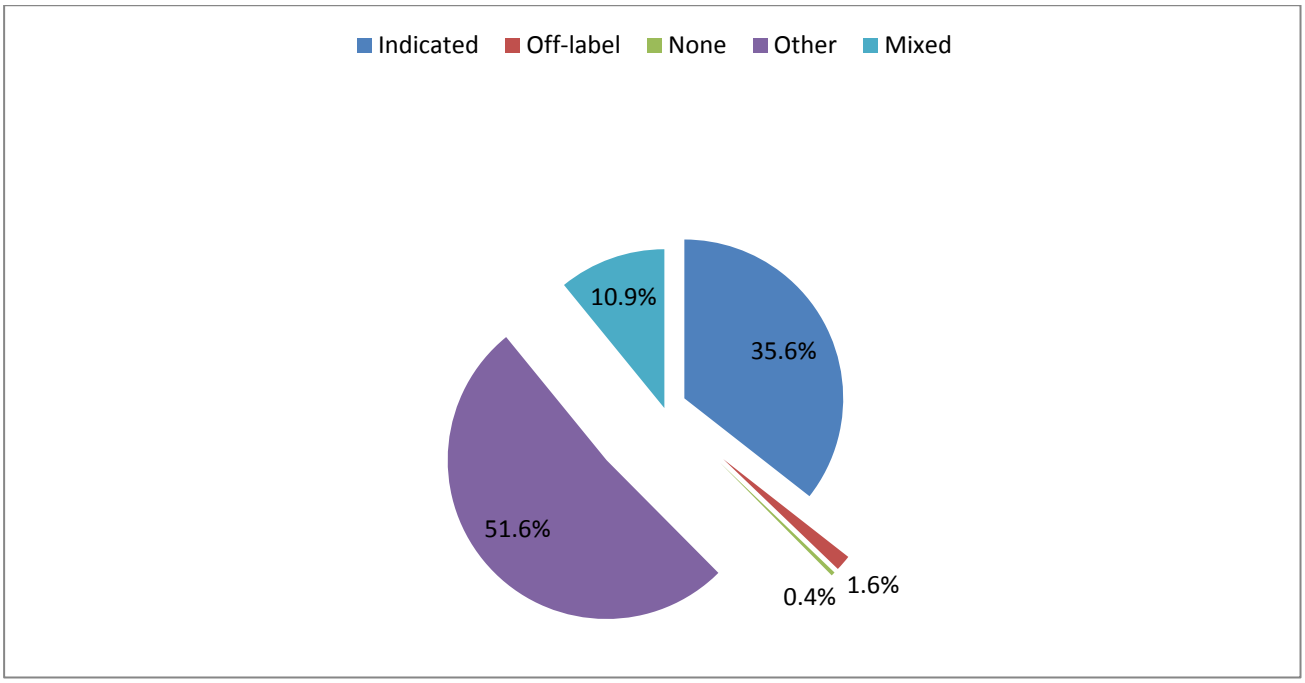

Figure 4.3 Claim categories for antidepressants during the study period

Patients in the claim category "ICD-10 code indicated" represented 35.6% (n = 180 264) of all patients during the study period, compared to those from the off-label category that represented 1.6% (n = 180 264). Patients in the "none" category represented 0.4% (n = 180 264), whereas other represented 51.6% (n = 180 264) and mixed represented 10.9% (n = 180 264).

For the purpose of the study, only the off-label and other category will be further discussed. These two categories were regarded as patients potentially receiving antidepressants off-label. Mixed claim codes consisted of claims with more than one ICD-10 claim code. Because of the uncertainlty of these claim codes, thses were not further discussed. Table 4.4 provides a description of antidepressant active ingredients with off-label ICD-10 claim codes according to the literature (refer to table 2.2 and Table A.3, Annexure A).

Table 4.4 Alphabetical list of antidepressants received off-label during the study (N = 2 635)

Antidepressant	Off-label claim category n (%)
Amitriptyline	2 170 (82.4)
Bupropion	40 (1.5)
Citalopram	52 (2.0)
Clomipramine	0
Dothiepin	0
Duloxetine	29 (1.1)
Escitalopram	112 (4.2)

Table 4.4 Alphabetical list of antidepressants received off-label during the study (N = 2 635) *continued*

Antidepressant	Off-label claim category n (%)
Fluoxetine	101 (3.8)
Fluvoxamine	7 (0.3)
Imipramine	0
Lithium	0
Lofepramine	0
Maprotiline	0
Mianserin	0
Mirtazapine	77 (2.9)
Moclobemide	0
Paroxetine	15 (0.6)
Reboxetine	0
Sertraline	14 (0.5)
Tranylcypromine	0
Trazodone	0
Trimipramine	5 (0.2)
Venlafaxine	13 (0.5)

The DU90% for off-label prescribing was achieved with amitriptyline, representing 82.4% (n = 2 635), escitalopram, 4.2% (n = 2 642) and fluoxetine, 3.8% (n = 2 642) of claims.

The following sections provide a summary of antidepressants with possible off-label indications.

4.9.1 Amitriptyline

In this section amitriptyline will be discussed in accordance with potential off-label usage.

A general summary of off-label category uses of amitriptyline as determined from Table A.3 (Annexure A) is presented in Table 4.5. It further gives a summary of the number of patients, number of prescriptions, average prescribed daily dosages and standard deviation, confidence interval and the number of DDDs represented by each indication for the study population. The DDD for amitriptyline is 75 mg daily (WHO, 2012).

Table 4.5 Off-label claim category and dosages for amitriptyline

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval (mg)	Number of DDDs[c]
A60	**Herpes neuralgic pain**	4 (0.002)	4 (0.001)	115.62* ± 26.51	-131.99 – 344.49	6.2
G43.0	**Migraine without aura**	119 (0.07)	364 (0.05)	45.16 ± 43.42	40.72 – 49.59	219.2
G43.1	**Migraine classic**	32 (0.02)	122 (0.02)	36.32 ± 38.53	29.41 – 43.322	59.1
G43.3	**Migraine complicated**	36 (0.02)	130 (0.02)	86.08 ± 58.96	75.84 – 96.31	149.2
G43.8	**Migraine other**	15 (0.008)	30 (0.004)	54.00 ± 54.21	33.76 – 74.24	21.6
G43.9	**Migraine unspecified**	286 (0.16)	956 (0.14)	48.00 ± 47.86	44.97 – 51.04	611.8
G44.0	**Headache cluster**	78 (0.04)	102 (0.02)	81.16 ± 58.20	69.73 – 92.59	110.4
G44.1	**Headache vascular**	44 (0.02)	135 (0.02)	49.37 ± 40.54	42.47 – 56.27	76.5
G44.2	**Headache tension**	1 093 (0.61)	1 660 (0.24)	77.40 ± 57.19	74.65 – 80.16	1 652.3
G44.3	**Headache chronic**	5 (0.003)	16 (0.002)	22.19 ± 6.05	18.97 – 25.41	4.1
G44.8	**Headache allergic**	38 (0.02)	110 (0.02)	48.44 ± 47.44	39.47 – 57.40	57.9
R51	**Headache**	363 (0.20)	487 (0.07)	87.30 ± 55.75	82.34 – 92.26	469.7
K58.0	**Irritable bowel syndrome with diarrhoea**	21 (0.01)	29 (0.004)	36.04 ± 48.20	18.28 – 55.65	13.9
K58.9	**Irritable bowel syndrome without diarrhoea**	36 (0.02)	91 (0.01)	41.71 ± 45.02	32.33 – 51.08	39.2

* = weighted average; a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Amitriptyline was prescribed for the treatment of migraine, in a total number of 1060.9 DDDs, compared to 2370.9 DDDs for headache, and 53.1 DDDs for irritable bowel syndrome (IBS).

Amitriptyline was prescribed for the treatment of migraine (without aura, classic, complicated, other and unspecified) in dosages of 36 ± 39 mg to 86 ± 59 mg daily (Table 4.5), which is in accordance with findings by Keskinbora and Aydinli (2008:981), where amitriptyline was found

effective for migraine in dosages from 10 mg to 150 mg daily (refer to Table 2.2). Bendsten and Jensen (2000:607) also found amitriptyline to be effective at a dose of 75 mg daily for chronic tension type headache. In accordance, the present study found the use of amitriptyline for the treatment of tension headache in 0.61% (n = 180 264) patients, at an average dose of 77.40 ± 57.19 mg [95% CI: 74.65 – 80.16]. In general, the present study showed that headache was treated with amitriptyline in dosages from 22 ± 6 mg to 87 ± 56 mg. Amitriptyline causes a modulation of the neurotransmitter system, thereby preventing migraine rather than changing the vascular tone (Keskinbora & Aydinli, 2008:981) (refer to paragraph 2.7.3.4.4).

Sohn *et al.* (2012:863) (refer to Table 2.2) established that a dose of 10 mg per day is effective for the treatment of IBS with or without diarrhoea. The present study showed that doses of 36 ± 48 mg to 42 ± 45 mg were prescribed per day, translating to 13.9 and 39.2 DDDs, respectively. A possible mechanism for the use of amitriptyline in IBS may be by modulating serotonin levels (Spiller *et al.*, 2007:1788). TCAs introduce several different mechanisms that may potentially explain it's positive effect on IBS (Halpert *et al.*, 2005:670). Adjustment of visceral sensitivity, ororectal transit interval and gut motility, may be prevalent mechanisms. Persistent stimulation of the frontal mid-cingulate cortex can give malfunction of pain control in IBS. Pain regulation is transmitted from the central nervous system (CNS); a central analgesic action by the TCAs may reverse the malfunction in the pain regulatory system (Halpert *et al.*, 2005:670). Accompanying psychological symptoms in IBS can be positively treated by antidepressants. Treatment with antidepressants for analgesic conditions occurs at lower dosages than for depression (Halpert *et al.*, 2005:670).

Although amitriptyline is only 5% as active as atropine, it still has the most effective anticholenergic action of the antidepressants. Symptoms like the motility of the gastro intestinal tract in IBS is decreased by the anticholernergic action of amitriptyline (Rajagopalan *et al.*, 1998:40; Steinhart *et al.*, 1981:56;). Pain reduction is not correlated with anxiety and depression at baseline with amitriptyline therapy that results to amitriptyline in IBS being independent of its antidepressant effects (Morgan *et al.*, 2005:606).

A general summary of the other category uses of amitriptyline as determined from Table A.3 (Annexure A) is presented in Table 4.6.

Table 4.6 Other claim category and dosages for amitriptyline

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval (CI)	Number of DDDs[c]
F20.0	**Paranoid schizophrenia**	5 (0.003)	35 (0.01)	54.29 ± 24.62	45.83 – 62.74	25.3
F20.4	**Post schizophrenic depression**	3 (0.002)	4 (0.001)	150.00 ± 0	0	0.7
F20.9	**Schizophrenia unspecified**	26 (0.01)	195 (0.03)	49.28 ± 44.76	42.96 – 55.60	128.1
F51.0	**Insomnia**	529 (0.29)	1 124 (0.16)	47.35 ± 48.36	43.76 – 50.62	709.6
F90.0	**Attention deficit with hyperactivity**	1 (0.001)	7 (0.001)	25.00 ± 0	0	2.3
G35	**Multiple sclerosis**	532 (0.3)	3 198 (0.46)	36.20 ± 35.39	34.97 – 37.46	1 543.6
M79.70	**Fibromyalgia**	15 (0.008)	46 (0.01)	39.31 ± 35.5	28.77 – 49.85	24.1
N95.0	**Postmenopausal bleeding**	1 (0.001)	7 (0.001)	47.14 ± 45.36	5.20 – 89.09	4.4
N95.1	**Menopausal and female climacteric states**	50 (0.03)	139 (0.02)	36.45 ± 40.16	29.71 – 43.18	67.6
N95.9	**Menopausal and perimenopausal disorder, unspecified**	21 (0.01)	72 0.01)	48.19 ± 45.61	37.48 – 58.91	48.2
R23.2	**Flushing**	1 (0.001)	3 (0.0004)	10 ± 0	0	0.4
G47.0	**Sleep disorder**	382 (0.21)	1 239 (0.18)	48.02 ± 53.07	45.07 – 50.98	793.3

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Amitriptyline was mostly prescribed in the other claim category for insomnia, with claims representing 0.16%, multiple sclerosis (0.46%), sleep disorder (0.18%) and schizophrenia 0.03% (n = 692 325).

Based on Table 4.6, amitriptyline was prescribed to patients with post schizophrenic depression, paranoid schizophrenia and unspecified schizophrenia in dosages ranging from 49 ± 45 mg [95% CI: 43.76 – 50.62] to 150 mg daily. Sommers *et al.* (1997:144) found amitriptyline ineffective as add-on treatment in combination with risperidone. However, in this study

amitriptyline was not researched as an add-on therapy.

An estimated 25% of schizophrenia patients also experience depression (Möller, 2008:339). Patients who experience schizophrenia are also prone to reduced social and vocational functioning. This may increase psychotic relapse and rehospitalisation (Buckley *et al.*, 2009:401). These patients are also linked to adverse life events that may include suicide attempts, loss of loved ones and attempted suicides. Ten percent of schizophrenic patients commit suicide (Hawton *et al.*, 2005:19). Schizophrenic patients with depression are a high risk for suicide at first diagnoses (Siris, 2012:35).

Amitriptyline was furthermore prescribed for the treatment of insomnia and sleep disorders in dosages of 47 ± 48 to 48 ± 53 mg daily. Insomnia occurs in 50% to 80% of patients with psychotic disorders (Harvard health publications, 2011). Sleep disorders are mainly present in patients with anxiety, depression, bipolar disorder and attention deficit hyperactivity disorder (ADHD). Antidepressants are regarded as better for long-term use than benzodiazepines and also show fewer side effects. The use of antidepressants has a dual relieving function because people with depression also experience insomnia. TCAs with sedating properties like amitriptyline and doxepin are commonly prescribed for insomnia (Harvard health publications, 2011). Trazodone, nefazodone and mirtazapine that work on serotonin receptors, may also be prescribed as antidepressants for insomnia. These drugs sedating properties are probably the mechanism that promotes sleep and has a relaxing effect on patients suffering from anxiety and mild depression. According to Ringdahl *et al.* (2004:217), amitriptyline should, however, be used with caution in elderly patients with insomnia and sleep disorders (Harvard health publications, 2011).

Menopausal symptoms (female climacteric states, postmenopausal bleeding or unspecified menopause) were treated with amitriptyline in dosages of 36 ± 40 mg [95% CI: 29.71 – 43.18] to 48 ± 46 mg [95% CI: 45.07 – 50.98] per day, fibromyalgia in dosages of 39 ± 36 mg [95% CI: 28.77 – 49.85] daily, and multiple sclerosis in dosages of 36 ± 35 mg [95% CI: 34.97 – 37.46] per day. Neuropathic pain and fibromyalgia have been treated successfully with amitriptyline in a small number of patients for many years, although without supportive evidence (Moore *et al.*, 2012). Kopsky *et al.* (2012) furthermore showed that burning neuropathic pain reduction could be achieved after administration of topical amitriptyline in a patient with multiple sclerosis. Pain relief of amitriptyline may well be due to several pharmacological mechanisms, which may include the inhibition of serotonin and norepinephrine reuptake at the presynaptic level, inhibiting N-Methyl-D-aspartic acid (NMDA) and alpha2-adrenergic receptors and partially blocking sodium, as well as the blockage of potassium and calcium channels (De Leon-Casasola, 2007:361).

4.9.2 Escitalopram

In this section, escitalopram will be discussed in accordance with potential off-label usage.

A general summary of the off-label category uses of escitalopram as determined from Table A.3 (Annexure A) is presented in Table 4.7. It further gives a summary of the number of patients, number of prescriptions, average prescribed daily dosages and standard deviation, confidence interval and the number of DDDs represented by each indication for the study population. The DDD of escitalopram is 10 mg daily (WHO, 2012).

Table 4.7 Off-label claim category and dosages for escitalopram

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F42.0	**Predominantly obsessional thoughts**	26 (0.01)	66 (0.01)	19.54 ± 11.26	16.77 – 22.31	129.0
F42.1	**Predominantly compulsive acts**	6 (0.003)	17 (0.002)	11.75 ± 3.92	9.75 – 13.79	20.0
F42.2	**Other compulsive disorder**	8 (0.004)	13 (0.002)	15.38 ± 5.19	12.25 – 18.52	20.0
F42.8	**Mixed obsessive thought and acts**	11 (0.01)	43 (0.01)	14.77 ± 5.56	13.06 – 16.48	63.5
F42.9	**Obsessive compulsive disorder unspecified**	21 (0.01)	42 (0.01)	23.45 ± 10.02	20.32 – 26.58	98.5
G43.0	**Migraine without aura**	1 (0.001)	1 (0.0001)	10.00 ± 0	0	10.0
G43.1	**Migraine classic**	1 (0.001)	1 (0.0001)	40.00 ± 0	0	4.0
G43.3	**Migraine complicated**	1 (0.001)	1 (0.0001)	20.00 ± 0	0	2.0
G43.9	**Migraine unspecified**	6 (0.003)	7 (0.001)	31.43 ± 10.69	21.54 – 41.31	22.0
N95.1	**Menopausal and female climacteric states**	24 (0.01)	59 (0.01)	17.20 ± 8.60	14.96 – 19.44	101.5

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Table 4.7 Off-label claim category and dosages for escitalopram *continued*

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
N95.3	**States associated with artificial menopause**	1 (0.001)	1 (0.0001)	20.00 ± 0	0	2.0
N95.9	**Menopausal and perimenopausal disorder, unspecified**	6 (0.003)	10 (0.001)	15.14 ± 5.13	11.48 – 18.81	15.1

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Treatment for obsessive compulsive disorders (OCD) with escitalopram represented a total number of 331 DDDs, treatment of migraine represented 38 DDDs and treatment of menopausal symptoms accounted for 118.6 DDDs.

Escitalopram was used to treat OCD (predominantly obsessive thoughts, predominal obsessive acts, other compulsive disorder, mixed obsessive thought and acts and obsessive compulsive disorder unspecified) in dosages of 12 ± 4 mg [95% CI: 9.57 – 13.79] to 23 ± 10 mg [95% CI: 20.32 – 26.58]. This finding was in conformity with findings by Stryjer *et al.* (2013:97), who showed that escitalopram is effective treatment for OCD in patients with schizophrenia in dosages of 10 mg to 20 mg (refer to Table 2.2). Fineberg and Craig (2007:235) stated that the SSRIs anti-obsessional properties are related to the inhibition of neuronal reuptake of serotonin in the central nervous system (CNS).

In the present study, migraine was treated with escitalopram in dosages of 10 mg to 40 mg per day. Based on literature escitalopram is effective treatment for migraine prophylaxis in dosages of 20 mg per day (Tarlaci, 2009:257). Rosas *et al.* (2013:1609) state that the mechanism that escitalopram my prevent migraine is by it's binding to 5HT1D receptor and may well have antimigraine action.

DeFronzo Dobkin *et al.* (2009:74) found that escitalopram was an effective treatment for menopausal symptoms in dosages of 10 mg to 20 mg. In accordance, the present study showed that escitalopram in dosages ranging from 15 ± 5 mg [95% CI: 11.48 – 18.81] to 20 mg were used to treat menopausal symptoms. Although the precise mechanism how escitalopram

improve hot flushes is unknown, there is strong evidence that indicates that estrogen is involved in the serotonergic system supporting hypotheses of the role of serotonin receptors in the pathogenesis of hot flushes (Freeman *et al.*, 2011:273).

A general summary of the other category uses of escitalopram as determined from Table A.3 (Annexure A) is presented in Table 4.8.

Table 4.8 Other claim category and dosages for escitalopram

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F20.0	**Paranoid schizophrenia**	9 (0.005)	18 (0.003)	15.00 ± 5.15	12.44 – 17.56	27.0
F20.2	**Undifferentiated schizophrenia**	1 (0.001)	1 (0.0001)	20 ± 0	0	2.0
F20.4	**Post schizophrenic depression**	4 (0.002)	15 (0.002)	13.24 ± 8.21	8.70 – 17.79	19.9
F20.9	**Schizophrenia unspecified**	30 (0.02)	211 (0.03)	17.12 ± 4.62	16.49 – 17.75	361.2
F51.0	**Insomnia**	11 (0.01)	29 (0.004)	24.14 ± 11.50	19.76 – 28.51	70.0
F90.0	**Attention deficit with hyperactivity**	1 (0.001)	1 (0.0001)	5.00 ± 0	0	0.5
G35	**Multiple sclerosis**	2 (0.001)	14 (0.002)	20 ± 0	0	28.0
G47.0	**Sleep disorder**	8 (0.004)	12 (0.002)	14.17 ± 5.15	10.90 – 17.44	17.0
G47.9	**Sleep disorder unspecified**	8 (0.004)	34 (0.01)	20.85 ± 10.84	17.06 – 24.63	70.9
K58.0	**Irritable bowel syndrome with diarrhoea**	1 (0.001)	1 (0.0001)	20.00 ± 0	0	2.0
K58.9	**Irritable bowel syndrome without diarrhoea**	2 (0.001)	2 (0.0003	14.38 ± 6.19	-41.21 – 69.96	2.9
N39.3	**Stress incontinence**	2 (0.001)	5 (0.001)	12.00 ± 4.47	6.45 – 17.55	6.0
N39.4	**Other specified urinary incontinence**	3 (0.002)	10 (0.001)	20.00 ± 0	0	20.0
G44.2	**Headache tension**	4 (0.002)	5 (0.001)	20.00 ± 0	0	10.0
R51	**Headache**	2 (0.001)	7 (0.001)	11.23 ± 3.27	8.20 – 14.27	7.8

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

The most prescribed other category claim for escitalopram was unspecified schizophrenia at 0.03%, sleep disorders at 0.01%, and insomnia at 0.004% (n = 692 325).

In Table 4.8 escitalopram for schizophrenia accounted for 410.1 DDDs, followed by sleep disorders (sleep disorder and insomnia) with 157.9 DDDs, headache with 52.0 DDDs and incontinence with 26 DDDs.

Escitalopram was prescribed for schizophrenia (paranoid schizophrenia, undifferentiated schizophrenia, post schizophrenic depression and unspecified schizophrenia) in dosages of 13 ± 8 mg [95% CI: 8.70 – 17.19] to 20 mg per day. Lancu *et al.* (2010:21), however, found escitalopram ineffective for the treatment of negative symptoms (emotional withdrawal, anhedonia, loss of initiative and restrictive affect) in schizophrenia. A good case for the prescription of antidepressants in schizophrenia is persistent when depressive symptoms occur in schizophrenic patients (Mulholland & Cooper, 2000:176). Approximately 50% of patients with schizophrenia suffer from obsessive compulsive symptoms in conjunction with psychosis, and among these 50% of patients 7.8% to 46% have complete OCD (Stryjer *et al.*, 2013:97).

Findings by Lader *et al.* (2005:353) showed that escitalopram was effective in treatment of sleep problems in depressed patients. In accordance, sleep disorders and insomnia were treated with escitalopram in dosages of 14 ± 5 mg [95% CI 10.90 – 17.44] to 24 ± 12 mg [95% CI 19.75 – 28.51]. Thase (1999:30), however, states that the SSRIs may trigger insomnia *via* stimulation of serotonin-2 receptors. Ensrud *et al.* (2012:854) found that patients with hot flushes were treated with escitalopram in dosages of 10 mg to 20 mg and experienced improvement in insomnia. Although it is found that serotonergic and noradrenergic systems are supposed to have a inhibiting influence on REM sleep (Drago, 2008:117). Sanchez *et al.* (2007:74) found escitalopram to prolong REM sleep latency.

In the present study, escitalopram was used to treat IBS in dosages of 14 ± 6 mg [95% CI: 41.21 – 69.96] to 20 mg [95% CI: 0]. Houghton *et al.* (1999:1441) suggest that an antagonist of 5HTD significantly increased orocaecal transit time towards normal values and then tend to decrease rectal sensitivity in paitients with IBS.

Incontinence was treated with escitalopram in dosages of 12 ± 4 mg [95% CI: 6.45 - 17.55] to 20 mg. Prescriptions for escitalopram in conjunction with an ICD-10 code for incontinence were present in 0.002% (n = 180 264). Duloxetine a serotonin and noradrenaline re-uptake inhibitor (SNRI) can also be used to treat incontinence in a dosage of 40 mg twice daily (BNF, 2009:452). Duloxetine stimulates two key neurotransmitters in the proximal end of the pudendal

nerve to control contraction of the external urethral sphincter (EUS), and by the stimulation of these two neurotransmitters the EUS helps to maintain continence by contraction and thus guarding against the increased bladder pressure and then preventing leakage (Sweeney, 2005:85).

Escitalopram was used in doses of 11 ± 3 mg [95% CI: 8.21 – 14.27] to 20 mg for the treatment of headache. However, according to Davidson *et al.* (2004:238) headache may be an adverse effect of escitalopram, where more than 10% of patients acquired headaches in a double-blind study. Rosas *et al.* (2013:1609) state that the mechanism that escitalopram my prevent migraine is by it's binding to 5HT1D receptor and may well have antimigraine action.

4.9.3 Fluoxetine

In this section fluoxetine will be discussed in accordance with potential off-label usage.

A general summary of the off-label category uses of fluoxetine as determined from Table A.3 (Annexure A) is presented in Table 4.9. It further gives a summary of the number of patients, number of prescriptions, average prescribed daily dosages and standard deviation, confidence interval and the number of DDDs represented by each indication for the study population. The DDD of fluoxetine is 20 mg daily (WHO, 2012).

Table 4.9 Off-label claim category and dosages for fluoxetine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
G44.0	**Headache cluster**	2 (0.001)	2 (0.0003)	75.00 ± 0	0	7.5
G44.2	**Headache tension**	69 (0.04)	73 (0.01)	75.37 ± 7.06	73.72 – 77.01	275.1
G44.8	**Headache other specified**	1 (0.001)	1 (0.001)	75.00 ± 0	0	3.8
K58.9	**Irritable bowel syndrome without diarrhoea**	3 (0.002)	3 (0.0004)	56.67 ± 31.75	-22.22 – 135.55	8.5
N94.3	**Premenstrual tension syndrome**	2 (0.001)	3 (0.0004)	16.67 ± 5.77	2.32 – 31.01	2.5
R51	**Headache**	24 (0.01)	25 (0.004)	75.93 ± 3.63	74.43 – 77.43	95.0

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Treatment of headache with fluoxetine represented a total number of 381.4 DDDs, whereas

treatment of IBS represented a total of 8.5 DDDs and treatment of premenstrual syndrome (PMS) accounted for 2.5 DDDs.

Saper *et al.* (1994:501) found fluoxetine effective treatment of chronic headache in dosages of 20 to 40 mg daily (refer to Table 2.2). The present study's findings showed that fluoxetine was given in doses as high as 75 ± 7 mg to 76 ± 4 mg [95% CI: 74.43 – 77.43] per day for headache (cluster, tension and other specified). There were conflicting findings in the literature, where Gherpelli and Esposito (2005:263) concluded that fluoxetine is an ineffective treatment in the management of chronic disease headache. The mechanism by which antidepressants prevent headaches remain doubtful and surely cannot be linked to underlying depression, but the SSRI does cause a decrease of beta-adrenergic receptor density. This decrease in receptor binding sites is not correlated with its altered function (Colombo *et al.*, 2004:172).

Fluoxetine was used to treat IBS without diarrhoea in dosages of 57 mg [95% CI: -22.22 – 135.55]. Vahedi *et al.* (2005:383) found fluoxetine effective in treatment of pain and constipation in patients with IBS in dosages of 20 mg. Vahedi and colleagues states that serotonin may have an important effect on the colonic motility and the pathophysiology in IBS. Rahimi *et al.* (2008:74), however, found the selective serotonin inhibitors (SSRIs) were ineffective treatments of abdominal pain, abdominal bloating and the relief of IBS symptoms.

PMS was treated with fluoxetine in dosages of 17 ± 6 mg [95% CI: 2.32 – 31.01]. This finding was in concurrence with Nazari *et al.* (2012) who found fluoxetine effective in treatment of PMS in dosages of 20 mg per day. The possible mechanism by which SSRIs act has been postulated as arising from the cyclical nature of PMS and may reflect SSRI action at a different receptor site than that in affective disorders (Dimmock *et al.*, 2000:1135).

A general summary of the other category uses of fluoxetine as determined from Table A.3 (Annexure A) is presented in Table 4.10.

Table 4.10 Other claim category and dosages for fluoxetine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F20.0	**Paranoid schizophrenia**	5 (0.003)	21 (0.003)	28.57 ± 10.14	23.95 – 33.19	30.0

Table 4.10 Other claim category and dosages for fluoxetine *continued*

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F20.4	**Post schizophrenic depression**	4 (0.002)	6 (0.001)	47.50 ± 30.12	15.89 – 79.11	14.3
F20.9	**Schizophrenia unspecified**	51 (0.03)	398 (0.06)	31.22 ± 16.93	29.55 – 32.89	621.3
F50.2	**Bulimia nervosa**	2 (0.001)	9 (0.001)	66.67 ± 26.45	46.33 – 87.00	30.0
F51.0	**Insomnia**	8 (0.004)	11 (0.002)	45.90 ± 29.82	25.88 – 65.94	25.3
F52.4	**Premature ejaculation**	3 (0.002)	4 (0.001)	76.25 ± 2.50	72.27 – 80.22	15.3
F90.0	**Attention deficit with hyperactivity**	2 (0.001)	2 (0.0003)	30.00 ± 14.14	-97.06 – 157.06	3.0
G35	**Multiple sclerosis**	4 (0.002)	15 (0.002)	20.00 ± 0	0	15.0
G43.0	**Migraine without aura**	2 (0.001)	5 (0.001)	20.00 ± 0	0	5.0
G43.9	**Migraine unspecified**	9 (0.01)	18 (0.003)	47.94 ± 10.69	21.54 – 41.32	43.2
G47.0	**Sleep disorder**	29 (0.02)	54 (0.01)	52.31 ± 26.84	44.99 – 59.64	141.2
G47.9	**Sleep disorder unspecified**	13 (0.01)	26 (0.004)	63.46 ± 24.36	53.62 – 73.30	82.5
N39.3	**Stress incontinence**	4 (0.002)	5 (0.001)	20.0 ± 0	0	5.0
N95.0	**Postmenopausal bleeding**	2 (0.001)	5 (0.001)	20.00 ± 0	0	5.0
N95.1	**Menopausal and female climacteric states**	20 (0.01)	61 (0.01)	28.89 ± 20.11	23.74 – 34.04	88.1
N95.9	**Menopausal and perimenopausal disorder, unspecified**	6 (0.003)	18 (0.003)	29.17 ± 21.09	18.68 – 39.66	26.2
N95.1	**Menopausal and female climacteric states**	20 (0.01)	61 (0.01)	28.89 ± 20.11	23.74 – 34.04	88.1
N95.9	**Menopausal and perimenopausal disorder, unspecified**	6 (0.003)	18 (0.003)	29.17 ± 21.09	18.68 – 39.66	26.2

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Fluoxetine accounted for 665.6 DDDs in the treatment of schizophrenia, compared to 249 DDDs in the treatment of insomnia and sleep disorders, 119.3 DDDs in the treatment for menopausal symptoms and 48.2 DDDs for migraine treatment.

Conflicting findings were found in the literature. For example, Spina *et al.* (1994:284) found that fluoxetine 20 mg per day might be beneficial in schizophrenic patients with negative symptoms, whereas Sepehry *et al.* (2007:609) found that the SSRIs did not improve negative symptoms in schizophrenia. Lecrubier (2007:113) further states that SSRIs remind prescribers that the SSRIs are certainly not a systematic or useful add-on therapy for negative symptoms in patients with schizophrenia. However, in this study the SSRIs were not researched as an add-on therapy. In the present study, fluoxetine was used to treat schizophrenia in dosages of 29 ± 10 mg [95% CI: 23.95 - 33.19] to 48 ± 30 mg [95% CI: 15.89 – 79.11].

Kara *et al.* (1996:1632) showed that 40 mg daily fluoxetine might be effective in the treatment of premature ejaculation. In the present study fluoxetine, however, was prescribed in dosages of 76.25 ± 2.50 mg [95% CI: 72.27 – 80.22]. According to McMahon (2004:63), stimulation of serotonin-2c receptors can increase ejaculation time and stimulating of seretonin-1A can decrease ejaculation time. The SSRIs increases serotonergic neurotransmission and activate the serotonin-2C receptor, thus increasing ejaculation time (Wang *et al.*, 2007:1004).

In the present study migraine was treated with fluoxetine in dosages of 20 mg [95% CI: 0] to 48 ± 11 mg [95% CI: 21.54 – 41.32]. According to Colombo *et al.* (2004:173) there is poor evidence that SSRIs prevent migraine.

In accordance to findings by Walsh *et al.* (2004:559), showing fluoxetine effective in dosages of 60 mg per day for the treatment of bulimia nervosa, the present study found that average dosages of 67 ± 26 mg [95% CI: 46.33 – 87] of fluoxetine were prescribed. According to Krüger and Kennedy (2000:498), patients with bulimia nervosa have lower basal serotonin levels in their cerebrospinal fluid than in healthy patients. Dieting is also known to reduce tryptophan, the forerunner of serotonin, thus given a SSRI will help to increase serotonin levels in patients suffering from bulimia nervosa. Krüger and Kennedy (2000:498) suggested that SSRI treatment should only start after nutritional improvement to increase tryptophan levels caused by the food depletion.

4.9.4 Mirtazapine

In this section mirtazapine will be discussed in accordance with potential off-label usage.

A general summary of the off-label category uses of mirtazapine as determined from Table A.3 (Annexure A) is presented in Table 4.11. It further gives a summary of the number of patients, number of prescriptions, average prescribed daily dosages and standard deviation, confidence interval and the number of DDDs represented by each indication for the study population. The DDD of mirtazapine is 30 mg daily (WHO, 2012).

Table 4.11 Off-label claim category and dosages for mirtazapine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F41.0	**Panic disorder**	7 (0.001)	11 (0.002)	23.87 ± 14.55	14.09 – 33.64	8.8
F41.1	**Generalized anxiety disorder**	21 (0.01)	91 (0.01)	17.80 ± 9.53	15.82 – 19.79	54.0
F41.2	**Mixed anxiety and depressive disorder**	20 (0.01)	96 (0.01)	23.52 ± 15.86	20.31 – 26.74	75.3
F41.9	**Anxiety disorder unspecified**	29 (0.02)	82 (0.01)	30.21 ± 16.16	26.66 – 33.76	82.6

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

The total number of DDDs for the treatment of other anxiety disorders (F41) with mirtazapine was 220.7. The claims represented 0.04% (n = 692 325) of all antidepressant prescriptions.

In the present study, mirtazapine was used in dosages of 18 ± 10 mg [95% CI: 15.82 – 19.79] to 30 ± 16 mg [95% CI: 26.66 - 33.76], to treat anxiety. These findings are similar to that by Gambi *et al.* (2005:486), where general anxiety disorder was treated with 30 mg of mirtazapine daily. The possible mechanism by which mirtazapine improves anxiety symptoms is by the enhancement of both serotonergic and noradrenergic transmission through alpha auto and hetero receptor antagonism and also by blockage of serotonin 2 and serotonin 3 receptors, respectively (Carli *et al.*, 2002:662). Mirtazapine further has low affinity for dopamamine receptors and is a potent antagonist on histamine 1 receptors (Croom *et al.*, 2009:428).

A general summary of the other category uses of mirtazapine as determined from Table A.3 (Annexure A) is presented in Table 4.12.

Table 4.12 Other claim category and dosages for mirtazapine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F20.0	**Paranoid schizophrenia**	3 (0.002)	9 (0.001)	50.00 ± 15.00	38.47 – 61.53	15.0
F20.9	**Schizophrenia unspecified**	18 (0.01)	112 (0.02)	28.53 ± 10.11	26.63 – 30.42	106.5
F40.1	**Social phobia**	3 (0.002)	6 (0.001)	23.75 ± 9.97	13.29 – 34.21	4.8
F43.0	**Acute stress reaction**	1 (0.001)	1 (0.0001)	30.00 ± 0	0	1.0
F43.1	**Post-traumatic stress disorder**	3 (0.002)	13 (0.002)	18.26 ± 11.42	11.35 – 25.16	7.9
F43.2	**Adjustment disorders**	2 (0.001)	4 (0.001)	22.50 ± 8.66	8.72 – 36.28	3.0
F43.9	**Reaction to severe stress, unspecified**	5 (0.003)	13 (0.002)	24.81 ± 20.17	12.62 – 36.99	3.3
F51.0	**Insomnia**	2(0.001)	4 (0.001)	24.38 ± 11.25	6.47 – 42.28	3.3
F90.0	**Attention deficit with hyperactivity**	1 (0.001)	2 (0.0003)	15.00 ± 0	0	1.0
G43.0	**Migraine without aura**	1 (0.001)	1 (0.0001)	15.00 ± 0	0	0.5
G47.0	**Sleep disorder**	9 (0.005)	33 (0.005)	23.41 ± 13.75	18.53 – 28.28	25.8
G47.9	**Sleep disorder unspecified**	8 (0.004)	27 (0.004)	24.31 ± 15.89	18.02 – 30.60	21.9
N95.1	**Menopausal and female climacteric states**	2 (0.002)	2 (0.0003)	15.00 ± 0	0	1.0
R51	**Headache**	1 (0.001)	1 (0.0001)	60.00 ± 0	0	2.0

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Mirtazapine in the other claim category represented 197 DDDs with 51 for insomnia and sleep disorders and 121.5 for schizophrenia.

Mirtazapine was used to treat sleep disorders in dosages of 23 ± 14 mg [95% CI: 18.53 – 28.28] to 24 ± 11 mg [95% CI: 6.47 – 42.28] per day. Based on a study by Aslan *et al* .(2002:668), mirtazapine is effective in reducing slow wave sleep in dosages of 30 mg daily, but does not decrease rapid eye movement (REM) significantly. Aslan and colleagues furthermore state mirtazapine may have these positive effects on sleep by deepening the sleep effects in

depressed patients.

Mirtazapine was found a useful second line therapy for post-traumatic stress disorder (PTSD) in dosages of 45 mg daily (Davidson *et al.*, 2003:190).This finding was for dosages much higher than in the present study where PTSD and other stress related conditions were treated in dosages of 18 ± 11 mg [95% CI: 11.35 – 25.16] to 25 ± 20 mg [95% CI: 12.62 – 36.99]. Mirtazapine's possible positive effect on PTSD may be due to its simultaneously serotonergic and noradrenergic transmission (Davidson *et al.*, 2003:190). Serotonergic system modulates mood, emotion, sleep and other physiological functions (Pithadia & Jain, 2009:72).

Mirtazapine was used to treat schizophrenia (paranoid and unspecified) in dosages ranging from 29 ± 10 mg [95% CI: 26.63 – 30.42] to 50 ± 15 mg [95% CI: 38.47 – 61.53]. The possible mechanism of mirtazapine as adjunctive treatment in schizophrenia is based on its receptor profile. According to Terevnikov (2013:34), mirtazapine is a potent inhibitor of post-synaptic serotonin 2a receptors which lacks D2 receptor affinity and relating to antipsychotic efficacy. Combination therapy of mirtazapine and dopamine 2 antagonists may improve the efficacy and tolerability in schizophrenia.

4.9.5 Citalopram

In this section citalopram will be discussed in accordance with potential off-label usage.

A general summary of the off-label category uses of citalopram as determined from Table A.3 (Annexure A) is presented in Table 4.13. It further gives a summary of the number of patients, number of prescriptions, average prescribed daily dosages and standard deviation, confidence interval and the number of DDDs represented by each indication for the study population. The DDD of citalopram is 20 mg daily (WHO, 2012).

Table 4.13 Off-label claim category and dosages for citalopram

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
N95.0	**Postmenopausal bleeding**	3 (0.002)	3 (0.0004)	29.33 ± 15.09	-106.12 – 164.87	4.4
N95.1	**Menopausal and female climacteric states**	35 (0.02)	121 (0.02)	35.29 ± 16.99	32.23 – 38.35	213.5

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Table 4.13 Off-label claim category and dosages for citalopram *continued*

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]	
N95.3	**States associated with artificial menopause**	2 (0.001)	8 (0.001)	20.00 ± 0	0	8.0	
N95.9	**Menopausal and perimenopausal disorder, unspecified**	12 (0.01)	26 (0.004)	45.00 ± 18.17	37.66 – 52.33	58.5	

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Treatment with citalopram for menopausal symptoms accounted a total of 280 DDDs.

Barton *et al.* (2010:3278) found citalopram efficient for the treatment of hot flushes in dosages of 10 to 30 mg daily, but concluded that doses of 10 mg were sufficient. In the present study, citalopram was used to treat menopausal symptoms in dosages of 20 mg to 45 ± 18 mg [95% CI: 37.66 – 52.33]. Weitner *et al.* (2002:343) proposes that estrogen decreases serotonin neurotransmission and having increased feelings of fatigue and sleeplessness. Thus the use of SSRI can lead to improved sleep *via* serotonin that remains longer in the synaps and thus leading to an amelioration of the negative mood states that is caused by decrease in estrogen. Freeman *et al.* (2011:273) also state that although the precise mechanism by which escitalopram, another SSRI, improve hot flushes is unknown – there is strong evidence that indicates that estrogen is involved in the serotonergic system supporting hypotheses of the role of serotonin receptors in the pathogenesis of hot flushes.

A general summary of the other category uses of citalopram as determined from Table A.3 (Annexure A) is presented in Table 4.14.

Table 4.14 Other claim category and dosages for citalopram

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F20.0	**Paranoid schizophrenia**	16 (0.01)	84 (0.01)	28.81 ± 8.97	26.86 – 30.76	121.0
F20.2	**Undifferentiated schizophrenia**	2 (0.001)	5 (0.001)	28.00 ± 17.89	5.79 – 50.21	7.0
F20.4	**Post-schizophrenic depression**	6 (0.003)	8 (0.001)	45.00 ± 14.14	33.18 – 56.82	18.0
F20.9	**Schizophrenia unspecified**	57 (0.03)	284 (0.04)	31.76 ± 14.11	30.11 – 33.41	451.0
F51.0	**Insomnia**	23 (0.01)	42 (0.01)	32.86 ± 19.16	26.89 – 38.82	69.0
F84.0	**Childhood autism**	1 (0.001)	1 (0.0001)	50.00 ± 0	0	2.5
F90.0	**Attention deficit with hyperactivity**	5 (0.003)	17 (0.002)	29.41 ± 14.35	22.03 – 36.79	25.0
G35	**Multiple sclerosis**	5 (0.003)	12 (0.002)	25.83 ± 10.84	18.95 – 32.72	15.5
G43.0	**Migraine without aura**	3 (0.002)	12 (0.002)	23.33 ± 11.55	15.99 – 30.67	14.0
G43.3	**Migraine complicated**	1 (0.001)	2 (0.0003)	60.00 ± 0	0	6.0
G43.8	**Migraine other**	1 (0.001)	2 (0.0003)	20.00 ± 0	0	2.0
G43.9	**Migraine unspecified**	18 (0.01)	26 (0.004)	44.62 ± 19.85	36.60 – 52.63	58.0
G44.2	**Headache tension type**	17 (0.01)	18 (0.003)	56.11 ± 12.43	49.93 – 62.29	50.5
G44.8	**Other specified headache syndromes**	1 (0.001)	1 (0.0001)	60.00 ± 0	0	3.0
G47.0	**Sleep disorder**	27 (0.02)	66 (0.01)	29.85 ± 11.7	26.97 – 32.72	98.5
G47.9	**Sleep disorder unspecified**	21 (0.01)	45 (0.01)	40.00 ± 20.73	33.77 – 42.23	90.0
K58.0	**IBS with diarrhoea**	1 (0.001)	1 (0.0001)	10.00 ± 0	0	0.5
K58.9	**IBS without diarrhoea**	8 (0.004)	8 (0.001)	57.19 ± 22.81	38.12 – 76.26	22.9
N39.4	**Other specified urinary incontinence**	3 (0.002)	10 (0.001)	22.00 ± 6.32	17.48 – 26.52	11.0
R51	**Headache**	7 (0.004)	7 (0.001)	60.00 ± 0	0	21.0

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

A total of 0.09% (n = 692 325) of prescriptions was represented by the other claim category of citalopram.This claim category also represented a total of 1 086.4 DDDs.

In the present study, tension type headache was treated with citalopram in doses of 56 mg [95% CI: 49.93 – 62.29]. According to Bendtsen *et al.* (1996:289), citalopram is not sufficient in dosages of 20 mg daily. Further studies by Rampello *et al.* (2004:327) suggest that citalopram and amitriptyline in combination may be beneficial for patients with tension-type headache. Alemdar and Selekler (2007:121) found that citalopram induced migraine attacks after taking citalopram, but that these findings should be confirmed with further studies. In the present study, citalopram was used to treat migraine in dosages of 20 mg to 45 ± 20 mg [95% CI: 36.20 – 52.63].

Salokangas *et al.* (1996:179) found citalopram given to patients in dosages of 20 mg to 40 mg to have no clear effect in psychopathological symptoms in patients with chronic schizophrenia, but that it does, however, improve the general well-being of these patients. Friedman *et al.* (2005:241) also showed that citalopram had no significant cognitive improvement for schizophrenia in dosages of 40 mg daily. In the present study schizophrenia (paranoid, undifferentiated, unspecified and post-schizophrenic) was treated with citalopram in dosages ranging from 28 ± 18 mg [95% CI: 5.59 – 50.21] to 45 ± 14 mg [95% CI: 33.18 – 56.82]. Escitalopram was also found ineffective treatment of the negative symptoms (emotional withdrawal, anhedonia, loss of initiative and restrictive affect) in schizophrenia (Lancu *et al.,* 2010:21).

Sleep quality and sleep latency were improved using citalopram 20 mg to 40 mg per day in patients with major depressive disorder (Shahsavand-Ananloo *et al.*, 2013:1160). These findings were similar to the present study where insomnia and sleep disorders were treated with 30 ± 11 mg [95% CI: 26.97 – 32.72] to 40 ± 21 mg [95% CI: 33.77 – 42.23]. According to Gillin *et al.* (1994:435) citalopram caused the activation of serotonin 1A receptor, whereby rapid eye movement (REM) was suppressed and sleep thus improved.

4.9.6 Bupropion

In this section bupropion will be discussed in accordance with potential off-label usage. A general summary of the off-label category uses of bupropion as determined from Table A.3 (Annexure A) is presented in Table 4.15. It further gives a summary of the number of patients, number of prescriptions, average prescribed daily dosages and standard deviation, confidence interval and the number of DDDs, represented by each indication for the study population. The DDD of bupropion is 300 mg daily (WHO, 2012).

Table 4.15 Off-label claim category and dosages for bupropion

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F41.1	**Generalised anxiety disorder**	10 (0.01)	16 (0.002)	187.50 ± 67.08	151.75 – 223.25	10.0
F41.2	**Mixed anxiety and depressive disorder**	22 (0.01)	69 (0.01)	221.19 ± 93.44	198.67 – 243.56	5.1
F41.9	**Anxiety disorder unspecified**	8 (0.004)	11 (0.002)	272.72 ± 147.25	173.81 – 371.65	10.0

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

The treatment of anxiety disorders with bupropion represented a total of 25.1 DDDs.

Bystritsky *et al.* (2008:49) found bupropion effective for the treatment of general anxiety disorder in dosages of 150 mg to 300 mg daily (refer to Table 2.2). Similar to Bystritsky and colleagues, the present study showed that bupropion was used to treat anxiety disorders (generalised, mixed anxiety and depressive disorder and unspecified) in dosages of 188 ± 67 mg [95% CI: 151.75 – 223.25] to 272 ± 147 mg [95% CI:173.81 – 371.65]. A possible mechanism by which bupropion reduced anxiety may be *via* its effect on noradrenaline neurotransmission and indirectly influencing serotonergic neurotransmission and then reducing anxiety (Gobbi*et al.*, 2003:238).

A general summary of the other category uses of bupropion as determined from Table A.3 (Annexure A) is presented in Table 4.16.

Table 4.16 Other claim category and dosages for bupropion

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F20.0	**Paranoid schizophrenia**	1 (0.001)	11 (0.002)	300 ± 0	0	11.0
F20.9	**Schizophrenia unspecified**	6 (0.003)	38 (0.01)	232.89 ± 96.76	201.09 – 264.70	29.5

Table 4.16 Other claim category and dosages for bupropion *continued*

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F43.0	**Acute stress reaction**	2 (0.001)	10 (0.001)	240.00 ± 104.88	164.97 – 315.02	8.0
F43.1	**Post-traumatic stress disorder**	1 (0.001)	5 (0.001)	188.57 ± 64.99	107.87 – 269.27	3.1
F43.2	**Adjustment disorders**	2 (0.001)	18 (0.003)	191.67 ± 69.13	157.29 – 226.05	11.5
F43.9	**Reaction to severe stress, unspecified**	4 (0.002)	8 (0.001)	206.25 ± 77.63	141.35 – 271.15	5.5
F51.0	**Insomnia**	3 (0.002)	6 (0.001)	150.00 ± 0	0	3.0
F90.0	**Attention deficit with hyperactivity**	18 (0.01)	46 (0.01)	241.30 ± 74.01	219.32 – 263.28	37.0
G43.0	**Migraine without aura**	1 (0.001)	3 (0.0004)	300.00 ± 0	0	3.0
G44.2	**Headache tension type**	2 (0.001)	6 (0.001)	275.00 ± 61.24	210.74 – 339.26	5.5
G47.0	**Sleep disorder**	1 (0.001)	1 (0.0001)	300.00 ± 0	0	1.0
G47.9	**Sleep disorder**	1 (0.001)	7 (0.001)	150.00 ± 0	0	3.5
N95.1	**Menopausal and female climacteric states**	1 (0.001)	3 (0.0004)	300 ± 0	0	3.0

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

A study done by Cañive *et al.* (1998:382) concluded that bupropion was an ineffective treatment in post-traumatic stress disorder (PTSD) in war veterans with no significant improvement in disturbance or prevention of PTSD. The present study only had one patient taking bupropion for PTSD in dosages of 189 ± 65 mg [95% CI: 107.87 – 269.27].

There were conflicting findings in the literature where Reimherr*et al.* (2005:249) showed that bupropion had a non-significant improvement of attention deficit hyperactivity disorder (ADHD) in dosages of 100 mg to 400 mg per day. Wilens *et al.* (2010:32), however, found that bupropion given in 100 mg to 400 mg do improve ADHD significantly. A potential mechanism how bupropion improves ADHD symptoms may be by its indirect enhancing effects on dopamine and noradrenalin (Ascher *et al.*, 1995:400). Attention deficit hyperactivity disorder was treated with bupropion in dosages of 241 ± 74 mg [95% CI: 219.32 – 263.28] (number of

DDDs: 37).

4.9.7 Duloxetine

In this section duloxetine will be discussed in accordance with potential off-label usage.

A general summary of the off-label category uses of duloxetine as determined from Table A.3 (Annexure A) is presented in Table 4.17. It further gives a summary of the number of patients, number of prescriptions, average prescribed daily dosages and standard deviation, confidence interval and the number of DDDs represented by each indication for the study population. The DDD of duloxetine is 60 mg daily (WHO, 2012).

Table 4.17 Off-label claim category and dosages for duloxetine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F20.0	**Paranoid schizophrenia**	2 (0.001)	10 (0.001)	60.00 ± 0	0	10.0
F20.2	**Undifferentiated schizophrenia**	1 (0.001)	14 (0.002)	60.00 ± 0	0	14.0
F20.4	**Post schizophrenic depression**	6 (0.003)	6 (0.001)	60.00 ± 0	0	6.0
F20.9	**Schizophrenia unspecified**	19 (0.01)	156 (0.02)	75.32 ± 41.68	66.78 – 83.85	195.8

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Treatment of schizophrenic symptoms with duloxetine represented a total of 225.8 DDDs.

Schizophrenia (paranoid, undifferentiated, post schizophrenic depression and unspecified) was treated with duloxetine in dosages ranging from 60 mg to 75 ± 42 mg [95% CI: 66.78 – 83.85]. These results are similar to findings by Mico' *et al.* (2011:308) who found duloxetine effective as a by-product to clozapine in clozapine resistant schizophrenia in dosages of 60 mg daily.

However, in the present study duloxetine was not researched as an add-on therapy in schizophrenia. Duloxetine increases noradrenaline levels by reuptake inhibition of noradrenaline (Rossiter *et al.*, 2012:494). A possible mechanism to treat negative symptoms in schizophrenia (which is present at low levels of noradrenaline) may well be by increasing the levels of noradrenaline (Yamamoto & Hornykiewicz, 2004:918). A general summary of the other category

uses of duloxetine as determined from Table A.3 (Annexure A) is presented in Table 4.18.

Table 4.18 Other claim category and dosages for duloxetine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F41.0	**Panic disorder**	9 (0.01)	33 (0.01)	48.46 ± 15.19	39.28 – 57.64	26.7
F41.1	**Generalized anxiety disorder**	13 (0.01)	53 (0.01)	49.02 ± 14.75	44.69 – 53.35	43.3
F41.2	**Mixed anxiety and depressive disorder**	22 (0.01)	93 (0.01)	41.74 ± 14.75	38.20 – 45.28	64.7
F41.9	**Anxiety disorder unspecified**	15 (0.01)	36 (0.01)	55.71 ± 10.76	50.82 – 60.61	33.4
F43.0	**Acute stress reaction**	2 (0.001)	2 (0.0003)	45.00 ± 21.21	-145.59 – 235.59	1.5
F43.1	**Post-traumatic stress disorder**	2 (0.001)	2 (0.0003)	45.00 ±21.21	-145.59 – 235.59	1.5
F43.2	**Adjustment disorders**	4 (0.002)	18 (0.003)	60.00 ± 0	0	18.0
F43.9	**Reaction to severe stress, unspecified**	4 (0.002)	9 (0.001)	55.71 ± 11.34	45.23 – 66.20	8.4
G35	**Multiple schlerosis**	5 (0.003)	24 (0.004)	43.75 ± 15.27	37.30 – 50.20	17.5
G43.0	**Migraine without aura**	4 (0.002)	11 (0.002)	60.00 ± 00	0	11.0
G43.3	**Migraine complicated**	2 (0.001)	7 (0.001)	50.00 ± 17.32	6.97 – 93.03	5.8
G43.8	**Migraine other**	1 (0.001)	1 (0.0001)	60.00 ± 0	0	1.0
G43.9	**Migraine unspecified**	2 (0.001)	5 (0.001)	60.00 ± 0	0	5.0
G44.2	**Headache tension type**	2 (0.001)	5 (0.001)	36.00 ± 13.41	19.34 – 52.66	3.0
G47.0	**Sleep disorder**	2 (0.001)	9 (0.001)	55.71 ± 11.34	45.23 – 66.20	8.4
G47.9	**Sleep disorder**	3 (0.002)	22 (0.003)	47.50 ± 15.45	37.68 – 57.32	17.4
N95.1	**Menopausal and female climacteric states**	3 (0.002)	14 (0.002)	60.00 ± 0	0	14.0

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

The other claim category of duloxetine represented a total of 0.05% (n = 692 325) of all antidepressant prescriptions in the study population.

In the present study duloxetine was used to treat multiple sclerosis (MS) in dosages of 37.3 mg to 50.2 mg (average PDD: 43.75 ± 15.27 mg). Solaro *et al.* (2013:115) found duloxetine effective for the treatment of depression in patients with MS in dosages of 60 mg per day. Fatigue is a definite confounder symptom in MS and duloxetine is effective against fatigue itself, although this hypothesis needs further investigation (Solaro *et al.,* 2013:116). According to Vollmer *et al.* (2011) duloxetine is also effective at reducing pain severity in patients with peripheral neuropathic pain associated with multiple sclerosis. According to Brown (2013), the analgesic mechanism of action of duloxetine is believed to occur in the central nervous system. There is reason to believe that it may also be effective in central pain conditions.

Duloxetine may have important therapeutic benefits in menopause-related symptoms when administered in dosages of 60 mg to 120 mg (Joffe *et al.*, 2007:949). These findings are similar to results obtained in the present study where 60 mg of duloxetine was used to treat menopausal and female climacteric states. According to Joffe *et al.* (2007:949) duloxetine's mechanism of action involves the improvement of vasomotor symptoms occurring regularly in menopausal women.

In the present study, migraine (without aura, complicated, other and unspecified) and tension type headache weretreated with duloxetine in dosages ranging from 36 ± 13 mg [95% CI: 19.34 – 52.66] to 60 mg. Even though this study is in conformity with a study by Taylor *et al.* (2007:1203), the authors concluded that preventative treatment of migraine and headache with duloxetine showed minimal effectiveness in dosages of 30 mg to 90 mg.

Although duloxetine is not registered for general anxiety disorder (GAD) in South Africa, it is effective treatment of GAD in dosages of 60 mg to 120 mg (Rynn *et al.*, 2008:187). The present study showed duloxetine was frequently used for anxiety disorders in dosages of 42 ± 15 mg [95% CI: 38.20 – 45.28] to 56 ± 11 mg [95% CI: 50.82 – 60.61]. The potential mechanism for the effect of duloxetine in GAD include by constantly reducing role functioning disabilities (imploving functional outcomes in patients with GAD) that are often associated with GAD (Endicott *et al.*, 2007: 523).

4.9.8 Paroxetine

In this section paroxetine will be discussed in accordance with potential off-label usage.

A general summary of the off-label category uses of paroxetine as determined from Table A.3 (Annexure A) is presented in Table 4.19. It further gives a summary of the number of patients, number of prescriptions, average prescribed daily dosages and standard deviation, confidence interval and the number of DDDs represented by each indication for the study population. The DDD of paroxetine is 20 mg daily (WHO, 2012).

Table 4.19 Off-label claim category and dosages for paroxetine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
N95.1	**Menopausal and female climacteric states**	11 (0.01)	35 (0.01)	22.46 ± 5.63	20.53 – 24.40	39.3
N95.9	**Menopausal and perimenopausal disorder unspecified**	3 (0.002)	9 (0.001)	30.00 ± 8.66	23.34 – 36.66	13.5
R52	**Acute pain**	1 (0.001)	1 (0.0001)	56.00 ± 0	0	2.8

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Treatment for menopausal symptoms with paroxetine represented a total of 55.6 DDDs.

Weitner *et al.* (2002:342) found paroxetine effective in treating hot flushes in dosages of 10 mg to 20 mg. In the present study paroxetine was used to treat menopausal symptoms in dosages of 22 ± 6 mg [95% CI: 20.53 – 24.40] to 30 ± 9 mg [95% CI: 23.34 – 36.66]. Weitner *et al.* (2002:343) propose that estrogen decreases serotonin neurotransmission and having increases feelings of fatigue and sleeplessness. Thus the use of SSRI can lead to improved sleep *via* serotonin that remains longer in the synaps and thus leading to an amelioration of the negative mood states that is caused by decrease in estrogen.

A general summary of the other category uses of paroxetine as determined from Table A.3 (Annexure A) is presented in Table 4.20.

Table 4.20 Other claim category and dosages for paroxetine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F20.0	**Paranoid schizophrenia**	2 (0.001)	19 (0.003)	47.02 ± 19.64	37.55 – 56.48	44.7
F20.9	**Schizophrenia unspecified**	10 (0.01)	75 (0.1)	32.67 ± 14.71	29.28 – 36.05	122.5
F51.0	**Insomnia**	1 (0.001)	1 (0.0001)	60.00 ± 0	0	3.0
F90.0	**Attention deficit with hyperactivity**	1 (0.001)	5 (0.001)	25.00 ± 0	0	6.3
G35	**Multiple sclerosis**	2 (0.001)	8 (0.001)	20.00 ± 0	0	8.0
G43.3	**Migraine complicated**	2 (0.001)	4 (0.001)	40.00 ± 40.00	-23.65 – 103.65	8.0
G43.9	**Migraine unspecified**	1 (0.001)	1 (0.0001)	20.00 ± 0	0	1.0
G44.2	**Headache tension type**	3 (0.003)	3(0.0004)	59.05 ± 1.65	54.95 – 63.15	8.9
G47.0	**Sleep disorder**	6 (0.003)	18 (0.003)	23.47 ± 8.19	19.40 – 27.54	21.1
G47.9	**Sleep disorder unspecified**	4 (0.002)	11 (0.002)	26.8 ± 15.17	16.62 – 37.01	14.7
K58.9	**IBS without diarrhoea**	2 (0.001)	4 (0.001)	30.00 ± 20.00	-1.82 – 61.82	6.0
R51	**Headache**	2 (0.001)	3 (0.0004)	44.00 ± 20.78	-7.63 – 95.63	6.6

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

A total of 250.8 DDDs was represented by the "other" claim category of paroxetine; the treatment of schizophrenia represented 167.2 of these DDDs.

Jockers-Scherübl *et al.* (2005:30) found that paroxetine had a significant treatment effect on the negative symptoms in schizophrenia in dosages of 30 mg per day. The present study showed that paroxetine was used to treat schizophrenia (paranoid and unspecified) in dosages of 33 ± 15 mg [95% CI: 29.28 – 36.05] to 47 ± 20 mg [95% CI: 37.55 – 56.48]. According to Mulholland and Cooper (2000:173), an SSRI should be considered as first line therapy in late post-psychotic depression. Millan (2000:854) hypothesizes that serotonin levels are decreased in schizophrenia.

4.9.9 Sertraline

In this section sertraline will be discussed in accordance with potential off-label usage.

A general summary of the off-label category uses of sertraline as determined from Table A.3 (Annexure A) is presented in Table 4.21. It further gives a summary of the number of patients, number of prescriptions, average prescribed daily dosages and standard deviation, confidence interval and the number of DDDs represented by each indication for the study population. The DDD of sertraline is 50 mg daily (WHO, 2012).

Table 4.21 Off-label claim category and dosages for sertraline

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
N95.1	**Menopausal and female climacteric states**	9 (0.01)	24 (0.003)	52.08 ± 10.21	47.77 – 56.39	25.0
N95.3	**States associated with artificial menopause**	1 (0.001)	1 (0.0001)	50.00 ± 0	0	1.0

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Sertraline for the treatment of menopausal symptoms represented 0.003% (n = 692 325) of all antidepressant prescriptions.

According to Grady *et al.* (2007:829), sertraline is ineffective for the treatment of hot flushes in dosages of 100 mg daily. In contrast, the present study showed that sertraline was used to treat menopausal symptoms (menopausal and female climacteric states and states associated with artificial menopause) in dosages of 50 mg to 52 ± 10 mg [95% CI: 47.77 – 56.39].

A general summary of the other category uses of sertraline as determined from Table A.3 (AnnexureA) is presented in Table 4.22.

Table 4.22 Other claim category and dosages for sertraline

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F20.0	**Paranoid schizophrenia**	3 (0.002)	6 (0.001)	54.17 ± 24.58	28.37 – 79.96	6.5
F20.9	**Schizophrenia unspecified**	19 (0.01)	126 (0.02)	82.54 ± 54.61	72.91 – 92.17	208.0
F51.0	**Insomnia**	3 (0.002)	3 (0.0004)	133.33 ± 93.82	-99.73 – 366.40	8.0
F90.0	**Attention deficit with hyperactivity**	3 (0.002)	7 (0.001)	82.14 ± 31.34	53.16 – 111.13	11.5
G35	**Multiple sclerosis**	1 (0.001)	11 (0.002)	50.00 ± 0	0	11.0
G43.9	**Migraine unspecified**	1 (0.001)	1 (0.0001)	187.50 ± 0	0	3.8
G44.2	**Headache tension type**	2 (0.001)	4 (0.001)	87.50 ± 25.00	47.72 – 127.28	6.8
G47.0	**Sleep disorder**	4 (0.002)	7 (0.001)	91.07 ± 49.32	45.45 – 136.69	12.8
G47.9	**Sleep disorder unspecified**	2 (0.001)	2 (0.0003)	50.00 ± 0	0	2.0

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Treatment of schizophrenia with sertraline represented a total of 214.5 DDDs in the "other" claim category.

Kirli and Caliskan (1998:110) found sertraline effective in dosages of 50 mg daily for post psychotic depressive disorder of schizophrenia. In the present study sertraline was used to treat schizophrenia (paranoid and unspecified) in dosages of 54 ± 25 mg [95% CI: 28.37 – 79.93] to 83 ± 55 mg [95% CI: 72.91 – 92.17]. In late post-psychotic depression an SSRI should be considered as first line therapy (Mulholland & Cooper, 2000:173) and the mechanism of their actions may involve other neuronal systems.

4.9.10 Venlafaxine

In this section venlafaxine will be discussed in accordance with potential off-label usage.

A general summary of the off-label category uses of venlafaxine as determined from Table A.3 (Annexure A) is presented in Table 4.23. It further gives a summary of the number of patients,

number of prescriptions, average prescribed daily dosages and standard deviation, confidence interval and the number of DDDs represented by each indication for the study population. The DDD of venlafaxine is 100 mg daily (WHO, 2012).

Table 4.23 Off-label claim category and dosages for venlafaxine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
G43.9	**Migraine unspecified**	1 (0.001)	3 (0.0004)	150.00 ± 0	0	4.5
M79.90	**Fibromyalgia**	2 (0.001)	12 (0.002)	75.00 ± 0	0	9.0
N95.1	**Menopausal and female climacteric states**	7 (0.004)	21 (0.003)	82.97 ± 30.70	69.00 – 96.95	17.4
N95.9	**Menopausal and perimenopausal disorder, unspecified**	3 (0.002)	9 (0.001)	108.33 ± 39.53	77.95 – 138.72	9.5

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Venlafaxine was used to treat menopausal symptoms (perimenopausal disorder unspecified, menopause and female climacteric states) in dosages of 83 ± 31 mg [95% CI: 69.00 – 96.95] to 108 ± 40 mg [95% CI: 77.95 – 138.72]. Evans *et al.* (2005:162) found venlafaxine effective to treat hot flushes in lower dosages of 37.5 mg to 75 mg. Evans and colleagues believe that the positive effect that venlafaxine hason mood elevation may increase the patient's ability to cope with hot flushes. According to Joffe *et al.* (2007:949) another SNRI duloxetine's mechanism of action involves the improvement of vasomotor symptoms occurring regularly in menopausal women.

A general summary of the other category uses of venlafaxine as determined from Table A.3 (Annexure A) is presented in Table 4.24.

Table 4.24 Other claim category and dosages for venlafaxine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F20.0	**Paranoid schizophrenia**	3 (0.002)	26 (0.004)	152.88 ± 96.00	114.11 –191.66	39.8
F20.4	**Post schizophrenic depression**	1 (0.001)	11 (0.002)	150.00 ± 0	0	16.5
F20.9	**Schizophrenia unspecified**	18 (0.01)	161 (0.02)	136.22 ± 66.72	125.84 – 146.61	219.3
F90.0	**Attention deficit with hyperactivity**	1 (0.001)	1 (0.0001)	75.00 ± 0	0	0.8
G35	**Multiple sclerosis**	1 (0.001)	2 (0.0003)	150.00 ± 0	0	3.0
G44.2	**Headache tension type**	1 (0.001)	1 (0.0001)	225.00 ± 0	0	2.3
G47.0	**Sleep disorder**	2 (0.001)	3 (0.0004)	150.00 ± 0	0	4.5
G47.9	**Sleep disorder unspecified**	3 (0.002)	3 (0.0004)	175.00 ± 114.56	-109.59 – 459.59	5.3
K58.9	**IBS without diarrhoea**	1 (0.001)	1 (0.0001)	75.00 ± 0	0	0.8
R51	**Headache**	1 (0.001)	1 (0.0001)	75.00 ± 0	0	0.8

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Treatment for other claim category of venlafaxine represented 293.1 DDDs and consisted of 0.03% (n = 692 325) of prescriptions of the study population.

Venlafaxine may have a role in the treatment of depression in patients with schizophrenia in dosages of 75 mg to 225 mg per day (Mazeh *et al.*, 2004:655). These findings were similar to findings in the present study where schizophrenia (paranoid, post schizophrenic and unspecified) was treated with venlafaxine in dosages of 136 ± 67 mg [95% CI: 125.84 – 146.61] to 153 ± 96 mg [95% CI: 114.11 – 191.66] per day. According to Mukaetova-Ladinska *et al.* (2010:166) in schizophrenia, it is found that serotonin and noradrenaline are depleted, which plays a significant role in schizophrenic rational processing. Venlafaxine, by preventing presynaptic re-uptake of noradrenaline, restores the neurotransmitters in the latter and then regulates the clinical symptoms.

Venlafaxine was used to treat sleep disorders in dosages of 150 mg to 175 ± 115 mg (95% CI: -109.59 – 459.59). These findings are in contrast with findings by Salín-Pascual *et al.* (1997:349) who found that venlafaxine given in dosages of 75 mg to 150 mg can actually cause sleep disturbances and reduce sleep in stages two and three.

4.9.11 Imipramine

In this section imipramine will be discussed in accordance with potential off-label usage.

A general summary of the off-label category uses of imipramine as determined from Table A.3 (Annexure A) is presented in Table 4.25. It further gives a summary of the number of patients, number of prescriptions, average prescribed daily dosages and standard deviation, confidence interval and the number of DDDs represented by each indication for the study population. The DDD of imipramine is 100 mg daily (WHO, 2012).

Table 4.25 Off-label claim category and dosages for imipramine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
K58.0	**IBS with diarrhoea**	1 (0.001)	1 (0.0001)	20.00 ± 0	0	0.2
K58.9	**IBS without diarrhoea**	6 (0.003)	23 (0.003)	30.54 ± 36.66	14.67 – 46.40	7.0

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Treatment of IBS with imipramine represented a total of 7.2 DDDs.

Abdul-Baki *et al.* (2009:3637) found imipramine effective for the treatment of IBS in dosages of 25 mg daily before bedtime. These findings were similar to the present study's findings where IBS with or without diarrhoea was treated with imipramine 20 mg to 31 ± 37 mg [95% CI: 14.67 – 46.40]. A possible mechanism may involve the antinoceptive effects of the antidepressants in treating IBS (Sainsbury & Ford, 2011:117). TCAs introduce several different mechanisms that may potentially explain its positive effect on IBS (Halpert *et al.*, 2005:670). Adjustment of visceral sensitivity, ororectal transit interval and gut motility, may be prevalent mechanisms. Persistent stimulation of the frontal mid-cingulate cortex can give malfunction of pain control in IBS. Pain regulation is transmitted from the central nervous system (CNS), and a central analgesic action by the TCAs may reverse the malfunction in the pain regulatory system (Halpert *et al.*, 2005:670). Accompanying psychological symptoms in IBS can be positively

treated by antidepressants. Treatment with antidepressants for analgesic conditions occurs at lower dosages than depression (Halpert *et al.*, 2005:670).

A general summary of the other category uses of imipramine as determined from Table A.3 (Annexure A) is presented in Table 4.26.

Table 4.26 Other claim category and dosages for imipramine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F20.0	**Paranoid schizophrenia**	3 (0.002)	11 (0.002)	19.54 ± 7.57	14.46 – 24.63	2.2
F20.9	**Schizophrenia unspecified**	4 (0.002)	46 (0.01)	64.67 ± 58.11	47.41 – 81.93	29.8
F41.0	**Panic disorder**	9 (0.01)	25 (0.004)	67.76 ± 62.53	41.95 – 93.57	16.9
F41.1	**Generalized anxiety disorder**	13 (0.01)	37 (0.01)	73.78 ± 71.65	49.89 – 97.67	27.3
F41.2	**Mixed anxiety and depressive disorder**	9 (0.01)	19 (0.003)	66.84 ± 66.18	34.95 – 98.74	12.7
F41.9	**Anxiety disorder unspecified**	57 (0.03)	87 (0.01)	138.04 ± 73.26	122.42 – 153.70	120.1
F51.0	**Insomnia**	8 (0.004)	16 (0.002)	61.98 ± 64.09	27.82 – 96.13	9.9
F90.0	**Attention deficit with hyperactivity**	5 (0.003)	12 (0.002)	64.59 ± 52.72	31.09 – 98.08	7.8
F90.0	**Attention deficit with hyperactivity**	5 (0.003)	12 (0.002)	64.59 ± 52.72	31.09 – 98.08	7.8
G35	**Multiple sclerosis**	43 (0.02)	233 (0.03)	37.99 ± 31.75	33.89 – 42.09	88.5
G43.0	**Migraine without aura**	3 (0.002)	5 (0.001)	54.50 ± 74.63	-38.17 – 147.17	2.7
G43.1	**Migraine classic**	1 (0.001)	14 (0.002)	25.00 ± 0	0	3.5
G43.8	**Migraine other**	1 (0.001)	2 (0.0003)	190.97 ± 4.91	146.85 – 235.09	3.8
G43.9	**Migraine unspecified**	17 (0.01)	21 (0.003)	131.03 ± 55.34	105.84 – 156.22	27.5
G44.0	**Headache cluster**	1 (0.001)	1 (0.0001)	187.50 ± 0	0	1.8
G44.1	**Headache vascular**	1 (0.001)	1 (0.0001)	187.50 ± 0	0	1.8
G44.2	**Headache tension**	106 (0.06)	123 (0.02)	105.68 ± 70.91	93.03 – 118.34	130.0
G44.8	**Headache allergic**	5 (0.003)	13 (0.002)	47.76 ± 54.29	14.95 – 80.56	6.2

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Table 4.26 Other claim category and dosages for imipramine *continued*

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
G47.0	**Sleep disorder**	13 (0.01)	21 (0.003)	81.19 ± 76.32	46.45 – 115.93	17.1
G47.9	**Sleep disorder unspecified**	5 (0.003)	10 (0.001)	22.00 ± 6.32	17.48 – 26.52	2.2
M79.90	**Fibromyalgia**	1 (0.001)	4 (0.001)	25.00 ± 0	0	1.0
N95.0	**Postmenopausal bleeding**	2 (0.001)	9 (0.001)	18.89 ± 5.46	14.69 – 23.09	1.7
N95.1	**Menopausal and female climacteric states**	5 (0.003)	13 (0.002)	101.92 ± 82.73	51.92 – 151.92	13.3
N95.3	**States associated with artificial menopause**	2 (0.001)	2 (0.0003)	150.00 ± 0	0	3.0
N95.9	**Menopausal and perimenopausal disorder, unspecified**	2 (0.001)	2 (0.0003)	168.75 ± 26.52	-69.49 – 406.99	3.4
R51	**Headache**	15 (0.01)	15 (0.002)	99.22 ± 73.62	58.45 – 139.99	14.9

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Treatment with imipramine represented a total number of 549.1 DDDs and 0.18% (n =180 264) of claims in the other claim category.

Shain *et al.* (1990:460) showed that imipramine may suppress REM sleep in depressed patients. In the present study imipramine was used in dosages of 22 ± 6 mg [95% CI: 17.48 – 26.52] to 81 ± 76 mg [95% CI: 46.45 – 115.93] to treat sleep disorders.

The present study showed that imipramine was used to treat multiple sclerosis in dosages of 38 ± 32 mg [95% CI: 33.89 – 42.09] daily. According to Dean (1969:87), however, imipramine has been shown as an ineffective treatment of multiple sclerosis in dosages of 25 mg three times a day (Dean, 1969:87).

Imipramine was used to treat panic disorder in dosages of 68 ± 63 mg [95% CI: 41.95 – 93.57]. These findings was in a lower dosage than a study by Ağargün *et al.* (1999:140) who found imipramine effective for sleep panic in dosages of 150 mg per day. Sleep panic attacks

areassociated with non-REM (rapid eye movement) events and it may be so that imipramine suppresses this event having a positive effect on sleep panic (Ağargün *et al.*, 1999:140).

Tension type headache treated with imipramine in dosages of 106 ± 71 mg [95% CI: 93.03 – 118.34] represented 0.06% (n = 180 264) of the claimed prescriptions. Mousavi *et al.* (2011:925) found imipramine to be an effective treatment of tension-type headache in dosages of 25 mg twice daily. Mousavi and colleagues state that by inhibition of pain pathways, or an increase of secretion of pain reducing substances in the central nervous system, may have an effect on tension-type headaches.

4.9.12 Trimipramine

In this section trimipramine will be discussed in accordance with potential off-label usage.

A general summary of the off-label category uses of trimipramine as determined from Table A.3 (Annexure A) is presented in Table 4.27. It further gives a summary of the number of patients, number of prescriptions, average prescribed daily dosages and standard deviation, confidence interval and the number of DDDs represented by each indication for the study population. The DDD of trimipramine is 150 mg daily (WHO, 2012).

Table 4.27 Off-label claim category and dosages for trimipramine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F51.0	**Insomnia**	1 (0.001)	1 (0.0001)	25.00 ± 0	0	0.2
G47.0	**Sleep disorder**	2 (0.001)	13 (0.002)	42.31 ± 12.01	35.05 – 49.57	3.7
G47.9	**Sleep disorder unspecified**	2 (0.001)	15 (0.002)	50.00 ± 0	0	5.0

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Sleep disorders were treated with trimipramine in dosages of 25 mg to 50 mg. These were similar to findings by Riemann *et al.* (2002:173) where trimipramine was found to be effective in increasing polysomnographical sleep efficiency in dosages ranging from 25 mg to 200 mg. The possible mechanism by which trimipramine acts on sleep may involve its increase of the percentage of REM sleep time. Trimipramine does not only normalise REM sleep, but may well

stimulate REM sleep beyond normal REM scores (Wiegand *et al.,* 1986:198).

A general summary of the other category uses of trimipramine as determined from Table A.3 (Annexure A) is presented in Table 4.28, using the ICD-10 coding system.

Table 4.28 Other claim category and dosages for trimipramine

ICD-10 code	ICD-10 description	Number of patients n (%)[a]	Number of prescriptions n (%)[b]	Dosage ± standard deviation (mean, mg)	95 % confidence interval	Number of DDDs[c]
F20.9	**Schizophrenia unspecified**	1 (0.001)	16 (0.002)	43.75 ± 11.18	37.79 – 49.71	4.7
F41.1	**Generalized anxiety disorder**	2 (0.001)	5 (0.001)	45.00 ± 11.18	31.12 – 58.88	1.5
F41.2	**Mixed anxiety and depressive disorder**	2 (0.001)	7 (0.001)	260.71 ± 103.94	164.59 – 356.84	12.2
F41.9	**Anxiety disorder unspecified**	2 (0.001)	17 (0.002)	226.47 ± 117.41	166.10 – 286.84	25.7
G43.9	**Migraine unspecified**	1 (0.001)	1 (0.0001)	50.00 ± 0	0	0.3
N95.1	**Menopausal and female climacteric states**	1 (0.001)	1 (0.0001)	100.00 ± 0	0	0.7

a = percentage patients calculated out of N = 180 264; b = percentage prescriptions calculated out of N = 692 325 and c = number of DDDs calculated as (mean x number of scripts / DDD)

Only eight (0.004%) patients received trimipramine in the "other" claim category and represented 45.18 number of DDDs.

4.10 Section summary

The antidepressants were prescribed for a number of off-label indications. These include: migraine and headache (the TCAs, SSRIs, SNRIs, mirtazapine and bupropion), IBS (TCA's, SSRIs and SNRIs), schizophrenia (TCAs, SSRIs, SNRIs, mirtazapine and bupropion), sleep disorders and insomnia (TCAs, SSRIs, SNRIs, mirtazapine and bupropion), multiple sclerosis (TCAs, SSRIs and SNRIs), menopausal symptoms (TCAs, SSRIs, SNRIs, mirtazapine and bupropion), anxiety disorders (TCAs and SNRIs) and ADHD (TCAs, SSRIs, SNRIs, mirtazapine and bupropion).

4.11 Chapter summary

This chapter contains the results and discussion of the empirical investigation phase of the study. Data obtained from the PBM Company for the year of 2010 were analysed in respect to a general overview of the data set, patients receiving antidepressants and the general prescribing patterns of the study population. Finally, the off-label prescribing of antidepressants of the study population was discussed and presented. The next (final) chapter brings the study to a close and will contain the conclusion, limitations and future recommendations of the study.

CHAPTER 5

Conclusions and Recommendations

5.1 Introduction

This chapter provides a general overview of the dissertation, followed by conclusions from the study. Finally, the limitations and strengths are emphasised, concluding with the recommendations for future research possibilities.

5.2 Dissertation content

This dissertation consists of five chapters. Chapter 1 comprises the background and rationale of the study and contributed to the literature in context. The research questions and objectives are determined, followed by the presentation of the different phases of the study. Chapter 2 contains a general discussion on what off-label medication is, the need for such prescribing, regulations and prescribing patterns in various countries, and concludes with identifying possible off-label indication with a possible mechanism of action, if provided in the literature.

Chapter 3 contains a description of the empirical investigation, which entails the study design, research method, data source, and selection of the study population. The study variables, classification systems used, measures of utilisation and statistical analysis are presented. This chapter concludes with the reliability and validity of the study assessed by applying a checklist of retrospective database studies, and ethical considerations.

In Chapter 4, the results and findings of the empirical investigation phase of the study are presented. This includes a discussion of the data set, patients receiving antidepressants and the study population.

This final chapter summarises the conclusions in line with the study objectives.

5.3 Conclusions

5.3.1 Conclusions based on findings from the literature study

In the following section, all the conclusions in relation to the literature study will be discussed based on the specific objectives.

Specific objective 1: *Conceptualise the meaning of "off-label" medication usage.*

The meaning of off-label is summarised and explained (refer Chapter 2, paragraph 2.2).

In conclusion, off-label usage can be described as the use of medication other than what it is registered for. This includes the use of medicines registered for adults in children, medication used for a different indication as it is registered for, used in a different administrative route and medication used where there is not enough scientific evidence for a specific indication. For the purpose of this study the term off-label will be used to describe all active ingredients that is not used for the indication that it is registered for.

Specific objective 2: *Determine the need for off-label prescribing*

There are several advantages for off-label prescribing. There is a definite need for off-label prescribing in cases where off-label is the last line of treatment or where there is no indication for a specific medication in children.

Specific objective 3: *Establish the difficulties that may arise from off-label prescribing*

Difficulties which may arise from off-label prescribing are the clinical and ethical considerations and the lack of scientific evidence of such medications being prescribed off-label. A huge concern is seen in paediatric prescribing practices were there is a lack in labelled evidence. Drugs that are safe in adults cannot be presumed automatically safe and effective in children (refer to Chapter 2, paragraph 2.4).

Specific objective 4: *Determine off-label prescribing practices in general*

First general regulations of various countries were evaluated. It was found that there are regulations in place to make sure that off-label prescribing practices be as safe as possible in certain countries (refer to paragraph 2.5.1). There is, however, limited information on off-label prescribing practices in South Africa.

Several studies showed that off-label prescribing is prevalent in many countries for many different indications (refer to Table 2.1). It seems, however, that there is less off-label use in adults documented in the published domain. It was also determined that antidepressants are one of the most relevant classes of drugs being prescribed off-label (refer to Table 2.1).

Specific objective 5: *Identify antidepressants with known off-label indications*

Antidepressants with off-label indications were identified and summarised in Table 2.2. The appropriate dosages were presented from the literature, as well as the age and indication of the off-label use. Finally, the mechanisms of the off-label indication in the patients were explained.

5.3.2 Conclusions based on findings from the empirical investigation

In the following section, the conclusions derived at in relation to the empirical investigation phase of the study will be presented, based on the specific objectives.

Specific objective 6: *Determine the prevalence of antidepressants with identified off-label indications on the pharmaceutical benefit management (PBM) company's database, stratified by age, gender and prescriber*.

Prescription claims data for a total of 1 220 289 patients were obtained from a medicine claims database of a South African Benefit Management (PBM) company's central database. These patients accounted for 14.7% of all medical aid schemes beneficiaries (n = 8 315 718) registered in terms of the Medical Schemes Act (Act 131/1998) during 2010, in South Africa (CMS, 2011:159). The data set consisted of information on more females than males. In 2010, patients on antidepressants represented a total of 15.2% (n = 1 220 289) of patients on the data set. Prescriptions and medicine items for these patients accounted for 8.3% (n = 8 515 428) and 3.5% (n = 20 527 777) of all prescriptions and medicine items claimed during the study period, respectively (refer to Table 4.1).

The most prescribed antidepressant in relation to age and gender were escitalopram, citalopram and amitriptyline.

The DU90% for prescribers was achieved with general practitioners (GPs) and psychiatrists, responsible for 75.7% and 14.9% (n = 702 885) of drugs, respectively. Based on the DU90% method, it was furthermore established that amitriptyline 82.4% (N = 2 635), escitalopram (4.2%) and fluoxetine (3.8%) were the most prescribed antidepressants for off-label indications (refer to Table 4.4).

Specific objective 7: *Determine the prescribed daily dosage of antidepressants with prescribed off-label indications.*

The antidepressants were prescribed for a number of off-label indications. These included: migraine and headache (the TCAs, SSRIs, SNRIs, mirtazapine and bupropion), IBS (TCAs, SSRIs and SNRIs), schizophrenia (TCAs, SSRIs,SNRIs, mirtazapine and bupropion), sleep

disorders and insomnia (TCAs, SSRIs, SNRIs, mirtazapine and bupropion), multiple sclerosis (TCAs, SSRIs and SNRIs), menopausal symptoms (TCAs, SSRIs, SNRIs, mirtazapine and bupropion), anxiety disorders (TCAs and SNRIs) and ADHD (TCAs, SSRIs, SNRIs, mirtazapine and bupropion). There seems to be similar off-label indications for some of the antidepressants, thses may be ascribed to a possible class effect for off-label use.

In Table 5.1 provides a summary of the antidepressants with known off-label indications identified on the database. Prescribed daily dose (PDD) and dosage ranges as determined from claims are given.

Table 5.1 Antidepressants prescribed off-label on the database, in relation to indication and dosage

Antidepressant	Off-label indication	Possible off-label indication	Prescribed daily dose (PDD) (range, mg)
Tricyclic antidepressants (TCAs)			
Amitriptyline	Herpes neuralgic pain		116*
	Migraine		36 – 86
	Headache		22 – 87
	Irritable bowel syndrome (IBS)		36 – 42
		Schizophrenia	49 – 150
		Sleep disorder	47 - 48
		Attention deficit hyperactivity disorder (ADHD)	25*
		Multiple sclerosis	36*
		Fibromyalgia	39*
		Menopausal symptoms	36 – 48
Imipramine	IBS		20 – 31
		Schizophrenia	19 – 65
		Other anxiety disorders	67 – 138
		Sleep disorders	22 – 81
		ADHD	65*
		Multiple sclerosis	38*
		Migraine	25 – 191
		Headache	48 – 188
		Fibromyalgia	25
		Menopausal symptoms	19 – 169
Trimipramine	Sleep disorders		25 – 50
		Schizophrenia	44*
		Other anxiety disorders	45 – 261
		Migraine	50*
		Menopausal symptoms	100*

* When only one PDD is given and not a range there is only one indication and not a group indication (e.g. There are a number of different headaches).

Table 5.1 Antidepressants with known off-label indication, in relation to indication and dosage *continued*

Antidepressant	Off-label indication	Possible off-label indication	Prescribed daily dose (PDD) (range, mg)
Selective serotonin re-uptake inhibitors (SSRIs)			
Citalopram	Menopausal symptoms		20 – 45
		Schizophrenia	28 – 45
		Sleep disorders	30 – 40
		Childhood autism	50*
		ADHD	29*
		Multiple sclerosis	26*
		Migraine	20 – 60
		Headache	56 – 60
		IBS	10 – 57
		Incontinence	22*
Escitalopram	Obsessive compulsive disorder		12 – 23
	Migraine		10 – 40
	Menopausal symptoms		15 – 20
		Schizophrenia	13 – 20
		Sleep disorders	14 – 24
		ADHD	5*
		Multiple sclerosis	20*
		IBS	14 – 20
		Incontinence	12 – 20
		Headache	11 – 20
Fluoxetine	Headache		75 – 76
	IBS		57*
	Premenstrual syndrome (PMS)		17*
		Schizophrenia	29 – 48
		Bulimia nervosa	67*
		Sleep disorders	46 – 63
		Premature ejaculation	76*
		ADHD	30*
		Multiple sclerosis	20*
		Migraine	20 – 48
		Incontinence	20*
		Menopausal symptoms	20 – 29

* When only one PDD is given and not a range there is only one indication and not a group indication (e.g. There are a number of different headaches).

Table 5.1 Table 5.1 Antidepressants prescribed off-label on the database, in relation to indication and dosage *continued*

Antidepressant	Off-label indication	Possible off-label indication	Prescribed daily dose (PDD) (range, mg)
Paroxetine	Menopausal symptoms		22 – 30
	Acute pain		56*
		Schizophrenia	33 – 47
		Sleep disorders	23 – 60
		ADHD	25*
		Multiple sclerosis	20*
		Migraine	20 – 40
		Headache	44 – 59
		IBS	30*
Sertraline	Menopausal symptoms		50 – 52
Antidepressant	**Off-label indication**	**Possible off-label indication**	**Prescribed daily dose (PDD) (range, mg)**
		Schizophrenia	54 – 83
		Sleep disorders	50 – 133
		ADHD	82*
		Multiple sclerosis	50*
		Migraine	188*
		Headache	88*
Serotonin and noradrenaline re-uptake inhibitors (SNRIs)			
Duloxetine	Schizophrenia		60 – 75
		Other anxiety disorders	42 – 56
		Stress disorders	45 – 60
		Sleep disorders	48 – 56
		Multiple sclerosis	44*
		Migraine	50 – 60
		Headache	36*
		Menopausal symptoms	60*
Venlafaxine	Migraine		150*
	Fibromyalgia		75*
	Menopausal symptoms		83 – 108
		Schizophrenia	136 – 153
		Sleep disorders	150 – 175
		ADHD	75*
		Multiple sclerosis	150*
		Headache	75 – 225
		IBS	75**

* When only one PDD is given and not a range there is only one indication and not a group indication (e.g. There are a number of different headaches).

Table 5.1 Table 5.1 Antidepressants prescribed off-label on the database, in relation to indication and dosage *continued*

Antidepressant	Off-label indication	Possible off-label indication	Prescribed daily dose (PDD) (range, mg)
Tetracyclic antidepressant			
Mirtazapine	Other anxiety disorders		18 – 30
		Schizophrenia	29 – 50
		Social phobia	24*
		Stress disorders	18 – 30
		Sleep disorders	23 – 24
		ADHD	15*
		Migraine	15*
		Headache	60*
		Menopausal symptoms	15*
Noradrenaline and dopamine re-uptake inhibitor			
Bupropion	Other anxiety disorders		188 – 272
		Schizophrenia	233 – 300
		Stress disorders	189 – 240
		Sleep disorders	150 – 300
		ADHD	241*
Antidepressant	**Off-label indication**	**Possible off-label indication**	**Prescribed daily dose (PDD) (range, mg)**
		Migraine	300*
		Headache	275*
		Menopausal symptoms	300*

* When only one PDD is given and not a range there is only one indication and not a group indication (e.g. There are a number of different headaches).

5.4 Limitations and strengths

The study had several limitations. Firstly, only one medicine claims database were used and thus can only be generalised to the specific database. There were a number of claims that only had repeat prescription ICD-10 codes and thus could not be included in the study. However, this study can be classified as a large cross-sectional descriptive study; and this increased the power and analysis of off-label prescribing.

5.5 Recommendations

Recommendations for future research include firstly, evaluating more than one database to analyse the usage of off-label medication in a broader field in the South African private health sector. Secondly future research should be done to evaluate the efficacy and safety of off-label practises, in order to contribute to the body of evidence in the literature.

5.6 Chapter summary

This chapter concluded the dissertation by linking the specific objectives of the study with the findings. The limitations were specified and recommendations for future research were made. Hereby all the study objectives were met.

Annexures

Table A.1 Classification of antidepressants (Rossiter *et al.*, 2012:484-495; Snyman, 2012:12-25)

Classification							
Heterocyclic	**MAOIs**	**SSRIs**	**SNRIs**	**Melatonergic agonist**	**Serotonin modulators (%-HT² blockers)**	**Dopamine-norepinephrine reuptake inhibitor**	**Tetracyclic**
Amitriptyline	**Moclobemide**	**Citalopram**	**Duloxetine**	**Agomelatine**	**Mirtazapine**	**Bupropion**	Maprotiline
Clomipramine	Tranylcypromine	**Escitalopram**	**Venlafaxine**		**Nefazodone**	**Reboxetine**	**Mianserin**
Dosulepin (Dothiepin)		**Fluoxetine**			**Trazodone**		
Doxepin		**Fluvoxamine**					
Imipramine		**Paroxetine**					
Lofepramine		**Sertraline**					
Trimipramine							

MOAI = monoamine oxidase inhibitors; HCAs = heterocyclic antidepressants; SSRIs = selective serotonin reuptake inhibitors; SNRIs = selective-norepinephrine reuptake inhibitor

Table A.2 Validation processes to insure the validity and reliability of the data by the PBM

Validation processes	Examples
Data integrity validation & Eligibility management	• Claim field format checks • Provider validation checks • Member Validation checks • Verify dependent code • Waiting period check • Duplicate check
Medicine utilisation management (active ingredient level against patient history)	• Refill limits (e.g. 12 fills per year for chronic medication) • Fill limitations per period (e.g. 1 fill per 26 days) • Product quantity limits (e.g. 200 analgesics/365 days) • Product requiring pre-authorisation (e.g. immune-modulating agents) • Patient specific exclusions (e.g. for pre-existing conditions and general waiting periods) • Pre-existing conditions (e.g. patient specific as advised by scheme) • Drug to age range limitations (e.g. Ritalin™ and generics will pay for patients 16 years and younger) • Drug gender limitations (e.g. hormone replacement therapy for women) • Invalid prescriber specialty (e.g. Diane™ prescribed by dermatologists) • Broad category exclusions (e.g. soaps/shampoos excluded) • Specific products excluded (e.g. urinary antiseptics) • Waiting periods (e.g. patient specific as advised by scheme)
Clinical management	• Ingredient duplication • Maximum daily dose exceeded • Therapeutic duplication • Drug-drug interactions • Drug-allergy interactions • Drug-age interactions • Drug-gender interactions • Drug-disease interactions • Drug-inferred health state interactions
Pricing management	• Continuous price file maintenance • Apply reference pricing e.g. generic reference pricing and therapeutic reference pricing (i.e. formulary based pricing for chronic diseases)
Formulary management	• Management of Chronic Disease List prescribed minimum benefits and non-chronic disease list conditions • Daily real-time benefit validation

Table A.3 ICD-10 codes for capturing of data

	Indication	ICD 10 code	Off-label indication	ICD 10 code
Agomelatine			Sleep-wake cycle increase	G47.2
Amitriptyline	Organic mood disorder	F06.3	Migraine prophylaxis	G43
	Depression	F30-F39	Migraine control	G43
	Anxiety + OCD	F40-F42		G43.0
	Noctural enuresis	F98.0		G43.3
				G43.8
				G43.9
			Headache	G44.0
				G44.1
				G44.2
				G44.3
				G44.8

Table A.3 ICD-10 codes for capturing of data *continued*

	Indication	ICD 10 code	Off-label indication	ICD 10 code
				R 51
			IBS	K58.0
				K58.9
			Herpes neuralgical pain	A60.0
				A60.1
				A60.9
Bupropion	Organic mood disorder	F06.3	Sexual dysfuction due to SSRI	F52
	Depression	F30-F39	General anxiety disorder	F41.1
	Nicotine Addiction	F17.2		F41.2
				F41.9
Citalopram	Organic mood disorder	F06.3	Flushing	R23.2
	Depression	F30-F39	Menopause	N95.0
		F92.0		N95.1
		F92.9		N95.3
	Anxiety	F40-F42		N95.9
			Premature ejaculation	F52.4
Cloimipramine	Cataplexy accomp narcolepsy	G47.4	Premature ejaculation	F52.4
	Endogenous depression	F33.2 and F33.3		
	Organic mood disorder	F06.3		
	Depression	F30-F39		
	OCD	F42		
Dothiepin				
	Organic mood disorder	F06.3		
	Depression	F30-F39		
		F92.0		
		F92.9		
	Anxiety	F40-F42		
Doxepin	depression psychoneurotic patients	F34.1	Insomnia	G47.0 and F51.0
	depression in alcoholics	F32		
Duloxetine	Diabetic peripheral neuropathic pain	G59.0	Stress incontinence after radical prostatectomy or cystectomy	N39.3
	Organic mood disorder	F06.3		N39.4

Table A.3 ICD-10 codes for capturing of data *continued*

	Indication	**ICD 10 code**	**Off-label indication**	**ICD 10 code**
	Depression	F30-F39	Treatment resistant schizophrenia	F20.0
	Anxiety	F40-F42		F20.2
				F20.4
				F20.9
Escitalopram	Organic mood disorder	F06.3	Flushing with pain	R23.3
	Depression	F30-F39	Obsessive compulsive disorder	F42.0
		F92.0		F42.2
		F92.9		F42.8
	Anxiety	F40-F42		F42.9
			Migraine	G43.0
				G43.1
				G43.3
				G43.9
			Menopause	N95.1
				N95.3
				N95.9
Fluoxetine	Organic mood disorder	F06.3	Premenstrual syndrome	N94.3
	Depression	F30-F39	IBS with pain	K58
		F92.0	Childhood autism	F84.0
		F92.9	Headache	G44.0
	Anxiety	F40-F42		G44.2
	OCD	F42		G44.8
	Bulimia nervosa	F50.2		R 51
			IBS	K58.9
Fluvoxamine	Organic mood disorder	F06.3	Binge eating disorder	F50.2
	Depression	F30-F39	Bulimia nervosa	F50.2
		F92.0	Panic disorder	F41.0
		F92.9		F41.1
	Obsessive compulsive disorder	F43		F41.2
Imipramine	Parkinsons	G20	IBS	K58
	alcohol abuse	F10.1		K58.0
	Behavioural disorders	F10 - F19		K58.9
	Incontinence	N39		
	Noctural enuresis	F98.0		
	Organic mood disorder	F06.3		

Table A.3 ICD-10 codes for capturing of data *continued*

	Indication	ICD 10 code	Off-label indication	ICD 10 code
	Depression	F30-F39		
		F92.0		
		F92.9		
Lithium Carbon	Depression	F30-F39		
	Organic mood disorder	F06.3		
Lofepramine	Depression	F30-F39	Multiple sclerosis	G35
	Organic mood disorder	F06.3		
Maproteline	Depression	F30-F39		
	Organic mood disorder	F06.3		
Mianserin	Depression	F30-F39	Dementia -improved sleep	F02
	Organic mood disorder	F06.3		
Mirtazapine	Depression	F30-F39		
	Organic mood disorder	F06.3	Methamphetamine decrease usage	Z81.4
			Generalized anxiety disorder	F41.1
				F41.2
				F41.9
				F41.0
Moclobemide	Depression	F30-F39	Multiple sclerosis	G35
	Organic mood disorder	F06.3		
	Social phobia	F40.1		
Nefazodone	Depression	F30-F39	Post traumatic stress disorder	F43.1
Paroxetine	Depression	F30-F39	Hot flushes	R23.2
		F92.0		
	Organic mood disorder	F06.3		
	Anxiety	F40-F42	Premature ejaculation	F52.4
			Acute pain	R 52
			Menopause	N95.1
				N95.9
Reboxetine	Depression	F30-F39	Appetite depressant	Y57.0
	Organic mood disorder	F06.3		

Table A.3 ICD-10 codes for capturing of data *continued*

	Indication	ICD 10 code	Off-label indication	ICD 10 code
Sertraline	Depression	F30-F39	Premature ejaculation	F52.4
		F92.0		
		F92.9		
	Organic mood disorder	F06.3		
	Anxiety	F40-F42	Post traumatic stress disorder	F43.1
			Binge eating disorder	F50.2
			Hot flushes	R 23.3
			Menopause	N95.1
				N95.3
Tranylcypromine	Depression	F30-F39		
	Organic mood disorder	F06.3		
Trazadone	Depression	F30-F39	Hypnotic	Y47
	Organic mood disorder	F06.3		
	Anxiety	F41		
Trimipramine	Depression	F30-F39	Polysomnographical sleep	G47.0 and F51.0
	Organic mood disorder	F06.3		G47.9
	Childhood enuresis	F98		
	OCD	F42		
Venlafaxine	Depression	F30-F39	Flushing	R23.2
		F92.0	Fibromyalgia	M79.7
		F92.9		M79.70
	Organic mood disorder	F06.3	Migraine	G43.9
	Anxiety	F40-F42	Attention deficit hyperactivity disorder	F90.0
			Menopause	N95.1
				N95.9

Table A.4 Summary of the effect sizes of prescription claims, in relation to age groups

Age group	***d*-value**
1 to 2	0.2
1 to 3	0.4
1 to 4	0.47
2 to 3	0.2
2 to 4	0.29
3 to 4	0.1

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