Overview of antidepressant usage and cost 2004 until 2006

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I can do everything through Him who gives me strength (Philippians 4:13).

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Last but the most important to the Lord, in the loneliest times of all I would say a prayer and I would know things were going to be fine because God was with me. I am nothing without the Lord's grace and strength.

ABSTRACT

Title: Overview of antidepressant usage and cost 2004 until 2006.

Keywords: Depression, antidepressants, managed care, drug utilisation review, pharmacoeconomics, generic substitution, age, gender, medicine treatment cost, cost savings.

Depression has an increasingly significant economic impact and quality of life burden on patients, employers and third party payers worldwide (Hylan *et al.*, 1998:53). Current projections indicate that the global burden of depression will rank second only to ischemic heart disease by the year 2020 (Hylan *et al.*, 1998:53). The prevalence of clinical depression in South Africa has been reported to range between 14 to 49 per cent of the general population (Triant, 2002:21). The cost of mental disorders in South Africa particularly when they are diagnosed late, are at least as high as R5 billion each year (The mental health information centre, 2002). According to the report of Mediscor medicines review for the year 2006 (Bester & Hammann, 2007) antidepressants contributed up to 5.0 per cent of the total medicine expenditure and was ranked third according to total medicine expenditure.

The objective of this study was to review the prescribing patterns and cost of antidepressants in a section of the private health care sector of South Africa by using a medicine claims database for the years 2004 to 2006. A retrospective drug utilisation study was done on data provided by the database of a pharmaceutical benefit management (PBM) company. The cost savings attributable to generic substitution were calculated by means of a cost minimisation study. Comparisons and analyses were done for 2004 to 2006, using the Statistical Analysis System (SAS for Windows, 9.1, 2002-2003).

Results of the study showed that antidepressant prescriptions accounted for 5.66% (n = 2 595 242), 5.05% (n = 1 621 739) and 4.51% (n = 996 787) of all prescriptions claimed during 2004, 2005 and 2006 respectively. The total cost for antidepressants for 2004 amounted to R 32 199 165.09; making depression the third most costly condition during 2004. During 2005 and 2006, these costs were ranked sixth and seventh respectively amongst all pharmacological classes on the database.

Prescriptions of antidepressants to female patients represented 42.26% (n = 44 915) compared to 17.86% prescribed to male patients. Antidepressant prescriptions ranked the highest for the age group older than 19 and younger than 44 years of age with a percentage of 42.72% of all prescriptions (n = 44 915); followed by antidepressant prescriptions for the age group older than 44 and younger than 59 years of age with a percentage of 35.06% (n = 44 915).

The most prevalent pharmacological category was the selective serotonin reuptake inhibitors (SSRIs) followed by tricyclic antidepressants. The most common prescribed antidepressants for 2004 was fluoxetine (18.87%, n = 157 810) while amitriptyline was the drug of choice during 2005 (19.11%, n = 86 521) and 2006 (20.09%, n = 47 740).

Drug interactions with a significance rating of one and two according to Tatro (2002: xiv), were respectively 79.45% (n = 5 247) in 2004, 65.76% (n = 2 415) in 2005 and 51.56% (n = 1 470) in 2006.

Generic antidepressants represented 58.67% (n = 157 810) of all prescriptions in its class in 2004, compared to 56.49% (n = 86 521) in 2005 and 63.30% (n = 47 470) in 2006. It was finally determined that the PBM company could have saved up to 10.87% (n = R 56 183 697.91) on mental health care cost during the study period if all innovator products on the database had been substituted with the least expensive generic product.

Recommendations for future research in this field were also made.

OPSOMMING

Titel: 'n Oorsig van die gebruik en koste van antidepressante in 2004 tot 2006.

Sleutelwoorde: Depressie, antidepressante, bestuurde gesondheidsorg, medisyneverbruiksevaluering, farmako-ekonomie, generiese vervanging, ouderdom, geslag, koste van behandeling met medisyne, kostebesparings.

Depressie het wêreldwyd 'n toenemende beduidende ekonomiese impak en las op die kwaliteit van lewe van pasiënte, op werkgewers en derdepartybetalers (Hylan *et al.*, 1998:53). Huidige vooruitskouings toon dat die wêreldwye las van depressie teen die jaar 2020 die tweede grootste, net na dié van ischemiese hartsiekte, sal wees (Hylan *et al.*, 1998:53). Dit is gerapporteer dat die voorkoms van kliniese depressie in Suid-Afrika tussen 14 en 49 persent van die algemene bevolking wissel (Triant, 2002:21). Die koste van geestesversteurings in Suid-Afrika, en veral as dit laat gediagnoseer word, is ten minste R5 biljoen per jaar (The mental health information centre, 2002). 'n Medisyne verbruiks verslag van 'n medisyne-eisehuis vir 2006 het getoon dat (Bester & Hammann, 2007) antidepressante 5.0 persent van die totale koste van medisyne bydra. Antidepressante was dus die derde grootste uitgawe van alle medisyne uitgawes vir die periode.

Die doel van hierdie studie was om die voorskryfpatrone en koste van antidepressante in 'n deel van die privategesondheidsorgsektor in Suid-Afrika te bestudeer deur 'n databasis van eise vir medisyne vir die jare 2004 tot 2006 te gebruik. 'n Retrospektiewe medisyneverbruiksevaluering studie is gedoen op die data van 'n medisyne-eisehuis. Die kostebesparing as gevolg van generiese vervanging is deur middel van 'n koste minimaliserings studie bereken. Vergelykings en ontledings vir 2004 tot 2006 is met behulp van die "Statistical Analysis System" (SAS vir Windows, 9.1, 2002-2003) gedoen.

Die resultate van die studie het getoon dat voorskrifte vir antidepressante 5.66% (n = 2 595 242), 5.05% (n = 1 621 739) en 4.51% (n = 996 787) van alle voorskrifte beloop het wat in 2004, 2005 en 2006 onderskeidelik geëis is. Die totale koste vir antidepressante het in 2004 'n bedrag van R32 199 165.09 beloop wat depressie die derde duurste toestand in 2004 gemaak het. In 2005 en 2006 was hierdie kostes onderskeidelik sesde en sewende van al die farmaseutiese klasse in die databasis.

Voorskrifte vir antidepressante aan vroulike pasiënte het 42.26% (n = 44 915) beloop teenoor 17.86% vir manlike pasiënte. Voorskrifte vir antidepressante was die meeste vir die ouderdomsgroep tussen 19 en 44 jaar met 'n persentasie van 42.72% van alle voorskrifte

(n = 44 915) gevolg deur voorskrifte vir die ouderdomsgroep tussen 44 en 59 jaar met 'n persentasie van 35.06% (n = 44 915).

Die farmakologiese groep wat die meeste voorgeskryf was, was die selektiewe serotonien-heropnameremmers (SSHR's) gevolg deur trisikliese antidepressante. Fluoksetien was die antidepressant wat in 2004 die meeste voorgeskryf is (18.87%, n = 157,810), terwyl amitriptilien die middel van keuse in 2005 (19.11%, n = 86 521) en 2006 (20.09%, n = 47 740) was.

Geneesmiddelinteraksies met 'n beduidende voorkoms van een en twee volgens Tatro (2002: xiv), was 79.45% (n = 5 247) in 2004, 65.76% (n = 2 415) in 2005 en 51.56% (n = 1 470) in 2006 onderskeidelik.

Generiese antidepressante het in 2004 58.67% (n = 157 810) van alle voorskrifte in hulle klas uitgemaak vergeleke met 56.49% (n = 86 521) in 2005 en 63.30% (n = 47 470) in 2006. Dit is laastens bepaal dat die medisyne-eisehuis in die studieperiode tot 10.87% (n = R56 183 697.91) op die koste vir geestesgesondheid kon gespaar het as alle oorspronklike produkte in die databasis met die goedkoopste generiese produk vervang was.

Aanbevelings vir verdere navorsing in hierdie veld is ook gemaak.

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CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

This dissertation will focus on the usage and cost-related aspects of antidepressant medicine, according to a medicines claims database. Data from the period, January 2004 to December 2006, will be used to investigate the usage and cost of antidepressant medicine in a section of the private health care sector of South Africa. The influence of age and gender variables on usage patterns will also be investigated for the year 2006. In the discussions, certain hypothetical scenarios will be created to determine possible cost savings generated by generic substitution of antidepressants.

1.2 PROBLEM STATEMENT

Depression has an increasingly significant economic impact and quality of life burden on patients, employers and third party payers worldwide (Hylan *et al.*, 1998:53). Current projections indicate that the global burden of depression will rank second only to ischemic heart disease by the year 2020 (Hylan *et al.*, 1998:53). The current costs of depression world wide are of similar magnitude with other major illnesses, such as cancer, acquired immune deficiency syndrome (AIDS), and coronary heart disease. However, compared with these chronic conditions, the costs associated with depression are more likely to be indirect costs such as productivity losses caused by absenteeism and sub-optimal job performance. Thus, the cost of depression is relatively hidden and more insidious than other chronic illnesses (Hylan *et al.*, 1998:53).

Mental health problems affect around 300 people out of every 1000 in Britain each year (Prescription Pricing Authority, 2005). Mental health problems can often be difficult to diagnose because the range and severity of symptoms can vary between individuals and these symptoms could also relate to more than one disorder. Mixed anxiety and depression are the most common problem, experienced by approximately 9 per cent of adults in Britain, followed by general anxiety in 5 per cent of adults (Prescription Pricing Authority, 2005).

According to the World Health Organization (WHO, 2001) an estimated 121 million people are suffering from depression in the world. An estimated 5.8 per cent of men and 9.5 per cent of women will experience a depressive episode in any given year. These figures can, however vary across different populations (WHO, 2001). An average physician will see between 60 and

100 people with depression each year and more than 80 per cent of patients with depression are cared for solely in primary care. However, around half of all people with depression in the community never get around to consulting their physician (Prescription Pricing Authority, 2005).

The prescribing of antidepressant medicine in Britain had increased by 36 per cent over the last 5 years to 7.3 million items (quarter to June 2005). Selective serotonin reuptake inhibitors (SSRIs) account for half of all antidepressant items as well as approximately fifty per cent of the cost of antidepressant medicine. Prescribing of SSRIs in Britain had increased by 45 per cent in the last 5 years; this was mainly due to decreases in price for fluoxetine and paroxetine. Based on the decrease in price, fluoxetine prescribing had increased by 22 per cent. Citalopram prescribing has more than doubled in the last five years to 1.2 million items (17 per cent of all antidepressant items). Prescribing of paroxetine has decreased by 38 per cent over the last 5 years to 0.52 million items. Prescribing of sertraline has increased to 0.45 million items. Prescribing of tricyclic and related antidepressants has remained fairly static over the last 5 years at 2.5 million items. The later group accounts for 35 per cent of all antidepressant prescribing and 14 per cent of cost. The majority of other antidepressant prescriptions were for venlafaxine with 0.68 million items (9 per cent of all antidepressant items) (Prescription Pricing Authority, 2005).

The social health challenges South Africa confronts are reflected in national statistics data, where South Africa is classified as an upper middle income, developing country (World Bank, 2007). Its population of more than 44 000 million speaks eleven languages and carries an 81.8 per cent literacy rate. The unemployment rate of 30 per cent reflects the lack of economic empowerment among disadvantaged groups and is linked to poverty and crime. It was estimated in 2000 that 50 per cent of South Africa live below the poverty line (Triant, 2002:20). Evidence suggests that there is a substantial burden of mental illness in South Africa, and it is likely that the country's political and social history plays a role. According to the "mental health model" of community psychology, many mental health problems arise from political, economic, and societal problems (Triant, 2002:20). The prevalence of clinical depression in South Africa has been reported to range between 14 to 49 per cent of the general population (Triant, 2002:21).

The cost of mental disorders in South Africa, particularly when they are diagnosed late, is at least as high as R5 billion each year (The mental health information centre, 2002). In addition to this, there are the human costs of mental disorders e.g. individual suffering, marital disruption and family breakdown (The mental health information centre, 2002). According to the report of Mediscor medicines' review for the year 2006 (Bester & Hammann, 2007) antidepressants contributed to 5.0 per cent of the total medicine expenditure and was ranked

third according to total medicine expenditure. According to this review the average antidepressants cost per patient per year was R747.00 (Bester & Hammann, 2007).

Triant (2002:21) conducted two community based studies (one in Mamre and the other one in KwaZulu Natal) that assessed mental disorders using two stages of screening. Both found over one-fifth of the population to be affected. In the rural town of Mamre in the Western Cape, the prevalence of psychiatric morbidity was found to be 27.1 per cent. Six per cent of this group had anxiety disorders and 14 per cent affective disorders, including dysthymia (Triant, 2002:21). Researchers in a South African rural community in the province of KwaZulu Natal determined a weighted prevalence of generalised anxiety and depressive disorders to be 23.9 per cent with the following being the breakdown of each condition: 3.7 per cent generalised anxiety, 4.8 per cent major depression, 7.3 per cent dysthymia, and 8.2 per cent concurrent major depression and dysthymia (Triant, 2002:21).

A study from Khayelitsha, which was done when it was still a new and informal settlement, showed a high prevalence rate of depression. In the study population of 99 women who were observed, 44 per cent were depressed and in the study population of men (n = 71), 25 per cent were depressed (Kale, 1995:1255). A more recent study of a group of low socio-economic patients in Pietermaritzburg demonstrated a depression prevalence rate of 28 per cent and showed that depression correlated positively with age and negatively with education (Triant, 2002:22).

According to a study in South Africa performed by Truter and Kotze (1997:1738) on a total of 2117 patients who were diagnosed with depression the following interesting trends were found. The tricyclic antidepressants (TCAs) were the most frequently prescribed antidepressant sub-group, representing 40.9 per cent of all the antidepressants prescribed. It was found that more females than males used antidepressants (42.4 per cent of females and 37.7 per cent of males). The prescribing patterns differed between females and males with respect to the antidepressant sub-groups. The SSRIs were the second most frequently prescribed antidepressant sub-group, representing 34.5 per cent of all the antidepressant prescriptions. Similar percentages of females and males were using SSRIs. Tricyclic antidepressants and the SSRIs together represent approximately 75 per cent of all the antidepressants prescribed (Truter & Kotze, 1997:1738).

A more recent study by Truter and Kotze (2006:301) showed that the average age of the patient population was 53 years in 1996 and 43 years in 2002/2003. The TCA prescriptions were 11 074 in 1996 and 9 888 for 2002/2003. Amitriptyline, dothiepin and imipramine together accounted for 69.57% of TCA prescriptions in 1996 and 91.64% in 2002/2003. Truter and

Kotze (2006:301) concluded that TCAs still remain an important therapeutic class in South Africa.

In the modern day and age the prevalence of depression is still growing because of societal pressures. The demand for antidepressants is increasing every day, but funds and the ability of people to pay for medical expenses is declining, because of factors such as poverty and unemployment that are ever increasing (Triant, 2002:20). It is therefore evident that research must be conducted on the usage patterns and cost of antidepressants in the South African private health care environment.

1.3 RESEARCH QUESTIONS

The following research questions can be formulated:

- What does depression entail?
- What managed care and pharmacoeconomics entail, and what is the significance of these in the South African health care sector?
- What were the changes in medicine usage patterns and costs of antidepressants for the period 2004 to 2006 in the private health care sector of South Africa?

1.4 RESEARCH OBJECTIVES

1.4.1 General research objectives

The general research objective of this study was to review the prescribing patterns and cost of antidepressants in a section of the private health care sector of South Africa by using a medicine claims processing company for the years 2004 to 2006.

1.4.2 Specific research objectives

1.4.2.1 Phase one: Literature review

The specific objectives of the literature review were

- to review depression as an illness and its treatment from the literature; and
- to discuss managed care, drug utilisation studies, pharmacoeconomic analysis and generic substitution as related to antidepressants.

1.4.2.2 Phase two: Empirical investigation

The specific objectives of the empirical study were as follows:

- Determine the prescribing patterns and cost of antidepressants relevant to other central nervous system stimulants (CNS) and all medicines claimed through the medicine claims processing company for 2004 to 2006.
- Compare the prescribing patterns and cost of generic and innovator medicine items for all medicines claimed through the database, CNS medicine items and antidepressants.
- Determine the general prescribing patterns and cost of the antidepressants claimed through the medicine claims processing company for 2004 to 2006.
- Determine the possible influence of generic substitution on the prescribing patterns and cost of antidepressants claimed through the medicine claims processing company.
- Analyse the prescribing patterns of antidepressants according to age and gender for 2006.
- Compare the prescribing patterns of different classes of antidepressants according to the Monthly Index of Medical Specialities (MIMS)-classification system.
- Investigate the prescribing patterns and cost of antidepressants based on active ingredients.
- Examine the drug interactions that may occur with antidepressant medicine therapy.
- Examine the prevalence and cost of the top ten antidepressants according to trade name.
- Determine the cost savings with generic substitution that can be achieved with generic substitution by conducting certain hypothetical scenarios.

1.5 RESEARCH METHOD

The research method consisted of two phases, namely a literature review and an empirical investigation.

1.5.1 Phase one: Literature review

The literature review was divided into two steps. The first step was to review depression including the definition, types, pathogeneses, treatment, treatment algorithms and pharmacologic actions of antidepressants.

The second step was a study of certain aspects of managed health care; including pharmacoeconomics, drug utilisation and generic substitution. Aspects that were discussed include the different types of analyses employed in pharmacoeconomics. Drug utilisation and generic substitution were defined and discussed with special reference to the usage patterns of antidepressant medicines.

1.5.2 Phase two: Empirical investigation

This phase consisted of five steps, namely:

- Selection of the study population.
- Selection of the measuring instruments.
- Data analysis.
- Report and discussion of the results of the empirical investigation.
- Recommendations based on the results of the empirical investigation.

1.5.3 Type of research

A retrospective drug utilisation study was done on data provided by the database of a medicines claims processing company. The cost savings attributable to generic substitution were calculated by means of a cost minimisation study. Comparisons and analyses were done for 2004 to 2006, using the Statistical Analysis System (SAS for Windows, 9.1, 2002-2003). Authorisation was obtained from the pharmaceutical benefit management company (PBM) and the research committee of the North-West University to do this analysis.

The number of medical aids on the PBM decreased with 56% from 2004 to 2006. The data that were available on the database were the following:

- The patients' medical aid information.
- Practice number for the prescriber and the pharmacy.

- Prescription number.
- Prescription date.
- Trade name.
- Nappi codes.
- Number of items prescribed.
- The amount paid by the medical scheme.

Patient confidentiality was maintained throughout the study by the allocation of a specific number by the PBM company to each patient, medical scheme, prescriber practice number and pharmacy number thus no identification of the patient, prescriber or dispenser was possible by the researcher.

Antidepressants were classified into seven categories by means of the MIMS classification. Prevalence, cost, age and gender were used as measuring instruments but will be discussed in section 4.7.

1.6 DIVISION OF CHAPTERS

The chapters were divided as follows:

Chapter 1: Introduction

Chapter 2: Depression: a short overview

Chapter 3: Aspects of managed health care and pharmacoeconomics as related to antidepressants

Chapter 4: Research methodology

Chapter 5: Results and Discussion

Chapter 6: Conclusions and Recommendations

1.7 CHAPTER SUMMARY

In this chapter the problem statement, research questions, research objectives and research methods were discussed. The following chapter will focus on various aspects of depression such as pathophysiology, aetiology, classification, diagnosis and therapy of depression.

CHAPTER 2

DEPRESSION: A SHORT OVERVIEW

2.1 INTRODUCTION

This chapter will focus on the definition of the different types of depression, the pathophysiology, aetiology, measurement of the severity of depression and diagnosis of depression. Only the most common diagnostic systems will be considered even though there are other systems that can be used for diagnostic purposes. Furthermore the management for depression (cognitive as well as drug therapy) will also be explained. Finally a literature review of drug interactions of antidepressants, patient compliance and risk of suicide and toxicity will also be discussed. The above-mentioned points strive to bring a comprehensive, yet concise overview of depression from a holistic perspective.

2.1.1 Definition of depression

Mood disturbances are often called affective disorders where "depression" can be seen as the down side and "mania" as the up side (Gelder *et al.*, 1999:127). Affective disorders can be classified into two classes namely "unipolar disorder" and "bipolar disorder". Unipolar disorder is the condition where the patient only experiences depression; while in the condition of bipolar disorder, the patient may experience depression at one stage and mania at another (Stahl, 2000:2). Wells *et al.* (2003:681) defined bipolar disorder as "cyclical episodes" which are characterised by recurrent extreme fluctuations in mood, energy and behaviour. In practice it may happen that a patient could experience depression and mania at the same time, i.e. "mixed episode" (Eisendrath & Lichtmacher, 2004:1029). In some cases a patient switches between mania and depression rapidly and this is referred to as "rapid cycling" (Roos, 1997:171). These episodes cause challenges in the correct diagnosis and management of depression (Stahl, 2000:2).

Depression is described by the World Health Organization (2003) as a mental disorder characterised by sadness, a loss of interest or pleasure, feelings of guilt or low self-esteem, disturbed sleep or appetite, low energy and reduced concentration. These problems can exacerbate by becoming chronic and have a negative impact on the everyday activities of life.

Only 50 per cent of citizens of South Africa that have depression as a condition receive treatment (Roos, 1997:170). Only half of these patients however, are treated successfully because of inadequate dosage or low compliance factors (Roos, 1997:170). The low

compliance may be due to misconceptions and poor education of the patient (Roos, 1997:170). The diagnosis of depression in South Africa may be further complicated by language and cultural differences. From another dimension, depression is often seen as ancestral rage or spirit possession and patients' belief that these external forces must be addressed rather than depression itself (Meys, 1998:313).

Because of stigma and misinformation regarding depression under the general public and health care professionals, symptoms of depression are often classified as unexplained (Stahl, 2000:2). The term used to describe this condition is "somatization" and perhaps could be the reason for misdiagnosis. Many of the patients with so-called unexplained symptoms are considered to have no real or treatable illness and thus are not treated. In most cases patients with unexplained symptoms have a treatable mental illness or are responding to stressful life events (Stahl, 2000:2).

2.2 THE PATHOPHYSIOLOGY OF DEPRESSION

Different hypotheses exist which describe the pathophysiology of depression. Some of the hypotheses, according to Wells *et al.* (2003:699) and Gelder *et al.* (1999:141) are:

- Permissive hypothesis: Low serotonin (5-HT) activity may precipitate the affective state. The levels of norepinephrine (NE) determine the type of depression, for example low NE may cause depression and high NE may cause mania.
- Postsynaptic changes in receptor sensitivity: Changes in sensitivity of NE or 5-HT_2 receptors may be associated with depression.
- Dysregulation hypothesis: In this theory the emphasis is not on the absolute increase or decrease of the activities of neurotransmitters but on the failure of the homeostatic regulation of neurotransmitter systems.
- Biogenic amine hypothesis: Inadequate monoamine neurotransmission may cause depression especially the NE neurotransmitter (Wells *et al.*, 2003:699).

In the early 1950's it became clear that the drug reserpine could cause depression (Potter & Hollister, 2001:498). Reserpine binds to storage vesicles in the central and peripheral adrenergic neurons; these vesicles are then inactivated and cannot concentrate nor store norepinephrine and dopamine. This depletion of the amines in the central nervous system (CNS) may lead to depression (Oates & Brown, 2001:882). This assumption formed the basis

for what is now known as the Monoamine hypothesis (Potter & Hollister, 2001:498). The neurobiology of depression according to Stahl (2000:21) is depicted in Figure 2.1.

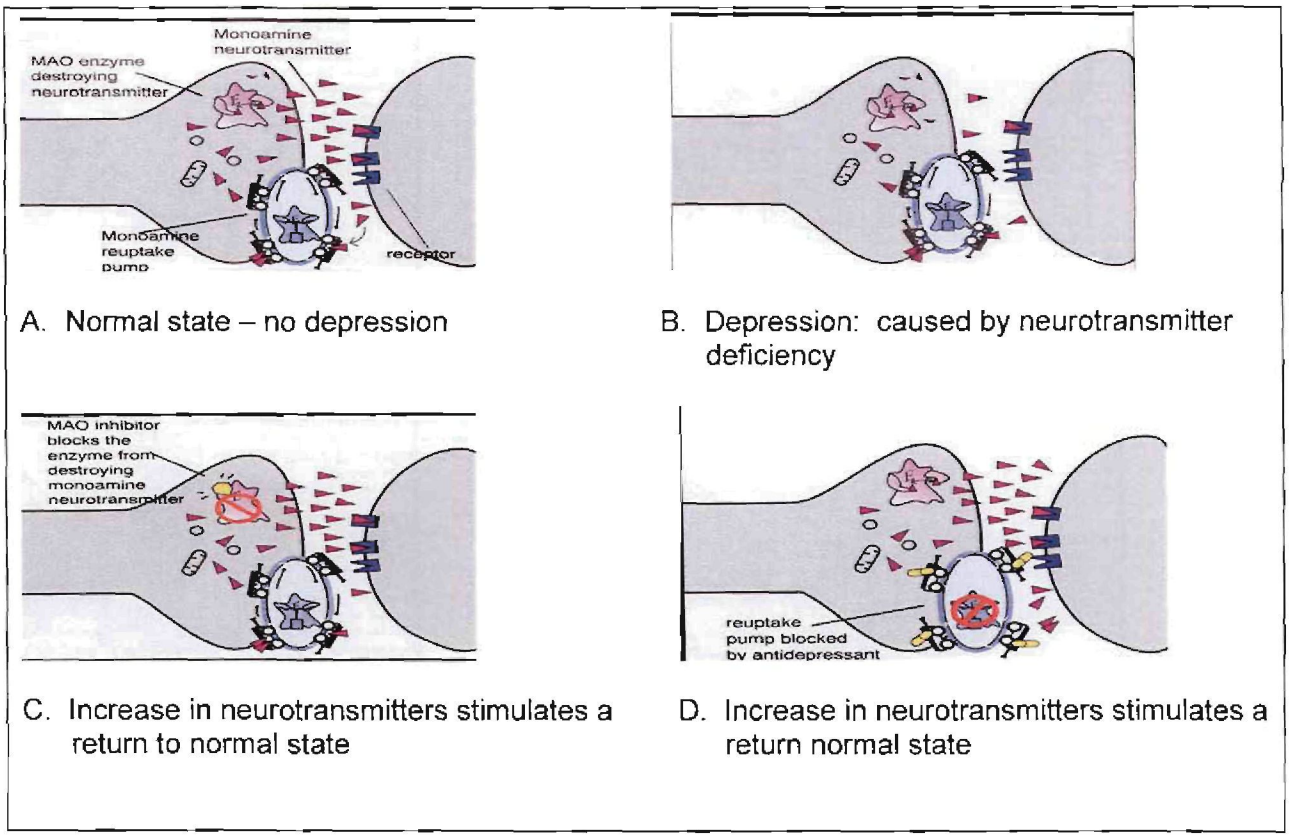


Figure 2.1: Neurobiology of depression (adapted from Stahl, 2000:21)

Figure 2.1A illustrates the normal releasing of the neurotransmitter norepinephrine (NE). The monoamine oxidase (MAO) enzyme, the NE reuptake pump and the NE receptors are all normal. Figure 2.1B demonstrates the monoamine hypothesis where the amine neurotransmitters are depleted. MAO inhibitors prevent MAO enzyme to destroy monoamine neurotransmitters. The monoamine neurotransmitters accumulate and relieve depression by enabling the monoamine neuron to return to normal as shown in figure 2.1C. Figure 2.1D is an example where tricyclic antidepressants are used to increase the neurotransmitter by blocking the neurotransmitter reuptake pump and thus relieving depression (Stahl, 2000:22).

In an article by Delgado and Moreno (2000:5) they reviewed the influence of norepinephrine (NE) and serotonin (5-HT) in depression and the therapeutic effects of antidepressant medicine from the perspective of human transmitter depletion studies. The data that were reviewed in this study suggested that noradrenergic and serotonergic systems are involved in antidepressant action, but the specific impairment that may cause depression is unclear and may vary in patients. The results from this study suggest that the cause of depression is more complicated than merely an alteration in the levels of 5-HT and /or NE. In some patients

depression may be caused by direct dysfunction in certain brain areas or neuronal systems modulated by monoamine systems. Delgado and Moreno (2000:5) concluded by stating that future research must focus on understanding the adaptive changes that follow enhancement of the synaptic levels of monoamines in neuronal circuits of the frontal cortex, amygdala and the hypothalamus. They also stated that research on the neurobiology of depression may be more informative if the focus shifted from investigating the areas of the brain that are modulated by monoamine rather than the monoamine systems themselves (Delgado & Moreno, 2000:5).

The knowledge of the normal functioning of mono-aminergic neurons clarifies the monoamine hypothesis further. The main monoamine neurotransmitters are norepinephrine, (also known as noradrenalin) and serotonin (5-HT) which will be discussed in sections 2.2.1 and 2.2.2 (Stahl, 2000:23).

2.2.1 Noradrenergic neurons

Norepinephrine is used by the noradrenergic neuron as a neurotransmitting agent (Cooper *et al.*, 2003:181). Enzymes synthesise monoamine neurotransmitters and other neurotransmitters in the cell body or nerve terminal. Most of the noradrenergic neurons are located in the locus coeruleus. The primary function of the locus coeruleus is to determine where the function of "attention" of the patient is focused. This enables the patient to react to a threat from the environment or signals such as pain coming from the body (Stahl, 2000:23).

Norepinephrine and the locus coeruleus play a vital role in the control of cognition, mood, emotion, movements and blood pressure. It is hypothesised that malfunction of the locus coeruleus may cause mood disorders such as depression, anxiety and attention disorders (Stahl, 2000:23).

2.2.2 Serotonergic neurons

Serotonergic neurons are concentrated in the brainstem area (i.e. the raphe nucleus). The brainstem serotonin receptors regulate functions such as mood, appetite, sexual responses, temperature regulation, hormone secretion, motor activity and sleep (Sanders-Bush & Mayer, 2001:275). Alterations in serotonin (5-HT) function may cause affective disorder (depression), obsessive-compulsive disorder, schizophrenia, anxiety states, phobic disorders, eating disorders, migraine and sleep disorders (Cooper *et al.*, 2003:297).

2.3 THE AETIOLOGY OF DEPRESSION

Aetiology may commonly be described as the pathological cause of illness (Kasper *et al.*, 2003:111). Various factors contribute to the occurrence of depression such as developmental problems (e.g. childhood events), genetic factors (neurotransmitter impairment) and psychosocial stresses (e.g. divorce) (Eisendrath & Lichtmacher, 2004:1029). Some of these factors will be discussed subsequently.

2.3.1 Sociosexual role

Women have a higher risk for developing depression relative to men and the prevalence for major depressive disorders in Western countries is 40 to 90 per 1000 females compared to 20 to 30 per 1000 men (Gelder *et al.*, 1999:137). In a study done by Truter and Kotze (1997:1739) on 2117 South African patients diagnosed with depression, 72.8 per cent were females. In another study conducted by Truter *et al.* (2006:301) it was found that 67.42 per cent in 1996 and 57.53 per cent in 2002/2003 were female patients. This variation in risk has led to considerable research but the cause is still not clear. Nolen-Hoeksema (1987:265) mentioned that it is possible that women are more in touch with their feelings; thus are more able to identify depression and report it. Nolen-Hoeksema (1987:277) however concluded, that this cannot be accepted as the only reason for the wide disproportion between men and women. Piccinelli and Wilkonson (2000:486) conducted a study to determine the putative risk factors leading to gender differences in depressive disorders. They did a critical review of the literature, dealing with artefactual and genuine determinants of gender differences in depression. Piccinelli and Wilkonson (2000:486) concluded that gender differences are real in depression. The determinants of these differences are not nearly established but at present adverse childhood experiences, depression and anxiety disorders in childhood and adolescence, sociocultural roles with related adverse experiences, psychological attributes related to vulnerability to adverse life events and coping skills are likely to be involved (Piccinelli & Wilkinson, 2000:491).

Women are also more prone to depression during times of hormonal changes. The incidence of hormonal changes is high during premenstrual periods and pregnancy (Meys, 1998:322). Depression is more likely during the first and third trimester of pregnancy. In the first trimester women can experience depression because of an unwanted pregnancy and during the third trimester the fears of the coming delivery or the normality of the foetus may also lead to depression (Gelder *et al.*, 1999:233).

2.3.2 Interpersonal factors

According to Eisendrath and Lichtmacher (2004:1029) depression is not unrelated to the external environment. It may be the cause of social and interpersonal disturbances (Eisendrath & Lichtmacher, 2004:1029). Kessler and Magee (1993:670) stated that disorganised environment during childhood may present as adult depression. Conditions such as drinking, mental illness, physical and verbal abuse may aggravate the effects of disturbed parental attachment and may show up as adult depression (Kessler & Magee, 1993:683) in later stages of life. In a study conducted by Truter *et al.* (2006:301) the average age of depression were 53 years in 1996 and 43 years of age in 2002/2003.

Depression may also influence the patient's everyday functioning and social skills (Roos, 1997:174).

2.3.3 Genetic factors

Bipolar disorder has the clearest indication of genetic transmission (Gelder *et al.*, 1999:138). Kendler *et al.* (as quoted in Beutler *et al.*, 2000:243) stated that there is less but still suggestive evidence that family history and genetic factors may cause chronic non-bipolar disorder and depression symptoms.

Sullivan *et al.* (2000:1552) conducted a meta-analysis of relevant data from primary studies to determine the gender epidemiology of major depression. They concluded that major depression in a familial disorder, and its hereditability mostly or entirely resulted from genetic influences. According to Sullivan *et al.* (2000:1552) environmental influences specific to an individual may also be a significant aetiology. Major depression is a complex disorder that does not result from either genetic or environmental factors on their own but rather from a combination of both. These findings are notably consistent and are likely to be applicable to most cases (Sullivan *et al.*, 2000:1552).

The Weisman and Jensen study (as quoted by Ladikos, 2003:4) found an increased incidence of major depressive disorder (MDD) particularly before puberty in children with depressed mothers. The peak age of onset of MDD in children was between 15 and 20 years of age (Ladikos, 2003:4). Prepubertal onset of MDD does not only increase the risk of suicide in adulthood but it may also lead to the development of bipolar disorder. Some investigators state that this early onset depression group should be the target for genetic studies (Ladikos, 2003:4).

Beutler *et al.* (2000:243) mentioned that for the most depressive disorders genetics present as a general rather than a specific risk factor.

2.4 CLASSIFICATION OF DEPRESSION

Potter and Hollister (2001:499) classified depression based on presumed origin. Hamilton (1979:5) divided depression into unipolar depression and bipolar disorder. According to Field (2000) these two disorders can be subdivided based on severity. Field (2000) went further by identifying subtypes of depression according to clinical features. A short discussion of this classification follows subsequently in paragraphs 2.4.1. and 2.4.2.

2.4.1 Types of depression based on presumed origin

According to Potter and Hollister (2001:498) depression may be differentiated into three types based on presumed origin e.g. "reactive", "endogenous" and "bipolar affective" as depicted in table 2.1.

Table 2.1: Differentiation between types of depression based on presumed origin (adapted from Potter & Hollister, 2001: 499)

Type	Diagnostic features	Comments
Reactive	Reactive depression occurs in response to real stimuli such as the following: adverse life events for example loss of a family member; physical illness like myocardial infarct or cancer; some medicines like antihypertensives, alcohol and hormones may have the adverse effect of depression; and other psychiatric disorders (e.g. senility).	More than 60% of all cases of depression are reactive. Core depressive syndrome consists of: depression, anxiety, bodily complaints, tension and guilt.
Major depressive (endogenous)	Major depressive disorder is a genetically determined biochemical disorder manifested by inability to experience ordinary pleasure or to cope with ordinary life events. It may occur at any age (childhood to old age).	About 25% of all depressions are endogenous. Present with core depressive syndrome and "vital" signs such as: abnormal rhythms of sleep; impaired motor activity; and change in libido and appetite; Usually responds well to specific antidepressants or electroconvulsive therapy. Tends to recur throughout life.
Bipolar affective (manic-depressive)	This type is characterised by episodes of mania. It usually presents as mania and depression, but may occasionally present as depression alone and in rare cases as mania alone.	This type constitutes about 10-15% of all cases of depression. It may be misdiagnosed as endogenous depression if hypo manic episodes are missed. Lithium carbonate can be used as a mood stabiliser. States of manic-depression may require antipsychotic drugs as well as antidepressant therapy.

Depression is a common condition with both psychological and physical manifestations (Potter & Hollister, 2001:498). The most common type of depression is reactive disorder as stated in table 2.1, but as explained it is also the least serious type (Potter & Hollister, 2001:498). Potter and Hollister (2001:498) warned that reactive disorder must, however, not be ignored seeing that it can affect the quality of life. Meys (1998:317) stated that the social and economic consequences of major depressive disorders are very big. According to Eisendrath and Lichtmacher (2004:1030), bipolar disorders may be difficult to diagnose because of the episodic mood shifts between mania and depression and the high co-morbidity with substance abuse.

2.4.2 Subtypes of depression according to severity

Unipolar depression is divided into *"major depressive disorder"* and *"dysthymic disorder"* that is the milder but more chronic form of unipolar depression (Field, 2000).

Double depression emerges when major depression and dysthymic disorder occur simultaneously. It presents as chronic mild depressive symptoms that peak into a major depressive condition and never return to the normal level, it merely returns to the mild depressive state (Field, 2000; Psychdirect, 2006; Shefferman, 2006).

Bipolar disorder also has a milder form called *"cyclothymic disorder"* where the patient alternates between a milder depression and milder mania than in the case of complete bipolar depression (Field, 2000). Cyclothymic disorder is a chronic condition and must be present for at least two years before it can be diagnosed as such (Eisendrath & Lichtmacher, 2004:1030). Bipolar disorder is classified into bipolar type I disorder where full episodes are experienced and bipolar type II disorder where the patient has severe depression but only a milder form of mania (Wells *et al.*, 2003:683).

Dysthymic disorder and cyclothymic disorder can be divided into six subtypes based on main clinical features as summarised in table 2.2 (Field, 2000).

Table 2.2: Subtypes of depression according to clinical features (Field, 2000)

Major depressive disorder	**Bipolar disorder**	
Dysthymic disorder	**Cyclothymic Disorder**	
Melancholic features	Depression	Mania
Atypical features	Melancholic	Psychotic
Psychotic features	Atypical	Catatonic
Catatonic features	-	Post-natal
Post-natal features	-	Seasonal onset
Seasonal onset (SAD)	-	-

- Depression with melancholic features: This form of depression is biologically based and is the incapability of the patient to experience pleasure (Wood, 2003). This disorder can only be diagnosed as such if there are at least three of the following symptoms present in combination with the incapability to experience pleasure: (1) distinct quality of depressed mood; (2) depression that is regularly worse in the mornings; (3) early waking; (4) significant anorexia or weight loss; (5) marked psychomotor agitation or retardation; or (6) excessive or inappropriate guilt (Field, 2000).

- Depression with atypical features: The patient experiences positive mood in reaction to positive life events but also experience at least 2 of the following bad conditions: (1) weight gain or increased appetite; (2) hypersomnia (sleeping 10 or more hours per day); (3) limbs feeling heavy; and (4) a long standing over-sensitivity to interpersonal rejection (Eisendrath & Lichtmacher, 2004:1030).

- Depression with psychotic features: The patient present with negative hallucinations and delusions (e.g. patients' belief that they are evil) (Field, 2000; Wood, 2003).

- Depression with catatonic features: This form of depression is accompanied by catatonic behaviour (Field, 2000).

- Depression with post-natal features. Post-natal depression must be distinguished from post-natal blues where patients experience rapidly changing moods, irritability and crying for no reason; this condition occurs in about 50 per cent of pregnant women (Meys, 1998:322). These feelings last only for a few weeks after childbirth and are not life altering. Post-natal depression, however, must meet the full criteria of a depressive episode. It presents itself in 13 per cent of pregnant women and occurs within 4 weeks after childbirth (Field, 2000).

- Depression with seasonal onset (also known as "Seasonal Affective Disorder" (SAD): This form of depression has its origin in periods of low levels of daylight (Gelder *et al.*, 1999:130). People with this disorder may develop mania in summer periods when days are longer (Field, 2000).

2.5 DIAGNOSIS OF DEPRESSION

The two most used diagnostic systems for the diagnosis of depression are the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Ed. (DSM-IV; American Psychiatric Association [APA], 1994), and the *International Classification of Mental and Behavioural Disorders* (ICD-10)

(WHO, 1992a). These diagnostic systems provide diagnostic guidelines based on clusters of systems rather than aetiological conceptualisations (APA, 1994:9).

Both these classification systems classify depressive syndromes based on the presence and severity of clinical symptoms and functional impairment. A team of experts should identify differences between the various types of depressions because the boundaries between the different classes are unclear and difficult to diagnose (WHO, 1992b:11).

2.5.1 DSM-IV diagnostic criteria

DSM-IV is the most used classification system in South Africa (Daubenton, 1998:65). According to the DSM-IV depression is classified as follows: Major Depressive Disorder (MDD) (single and recurrent), Dysthymic Disorder, and Depressive Disorder (not otherwise specified) (NOS) (Nezu *et al.*, 2000:10).

MDD can only be diagnosed if the patient meets the full criteria. MDD is considered recurrent if the patient experiences two depressive episodes within a period of at least two consecutive months between the episodes (Nezu *et al.*, 2000:10).

The DSM-IV considers the following factors before a diagnosis of major depression is made (Stahl, 2000:4):

- Five (or more) of the following symptoms causing a change in life style, must be present in the same two-week period. One of the symptoms must be either depressed mood or loss of interest or pleasure. This does not include symptoms that are caused by a general medical condition or medication.

  - Depressed mood most of the day, almost every day as reported by the patient or people that are in contact with the patient. In children and adolescents it may be identified as irritability.

  - Loss of interest or pleasure in most of the everyday activities.

  - Considerable variation in weight e.g. a change of more than 5 per cent of body weight in a month. Children that do not gain weight as they should, must be noted.

  - Sleep disturbances almost every day.

- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Weariness or loss of energy almost every day.
- Inappropriate feelings of guilt and worthlessness nearly every day.
- Concentration problems or indecisiveness most of the time.
- Threats of suicide and frequent thoughts of death.

❖ The symptoms do not represent those of a mixed episode.

❖ The symptoms influence social, occupational or other areas of functioning negatively.

❖ Symptoms are not due to an existing medical condition or use of various medical substances.

Symptoms occur for longer than two months or are characterised by loss of quality of life (Stahl, 2000:4).

Dysthymic disorder is more chronic but less severe than MDD but the symptoms are very similar. In dysthymic disorder the patient is depressed for the greater part of the day, almost every day over a two-year period. For a patient to be diagnosed with dysthymic disorder he or she must experience depressed mood and at least two of the following symptoms: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness (Nezu *et al.*, 2000:10).

Depressive disorder-NOS is a disorder that has depressive features but does not present with all the symptoms of MDD or Dysthymic disorder. This disorder is diagnosed based on presumed aetiologies. Depressive disorder-NOS is caused by a general medical condition or medical substance (Nezu *et al.*, 2000:10).

Affective disorders are classified as syndromes. The disorder presents itself with a cluster of symptoms only one of which is an abnormality in mood. The key feature that must be considered in affective disorders is quality of mood, the degree of mood change and the duration of abnormal mood (Stahl, 2000:3).

2.5.2 ICD-10 classification system

The ICD-10 diagnostic system is more widely used in international research and consists of definitions and categories that are not compatible with the DSM-IV. According to the ICD-10 system, depression can be divided into the following categories based on various features (WHO, 1992a):

- Recurrent depressive disorder (F33): This disorder is characterised by repeated episodes of depression that can be classified into mild, moderate and severe without any history of mania. This category can still be used if there is only a mild elevation of mood that fulfils the criteria of hypomania immediately after a depressive episode (sometimes this elevation of mood may be caused by the treatment of depression) (WHO, 1992a).

- Depressive episode (F32): The patient experiences depressed mood, loss of interest and enjoyment, and loss of energy that causes fatigability and reduction in activity. The patient gets tired after minimal effort. Other symptoms include the following:

  - Impaired concentration and attention.
  - Low self-esteem and self-confidence.
  - Feelings of guilt and unworthiness.
  - Bleak and pessimistic views of the future.
  - Ideas of self-harm or suicide.
  - Sleep disorders.
  - Poor appetite (WHO, 1992a).

The depressed mood varies little from day to day and does not really respond to life events, but may vary as the day goes on. Every patient experiences different symptoms and atypical presentations are common in adolescence. Anxiety, distress, and motor agitation may be more prominent than the depressed mood. Mood change may also go unnoticed because of symptoms like irritability, excessive consumption of alcohol, melodramatic behaviour, and exacerbation of pre-existing phobic or obsessional symptoms, or by hypochondriacal

preoccupations. Depressive episodes may also be subdivided into mild, moderate or severe as discussed in section 2.5.2.1-2.5.2.4 (WHO, 1992a).

2.5.2.1 Mild depressive episode (F32.0)

The most common symptoms for this disorder are depressed mood, loss if interest and increased fatigability. A definite diagnosis can only be made if two of these symptoms and two of the symptoms discussed under "F32" - depressive episode - are present. None of the symptoms should be severe and minimum duration for an episode is two weeks (WHO, 1992a).

A patient with mild depressive disorder will be uncomfortable with the symptoms and the patient's normal activities may be impaired but the patient will still continue to perform these activities (WHO, 1992a).

2.5.2.2 Moderate depressive episode (F32.1)

Moderate depressive episode is only diagnosed as such if two or three symptoms of a mild depressive episode and at least three of the symptoms for a depressive episode are present. The minimum period for this episode to continue is two weeks. The patient will find it difficult to continue social, work or domestic activities (WHO, 1992a).

2.5.2.3 Severe depressive episode without psychotic symptoms (F32.2)

The patient usually experiences considerable distress or agitation, unless retardation is a marked characteristic. The patient is likely to experience low self-esteem, feelings of uselessness or guilt and suicide may be a danger in severe cases. Somatic syndrome is presumed to be present in most of the severe depressive episodes (WHO, 1992a).

The three symptoms of mild and moderate depressive episodes as well as at least four of the symptoms of a depressive episode should be present and to a severe extent to classify it under F32.2. If the agitation or retardation is significant the patient may be unable or unwilling to describe the other symptoms in detail. The duration of the depressive episode should usually be at least two weeks but if the symptoms are severe and appear suddenly a diagnosis may be made in less than two weeks. In cases of severe episodes the patient is usually unable to continue social, work or domestic activities (WHO, 1992a).

2.5.2.4 Severe depressive episode with psychotic symptoms (F32.3)

In this case the episode meets the full criteria for a severe depressive episode without psychotic symptoms and in addition the patient must experience psychotic symptoms such as delusions,

hallucinations or depressive stupor. The delusions that a patient experience are those of sin, poverty or imminent disasters and the patient accepts responsibility for this. The patient may experience auditory or olfactory hallucinations and the voices that the patient hears are usually accusatory. Severe psychomotor retardation may be classified as mood-congruent or incongruent (WHO, 1992a).

2.6 LIMITATIONS OF DIAGNOSTIC CLASSIFICATION SYSTEMS

The classification systems rely on random decisions about the number and duration symptoms. It is difficult to distinguish between the main disorder and the subtypes seeing that the symptoms are very similar between the different disorders (Field, 2000).

According to Field (2000) depression and borderline personality disorders have many features in common and this may complicate the diagnosis. A patient with borderline personality disorder has a history of self-harm, out-of-control emotions, suicidal and over sensitivity to abandonment (Blyth, 1998:366). They may also experience anxiety and panic. In depression when the patient experiences all these symptoms a diagnosis is very difficult to make (Field, 2000).

2.7 MEASURES THAT ASSESS THE SEVERITY OF DEPRESSION

The measures to assess the severity of depression fall outside the scope of pharmacy and are usually used by psychiatrists but are briefly discussed in this chapter to ensure that all angles of depression have been touched upon.

Self-reported or clinician-rated symptom scales are used to determine the severity and response to treatment for depression (Ruhè *et al.*, 2005:46). It is believed that clinician-rated symptom scales are more accurate, than self-reported scales in patients with cognitive impairments and more severe or psychotic depressions (Ruhè *et al.*, 2005:46). According to Carmody *et al.* (2006:601) the two most popular clinical ratings are the Hamilton rating scale for depression (HRSD) and the 10-item Montgomery Asberg Depression Rating Scale (MADRS).

2.7.1 The Hamilton rating scale for depression (HRSD)

The HRSD is a twenty-one item clinician-rated instrument that is completed after an in-depth clinical interview with the patient and family members. Symptoms are rated according to severity as experienced by the patient days or weeks prior to the interview (Nezu *et al.*, 2000: 58).

Hamilton suggested that questions should be asked in a variety of manners to get information and that direct questions should be avoided seeing that this will limit the quality of information (Nezu *et al.*, 2000: 58). The HRSD is assessed as follows:

The purpose of the measure. This rating scale is used to determine the severity of the depressive symptoms as well as to evaluate changes in the patient's condition due to therapy as time goes by (Nezu *et al.*, 2000:58).

Administration of the measure. The interview prior to the HRSD assessment should take at least 30 minutes to obtain the necessary information. After the information has been collected the completion of the form takes about 10 minutes (Nezu *et al.*, 2000:58).

Measure Scoring. There are many variations of the HRSD and how the scoring is done depends on the type you are using. In Appendix A an example of the HRSD is given and how scoring should be done. It is important to specify the method of scoring that is used when results are reported (Nezu *et al.*, 2000:58).

Interpretation of the measure. When symptoms of the depressive illness are very severe a high score will be attained. There are two stable factors in the HRSD that were identified by some of the factor analyses namely the general factor of depressive illness and a bipolar factor representing varying degrees of psychomotor symptoms ranging between agitation and retardation (Nezu *et al.*, 2000:58).

2.7.2 The Montgomery-Asberg depression rating scale (MADRS)

The MADRS is a clinician-rated measure, which is used in adults that are receiving antidepressant treatment. The measure consists of ten items and every item represents a symptom that is sensitive to change such as sadness, sleep and inner tension. Items are rated on a seven-point scale with explanatory anchors at even numbered ratings. An example of the MADRS (and how it should be scored) is given in Appendix B. Information is gathered from an interview with the patient. Missing information must be collected from other sources such as family (Nezu *et al.*, 2000:76). Factors concerning the MADRS are discussed in the following paragraphs.

Purpose of the measure. The primary usage for the MADRS is to evaluate the symptoms of depression, with the focus being on the success of the treatment (Nezu *et al.*, 2000:76).

Administration of the measure. In contrast to the HRSD the MADRS only takes 5 minutes to complete and does not require any specialised training. The clinical interview and the MADRS are conducted simultaneously (Nezu *et al.*, 2000:76).

Measure scoring. Individual item ratings and the total scores may be included in scoring and the medication outcome is assessed by the inclusion of both these scores as change scores (Nezu *et al.*, 2000:77).

Interpretation of the measure. The primary role MADRS is the examination of changed scores on either individual items or summed scores (Nezu *et al.*, 2000:77).

Clinical utility. The MADRS has some advantages that can distinguish it from the HRSD. The MADRS does not require trained professionals and takes little time to administer (Nezu *et al.*, 2000:77).

2.8 THERAPY FOR DEPRESSION

According to Hull (1997:262) the most effective way to treat depression is a combination of cognitive therapy and antidepressant medication. Cognitive therapy focuses on cognitive symptoms such as helplessness, hopelessness, demotivation, low self-esteem and guilt (Hull, 1997:262). The cognitive methods and antidepressant therapy for depression will be discussed in sections 2.8.1 and 2.8.2.

2.8.1 Cognitive therapy

The most important aspect of this therapy is to challenge the patient's thoughts and beliefs. This is done by collecting information that may disprove the patient's interpretation and beliefs of events. This may help patients to realise that the thoughts they have are only that and not a true reflection of reality. There are various techniques to achieve this. These techniques according to Field (2000) are:

Thought catching. This method involves the collection and listing of thoughts after a traumatic incident. Therapy starts with the identification of the event that may have caused the depression and then a list is compiled of all the thoughts that the patient experienced (Field, 2000). The therapist and the patient then decide which thoughts are a reasonable representation of reality and which thoughts are brought about by the event (Gelder *et al.*, 1999:372). The thoughts that are only brought about by the event are called negative automatic thoughts (NAT). Answers for these thoughts are then produced and rehearsed so that the patient can develop a coping mechanism for future NAT (Field, 2000).

Task Assignment. Tasks are designed (mostly by the patient) that represent activities that the patient would normally avoid for example going out of the house. The patient would describe the fear and explain what could go wrong if the task is performed. The patient must then go out between sessions and execute the task. At the next session the patient can explain how the task was done and to what extent the fears became reality. This technique is used to help the patients overcome their fears and continue normal living (Field, 2000).

Reality Testing. This process is used to disprove certain beliefs that a patient may have. Tasks are then assigned to show the patient what would happen in reality if the activity is performed (for example, telephone a friend to disprove the belief that no-one wants to speak to the person) (Field, 2000).

Cognitive rehearsal. After the tasks have been executed, cognitive practise can help the patient to learn certain skills to overcome problems. If there is a possibility that a similar situation may occur in the near future the patient is encouraged to think about every aspect of the future event. If a difficult situation arises the patient should write it down and a task should be designed in order to work through the situation and come to a positive conclusion. For every stumbling block a solution should be generated. This will help the patient to develop skills in problem solution (Field, 2000).

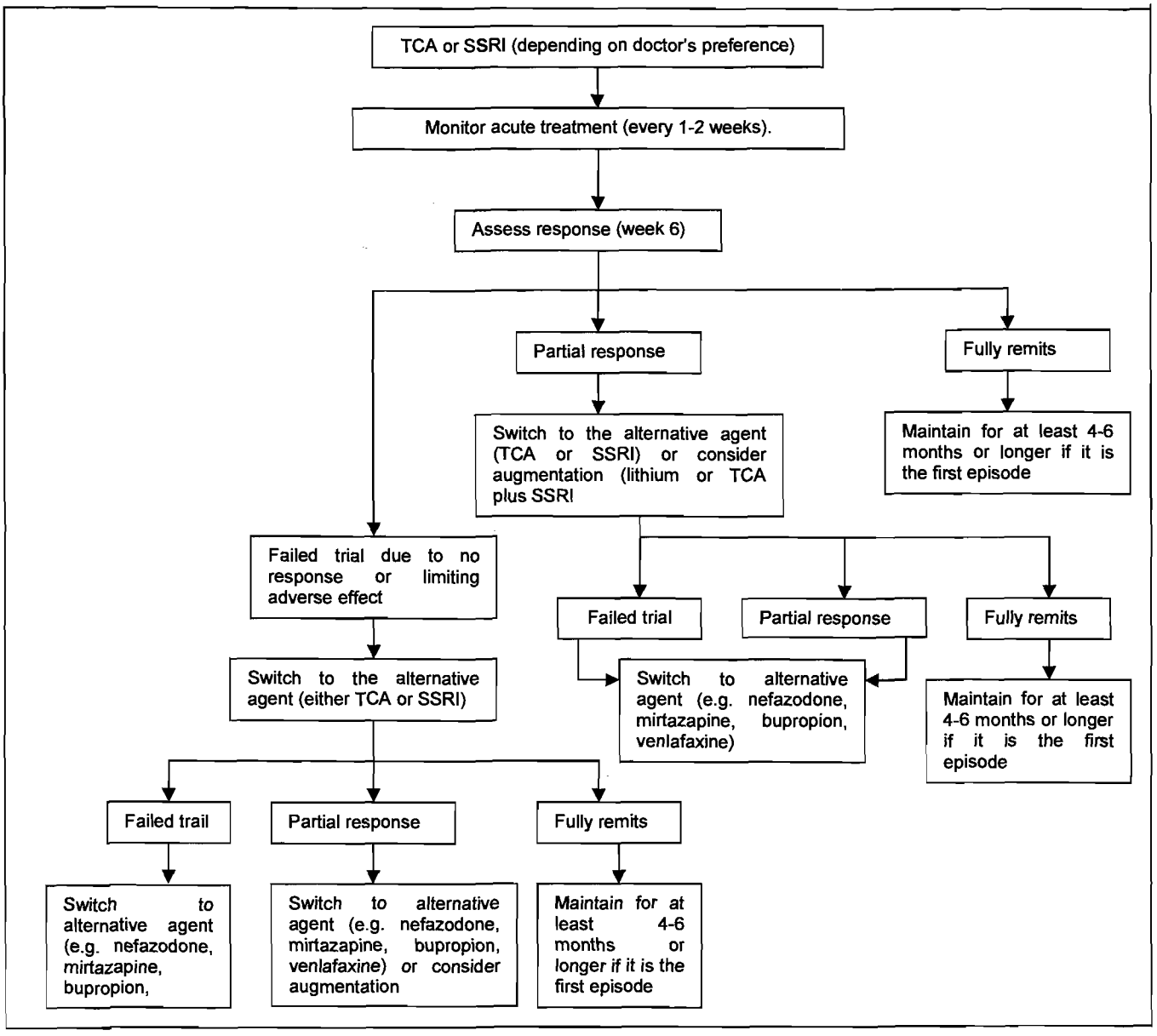
Alternative Therapy. This method is used to help the patient to overcome feelings of vulnerability and focus on coping mechanisms. Patients develop situations that represent those that they are unable to cope with. The patient must then create solutions for any situation that may arise, all the solutions must be considered no matter how outrageous they may seem. The advantages and disadvantages of all the alternatives including cost must then be measured. This therapy promotes creative thinking and helps the patient to break the cycle of negative thoughts (Field, 2000).

Dealing with underlying fears and beliefs. Finally, the therapist must study underlying fears and core beliefs that may arise from certain thoughts or avoidance behaviours. The origin of these beliefs must be discussed with the therapist. Tasks should be assigned to challenge these core beliefs (Field, 2000).

In mild depression, cognitive therapy alone may be useful and be as successful as drug therapy. In severe cases it may be necessary to first stabilise the patient on antidepressants and then start with cognitive therapy (Field, 2000).

2.8.2 Drug therapy

In a study conducted by Timms (2007), it was revealed that after three months of treatment 50 to 65 per cent of patients who received antidepressant therapy showed notable improvement and 25 to 30 per cent of the patients who were treated with a placebo showed improvement. This indicated that antidepressants are helpful but some of the benefits of this treatment are due to the placebo effect (Timms, 2007). For every illness there must be a well defined treatment plan to optimise therapy. The treatment plan for depression according to Roos (1997:177), Wells *et al.* (2003:716) and Eisendrath and Lichtmacher (2004:1033) is illustrated in figure 2.2.



TCA = Tricyclic antidepressants; SSRI = Selective serotonin reuptake inhibitor

Figure 2.2: Algorithm for treatment of depression (Eisendrath & Lichtmacher, 2004:1033; Roos, 1997:177; Wells *et al.*, 2003:716).

According to Taylor (2002) bipolar mood disorder must be treated with lithium salt or carbamazepine, but usually after the manic episode has been controlled with an antipsychotic such as haloperidol.

The maintenance therapy for bipolar mood disorder is lithium, taken orally in divided doses. Lithium dosage is determined by monitoring the blood levels of the medicine, because of its narrow therapeutic index it must be monitored closely. Another alternative for maintenance therapy is carbamazepine orally two to three times per day or sodium valproate orally three times per day as a mood stabiliser (Taylor, 2002).

Taylor (2002) states that major depressive disorder must be treated with tricyclic antidepressants (TCAs) except in patients with cardiac conduction disturbances or high suicide risk and seeing that it is lethal in overdose the dosage must be started at lower than therapeutic doses and titrated up to therapeutic dosage within seven days. Selective serotonin re-uptake inhibitors (SSRIs) should be used for patients with contra-indications to TCAs but must only be prescribed by a psychiatrist. Major depressive disorder must be treated for a duration of at least six months (Taylor, 2002).

Antidepressants are divided into three groups based on the pharmacologic effect that they have in the brain. Figure 2.3 illustrates the various classes of antidepressants (Katzung *et al.*, 2002:269).

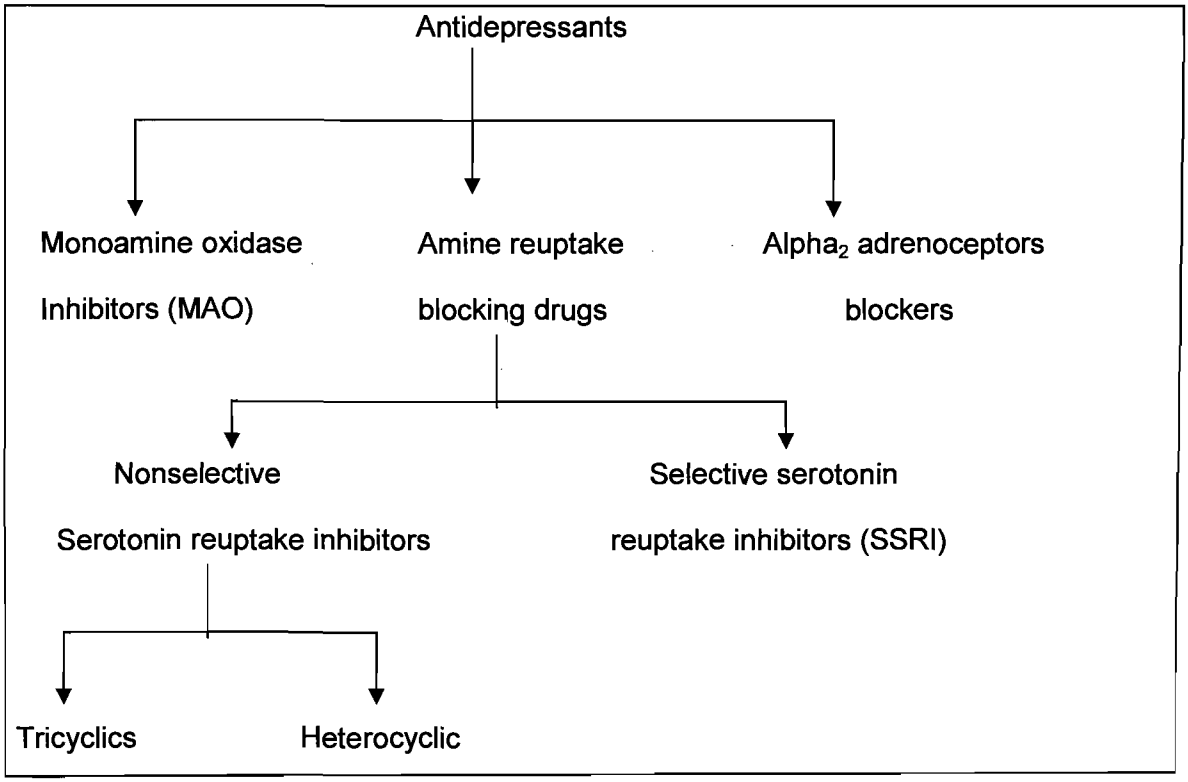


Figure 2.3: Major classes of antidepressant drugs (Katzung *et al.*, 2002: 269)

Amine reuptake blocking drugs are further subdivided into two groups based on the way they interact with the 5-HT transporters (figure 2.3.) (Katzung *et al.*, 2002:269).

In Britain SSRIs and tricyclic antidepressants (TCAs) account for 90 per cent of all the antidepressants prescribed (Gunnell & Ashby, 2004:34). A study conducted by Truter and Kotze (1997:1739) on 2117 patients diagnosed with depression in South Africa gave the following results: the tricyclic antidepressants formed the most frequently prescribed antidepressants group representing 40.9 per cent of all antidepressants prescribed, with SSRIs ranked second with a percentage of 34.5. In another study, Truter *et al.* (2006:301) found that amitriptyline, dothiepin and imipramine together accounted for 69.57 per cent of all TCAs prescribed in 1996 and increased to 91.64 per cent of all TCAs prescribed during 2002/2003.

2.8.2.1 Effects of specific antidepressants

Table 2.3 shows the degree of activity of different antidepressants and the effect they have on various neurotransmitters. Most of these agents named in table 2.3 are available in South Africa and indicated in the table (Gibbon, 2005:437) and (Snyman, 2006:14). Following table 2.3 is a discussion of the effects of antidepressants according to Potter and Hollister, (2001:504), Katzung *et al.* (2002:269) and Baldessarini, (2001:452).

Table 2.3: Pharmacologic differences among several antidepressants (Baldessarini, 2001:452; Katzung *et al.*, 2002:269; Potter & Hollister, 2001:504; Wells *et al.*, 2003:704).

CLASSIFICATION	Active ingredient	Available in South Africa	Sedative action	Anti-muscarinic Action	Block of Amine Pump for:		
					Serotonin	Norepinephrine	Dopamine
Tricyclic Derivatives	Amitriptyline	√	+++	+++	+++	++	0
	Imipramine	√	++	++	+++	++	0
	Clomipramine	√	+++	++	+++	+++	0
	Doxepin	X	+++	+++	++	+	0
	Trimipramine	√	+++	?	++	+	0
Selective Serotonin Re-uptake Inhibitors (SSRI's)	Fluoxetine	√	+	+	+++	0,+	0,+
	Paroxetine	√	+	0	+++	0	0
	Citalopram	√	0	0	+++	0	0
	Fluvoxamine	√	0	0	+++	0	0
	Sertraline	√	+	0	+++	0	0
Monoamine Oxidase Inhibitors	Tranylcypromine	√	0	?	+	++	√
	Phenelzine	X	+	?	++	++	√
	Selegiline	√	0	?	√	?	?
	Mirtazapine	√	+++	0	0	0	0
Inhibits the re-uptake of both serotonin and noradrenalin	Venlafaxine	√	0	0	+++	++	0,+

0=none; +=Slight; ++=Moderate; +++=Hi; ?=not established; √=does have an effect

Tricyclic agents. These agents have three benzene rings in their chemical structure and from there the name tricyclic agents (Gelder *et al.*, 1999:345). These first-generation antidepressants show varying degrees of selectivity for the reuptake pumps for norepinephrine and serotonin (Potter & Hollister, 2001: 505).

According to Gibbon (2005:438) tricyclic antidepressants (TCAs) are mainly indicated for depression which includes major depression, depression with anxiety, and depression associated with somatic complaints. Because of their sedative action they may be useful in inducing and maintaining sleep and may have some benefits in bipolar disorder, although they have the potential to induce mania (Gibbon, 2005:438).

Imipramine has shown efficiency in panic and phobic disorders and clomipramine may be used in obsessive compulsive disorder. Amitriptyline, in low doses, may be beneficial in chronic pain situation such as rheumatoid arthritis and as prophylaxis in migraine (Gibbon, 2005:438).

Selective serotonin reuptake inhibitors (SSRI). Fluoxetine was the first SSRI that was approved for clinical use (Berk, 1997:285). Paroxetine and sertraline differ from fluoxetine in the sense that they have shorter half-lives and have different potencies as inhibitors of specific P450 isoenzymes (Potter & Hollister, 2001:505). According to Berk (1997:285) SSRIs have become one of the first-line medicines in the treatment of depression. Gibbon (2005:439) states that SSRIs are mainly used in the management of depressive disorders and are as effective as TCAs. The reason for this is that they do not have anticholinergic and cardiac side-effects, they do not cause weight gain and they are safer in overdose than other antidepressants. Thus a patient would rather take an SSRI than other antidepressants despite side-effects like nausea, vomiting, fatigue and sexual dysfunction (Potter & Hollister, 2001:505; Wells *et al.*, 2003:706). The SSRIs that are available in South Africa are fluoxetine, citalopram, sertraline, paroxetine and fluvoxamine (Snyman, 2006:20).

Monoamine oxidase inhibitors (MAO). These antidepressants are particularly effective in the treatment of depressive disorders with atypical features such as hypersomnia, increased appetite and weight gain (Gibbon, 2005:442). The primary role of MAO-A is to metabolise norepinephrine, serotonin and tyramine. MAO-B's major function is to metabolise dopamine (Potter & Hollister, 2001:505). Older MAO inhibitors such as tranylcypromine block MAO irreversibly and this leads to a release of ingested catecholamines such as tyramine in the bloodstream; which can cause a potentially fatal hypertensive reaction – the so-called "cheese-reaction" (Berk, 1997:287). The irreversible MAO inhibitors thus have a high risk of hypersensitive reactions to food such as cheese that contain tyramine. According to evidence

available to date, the reversible, short-acting MAO inhibitor moclobemide is less likely to show this interaction (Gelder *et al.*, 1999:349).

Serotonin and noradrenaline reuptake inhibitors (SNRIs). Venlafaxine inhibits the reuptake of serotonin and inhibits the transport of norepinephrine to a lesser degree but does not have the characteristic cholinergic effects of tricyclic antidepressants and is not sedative (Gelder *et al.*, 1999:347). At high doses the patient will experience a moderate increase in heart rate and blood pressure because of the inhibition of norepinephrine inhibition. Doses in the range of 300 mg/day or greater may present broader therapeutic effects than SSRIs but the doses should gradually be increased to control adverse effects (Potter & Hollister, 2001:505). Venlafaxine is mostly used in patients where the anticholinergic effects are contra-indicated (Gibbon, 2005:444).

2.8.2.2 Adverse effects of antidepressants

Some patients may be more sensitive to side-effects than others, thus it may be difficult to predict the side-effects that a specific antidepressant may have (Healy, 2002:71). Snyman (2006:13a) classified antidepressants into seven groups namely tricyclic antidepressants, non-tricyclic antidepressants, mono-amine oxidase inhibitors, selective serotonin re-uptake inhibitors, lithium and others. A dry mouth is an almost universal side-effect for antidepressants (Healy, 2002:72). Other adverse effects will be discussed under these headings and the adverse effects will be summarised in table 2.4.

2.8.2.2.1 Tricyclic antidepressants

Tricyclic antidepressants such as clomipramine, lofepramine, imipramine and amitriptyline, to name only a few, have sedative effects, sympahtomimetic effects such as tremors, antimuscarinic effects like blurred vision and constipation, cardiovascular effects such as hypotension and conduction defects, neurological effects like seizures may be experienced, sexual disturbances and weight gain can also be experienced (Gelder *et al.*, 1999:350; Potter & Hollister, 2001:509). Sweating is also not uncommon with tricyclic antidepressants (Healy, 2002:73). Other side-effects of this antidepressant group are depicted in table 2.4.

2.8.2.2.2 Non-tricyclic antidepressants

The two active ingredients, mianserin and maprotiline are represented in this group. A patient that receives mianserin therapy my experience effects such as drowsiness, weight gain, arthritis and hypomania/mania which may be precipitated in patients with bipolar disorder

(Gibbon, 2005:444). Potter and Hollister (2001:509) stated that maprotiline is similar to tricyclic antidepressants with additional dose-related seizures.

2.8.2.2.3 Mono-amine oxidase inhibitors

Tranylcypromine and moclobemide are classified as mono-amine oxidase inhibitors (Snyman, 2006:19). The presentation of nervousness and oedema is higher for moclobemide than for venlafaxine and paroxetine; and there is also a significantly higher rate of agitation for moclobemide compared to paroxetine (Vanderkooy *et al.*, 2002). Moclobemide showed no more sexual adverse effects compared to other antidepressants (Vanderkooy *et al.*, 2002). Other adverse effects of mono-amine oxidase inhibitors are summarised in table 2.4.

2.8.2.2.4 Selective serotonin re-uptake inhibitors (SSRIs)

There are quite a lot of SSRIs available on the market like paroxetine, citalopram, paroxetine and sertraline to name only a few (Snyman, 2006:20). More patients experienced constipation on paroxetine than on moclobemide. The incidence of tremor and sweating is much higher for sertraline than moclobemide; sertraline also shows more tremors than paroxetine (Vanderkooy *et al.*, 2002). In the short-term SSRIs may have an appetite-suppressing property (Healy, 2002:75). Men that received paroxetine treatment reported delayed ejaculation more than men that received bupropion or sertraline treatment (Vanderkooy *et al.*, 2002). For the other side-effects of SSRIs refer to table 2.4.

2.8.2.2.5 Serotonin and noradrenaline re-uptake inhibitors

Venlafaxine and duloxetine are categorised in this group (Snyman, 2006:32). Nausea was more common in venlafaxine than in moclobemide and bupropion (Vanderkooy *et al.*, 2002). Venlafaxine may also cause dose-related elevations of diastolic blood pressure (Wells *et al.*, 2003:702). Other adverse effects of this group are summarised in table 2.4.

2.8.2.2.6 Lithium

The dose related toxic effects of lithium are weakness, drowsiness, thirst and gastrointestinal intolerance. Increased toxicity is characterised by more severe central nervous system effects. Independent of the dose of lithium symptoms such as nausea, vomiting, diarrhoea and weight gain may also occur with the use of lithium (Gibbon, 2005:427).

2.8.2.2.7 Other antidepressants

Active ingredients such as reboxetine, sulpiride, flupenthixol, trazodone, fluphenazine, mirtazapine and bupropion are classified in this group (Snyman, 2006:35). Weight loss was more frequent with bupropion than with paroxetine (Vanderkooy *et al.*, 2002). Bupropion showed a higher increase in libido in men and women than paroxetine or sertraline. Nervousness, agitation and postural hypotension are more common in bupropion than in paroxetine. The presence of nervousness and oedema is also more in bupropion than in paroxetine and venlafaxine (Vanderkooy *et al.*, 2002). The other adverse effects of this group of antidepressants are illustrated in table 2.4.

Table 2.4: Adverse effects of antidepressants (Gelder *et al.*, 1999:350; Gibbon, 2005:437; Potter & Hollister, 2001:509; Snyman, 2006:14).

Medication		Adverse effects	Available in South Africa
Tricyclics (clomipramine) Sedative Sympahtomimetic Antimuscarinic Cardiovascular Psychiatric Neurologic Metabolic-endocrine		 Sleepiness, additive effects with other sedative drugs Tremor, insomnia Blurred vision, constipation, urinary hesitancy, confusion Orthostatic hypotension, conduction defects, arrhythmias Aggravation of psychosis, withdrawal syndrome Seizures Weight gain, sexual disturbances	√
Non-tricyclic antidepressants: Maprotiline		Similar to tricyclic agents; with dose-related seizures.	√
Mono-amine oxidase inhibitors		Sleep disturbances, dry mouth, dizziness, constipation, headache, tremor, weight gain, postural hypotension, sexual disturbances	√
Serotonin and noradrenaline re-uptake inhibitors: Venlafaxine		Nausea, somnolence, sweating, dizziness, sexual disturbances, hypertension, anxiety and hypersensitivity reactions such as skin rash.	√
Fluoxetine and other selective serotonin reuptake inhibitors		Insomnia, headache, tremor, gastrointestinal symptoms, weight loss, rashes, decreased libido, sexual dysfunction, anxiety (acutely)	√
Other	Mirtazapine	Somnolence, increased appetite, weight gain, constipation, nausea, tremor and dizziness	√
	Trazodone	Drowsiness, headache, weight loss, dizziness, insomnia, nausea, agitation	√
	Bupropion	Dizziness, dry mouth, sweating, tremor, aggravation of psychosis, potential for seizures at high doses	√

Posternak and Zimmerman (2002:237) conducted a study to determine whether a patient who has experienced intolerable adverse effects on one antidepressant can safely and effectively be switched to a second antidepressant while the depressive disorder is in remission. They concluded that the study provides preliminary evidence that switching antidepressants while in

remission may be a safe and effective strategy for managing antidepressant induced adverse effects (Posternak & Zimmerman, 2002:237).

Most common unwanted effects are minor, but patient compliance may seriously be jeopardised (Potter & Hollister, 2001:508). A patient with a severe condition will be more likely to tolerate the side effects than a patient with minor symptoms (Healy, 2002:71).

2.9 DRUG INTERACTIONS OF ANTIDEPRESSANTS

Drug interactions occur when the effect of one medicine is altered by the presence of another medicine, food or any other environmental chemical agent. The effects can be harmful if an increase in the normal levels of the drug is caused by the interaction. The interaction may also cause a reduction in effectiveness that may be just as damaging as the increase in medicine levels (Baxter, 2006:1).

Tatro (2002:xiv) explains drug interactions on a hieratical scale where a number one through to five will be assigned to each interaction (refer to table 2.5). This number is known as the significance rating of the interaction. "One" is a severe and well-documented interaction and "five" is an interaction that is unlikely to occur (Tatro, 2002: xiv).

The severity of an interaction is associated with the significance rating as summarised in table 2.5 and is used to compare the risk of therapeutic alternatives to the benefits of these alternatives. The negative effects of an interaction can be avoided by altering the dosage or adjustment of the administration schedule. According to Tatro (2002:xiv) there are three degrees of severity:

- Major: the effects of the interaction may cause death or permanent damage.
- Moderate: the interaction may cause a set back in the patients' current medical condition. This may require additional treatment, hospitalisation or extended hospital stay.
- Minor: the effects of this interaction may be asymptomatic or may be irritating but do not alter the therapeutic outcome. No extra treatment or clinical interventions are needed (Tatro, 2002:xiv).

Table 2.5: Classification of drug interactions (Tatro, 2002: xiv)

Significance rating	Severity
1	Major
2	Moderate
3	Minor
4	Major/moderate
5	Minor
	Any

The rapidity with which the symptoms of an interaction appear determines the urgency with which preventative measures should be applied to prevent the consequences of the interaction. Two levels of onset are used (Tatro, 2002:xiv):

- Rapid: the effects will appear within twenty-four hours after the interacting drug was administered. Immediate action must be taken to prevent symptoms of the interaction.

- Delayed: It may take days to weeks after the administration of the interacting drug for symptoms of the interaction to appear. This kind of interaction is not life threatening and does not require immediate action (Tatro, 2002:xiv).

Table 2.6 indicates the most important drug-drug interactions of antidepressants. The significance rating, severity and onset as discussed in above paragraphs are also assigned to most of the interactions (Katzung *et al.*, 2002: 273; Tatro, 2002: xiv).

One of the interactions in table 2.6. that must be emphasised is the interaction between MAO inhibitors (e.g. Tranylcypromine) and the SSRIs. This interaction causes an increase in the stores of monoamine oxidase and the inhibition of the reuptake of monoamine oxidase after it has been released. The concomitant administration of these two types of drugs may lead to an increase of serotonin levels (Potter & Hollister, 2001:505).

This increase in serotonin is described as the "serotonin syndrome" and is characterised by myoclonus (jerks and twitches), tremors of the tongue and fingers, shivering and sweating, restlessness, agitation, in some cases diarrhoea and it may be life threatening (Healy, 2002:80)

Warfarin is contra-indicated with most of the SSRIs because SSRIs may lead to an increase of warfarin plasma levels which may lead to bleeding (Baxter, 2006:311). According to Gelder *et al.* (1999:347) lithium increases the 5-HT function when given with an SSRI and should thus be avoided (the combination is, however, sometimes used by specialists).

Tricyclic antidepressants interact with the adrenergic neurone blockers such as guanethidine and clonidine (Gelder *et al.*, 1999:346). According to Katzung *et al.* (2002:273) this interaction may lead to a decrease in the antihypertensive effects of the adrenergic neurone blockers as indicated in table 2.6. According to Baxter (2006:311) the levels of tricyclic antidepressants can increase from 20 per cent to tenfold the original level when used with an SSRI and this may lead to tricyclic toxicity. Tricyclic antidepressants increase the levels of citalopram and possibly fluvoxamine which can cause serotonin syndrome (Baxter, 2006:999).

Table 2.6: Drug interactions observed with antidepressant medications (adapted from Katzung *et al.*, 2002: 273; Tatro, 2002: xiv; Wolters Kluwer Health, 2006)

Drug		Taken with	Significance rating	Severity	Onset	Consequence
SSRI's	Fluoxetine	Lithium	4	Moderate	Delayed	Increased blood levels of the second drug; doses may need to be decreased
		Tricyclics	2	Moderate	Delayed	
		Warfarin	4	Moderate	Delayed	
	Fluvoxamine	Alprazolam	3	Minor	Delayed	Increased blood levels of the second drug; doses may need to be decreased
		Theophyline	4	Moderate	Delayed	
		Tricyclics	2	Moderate	Delayed	
		Warfarin	4	Moderate	Delayed	
	Paroxetine	Tricyclics	2	Moderate	Delayed	Increased blood levels of the second drug; doses may need to be decreased
		Warfarin	4	Moderate	Delayed	
	Sertraline	Tricyclics	2	Moderate	Delayed	Increased effects; doses may need to be decreased
		Warfarin	-	-	-	
MAO Inhibitors		Tricyclics	1	Major	Rapid	Hyperpyretic crisis, convulsions and death have occurred.
		Sympathomimetics	1	Major	Rapid	Hypertensive crisis
		SSRI's	1	Major	Rapid	Serotonin syndrome
Tricyclics (TCA's)		CNS depressants (ethanol, sedative hypnotics, etc.)	-	-	-	Serotonin syndrome
		Clonidine	-	-	-	Decreased antihypertensive effects
		Guanethidine	-	-	-	
		Methyldopa	-	-	-	
		SSRI's	2	Moderate	Delayed	Serotonin syndrome

Another important interaction that must be noted is the one of monoamine oxidase inhibitors (MAOI) with certain foods and drinks that contain tyramine such as cheese and some red wines. Tyramine is normally inactivated by the body's monoamine oxidases. Seeing that MAOI inactivates the monoamine oxidases the tyramine which enters the bloodstream and releases noradrenaline, this may lead to a hypertensive crisis that could be fatal (Gelder *et al.*, 1999:350.)

2.10 PATIENT COMPLIANCE TO ANTIDEPRESSANT THERAPY

Non-compliance to antidepressant treatment is mostly observed during the acute, continuation and maintenance phases of treatment (Cohen *et al.*, 2004:49). A possible reason for this may be that a patient may consent to take antidepressants but as soon as the patient feels better; therapy is stopped and the patient is not compliant anymore (Healy, 2002:258). A study that was conducted by Cohen *et al.* (2004:40) showed that 60 per cent of patients that receive antidepressant treatment are not compliant, 28 per cent of these patients stop taking their medication in the first month and 44 per cent discontinue their treatment in the third month of treatment.

Possible reasons for non-compliance may be the patient's beliefs e.g. the belief that depression is a condition that does not require treatment. The patient may be misinformed about antidepressant therapy; and may for example, think antidepressants are addictive or that he/she can simply stop therapy as soon as he/she feels better. Other factors that may contribute to non-compliance are that the patient experiences negative side-effects or the doctor's prescribing behaviour (Thompson *et al.*, 2000:157).

A patient's characteristics and personality may be an indication for a risk of treatment non-compliance. The knowledge of a patient's unique personality may be used to formulate an individual treatment plan for the patient. A person that is an extrovert may be non-compliant seeing that he/she likes people, excitement and activity. These patients thus might be too busy to remember to take their medicine. On the other hand a patient that is very modest may be very compliant because he/she respects authority and may have more insight in his/hers condition (Cohen *et al.*, 2004:49).

Efficacy and the side-effect profiles of antidepressant treatment may be influenced by non-compliance. Antidepressant therapy that is taken irregularly may be seen as ineffective which may lead to unnecessary dosage or treatment change. Treatment non-compliance is seen as one of the most preventable causes for treatment failure (Cohen *et al.*, 2004:49).

2.10.1 Tools to facilitate compliance

Visual aid is an educational tool that can be used in patients that start on antidepressant therapy to improve compliance. It has the advantage that it is simple to use and very time-efficient. This tool helps the patient to understand what to expect during the acute phase of antidepressant therapy and it stresses the importance of long-term treatment adherence (refer to figure 2.4). This method promotes a discussion between patient and practitioner about antidepressant therapy, which will lead to a more informed patient and better treatment compliance (Gardner, 2001).

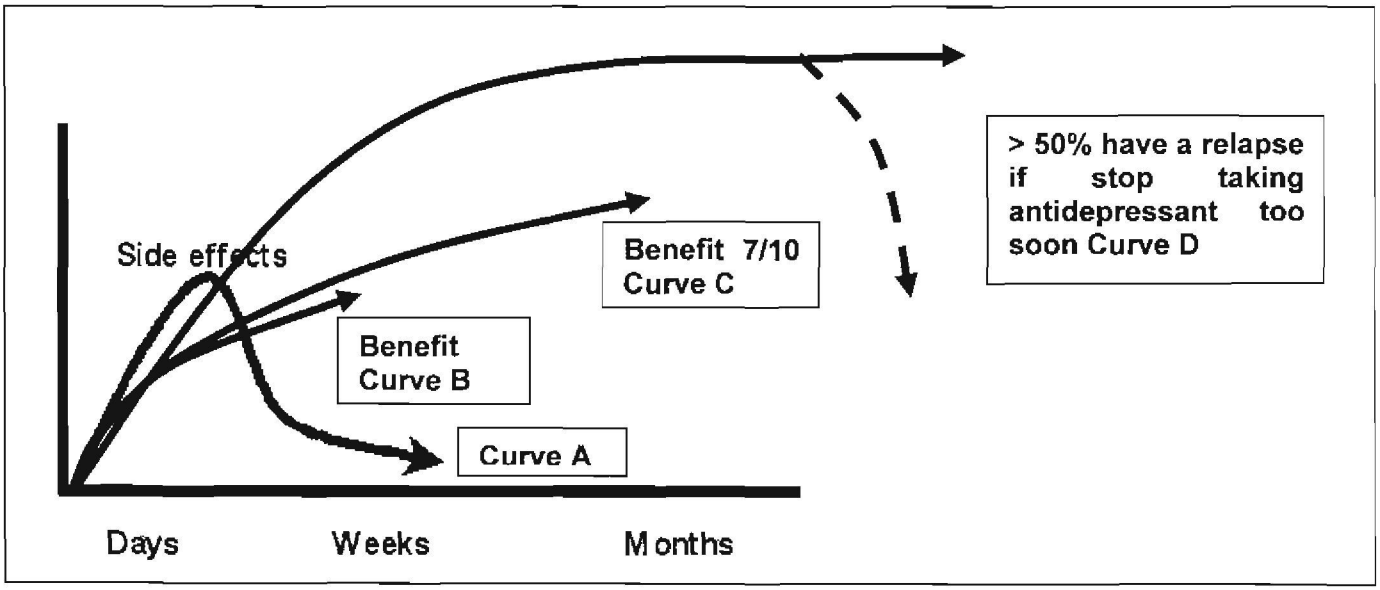


Figure 2.4: Visual aid to facilitate patient compliance (adapted from Gardner, 2001)

Figure 2.4. can be explained as follows:

- Early in the treatment side-effects can occur, this may seem to outweigh the apparent benefits of treatment. In most cases (~8/10) the side effects are bearable and disappear within the first few days or weeks of treatment. Two out of ten patients stop treatment within the first few weeks because of intolerable side-effects (curve A) (Gardner, 2001).

- Many patients do not experience any benefits of antidepressant therapy for weeks after treatment has commenced. Most patients only see results after four weeks of treatment but thereafter they keep improving as treatment is continued (curve B) (Gardner, 2001).

- Close to eight weeks after treatment have been started seven out of ten patients will have positive results and fifty per cent of these patients will no longer experience any depression symptoms (curve C) (Gardner, 2001).

- Three out of ten patients do not get the wanted effects of antidepressant therapy either because of side-effects, non-compliance or a mixture of factors. No practitioner can determine prior to treatment how a patient will react to certain therapy (curve C). In this case the patient's therapy can be changed to get the desired effects (Gardner, 2001).

- In more than fifty per cent of cases a patient's depressive symptoms can return if they stop therapy too early even if they had a good response to treatment (curve D) (Gardner, 2001).

- If positive results are attained treatment should normally be continued for six months after treatment has been initiated (Gardner, 2001).

2.11 RISK OF SUICIDE AND TOXICITY OF ANTIDEPRESSANTS

Medicines most used in overdose are anxiolytics, non-opiate analgesics and antidepressants (Gelder *et al.*, 1999:250). The risk of suicide does not seem to differ between different antidepressants but the fatality rate is higher in tricyclic antidepressant overdoses than in selective serotonin reuptake inhibitors (SSRIs) (Eisendrath & Lichtmacher, 2004:1033). Tricyclic antidepressants (TCA) overdoses have the highest hospitalisation and fatality rate compared to any other prescribed drug overdose (Palmer *et al.*, 1998:3). TCA and SSRIs have different toxicity profiles which result in different overdose mortality rates and medicines in the TCA group also have different toxicities (Palmer *et al.*, 1998:3).

In 2007, the Food and Drug Administration ordered that antidepressant medication carry a warning of increased suicide risk in young adults 18 to 24 years (Friedman & Leon, 2007:2343). It was not clear whether the suicidal thoughts were because of the depression or because of the treatment. Three hundred and seventy-two randomised clinical trails on antidepressants were conducted by 12 pharmaceutical companies. The question of whether suicidal thoughts were caused by depression or treatment may be answered by the following facts; more than 20 per cent of the data came from 43 studies of treatment for nonpsychiatric indications and 34 trails for nonbehavioural indications. Concluding that the risk per person per year of treatment was substantially lower in trials for nonpsychiatric indications, suggesting that depression played a key role in suicidality (Friedman & Leon, 2007:2345).

About three per cent of all TCA overdoses are fatal. TCA doses higher than 600mg may be potentially fatal and doses of higher than 4000mg are routinely fatal in all patients (Palmer *et al.*, 1998:3). In patients that are at risk for suicide prescriptions must be limited to 50 units of 25mg doses on a "no refill" basis and if there is a serious possibility of suicide, medication

should be issued to a responsible family member. Both accidental and planned overdoses are common and should be handled as a serious medical emergency. Symptoms that occur during an overdose are as follows (Potter & Hollister, 2001:509).

- Coma with shock and sometimes metabolic acidosis.
- Respiratory depression and the possibility to develop sudden apnoea.
- Agitation and delirium while conscious and unconscious.
- Neuromuscular irritability and seizures.
- Hyperpyrexia.
- Bowel and bladder paralysis.
- Various cardiac manifestations, including conduction and arrhythmias (Potter & Hollister, 2001:509).

Cardiac manifestations as mentioned above are difficult to handle (Baldessarini, 2001:467). The anti-arrhythmic drugs that have the least effect on cardiac conduction should be used. The patient's cardiac condition should be monitored continuously and the necessary facilities should be available if resuscitation is needed. Arterial blood gases and pH should be measured frequently seeing that hypoxia and metabolic acidosis may occur due to the arrhythmias (Potter & Hollister, 2001:509).

Fatality due to SSRI overdose is extremely rare and normally occurs only in patients that have taken it in combination with other substances like alcohol or other medicines. In SSRI overdoses only supportive treatment can be given since the drug cannot be removed by dialysis because of the high volume of distribution (Potter & Hollister, 2001:510).

Overdose due to MAO inhibitors is not common. Symptoms that may be expected are agitation, delirium, and neuromuscular excitability and are followed by obtained consciousness, seizures, shock and hyperthermia. Supportive treatment is usually all that is needed (Potter & Hollister, 2001:510).

While *"successful suicides"* by overdose are more common among TCA users, suicide by other means than poisoning is more common among non-TCA users. This indicates that patients that are at risk for suicide will rather receive SSRI treatment but if they want to commit suicide they will succeed (Palmer *et al.*, 1993:3).

2.12 LEGISLATION THAT LIMITS ACCESS TO ANTIDEPRESSANTS

According to O'Neill-Kerr (1997:238) the risk of suicide is increased by both major depression and bipolar mood disorder. Gelder *at al.* (1999:250) identified antidepressants as one of the most frequently used medicines in suicide. Because of their toxicity (refer to section 2.11), access should be limited.

According to the Medicines and Related Substance Control Act 101 of 1965 (Act 101/1965) as amended in 1997, all the antidepressants are schedule 5 medicines. The Medicines and Related Substance Control Act 101 of 1965 as amended in 1997, states that in the case where schedule 5 medicine is used as an antidepressant it should not be prescribed for longer than six months unless an authorised prescriber has consulted a psychiatrist or where one psychiatrist consulted with another psychiatrist (South Africa, 1997:16). In cases of emergency, schedule 5 medicines may be given, but only enough to last 48 hours. The prescriber that has given the order must issue a written prescription within 72 hours (South Africa, 1997:16).

2.13 CHAPTER SUMMARY

This chapter focussed on the pathophysiology, aetiology and classification of depression. These factors are important to consider in the diagnosis of depression. The cognitive treatment as well as the treatment of depression using medication was discussed. The medication treatment was mainly focussed on the pharmacological sub-groups as classified in the Monthly Index of Medical Specialities (MIMS); emphasis was not as much on individual agents. Medicine interactions and patient compliance were considered to effectively enhance antidepressant treatment. This chapter concluded with a discussion on the risk of suicide and pointed out legislation that limits access to antidepressants in South Africa.

The next chapter will focus on theoretical aspects of medicine usage and cost such as managed care, drug utilisation review, pharmacoeconomics and generic substitution, as related to antidepressants.

CHAPTER 3

ASPECTS OF MANAGED HEALTH CARE AND PHARMACOECONOMICS AS RELATED TO ANTIDEPRESSANTS

3.1 INTRODUCTION

This chapter will focus on the subjects of managed care, aspects of drug utilisation review, generic substitution and pharmacoeconomic analysis. Pharmacoeconomic analysis will be explained in detail with reference to antidepressants as it forms part of the scope of the objectives of the study. Issues surrounding medicine pricing legislation will also be discussed.

The goal of the National Drug Policy is to ensure an adequate and reliable supply of safe, cost-effective medicines of acceptable quality to all citizens of South Africa and the rational use of medicines by prescribers, dispensers and consumers (South Africa, 1996).

The most notable deficiency in the South African pharmaceutical sector is the lack of equity in access to essential medicines, with a consequent impact on the quality of care. Rising medicine prices also give an increasing cause for concern, as did evidence of irrational use of medicines and cost-ineffective procurement and logistic practices (South Africa, 1996).

The South African Government is faced with four challenging problems in the health care market.

- The public sector does not have the resources to provide sufficient health care to the large population not covered by medical aids.
- The number of people that are covered by medical aids is declining.
- The increasing cost of private health care has continually exceeded inflation and has now reached a point where private health care has been unable to grow due to its high cost.
- The public and private sectors must be improved to increase the quantity and quality of health care received by a larger number of the South African population, but the challenge lies in how to go about it (Luiz & Wessels, 2004:1).

Mental illness has been increasingly recognised as a major social and economic burden on individuals and society because it increases health care cost, decreases productivity and reduces quality of life (Love, 2002:3). According to Greenberg *et al.* (as quoted by Hylan *et al.*, 1998:53) the cost for depression is similar to that of cancer, AIDS, and coronary heart disease; but the cost of depression is usually because of productivity loss thus the cost of depression is more hidden than in the case of other diseases.

These statistics present a good indication of why tools such as managed care, drug utilisation review, generic substitution and pharmacoeconomic analysis must be used in the South African health care sector to contain costs of medicines such as antidepressants.

3.2 MANAGED CARE

In this section managed care will be defined and discussed as related to the South African health care sector.

Managed care is defined by Kane *et al.* (1996) as efforts to coordinate, rationalise, and channel the use of services to achieve desired access, service, and outcomes while controlling cost. The Medical Schemes Act (131/1998) defines managed care as a "clinical and financial risk assessment and management of health care, with the view to facilitate appropriateness and cost-effectiveness of relevant health care services within the constraint of what is affordable, through the use of rule-based and clinical management-based programmes". The Council of Medical Schemes (2003) defines managed care within the South African setting as a term used to refer to a diverse range of health care organisational strategies aimed at controlling cost, improving access and assuring better quality of care provided to patients covered by medical schemes.

The basis of managed health care is that it begins with cost cutting measures such as demanding discounts and proceeds to its most advanced form where it transfers the risk from the medical aid to the health provider, and thus the provider becomes motivated to reduce costs (Luiz & Wessels, 2004:3). The managed care approach controls cost through measures such as utilisation review to monitor wasteful practices by providers and patients, consumer education to reduce unnecessary health care utilisation, practice guidelines and formularies to promote cost-effective management of particular medical conditions; control access to expensive services and negotiating discounts on supplies and services (Kinghorn, 1996:335).

The Council of Medical Schemes (2003) recognises the potential advantage of managed health care to the extent that it can.

- encourage the use of most cost-effective health care delivery mechanisms, and thus accomplish cost reduction;
- align the financial incentives of providers and financiers to reduce bad incentives for unnecessary care;
- establish mechanisms to maintain or improve quality of care;
- promote the development of standardised treatment plans;
- support patients in gaining access to the most suitable treatment interventions;
- promote an integrated approach to managing the health care needs of patients (Council for Medical Schemes, 2003).

Managed care revolves around trying to provide quality health care within the capitated financial environment, pharmaceutical formularies and outcome guidelines (Kriel, 2003:16). The delivery of services in a capitated environment follows the managed care model (figure 3.1) where the employer negotiates with the managed care organisation and the managed care organisation negotiates with the provider for the most affordable rates. The providers deliver health care services to the patients within the guidelines of the managed care organisation (Kriel, 2003:16).

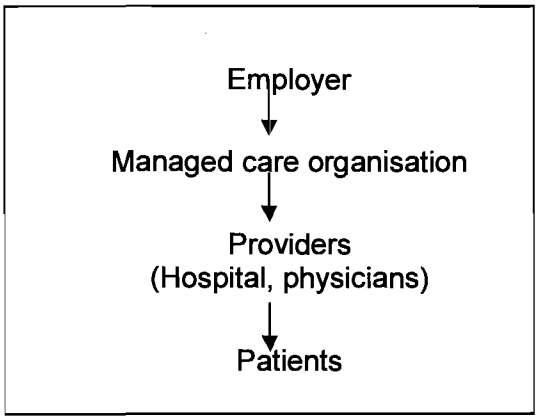


Figure 3.1: Managed care model (Kriel, 2003:16)

Managed care was formally introduced in South Africa in 1995 with the aim to control the cost of health care (Rothberg *et al.*, 1999). Managed care was successfully implemented in the Vaalmed staff model plan and the Eastern Cape UDIPA full capitation option run by the Uitenhage independent practices association (IPA). Less successful examples were the Mines Benefit Society's pre-paid health plan and Medico's capitation plan (Rothberg *et al.*, 1999). These two companies failed because they suffered from the burden of controlling costs in environments loaded with pensioners and the requirement to assume the risk for areas which were becoming more unmanageable (Rothberg *et al.*, 1999).

As health care cost continues to spiral upwards, medical schemes are turning to managed care programmes to cut the costs of services and keep benefits affordable. The aim of these managed care programmes is to ensure that patients receive the most appropriate and cost-effective services that the scheme can afford. According to Du Preez, if you ever had to telephone your medical aid fund for authorisation before being admitted to hospital or have had to register on a chronic disease programme, you have experienced managed care (Du Preez, 2003). Some of the managed care organisations that are currently registered are Calabash Health Solutions®, Ingwe risk management®, Medscheme®, Prosperity health® and Sovereign health® (Council for Medical Schemes, 2005).

Managed care can be divided into three contractual links as illustrated in figure 3.2. Jurisich and Da Silva (1996) define a contractual link as the way the service providers are tied to the managed care organisation. These contractual links will be discussed in subsections 3.2.1-3.2.3.

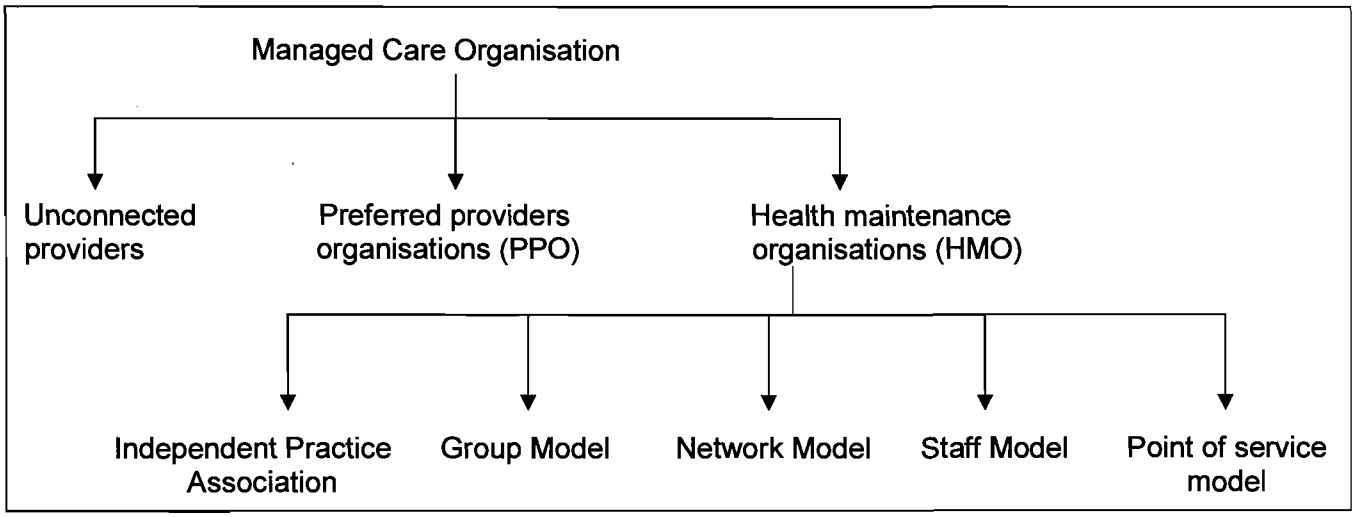


Figure 3.2: The contractual links for managed care organisations (adapted from Fairfield *et al.*,1997 and Jurisich & Da Silva, 1996).

3.2.1 Unconnected providers

When service providers are operating as unconnected entities; the patient has the right to choose his/her own service provider, no managed care organisation is involved in these sections. Any financier to whom the patient is contracted to has no contractual links with the providers of services (Jurisich & Da Silva, 1996). This entities are called unconnected providers.

3.2.2 Preferred provider organisations (PPO)

Preferred provider organisations (PPO) is defined by Rickel and Wise (2000:105) as a partnership between a hospital and a group of health care professionals to provide services to a group of patients. Fairfield *et al.* (1997) define PPO as a third party that takes over the administration and utilisation management on behalf of the insurer. In the preferred provider organisation the patient is free to choose either the preferred provider (the health care entity that is contracted with the PPO plan) or any other health care entity of his choice. Should the patient, however, choose the preferred provider his co-payment is then typically reduced (Hagen, 1999:6).

3.2.3 Health maintenance organisations (HMO)

Fairfield *et al.* (1997) define health maintenance organisations (HMO) as a prepaid, organised delivery system where the organisation assumes the financial risk for the care that is provided to its members. Financial risk may be transferred to clinicians and other financial incentives (Fairfield *et al.*, 1997). Capitation is explained by Rickel and Wise (2000) as a situation where the managed care company pays a fixed fee to a physician for an enrolled patient's care over a specific period of time regardless of whether the patient is seen or not.

Figure 3.2 indicates that there are five main types of HMOs. These types will be discussed subsequently.

- Staff model – The staff model is an HMO that employs health care providers on a salary basis and sees members mostly in its own medical facilities (Rickel & Wise, 2000:107). Rognehaugh (1998:234) defines the staff model as an HMO model that enters into a relationship with its physicians as employees; premiums are paid to the HMO which in turn pays the physicians as staff members. Staff models are increasingly exploring new incentive pay structures instead of the normal flat salary (Rognehaugh, 1998:234).

- Group model – This model involves contracts between the HMO and either a single or multiple group of physicians and hospitals; these groups may be organised as a partnership, professional cooperation or other associations. The health plan compensates the group for services rendered at a contracted rate and arranges hospital services agreements for the inpatient or ancillary care needs (Rognehaugh, 1998:95).

- Network model and independent practice association model were initially different; these models are now, for all practical purposes, indistinguishable. The HMO builds a network of existing practices and providers and contracts them to provide care for the enrollees. The patients must choose a primary care doctor (who acts as a gatekeeper to specialist services) from among the network of providers (Fairfield *et al.*, 1997). Hagen (1999:19) defines a gatekeeper as an individual who controls a patient's access to and use of health services. The providers contracted with the HMO keep the right to provide services to other patients out of the HMO spectrum as well (Fairfield *et al.*, 1997).

- Point of service model – Rickel and Wise (2000:105) define point of service as a plan which permits members to go outside of the plan for services at extra cost. The patient is free to choose his or her own service provider, however, these plans are more expensive than in the case of the above-mentioned models (Hagen, 1999:7).

Although the introduction of managed care into the South African health care sector was (and in some cases, still is) strongly resisted by some of the major stakeholders and vested interest groups, managed care systems are now firmly established and are likely to become even more important in the future (Fourie, 1999).

An evaluation of the South African health care setting forecasts a growing focus on managed care initiatives in the future. Tools such as formularies, disease management programmes, contracts, utilisation review programmes, clinical guidelines and quality assurance programmes appear to be receiving increased attention (Health Professions Council of South Africa, 2005).

3.3 DRUG UTILISATION REVIEW (DUR)

Drug utilisation review programmes can be used as a tool to contain medicine costs (refer to section 3.2) (Kinghorn, 1996:335). In this section, drug utilisation review will be discussed under the following headings: history, description, types, criteria, limitations and future.

3.3.1 History of DUR

Population-based drug utilisation studies were pioneered in Europe during the late 1960's and early 1970's (Serradell *et al.*, 1987:994). DUR studies were developed in Europe for quantitative and qualitative studies of the use of medicines in the population, the factors affecting their use, and the problems resulting from this usage (Sacristán & Soto, 1994:300). The primary focus of these studies were determined by the needs of the programme administrators but the drug use statistics published in these studies were not linked to the population data. In later studies a shift towards a more epidemiological approach occurred and the population denominator became more important. In addition more adequate measures for drug utilisation data were developed (Serradell *et al.*, 1987:994).

In the 1980's, following decades of research on quality of drug therapy, preventable adverse drug reaction, inadequate patient compliance, and cost containment procedures; interest arose to promote a large scale drug utilisation review (DUR) and drug use initiatives. Subsequently federal legislation, the Omnibus Budget Reconciliation Act of 1990 (OBRA'90), was passed in the United States that required online prospective DUR and retrospective DUR for ambulatory medical aid patients (The U.S. Pharmacopoeia Drug Utilisation Review Advisory Panel, 2000).

In these mandatory retrospective DUR studies computer software was used to identify drug-drug interactions, overuse (e.g. early refills), drug-disease interaction, duplicate therapy, excessive or insufficient dose and drug-pregnancy contra-indications (Hennessy & Strom, 2003).

3.3.2 Discussion of DUR

Drug utilisation review (DUR) was defined by the WHO (2003) in 1977 as the marketing, distribution, prescription, and use of medicines in society with special emphasis on the resulting medical, social and economic consequences. Rognehaugh (1998:69) defines DUR as a quantitative review to establish the medical appropriateness of providers to patients for particular medical conditions, performed by peers with feedback and education given to the providers. Edgren, (1999) defined DUR as an authorised, structured and continuing programme that reviews, analyses and interprets collective patterns of medication use measured against predetermined standards and criteria established for specific health care delivery systems.

Walters and Smart (1994:820) defined DUR for the South African health care setting as an authorised, structured, ongoing system for the monitoring of medicine use through comparison

with specific standards and initiation of corrective actions when medicine use patterns are inconsistent with these standards.

DUR studies can be used to estimate the prevalence of an illness in a specific area, based on consumption data for the medicine used to treat a disease (Truter, 1997:19). It can also be used to study different prescribing practices (Truter, 1997:19). DUR is not only used in the detection of medication problems but also to establish measures or interventions to solve them (Truter, 1997:20). DUR may be used to improve the quality of care, control of medical care costs and the identification of fraud and abuse of medicines or services (Truter, 1995:338). DUR may be valuable in the promotion of rational and cost-effective use of medicine in the South African health care system (Truter, 1995:339). One of the economic objectives of the National Drug Policy is the promotion of cost-effective and rational use of medicines (South Africa, 1996). Truter (1997:20) is also of the opinion that this objective can be achieved by DUR studies.

3.3.3 Classification of DUR

Studies in drug utilisation include quantitative and qualitative aspects of medicine use. Quantitative and qualitative DUR studies may be combined into a single effort to produce information about patterns and number of medicine items used as well as quality of medicine use (Kreling & Mott, 1993:416).

A variety of approaches can be adopted for both quantitative and qualitative DUR studies. These approaches include automated computerised review of prescription medicine data base, committee review of patient charts and prescription drug profiles, and pharmacist reviews of medication charts and prescription drug profiles (Kreling & Mott, 1993:416).

Quantitative and qualitative DUR studies will be defined and discussed in paragraphs 3.3.3.1-2.

3.3.3.1 Quantitative DUR studies

Strom (1994:697) defines quantitative drug utilisation studies as descriptive studies of the frequency of medicine usage. Quantitative DUR measures the number and patterns of medicine usage (Iñesta, 1992:353). These studies involve collecting, organising and displaying estimates or measurements of medicine usage. The results of these activities usually take the form of absolute or relative quantitative data describing the use of medicines within specified time frames and drug, patient and/or prescriber categories (Kreling & Mott, 1993: 416). Drug utilisation data that are the results of these studies can be used to estimate medicine utilisation

in study populations by age, gender, social class and morbidity, and to identify areas of possible over or under utilisation (Lee & Bergman, 1994:380). These studies may be episodic or continuing activities normally performed by a pharmacist or pharmacy department (Kreling & Mott, 1993: 416).

The objective of a quantitative DUR study is to quantify the present state of medicine use, developmental trends and time course profiles of medicine use (Iñesta, 1992:353).

According to Iñesta (1992:353) quantitative DUR studies have the following uses:

- To know or to estimate over-use, under-use or misuse of medicines.
- As markers for very basic estimates of disease prevalence.
- To monitor the effects of informational or regulatory activities.
- To estimate rates of adverse drug reactions using the number of exposed patients as a denominator (Iñesta, 1992:353).

3.3.3.2 Qualitative DUR studies

According to Iñesta (1992:353) qualitative drug utilisation studies are studies that assess the appropriateness of medicine used. Strom (1994:697) also defines qualitative drug utilisation studies as studies that assess the appropriateness of medicine use. The detection and evaluation of inappropriate medicine use should lead to the improvement of medicine use through changes in therapeutic practices. These changes can, however, only be implemented with informative, educational and administrative actions (Iñesta, 1992:353).

Qualitative DUR studies include collecting, organising, analysing and reporting information on the rationality of drug use. These studies focus on the use of certain criteria (predetermined elements against which aspects of quality, medical necessity and appropriateness of medical care may be compared) to provide an evaluation of the quality of drug use (Kreling & Mott, 1993:416).

3.3.4 Types of DUR studies

Drug utilisation review studies are also divided into retrospective, concurrent and prospective reviews. These three types of DUR studies will be discussed in subsections 3.3.4.1-3.

3.3.4.1 Retrospective DUR Studies

A retrospective DUR study is where the evaluation of therapy and intervention is performed after the patient had completed the prescribed therapy (Blackburn, 1993:15). According to Kreling and Mott (1993:417) retrospective studies can be used to identify previous trends in medicine use and may be used to develop future interventions designed to enhance medicine usage patterns. Because of the timing of retrospective studies, it has little immediate impact on patient care or the avoidance of inappropriate medicine use (Kreling & Mott, 1993:417).

Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants may cause anxiety and insomnia (refer to table 2.4). Jacobsen (as quoted by Rascati, 1995:786) states that trazodone and benzodiazepines can be prescribed to counter these side-effects. Rascati (1995:786) conducted a retrospective DUR study to determine to what extent this dual prescribing is done by analysing Medicaid prescriptions for the year 1993. The conclusion that was made from this study was that concomitant use of SSRIs or clomipramine was high with at least one third of the SSRI/clomipramine users in the study population also receiving anxiety/sleep medication. The concomitant use of SSRIs or clomipramine with trazodone occurred less frequently (Rascati, 1995:790).

Gelder *et al.* (1999:137) indicated that women have a higher risk for depression than men (refer to section 2.3.1). Parker *et al.* (2003:1473) have conducted a retrospective and prospective naturalistic uncontrolled study to determine gender and age differences in SSRI and TCA antidepressant response. This study failed to find any evidence of women having a preferential response to SSRI or TCA therapy. Older age was, however, associated with TCA response and younger patients did response better to SSRI treatment. The conclusion was, however, made that due to a lack of studies that examine gender and age differential effects these effects have still to be established (Parker *et al.*, 2003:1473).

3.3.4.2 Concurrent DUR Studies

Concurrent DUR studies are conducted while provision of medicine is taking place. If a potential problem occurs while dispensing, the process comes to a halt until authorisation has been received on what steps to follow (Truter, 1995:338). These types of studies are more expensive and time consuming than retrospective studies and there has to be a well organised computer system or a manual medicine profile system in place (Truter, 1995:338).

3.3.4.3 Prospective DUR Studies

Prospective studies are defined by Blackburn (1993:15) as programmes where the evaluation of therapy, and intervention if necessary, occurs before the patient starts with therapy. Prospective review studies require the examining of current medicine orders for appropriateness and correctness (Kreling & Mott, 1993:417). Prospective studies rely on criteria derived from published literature, clinical experience and basic pharmacological principles to provide an evaluation of medicine therapy (Kreling & Mott, 1993:417). According to Truter (1995:338) a practitioner performs a prospective study by using data that are collected from a complete medicine and medical history obtained from an interview with the patient and from previous medical records. These studies are beneficial to the patient because the studies identify and prevent medicine therapy problems before they occur (Kreling & Mott, 1993:417).

A prospective DUR study conducted by Oquendo *et al.* (2002:1746) tested adequacy of antidepressant treatment and its impact on suicidal acts in the 2 years of hospitalisation for major depression. Patients (n=136) with major depression were interviewed at 3 months, 1 year and 2 years after admission. Major depression in the follow-up period increased the risk of a suicide attempts sevenfold. For each suicide attempt in a subject's history, the risk for a suicide attempt in the follow-up period increased by 30 per cent. The conclusion made from this study was that antidepressant treatment of depressed patients is strikingly inadequate, even in suicide attempters, known to be at higher risk for suicidal acts. Further controlled studies of antidepressants are needed to evaluate effects on suicidal acts (Oquendo *et al.*, 2002:1746).

Tricyclic antidepressants' (TCA) overdoses have the highest hospitalisation and fatality rate compared to any other prescribed drug overdose (Palmer *et al.*, 1998:3) (refer to section 2.11). Phillips *et al.* (1997:439) conducted a prospective study to test the hypothesis that fluoxetine causes less morbidity and mortality than TCAs. The study included a prospective case series of urban hospital systems. Of the hundred and seventy-nine medicine ingestion deaths from the coroners' records thirty-eight were from tricyclic antidepressants and none from fluoxetine. It was concluded that tricyclic antidepressant overdoses resulted in more toxicity and more frequent admissions to the intensive care unit than in the case of fluoxetine overdose (Phillips *et al.,* 1997:439). If a patient presents with a suicide risk (determined by an interview and medical history) tricyclic antidepressants will be avoided.

This dissertation places the focus on the data that have occurred after the patient had completed the therapy and is used to identify previous trends in medicine use. This study can

thus be classified as a retrospective drug utilisation study (both qualitative and quantitative) regarding the prescribing patterns and cost of antidepressants.

3.3.5 Future of DUR studies

According to Edgren (1999) DUR will evolve significantly in the following areas:

- The HMO/PPO environment: DUR will be used as indicators of quality in medical practices, this is already occurring in some practices. DUR studies will also be used as risk indicators.
- Physicians: DUR studies will provide a concurrent evaluation of prescribing practices.
- Patients: Patients want more information to enable them to compare provider performance. DUR studies will make this information available.
- Employers: Employers control the managed health care machine. Employers do not want information on the health care of individual employees but they are increasingly interested in targeting health care resources (Edgren, 1999).

Any method that contributes information on the cost and effects of medicines will be used in a pharmacoeconomic study. DUR can be utilised to obtain information on cost and effects of medicines. This is the basis of the relationship between pharmacoeconomic studies and DUR (Sacristán & Soto, 1994:302). Further focus on pharmacoeconomic studies will be discussed in section 3.4 of this chapter.

3.4 PHARMACOECONOMICS

Medicines account for roughly 30 per cent of the total health care bill in South Africa, which is high, compared to many other countries (Luiz & Wessels, 2004:3). The Mediscor report for 2006 found that the expenditure for antidepressants was 5.0 per cent of the total medicine expenditure in 2005 and 2006 (Bester & Hammann, 2007).

There are thus increasing demands on decision makers for cost containment. Pharmacoeconomics uses tools to identify, measure and compare the costs and consequences of medical interventions, including medicine therapy (Struwig, 2005:2). Economic evaluations of health care alternatives are becoming more common as health care providers seek the optimal use of limited recourses (Struwig, 2005:2, Valodia, 2007:6).

According to Walley (2006) health economics is the science of assessing costs and benefits. The aim of health economics is to identify the most efficient therapy, so that the greatest benefit can be achieved from a given amount of money or resources. An important factor to keep in mind is that efficiency may not be the most important objective – for instance caring for a dying patient or treating a patient with a serious disease with little hope must be a priority (Walley, 2006). Economic evaluations are conducted to assess efficiency – the relationship between outputs (consequences) and inputs (costs). The ultimate goal of economic evaluations is to enable the decision maker to allocate resources more efficiently (Larson, 2001:4).

Pharmacoeconomics was defined by Townsend (1987:134) as the description and analysis of the costs of medicine therapy. Cantor (2002) defines pharmacoeconomics as the identification, measurement and comparison of pharmaceutical products and services based on clinical benefits and economic costs. It is an interdisciplinary science that incorporates elements from pharmacy, clinical medicine, clinical epidemiology, statistics, psychology, economics and ethics (Cantor, 2002). Einarson and Iskedjian (2005) define pharmacoeconomics as the simultaneous comparison of medicines against alternative (medicine or non-medicine) treatments with reference to both costs and outcomes.

Pharmacoeconomics is a branch of health economics that particularly considers medicine therapy (Walley, 2006). Pharmacoeconomic research identifies measures and compares the costs (i.e. resources consumed) and consequences of pharmaceutical products and services (Bootman *et al.*, 1991:4). It can be used by pharmaceutical companies who in developing a new medicine, after complying with efficacy, safety and tolerability standards must overcome a fourth hurdle of cost effectiveness. It should also interest clinical pharmacologists, either in their roles assessing new medicines or in conducting clinical trials that now often include economic evaluations (Walley, 2006).

Figure 3.3 illustrates some of the stakeholders that are involved in pharmacoeconomic analysis in the South African health care setting.

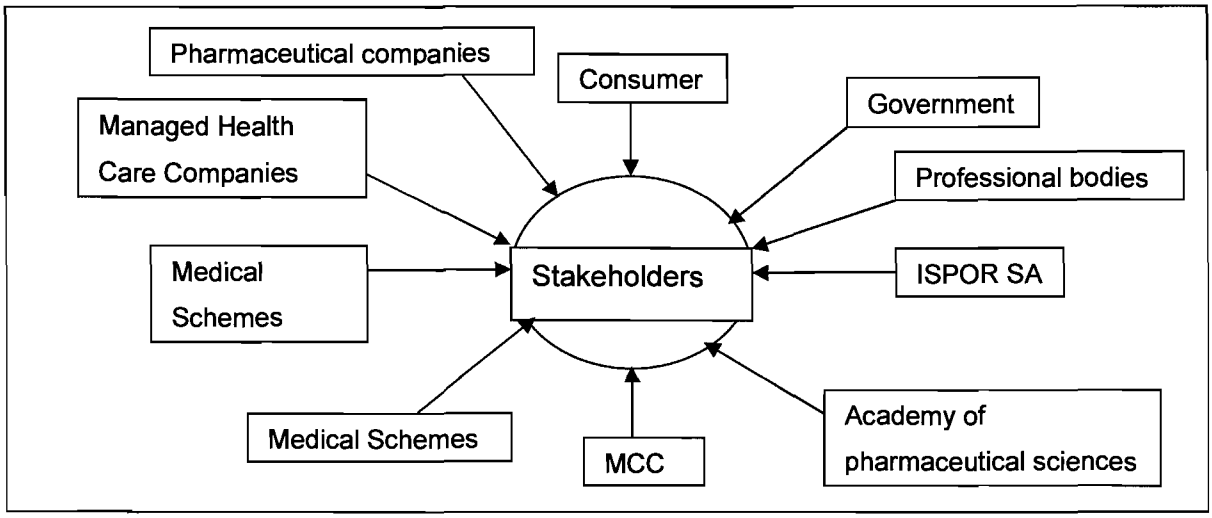


Figure 3.3: Stakeholders in pharmacoeconomics in South Africa (Valodia, 2007:14)

In this dissertation a few of these stakeholder entities are involved, the patient who consumes antidepressants, the government who promotes safe and effective medicines at the lowest possible price and the managed health care companies and medical schemes from which the data for this dissertation were obtained.

In figure 3.4 the factors that influence medicine prices and medicine expenditure will be illustrated.

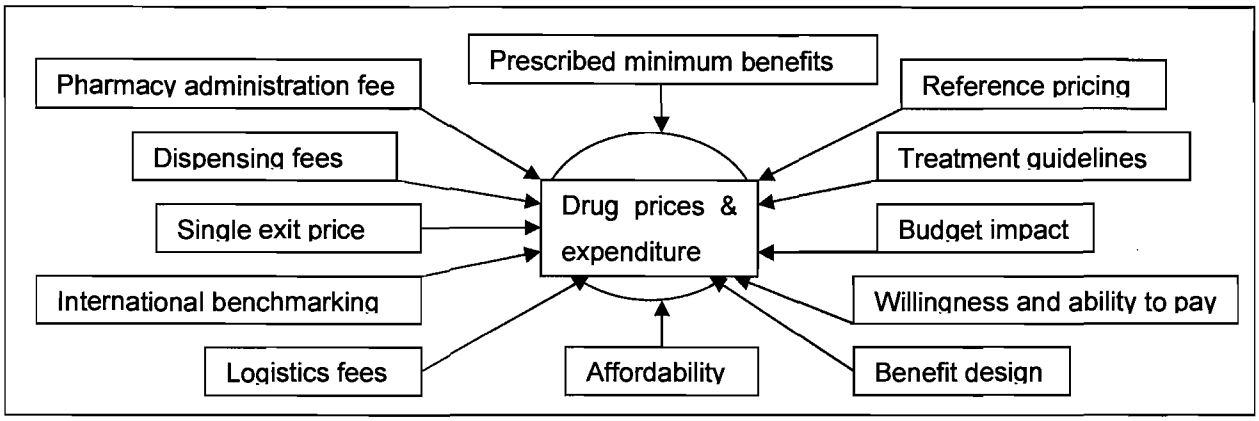


Figure 3.4: Factors influencing medicine prices and medicine expenditure in South Africa (Valodia, 2007:15).

Pharmacoeconomic analysis must be applied to all the mentioned factors (figure 3.4) to ensure affordability of medicines. Pharmacoeconomic analyses are categorised into cost-of-illness, cost-benefit, cost-effectiveness, cost-utility, and cost-minimisation studies (Drummond *et al.*,1999:2; Elliot & Payne, 2005:91).

The above-mentioned pharmacoeconomic analyses create a common ground on which to evaluate the contrasting information categories for prescription medicines: efficacy or effectiveness, safety, quality of life and other preference measurements, and cost (Bonk, 1999:10). In the following subsections the applications of the pharmacoeconomic tools will be discussed with regard to mental illness, depression and antidepressants.

3.4.1 Cost-of-illness analysis

Cost-of-illness quantifies cost of a disease without considering any of its treatments (Bonk, 1999:25). According to Bootman *et al.* (1991:5) cost-of-illness studies identify and evaluate the direct and indirect costs of a disease.

Hylan *et al.* (1998:53) state that depression has an increasingly significant economic and quality of life burden on patients, employer and third party payers worldwide (refer to section 1.2).

A study was done by Kirigia and Sambo (2003:2) to determine the total cost of mental and behavioural disorders (MBD), of which depression was part of the study, from a societal perspective (specifically the family and the Ministry of Health). This study used standard cost-of-illness methods to estimate direct costs i.e. the costs carried by the health care system and the family in directly treating MBD and indirect costs i.e. loss of productivity carried by the patient, family and employer. The conclusion that was made from this study was that there is an urgent need for research in all African countries to determine the national-level epidemiological burden of MBD, measured in terms of the prevalence, incidence, mortality and probability, the disability-adjusted life-years lost and the economic burden of MBD, broken down by different productive and social sectors and occupations of patients and relatives (Kirigia & Sambo, 2003:2).

3.4.2 Cost-benefit analysis

Bonk (1999:10) states that cost-benefit analysis identifies and measures the costs of treating the disease and the treatment outcomes in monetary terms. Cost-benefits analysis consists of identifying all the benefits that accumulate from treatments and converting these to a monetary value in the year in which they occur. This value is then discounted to its equivalent present value at the selected interest rate. This is then compared to other treatment programmes. If all relevant factors remain constant, the programme with the largest present value of benefits minus costs is the best in terms of its economic value (Bootman *et al.*, 1991:6). Carriere and Huang (2001:21) state that the outcomes of therapeutic intervention are measured in monetary

terms by net benefits [(Net Benefits = total benefits–total costs or benefits-to-cost ratio) (Benefits-to-Cost ratio=total benefits/total cost)]. Cost-benefit analysis can be conducted for a single or multiple therapeutic interventions to provide foundations for decision making to achieve the desired objectives (Carriere & Huang, 2001:21). This approach is not often used in pharmacoeconomic studies (Walley, 2006).

Torné and Isaac (1996:359s) conducted a cost-benefit analysis to determine the costs and benefits of augmentation of paroxetine with the $5HT_{1A}$ receptor blocker pindolol during a randomised, placebo controlled trial. The economic analysis incorporated all the costs involved, including clinical and laboratory costs, costs of infrastructure and medicines. Torné and Isaac (1996:359s) applied the techniques of shadow pricing and inter-temporal discounts of social taxes. The result revealed that the main benefits are the speed and magnitude of the improvement of quality of life and leisure, and the savings in clinical resource utilisation. Torné and Isaac (1996:359s) concluded that economic analysis becomes increasingly important in the evaluation of treatment and that it must be included in clinical trials wherever possible.

3.4.3 Cost-effectiveness analysis

Carriere and Huang (2001:23) explain cost-effectiveness analysis (CEA) as a method for comparing health outcomes (effectiveness) and the net costs from a therapeutic intervention against other alternatives with similar health outcomes. CEA measures outcomes in terms such as mortality, disability or quality of life unlike in the case of cost-benefits analysis where outcomes are measured in monetary terms. According to Bonk (1999:10) cost-effectiveness analysis measures the cost of treating a disease, but treatment outcomes are expressed in clinical measurements. The health outcome concerned in CEA is a single dimensional health measure (Carriere & Huang, 2001:23). The net costs from a therapeutic intervention are the costs for providing the treatment and applying the resources for the intervention after subtracting the non-health benefits from the programme measured in monetary terms. Decision makers would choose the intervention that is the most effective and least expensive (Carriere & Huang, 2001:24).

Kim and Holloway (2003:1272) conducted a decision and cost-effectiveness analysis to determine the burdens and benefits of placebo therapy in antidepressant clinical trials. They used a static model to determine whether a patient would be entered in an individualised psychiatric treatment trial or an eight-week placebo-controlled randomised clinical trial. Model outcomes included the probability of treatment response at 8 weeks and cost-effectiveness. The authors also discovered that a participant in a typical antidepressant efficacy trial has a

chance of treatment response almost 25 per cent less than that with individualised treatment. They also found that a patient can save approximately $164 for every 10 per cent chance of response sacrificed by entering the placebo-controlled trial. Kim and Holloway (2003:1272) also concluded that evidence-based estimates of the burdens and potential benefits may be more useful for institutional review boards and potential subjects than unstructured records of risks and benefits.

3.4.4 Cost-utility analysis

Bootman *et al.* (1991:8) describe cost-utility analysis as an economic tool in which the outcomes of the intervention are measured in terms of patient preference or the quality of the outcome. It is similar to CEA with the added dimension of particular point of view – mostly that of the patient (Bootman *et al.*, 1991:8). Cost is also expressed in monetary terms as is the case with CEA. The outcome of therapy is measured as a unit of utility e.g. quality-adjusted life-year (QALY) or cost per QALY gained (Bootman *et al.*, 1991:8; Walley, 2006).

Only 50 per cent of patients in South Africa that have depression receive treatment for it because of misdiagnosis (Roos, 1997:170) (refer to section 2.1.1). Valenstein *et al.* (2001:345) conducted a study to examine the cost-utility of screening for depression compared with no screening. The outcome measures for this study were costs and quality-adjusted life-years (QALYs). The cost of annual screening from a society perspective in primary care patients would be $192 444/QALY. Screening every 5 years would accumulate to $50 988/QALY and $32 053/QALY if it is only done once off. From the payers' perspective the cost of annual screening would be $225 467. Valenstein *et al.* (2001:345) made the conclusion that annual and periodic screening for depression cost more than $50 000/QALY, but one time screening is cost-effective. According to the authors the cost-effectiveness of screening may improve if treatment becomes more effective.

In another cost-utility analysis Serrano-Blanco *et al.* (2006:39) determined the cost-utility of selective serotonin reuptake inhibitors (SSRIs) for treating depressive disorders prescribed in primary care (PC). Incremental cost-utility ratios (ICUR) were collected from several comparisons among different SSRIs. Serrano-Blanco *et al.* (2006:39) concluded that fluoxetine seemed to be a better cost-utility SSRI option for treating depression in a primary care setting.

A study conducted by Hakkaart-Van Roijen *et al.* (2006:323) to assess the cost-utility of brief psychological treatment compared to cognitive-behavioural therapy (CBT) and normal medicine treatment, showed that the mean direct costs for the brief treatment were lower than those of

CBT and medicine therapy. However, after adding indirect costs there were no differences in the three groups. They also found no difference in QALYs between the three therapy methods. Hakkaart-Van Roijen *et al.* (2006:323) concluded that the cost-utility did not differ between the three treatment methods.

3.4.5 Cost-minimisation analysis

Cost minimisation analysis (CMA) involves measuring only costs and is only applicable where the outcomes are identical (Walley, 2006). Carriere and Huang (2001:24) explain CMA as a method designed to identify preferred choice between possible alternatives with comparable outcomes by examining the cost associated with each of those alternatives. This analysis can be used to determine whether a generic medicine item or innovator medicine item should be prescribed (lower cost but the same health outcomes) (Walley, 2006).

In this dissertation/study, the prevalence and costs of antidepressants will be calculated from data from a South African pharmaceutical benefit management (PMB) company (refer to chapter 5). The principles of cost minimisation analysis will be applied to determine possible cost savings through generic substitution (refer to section 5.7).

3.5 GENERIC SUBSTITUTION

Rognehaugh (1998:91) defines a generic equivalent as a medicine not protected by a trademark and that has the same active ingredient as those sold under a brand name. A generic medicine can be defined as a medicine that contains the same active ingredient than the innovator medicine that is no longer protected by a patent. There is no restriction on the number of generic items, each with a similar formulation, but not necessarily identical to the original, that can enter the market. All the generic items must, however, comply with the same quality and safety requirements demanded of the innovator product (The Association of the British Pharmaceutical Industry, 1999).

According to Pillay (2006) generic medicine in South Africa refers to medicines that are registered with the Medicines Control Council; and includes medicine that has never been protected by patent legislation. These medicines are usually manufactured by other companies than the company that originally held the patent (Pillay, 2006).

The goal of generic substitution is to reduce the cost of a medicine whilst achieving the same medical effect (Engström *et al.*, 2006). The aim of the National Drug Policy of South Africa

regarding drug pricing is to promote the availability of safe and effective medicines at the lowest possible cost. One of the methods to achieve this is by generic substitution (South Africa, 1996). The Medicines and Related Substance Control Act (101/1965) as amended in 1997 states that a pharmacist shall inform patients of the benefits of generic substitution and dispense generic medicines unless otherwise stated or not prefferred by the patient (South Africa, 1997:26).

The factors that may cause an increase in the sales of generic medicines are the following:

- By 1980, most states had passed drug-product substitution laws that enabled pharmacists to dispense generic medicine even when an innovator medicine had been prescribed (Cook, 1998).
- Some government health programmes and private health insurance plans actively promote generic substitution (Cook, 1998).
- Managed care initiatives that promote generic utilisation, such as the wider implementation of more rigid generic reference pricing (Bester *et al.*, 2006:7).
- The introduction of formularies that promote the use of generic medicines for the treatment of various diseases, including the prescribed minimum benefits (Bester *et al.*, 2006:7).
- Greater knowledge of the availability of generic products by patients and prescribers (Bester *et al.*, 2006:7).
- Mandatory generic substitution at pharmacy level (Bester *et al.*, 2006:7).

The following results were obtained in a study conducted by Levinson (2006), for the Department of Health and Human Services in the USA, to determine the extent of generic drug utilisation in State Medicaid programmes during 2004:

- Generic medicine items were dispensed in 89 per cent of all cases where a generic substitute was available.
- Forty-one per cent of all prescriptions were for medicines that had no generic equivalents.
- Fifty-four per cent of all the medicines dispensed were generics (Levinson, 2006).

In a study done by Karim *et al.* (1996:198) to evaluate the potential savings from generic prescribing and generic substitution in South Africa it was found that only 23 per cent of medicines prescribed had generic equivalents. Of the 23.5 per cent of medicines that had generic equivalents only 21 per cent were prescribed as generic medicines. The conclusion that Karim *et al.* (1996:198) made was that generic prescribing and substitution would have the potential to reduce medicine costs by nearly 10 per cent if practised to the maximum capasity. Current restrictive prescribing and dispensing practices result in marginal cost savings from generic prescribing and substitution. Generic prescribing and substitution can be promoted by continuous education programmes for private medical practitioners in South Africa (Karim *et al.*, 1996:198).

According to the Mediscor Medicines Review for 2006 the utilisation of generic medicine items in South Africa increased with 18.4 per cent from 2004 to 2006, with 45.4 per cent of innovator items substituted in 2006 compared to the 54 per cent in the USA (Bester & Hammann, 2007). Although there was an increase in generic substitution, it has not yet achieved its full potential in South Africa.

3.6 MEDICINE PRICING IN SOUTH AFRICA

The aim of the South African government is to ensure that patients obtain value for money when purchasing pharmaceutical products in either the public or private health care sectors. Modern medicines are expensive to develop and it is accepted that the county should contribute to the costs of research and development, however, these costs should be accurately estimated and according to the county's ability to pay. According to the pricing committee the purchase prices of medicines in the private sector should relate to their therapeutic performance, taking into account the national socio-economic factors. (South Africa, 2006:498).

In 2004, the government introduced a single exit price for medicines and put a stop to discounts and additional levies on medicines. These medicine pricing regulations only provided for an additional dispensing fee to the single exit price (Board of healthcare funders of Southern Africa, 2006). The timescales for the implementation of this legislation were as follows; 2 May discounting by manufacturers, wholesalers and retailers will become unlawful; 26 May the list of single exit prices must be lodged with the Director-General and sales must be done according to these prices and within 90 days from the 2nd of May all these regulations must be fully implemented, with audited single exit prices in operation (Tshabalala-Msimang, 2004).

The single exit price was defined in the regulations relating to a transparent pricing system for medicines and scheduled substances in terms of the medicine and related substance act (101/1965) as the price set by the manufacturer or importer of a medicine combined with the logistics fee and VAT and is the price of the lowest unit of medicine within a pack multiplied by the number of units in the pack (South Africa, 2004:466). The aim of the new dispensing fee is to discourage the inappropriate use of high-cost products, thereby making health care accessible to more South Africans (Board of healthcare funders of Southern Africa, 2006).

These regulations and the dispensing fee became subject to legal challenges and the Department of Health was eventually ordered to reconsider the dispensing fee (Board of healthcare funders of Southern Africa, 2006). The Pharmacy Stakeholders Forum Filled an urgent application in the Pretoria High court on the 18th of December 2006, challenging the new medicines price regulations (Qualsa, 2007). In the Government Gazette (no. 29443) certain amendments to regulations was proposed by the Minister of Health relating to the transparent pricing system and the deadline for comments on the amendments was the 19th of March 2007 (Board of healthcare funders of Southern Africa, 2007). However uncertainty remains regarding the pricing system of medicines in South Africa (Qualsa, 2007).

3.7 CHAPTER SUMMARY

The economic burden of health care in South Africa may be reduced if methods of cost saving (*inter alia* as discussed in this chapter) are practised to their full potential. This chapter focused on various aspects of managed care, drug utilisation, pharmacoeconomics and generic substitution. Examples as related to antidepressants were also used to explain these terms.

The following chapter entails a discussion of the research methodology of this study. Aspects such as research objectives, research design, data source used for the empirical investigation, data analysis, measuring instruments and reliability and validity of the research instruments will be discussed.

CHAPTER 4

RESEARCH METHODOLOGY

4.1 INTRODUCTION

In this chapter the research objectives, empirical research methodology, data sources and database on which the study was based, will be discussed in detail.

4.2 GENERAL RESEARCH OBJECTIVE

The general objective of this study was to investigate the prescribing patterns and cost of antidepressants in a section of the private health care sector of South Africa by using a medicine claims processing company for the years 2004 to 2006.

4.3 SPECIFIC RESEARCH OBJECTIVES

The research project consisted of two phases, namely a literature review and an empirical investigation. The research objectives of the two phases included the following:

4.3.1 Phase one: Literature review

The specific objectives of the literature review were

- to review depression as an illness and its treatment from the literature; and
- to discuss managed care, drug utilisation studies, pharmacoeconomic analysis and generic substitution as related to the usage of antidepressants.

4.3.2 Phase two: Empirical investigation

The specific objectives of the empirical study were as follows:

- Determine the prescribing patterns and cost of antidepressants relevant to other central nervous system stimulants (CNS) and all medicines claimed through the medicine claims processing company for 2004 to 2006.
- Compare the prescribing patterns and cost of generic and innovator medicine items for all medicines claimed through the database, CNS medicine items and antidepressants.

- Determine the general prescribing patterns and cost of the antidepressants claimed through the medicine claims processing company for 2004 to 2006.
- Determine the possible influence of generic substitution on the prescribing patterns and cost of antidepressants claimed through the medicine claims processing company.
- Analyse the prescribing patterns of antidepressants according to age and gender for 2006.
- Compare the prescribing patterns of different classes of antidepressants according to the Monthly Index of Medical Specialities (MIMS)-classification system.
- Investigate the prescribing patterns and cost of antidepressants based on active ingredients.
- Examine the drug interactions that may occur with antidepressant medicine therapy.
- Examine the prevalence and cost of the top ten antidepressants according to trade name
- Determine the cost savings with generic substitution that can be achieved with generic substitution by conducting certain hypothetical scenarios.

4.4 RESEARCH DESIGN

The research was done on data that were obtained from a medicine claims processing company. Data were collected after the medicine has been issued to the patients, thus the study could be defined as a retrospective drug utilisation study (with both qualitative and quantitative aspects) (refer to section 3.3.3.1 - 3.3.4.1).

4.5 DATA SOURCE USED FOR THE EMPIRICAL INVESTIGATION

The data used in this study were obtained from a medicine claims processing company, Interpharm Data Systems®. Interpharm Data Systems® is an organisation that manage the benefits of medical schemes and -insurance companies in South Africa by providing a real-time auditing process to claims from pharmacies and service providers. In 2004, this company performed claim switching for 50 per cent of South Africa's medical providers (Shapshak, 2004).

The data obtained were for a period of three years from January 2004 to December 2006. The database consists of a total number of 5 213 765 prescriptions, containing a total number of 11 283 410 medicine items with a total cost of R1 346 210 929 (refer to table 5.2). The data were

analysed according to periods of four months each, for each individual year of study (refer to table 5.1).

Each prescription record contained a unique number to identify each patient, medical practice, pharmacy or medical scheme. These numbers were randomly allocated by the medical scheme administrator providing the data to ensure confidentiality. Thus confidentiality of information was maintained throughout the study (also see section 4.8). The database consists of the following information: (1) a specific code for the medical scheme (the specific medical scheme could not be identified), (2) medical scheme member number, (3) dependant number, (4) prescription number, (5) date of dispensing the prescription, (6) trade name of the medicine item, (7) Nappi codes of the medicine item, (8) amount of the medicine item prescribed, and (9) the amount paid by the medical scheme. Data regarding the age and gender of a patient were available for 2006 only.

4.6 DATA ANALYSIS

The data were analysed using the Statistical Analysis System® SAS 9.1® (SAS Institute Inc., 2002-2003).

4.6.1 Classifications systems

Various classification systems were used to classify medicine claimed through the database such as the Monthly Index of Medical Specialities (MIMS) classification and the Nappi classification.

4.6.1.1 MIMS classification

According to the MIMS classification (Snyman, 2007:15), antidepressants are classified into seven pharmacological groups, namely: tricyclic antidepressants (TCA), non-tricyclics, mono-amine oxidase inhibitors (MAOs), serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline re-uptake inhibitors (SNRIs), lithium and others.

The prescribing patterns and cost of the antidepressants according to the MIMS classification for pharmacological class will be calculated in section 5.4 (also refer to Appendix C, table 3-4c).

4.6.1.2 The Nappi code

The Nappi code is a unique nine digit number implemented with electronic transactions in mind. This code is unique for each product name, pack size, strength, manufacturer plus exclusions

(Snyman, 2004:6a). For the purpose of this study the antidepressants on the database were identified by means of the Nappi code.

4.6.2 Statistical analysis

In the empirical investigation various statistical methods were used to analyse the data. A short discussion of each follows subsequently.

4.6.2.1 Arithmetic mean (average)

The arithmetic mean is defined as the sum of all the observations divided by the total number of observations in the total data set (Banerjee, 2003:3). Brase and Brase (1999:94) define the arithmetic mean as an average that uses the exact value of each entry for the arithmetic mean. The arithmetic mean was calculated as follows:

Where:

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

x = value in the data set

$\sum$ = the sum

n = number of observations

The arithmetic mean was used during data analysis (refer to section 5.2 to 5.7) to determine the average cost and the average number of items per prescription.

4.6.2.2 Standard deviation

The standard deviation is defined by Banerjee (2003: 5) as a measure of the spread of data about the mean, weighting each individual item by its distance from the centre of the distribution. The standard deviation is the square root of the variance and produces a good descriptive measure of variability (Cohen & Lea, 2004:14). The standard deviation(s) was calculated as follows:

$$s = \sqrt{\frac{\sum \left(x - \bar{x}\right)^2}{n-1}}$$

Where:

s = standard deviation

x= value in the data set

$\bar{x}$ = arithmetic mean

n = number of observations

This equation was used during data analysis to determine the standard deviation of the average cost and the average number of items per prescription. The standard deviation is an indication of the distribution of data around the average cost or the average number of items per prescription. In some cases throughout chapter five the standard deviation was larger than the average cost which indicates an uneven distribution of data around the mean.

4.6.2.3 Cost-prevalence index

According to Serfontein (1989:180) index numbers in general are used to investigate drug utilisation patterns. The cost-prevalence index indicates the relationship between the total number of medicine items prescribed or claimed and the total medicine cost (Serfontein, 1989:181). The cost-prevalence index (CPI) was calculated as follows:

$$Cost-prevalence\quad index = \frac{Cost(\%)}{\Pr evalence(\%)}$$

Where:

- If the cost index < 1 then the medicine items are inexpensive.
- If the cost index = 1 there is a balance between the cost and the prevalence of the medicine item.
- If the cost index > 1 then the medicine item is fairly expensive.

The cost prevalence index was used during data analysis (refer to sections 5.2-6) to determine the expensiveness of a product relative to the number of medicine items prescribed.

4.6.2.4 Effect sizes (d-values)

According to Cohen (1988:3) the effect size can be defined as the degree to which a phenomenon is present in the study population. Effect size is an indication of the number of standard deviations, two populations means are apart (Cohen & Lea, 2004:125). The effect size (*d*) was calculated as follows:

$$d = \frac{\overline{x_a} - \overline{x_b}}{s_{\max}}$$

Where:

d = effect size

$\overline{x_a}$ = average medicine treatment value of a

$\overline{x_b}$ = average medicine treatment value of b

The *d*-value can be interpreted as follows (Steyn, 1999:3):

- *d* = 0.2 Small effect. These results were regarded as insignificant.
- *d* = 0.5 Medium effect which is observable. Results may be significant.
- *d* = 0.8 Large effect which is of high practical importance (Steyn, 1999:3).

The effect size was used during data analysis to determine whether the differences between averages are of practical significance for example to determine whether the average cost of innovators is practical significantly higher than that of generic products (refer to sections 5.2-6).

4.6.2.5 Cost savings

For the purpose of this study cost savings can be seen as the cost of medicine that can be saved if medicine items are substituted with other medicine items containing the same active ingredient and strength, in practice this will refer to the "innovator" and "generic" products.

In this study cost savings for the following four hypothetical scenarios were calculated:

Scenario 1

- Where 100 per cent of the innovator item was replaced with the most expensive generic medicine item.

Scenario 2

- Where 50 per cent of the innovator item was replaced with the most expensive generic medicine item.

Scenario 3

- Where 100 per cent of the innovator item was replaced with the least expensive generic item.

Scenario 4

- Where 50 per cent of the innovator item was replaced with the least expensive generic item.

Cost savings were calculated according to the following equation (refer to section 5.7):

Cost Saving =Total cost (innovator item)
– [Average cost (generic item) x n (total number of innovator items)]

Cost savings were calculated in section 5.7 for each active ingredient according to strength except where the innovator is less expensive than the generic or where there is no generic product available.

4.7 MEASURING INSTRUMENTS

Measuring instruments such as prevalence, cost, age and gender were used to analyse prescribing patterns of antidepressants. These measuring instruments will be discussed in the following subsections.

4.7.1 Prevalence

According to Waning and Montagne (2001:20) prevalence is the number of existing cases of an illness in a defined population at a specific time. In this study, prevalence and frequency were

used as synonyms to indicate the number of medicine items/prescriptions claimed for a specific time period.

In chapter five the prevalence of medicines will be determined for the following categories:

- The prevalence of all medicines claimed through the database for the year 2004 to 2006 (refer to section 5.2).
- The prevalence for central nervous system (CNS) medicines for the year 2004 to 2006 (refer to section 5.2).
- The prevalence of antidepressants for the year 2004 to 2006 (refer to section 5.3).
- The prevalence of generic and innovator medicines in general, and specifically for CNS agents and antidepressants (refer to sections 5.2.2 and 5.3.3).
- The prevalence of antidepressants according to age and gender (refer to section 5.3.3).
- The prevalence of antidepressants according to active ingredient (refer to section 5.5).

4.7.2 Cost

Cost is defined by Vogenberg (2001:3) as the value of resources consumed. In this study cost was expressed as a rand-value (R).

The cost of the following categories of medicines will be discussed in chapter five:

- The cost of all medicines claimed through the database for the years 2004 to 2006 (refer to section 5.2).
- The cost for central nervous system (CNS) medicines for the years 2004 to 2006 (refer to section 5.2).
- The cost of antidepressants for the years 2004 to 2006 (refer to section 5.3).
- The cost of generic and innovator items of all medicines prescribed as well as CNS agents and antidepressants (refer to sections 5.2 and 5.3.3).
- The cost of antidepressants according to age and gender (refer to section 5.3.3).
- The cost of antidepressants according to active ingredient (refer to section 5.5).

Cost will also be used to calculate the average cost and total cost of treatment. Cost-minimisation analysis (refer to section 3.4.5) will be used to determine possible cost savings of antidepressants through generic substitution (refer to section 5.7).

4.7.3 Age

Age is generally derived from the date of birth of a person and is an indication of the completed life years of that person (Kids' well-being Indicators Clearinghouse, 2007). The age of the patient in this study was determined according to the date of birth of the patient indicated on the prescription that was dispensed.

In this study the age of patients who received antidepressant prescriptions during 2006 were divided into five categories as follows:

- 0 ≤ 9 years
- > 9 and ≤ 19 years
- > 19 and ≤ 44 years
- > 44 and ≤ 59 years
- > 59 years

4.7.4 Gender

The World Health Organization (2007) defines the sex of an individual as the biological and physiological characteristics that define men and women; and gender as the socially constructed roles, behaviours, activities, and attributes that society considers appropriate for men and women. In other words male and female are sex categories and masculine and feminine are gender categories (WHO, 2007). Sex thus refers to an individual's gender classification: male or female (WHO, 2007).

For the purpose of this study gender and sex will be seen as synonyms and will be used to indicate whether a prescription was prescribed for a male or a female.

The information on age and gender was available only for 2006 on the Interpharm® database and was not indicated on all prescriptions. This was indicated as a limitation in section 6.2.

4.8 RELIABILITY AND VALIDITY OF THE RESEARCH INSTRUMENTS

The data were obtained directly from the medicine claims database and there was no direct manipulation of the data done by the researcher. Research was conducted from the viewpoint that all data obtained from the medicine claims database were correct and accurate. Data for analysis were obtained from one medicine claims database, thus limiting external validity, implying that results can only be generalised to the specific database, as well as the specific study population. No specific details such as patients, medical practice, pharmacy or medical scheme could be identified; thus confidentiality of information was maintained throughout the study.

4.9 RESULTS AND DISCUSSION

The results and discussion of this study will be documented in chapter five and Appendix C.

4.10 CONCLUSIONS AND RECOMMENDATIONS

The conclusions and recommendations from the literature and empirical investigation will be discussed in chapter six.

4.11 CHAPTER SUMMARY

This chapter focused on research methodology and measuring criteria of this study. In the next chapter the results and discussion of this study will be documented.

CHAPTER 5

RESULTS AND DISCUSSION

5.1 INTRODUCTION

This chapter will focus on the results obtained from a retrospective study done on data of a medicine claims processing company, for the years 2004 to 2006.

Data were analysed based on "usage" and "cost" as depicted in figure 5.1. In addition the data of 2006 were used to evaluate prescribing patterns according to age and gender. These two variables were only added to the data for 2006.

Firstly the prescribing patterns and cost of antidepressants were compared to the total number of medicine items prescribed on the database and the number of central nervous system (CNS) agents prescribed for each study year. Secondly the antidepressants were divided into generic and innovator medicine items which were examined based on prescribing patterns and cost. The antidepressants were further analysed according to pharmacological classes and active ingredients [refer to Appendix C for classification according to the MIMS (Snyman, 2007:15)]. Finally the cost savings with generic substitution for each active ingredient were calculated and discussed, except where there was no generic product or where the generic product was more expensive than the innovator product.

5.1.1 Annotations regarding data analysis/reporting of results

In this section some aspects with regard to the interpretation of results will be discussed.

- This study was conducted for data that ranged from 2004 to 2006. These three years of study were divided into periods of four months each as indicated in table 5.1.

Table 5.1: Study years divided into periods

Year	Jan-Apr	May-Aug	Sept-Dec
2004	P1	P2	P3
2005	P4	P5	P6
2006	P7	P8	P9

- Numerical values were mostly rounded off to two decimal places. It may thus happen in some cases that the percentages do not add up to a hundred (refer to Appendix 6-8c).

- Only effect sizes that were of practical importance ($d \geq 0.8$) (refer to section 4.6.2.4) were indicated in the results.

- Age and gender were indicated on some prescriptions only; therefore the number of prescriptions discussed in the section of age and gender will not add up to the total number of patients, prescriptions and antidepressants prescribed.

Figure 5.1 is an illustration of how data will be analysed.

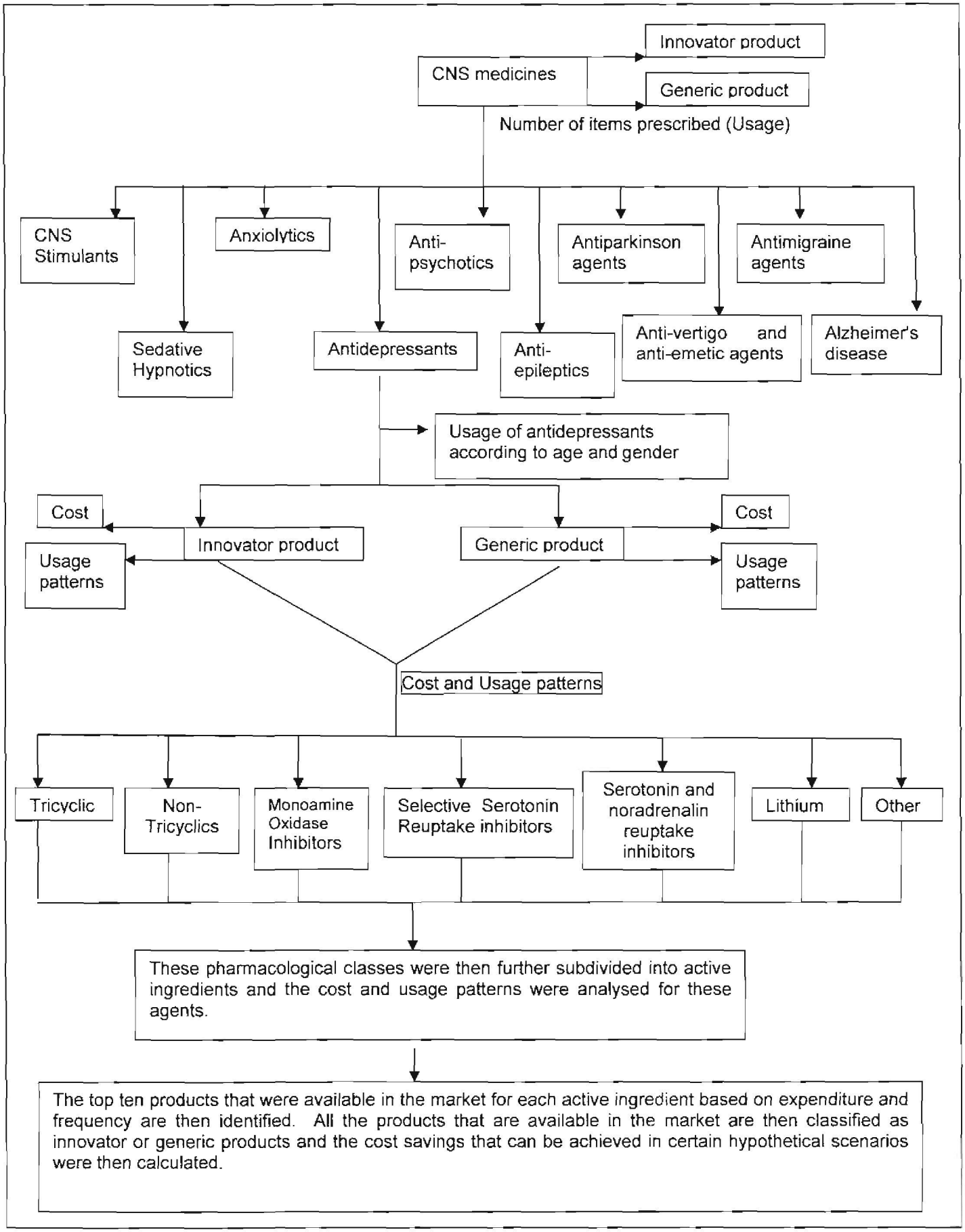


Figure 5.1: Analyses of data

5.1.2 Definitions

Certain terms referred to in this chapter can be defined as follows:

Active ingredient: An active ingredient can be defined as any component of a drug product intended to deliver a pharmacological effect or other direct effect in the diagnosis, cure, alleviation, treatment or prevention of a disease, or to influence the structure or any function of the human or animal body (Food and Drug Administration, 2007). Active ingredients include those components of the medicine that may undergo chemical change during the manufacturing process of the medicine and are present in the medicine products in a modified form intended to give the specified activity or therapeutic effect (Food and Drug Administration, 2007).

The antidepressants' active ingredients for this study were identified as stated in the Monthly Index of Medical Specialities (MIMS) (Snyman, 2007:15) and the South African Medicines Formulary (Gibbon, 2005:437) (refer to section 5.5 and Appendix C, table 11c).

Medicine: The Medicine and Related Substances Control Act (101/1965) defines medicine as any substance or mixture of substances to be suitable for the use in:

- Diagnosis, treatment, mitigation, modification or prevention of a disease, or abnormal physical or mental state, or the symptoms thereof in man, or
- Restoring, correcting, or modifying any somatic, physic, or organic function in man, and includes veterinary medicine (South Africa, 1997).

For the purpose of this study the terms medicine, drugs and medicine items will be used as synonyms.

Innovator items: Innovator items are medicine items that are assigned a patent on their chemical formulation or manufacturing process, undergo extensive testing before they are approved, and are then sold under a brand name e.g. Prothiaden (Cook, 1998:2).

Generic items: A generic medicine contains the same active ingredient as an innovator medicine. Any company can develop such a medicine the moment the innovator is no longer protected by a patent. All the generic items must, however, comply with the same quality and safety requirements demanded of the innovator product (The Association of the British Pharmaceutical Industry, 1999). According to Pillay generic medicine refers to medicines that are registered in South Africa but has never been protected by patent legislation. These medicines are usually manufactured by other companies than the company that originally held the patent (Pillay, 2006).

In South Africa both innovator and generic medicines are approved and registered by the Medicine Control Council (MCC) (South Africa, 2007).

5.1.3 Acronyms pertaining to this analysis

CNS: Central nervous system

MAO: Monoamine oxidase

MCC: Medicine Control Council

SSRI: Selective serotonin reuptake inhibitors

SNRI: Serotonin and noradrenalin reuptake inhibitors

TCA: Tricyclic antidepressants

CPI: Cost-Prevalence Index

SD: Standard deviation

5.2 GENERAL MEDICINE PRESCRIBING PATTERNS AND COSTS OF THE STUDY POPULATION

5.2.1 General prescribing patterns of antidepressants

The prevalence of antidepressants was compared to the total number of medicine items claimed through the database and to the total number of central nervous system medicines to establish the impact that antidepressants have on the total medicine costs.

The **average number of general medicine items per prescription** did not change from 2004 to 2006 (refer to table 5.2). The total number of medicine items prescribed decreased from 5 305 846 in 2004 to 3 606 992 in 2005 and in 2006 there was a further decrease of 34.28% to 2 370 572 items prescribed. This decrease in the prevalence of medicine items may be attributable to the 56% decrease in the number of medical aids administrated by the medical claims processing company from 2004 to 2006. The number of medical aids registered on the PBM was 80 in 2004, it decreased to 68 in 2005 and a further decrease to 35 medical aids was observed in 2006.

CNS medicines accounted for 8.6% of the total number of medicines (n = 5 305 846) prescribed in 2004. In 2005 the number of CNS medicine items declined to 7.4% of all medicine items

prescribed (n = 3 606 992) in 2005, and in 2006 6.45% of all medicine items (n = 2 370 572) that were prescribed were CNS medicines.

In 2004, 2005 and 2006 **antidepressant prescriptions** accounted for 5.66% (n = 2 595 242) in 2004, 5.05% (n = 1 621 739) in 2005 and 4.51% (n = 996 787) in 2006 respectively of all prescriptions claimed. In 2004 antidepressants were ranked seventh compared to other pharmacological classes on the database according to the total number of items prescribed (refer to Appendix C; table 1c). During 2005 and 2006 the percentage prevalence of antidepressants prescribed decreased and antidepressants presented as the eleventh most often prescribed pharmacological class on the database.

During 2004 **antidepressants** accounted for 2.97% (n = 5 305 846) of all medicine items prescribed. Antidepressants represented 2.40% (n = 3 606 992) of all items prescribed in 2005 and 2.01% (n = 2 370 572) in 2006. However, 34.72% (n = 454 551) in 2004, 32.50% (n = 266 228) in 2005 and 31.25% (n = 152 787) in 2006 of all CNS medicines provided were antidepressants. It appears that the usage of antidepressants varied just above 2% - and just below 3% of all medicines prescribed during the study period.

Table 5.2: The prevalence and cost of antidepressants in comparison with the total number of medicines prescribed

		Total number of prescriptions	Total number of items prescribed (%)*	Average number of items per prescription ± SD	Total cost of items prescribed (R) (%)**	Average cost per item ± SD (R)	Average Cost per prescription (R)	CPI***
Total Data Base	2004	2 595 242	5 305 846	2.04 ± 1.27	661 221 000	124.62 ±228.55	254.78 ±397.84	-
	2005	1 621 736	3 606 992	2.22 ± 1.37	405 829 097	112.51 ±226.99	250.24 ±403.60	-
	2006	996 787	2 370 572	2.38 ± 1.44	279 160 832	117.76 ±237.81	280.06 ±434.37	-
Total CNS Agents	2004	374 430 (14.43)	454 551 (8.57)*	1.21 ± 0.53	74 336 775.60 (11.24)**	163.54 ±197.91	198.53 ±275.39	1.31
	2005	220 740 (13.61)	266 228 (7.38)*	1.21± 0.52	38 417 865.76 (9.47) **	144.30 ±192.12	174.04 ±259.62	1.28
	2006	127 624 (12.80)	152 787 (6.45)*	1.20 ± 0.51	23 591 353.48 (8.45) **	154.41 ±224.46	184.85 ±299.22	1.31
Total Anti-depressants	2004	146 905 (5.66)	157 810 (2.97)*	1.07 ± 0.28	32 323 356.77 (4.89) **	204.82 ±186.14	220.03 ±213.34	1.65
	2005	81 830 (5.05)	86 521 (2.40)*	1.06 ± 0.24	15 245 709.85 (3.76) **	176.21 ±178.81	186.31 ±198.33	1.57
	2006	44 938 (4.51)	47 740 (2.01)	1.06 ± 0.25	8 614 631.29 (3.09) **	180.45 ±204.20	191.70 ±229.21	1.54

****CPI= Cost Prevalence Index*

**% Prevalence = Number of CNS or Antidepressant prescriptions divided by the total number of medicine prescriptions for the year multiplied by a hundred. (n2004 = 2 595 242, n2005 = 1 621 736, n2006 = 996 787)*

**% Prevalence = Number of CNS agents or Antidepressant items divided by the total number of medicine items prescribed for the year multiplied by a hundred. (n2004 = 5 305 846, n2005 = 3606 992, n2006 = 2 370 572)*

***% Cost = Cost of CNS agents or antidepressants divided by the total cost of all medicine items prescribed for the year multiplied by a hundred. (n2004 = R 661 221 000.00; n2005 = R 405 829 097.00, n2006 = R 279 160 832.00).*

The external environment in which people live may lead to depression (refer to section 2.3.2), but the way in which this had an influence on the variance of consumption of antidepressants was not investigated in this study.

The **total medicine expenditure** as claimed through this medicines claims database for 2004 was R 661 221 000.00. The **total cost of CNS medicines** was R 74 336 775.60; accounting for 11.24% of the total cost of all medicine items claimed during 2004. **Antidepressants** represented 4.89% (n = R 661 221 000.00) of the total medicine expenditure for 2004. In 2005 **antidepressants** represented 3.76 % (n = R 405 829 097.00) of the total medicine costs and 39.68% of the CNS medicines (n = R 38 417 865.76) (refer to table 5.2).

In 2006 the **total medicine expenses** on the database was R 279 160 832.00. The **CNS medicines** accounted for 8.45% (n = R 279 160 832.00) of these expenses with an amount of R 23 591 353.48. **Antidepressants** represented 3.09% (n = R 279 160 832.00) of the total medicine expenditure and 36.52% (n = R 23 591 353.48) of the CNS medicines prescribed in 2006 (refer to table 5.2).

The **average cost for all medicines** claimed through the database decreased with 9.7% from R 124.62 ± R 228.55 per medicine item during 2004 to R 112.51 ± R 226.99 per item during 2005 and increased slightly during 2006 with 4.67% to R 117.76 ± R 237.81 per items. The average cost of all medicine items was, however, still lower in 2006 than in 2004. The **average cost for an antidepressant medicine item** also decreased from R 204.82 ± R 186.14 in 2004 per item to be R 180.45 ± R 204.20 during 2006 (refer to table 5.2).

The transparent pricing system as stated in the Medicine and Related Substances Control Amendment Act of 1997 (section 22G) was implemented the 2nd of May 2004 (Tshabalala-Msimang, 2004). This pricing system led to various court cases and has not yet been finalised in 2007. The decrease in total medicine prices from 2004 to 2005 may be mainly attributed to the implementation of the new pricing system. The decrease in the total medicine expenditure may also be linked to the 56% decrease in medical aids administrated by the PBM. In table 5.2 the **cost-prevalence index** (CPI) for CNS agents as well as antidepressants was calculated for

each year and this indicates that the cost of CNS agents and antidepressants was both relatively expensive compared to the total medicine expenditure seeing that in all the cases the cost-prevalence index was higher than 1.

In 2004 the **total cost for antidepressants** on the database was R 32 199 165.09. This made depression the third most costly condition during 2004. In 2005 the total cost was R 15 178 669.05 and the cost of depression was ranked sixth among all pharmacological classes on the database (refer to Appendix C; table 1c). In 2006 antidepressants were ranked seventh according to total medicine expenditure (refer to Appendix C; table 1c). Taken into consideration that the cost of depression is likely to be associated with hidden cost e.g. productivity losses caused by absenteeism and sub-optimal job performance (refer to section 3.1), the total cost of depression may be substantially more than merely the treatment costs.

5.2.2 The utilisation of innovator medicine items compared to generic medicine items

In table 5.3 the utilisation patterns of innovator and generic medicine items were compared for the total study population, the central nervous system and antidepressant medicines.

Table 5.3: A comparison between the utilisation of innovator and generic medicine items

		2004		2005		2006	
		Innovator	Generic	Innovator	Generic	Innovator	Generic
Prevalence	Total Database (%*)	66.44	33.56	64.61	35.39	59.73	40.27
	CNS Agents (%#)	49.69	50.31	50.40	49.60	47.11	52.89
	Antidepressants (%@)	41.33	58.67	43.51	56.49	36.91	63.30
Total Cost (R)	Total Database (%*)	549 255 136.00 (83.07)	111 965 864.00 (16.93)	333 863 321.00 (82.27)	71 965 775.97 (17.73)	215 288 806.00 (77.12)	63 872 025.91 (22.88)
	CNS Agents (%#)	56 026 888.99 (75.37)	18 309 886.61 (24.63)	30 756 059.60 (80.06)	7 661 806.16 (19.94)	18 545 168.45 (78.61)	5 046 185.03 (21.39)
	Antidepressants (%@)	22 133 754.53 (68.48)	10 189 602.24 (31.53)	11 851 458.86 (77.74)	3 394 250.99 (22.26)	6 364 168.22 (73.88)	2 250 463.07 (26.12)
Average Cost ± SD (R)	Total Database	155.80 ±270.06	62.88 ±74.29	143.27 ±272.21	56.37 ±73.74	152.04 ±294.67	66.91 ±85.48
	CNS Agents	248.04 ±237.67	80.07 ±89.66	229.22 ±230.26	58.02 ±75.97	257.67 ±280.77	62.44 ±84.22
	Antidepressants	339.32 ±204.17	110.06 ±89.23	312.04 ±187.96	69.96 ±60.14	363.25 ±226.61	74.47 ±74.11
Effect Size	Total Database	0.34		0.32		0.29	
	CNS Agents	0.71		0.74		0.70	
	Antidepressants	1.12		1.29		1.27	
CPI	Total Database	1.25	0.50	1.27	0.50	1.29	0.57
	CNS Agents	1.52	0.49	1.59	0.40	1.67	0.40
	Antidepressants	1.66	0.54	1.79	0.39	2.00	0.41

Prevalence % = The number of generic or innovator items prescribed divided by the total number of medicine items prescribed for the study period multiplied by 100. (n2004 = 5 305 846; n2005 = 3 606 992; n2006 = 2 370 572).*

Prevalence %# = The number of generic or innovator CNS agents prescribed divided by the total number of medicine items prescribed for the study period multiplied by 100. (n2004 = 454 551; 2005 = 266 228; n2006 = 152 787.00).

Prevalence %@=The number of generic or innovator antidepressants prescribed divided by the total number of antidepressants prescribed for the study period multiplied by 100. (n2004 = 157 810; 2005 = 86 521; n2006 = 47 470).

Cost %= The cost of generic or innovator items prescribed divided by the total cost of medicine items prescribed for the study period multiplied by 100. (n2004 = R 661 221 000.00; n2005 = R 405 829 097.00; n2006 = R 279 160 832.00).*

Cost %#= The cost of generic or innovator CNS agents prescribed divided by the total cost of medicine items prescribed for the study period multiplied by 100. (n2004 = R 74 336 775.60; n2005 = R 38 417 865.76; n2006 = R 23 591 353.48).

Cost %@=The cost of generic or innovator antidepressants prescribed divided by the total cost of all antidepressants prescribed for the study period multiplied by 100. (n2004 = R 32 323 356.77; n2005 = R 15 245 709.85; n2006 = R 8 614 631.29).

Table 5.3 revealed the following:

- The **total percentage of innovator items** on the database declined by 6.7% between 2004 and 2006, and a **total cost percentage** decrease of 5.95% was observed (refer to table 5.3).

- **CNS innovator** medicine items remained relatively stable during the study period with a relatively steady decrease of 2.58% from January 2004 to December 2006. This decrease in innovator items can be directly linked to the 2.58% increase in **generic CNS agents**. However, a decrease of 3.24% was documented in the **total cost percentage** of CNS generic items from 2004 to 2006 (refer to table 5.3).

- The prevalence of **antidepressant generic items** increased by 4.63% from 2004 to 2006, while the **total cost percentage** of **innovator antidepressants** increased with 5.4% during the study period. This is an indication that innovator items still have a substantial impact on the mental health care costs (refer to table 5.3).

The **effect size (*d*-value)** for the difference between the average cost of the innovator and generic items was calculated for the total database, CNS agents and antidepressants for each study year. The antidepressants were the only group where the effects size for each year was

higher than 0.8 which indicated that the innovator products were practical significantly more expensive than the generic products (refer to table 5.3).

The **cost-prevalence index** (CPI) for innovator items was fairly expensive compared to generic medicine for each study year because the value of the CPI is larger than 1. The CPIs for these groups are all depicted in table 5.3.

5.3 ANALYSIS OF ANTIDEPRESSANT MEDICINE

5.3.1 General prescribing patterns and cost for antidepressants

In table 5.4 the general prescribing patterns for antidepressants are described for each study period. This description includes the number of items prescribed, the average number of antidepressants per prescription, total cost, the average cost per antidepressant prescription and average cost per antidepressant on the database.

Table 5.4: The contribution of antidepressants towards the total database

Study period	Prevalence (items) (%)	Prescriptions (%)
P1	3.20	5.72
P2	2.73	5.31
P3	3.06	5.95
P4	2.44	5.02
P5	2.25	4.84
P6	2.54	5.34
P7	2.02	4.49
P8	1.95	4.40
P9	2.08	4.64

Prevalence % = Number of antidepressant items for the specific study period divided by the total number of items claimed during the study period multiplied by a hundred (n1 = 1 363 571; n2 = 1 953 833; n3 = 1 988 442; n4 = 1 124 635; n5 = 1 384 135; n6 = 1 098 222; n7 = 778 669; n8 = 834 501; n9 = 757 402).

Prescriptions % = Number of antidepressant prescriptions for the specific study period divided by the total number of prescriptions claimed during the study period multiplied by a hundred (n1 = 713 470; n2 = 935 640; n3 = 946 132; n4 = 517 926; n5 = 609 044; n6 = 494 766; n7 = 329 487; n8 = 348 210; n9 = 319 090).

In table 5.4 it is depicted that the usage of antidepressants varied between 5.31% and 5.95% of the total number of prescriptions claimed during each study period for 2004. In 2005 the usage of antidepressants varied between 4.84% and 5.34% of the total number of prescriptions claimed through the medicine claims processing company, therefore, only slightly lower than 2005. The usage of antidepressants in 2006 was between 4.40% and 4.64% of the total number of prescriptions claimed. This indicated that the usage of antidepressants remained relatively constant for 2004 to 2006.

The increase in the number of antidepressant items that was observed in certain study periods as depicted in table 5.5 may be attributable to an increase in the number of patients. The composition and change of medical schemes, members and dependants, as illustrated on the database(s) for the study periods, are factors that are only noted for possible influence on the medicine usage. In other words the "business side" and "risk management" fall outside the scope of this study, as this is from the viewpoint of this study uncontrollable.

Table 5.5: General breakdown of prescribing patterns for antidepressants

Time	Number of items prescribed	Average number of items per prescription	Total cost (R)	Average cost per prescription ± SD (R)	Average cost per item ± SD (R)
P1	43 606	1.07±0.27	10 723 459.88	262.77±236.28	245.92±206.77
P2	53 340	1.07±0.27	11 316 617.00	227.37±222.67	212.16±193.67
P3	60 864	1.08±0.29	10 283 279.89	182.58±177.98	168.96±154.24
Total 2004	**157 810**	**1.07±0.28**	**32 323 356.77**	**220.03±213.34**	**204.82±186.14**
P4	27 402	1.05±0.24	4 896 978.31	188.52±195.34	178.71 ±176.59
P5	31 133	1.05±0.24	5 528 497.21	187.71±198.07	177.58±179.13
P6	27 986	1.06±0.25	4 820 234.33	182.58±201.65	172.24±180.57
Total 2005	**86 521**	**1.06±0.24**	**15 245 709.85**	**186.84±198.83**	**176.21±178.81**
P7	15 749	1.06±0.25	2 896 081.01	195.55±238.75	183.89±212.02
P8	16 243	1.06±0.25	2 885 045.97	188.41±218.96	177.62±197.36
P9	15 748	1.06±0.26	2 833 504.31	191.26±229.80	179.93±203.12
Total 2006	**47 740**	**1.06±0.25**	**8 614 631.29**	**191.70±229.21**	**180.45±204.20**

The number of antidepressant medicine items was slightly higher for the period September to December 2004 with 38.57% (n = 157 810) of the total number of antidepressants prescribed compared to the other periods (P2 = 33.8% and P1 = 27.6% respectively). Table 5.5 shows that the **total cost** of these items increased from the first time-period (January-April 2004) to the second period (May-August 2004), where after a decline in total cost was observed during the last period of 2004, to value below that of the initial first period (a total reduction of 4.2%). This trend can be explained by the decrease in the average cost of antidepressants from January to December 2004 (P1-P3) (refer to table 5.5). This decrease was mainly due to the implementation of the transparent pricing system in May 2004 (Tshabalala-Msimang, 2004).

***d*-Values** calculated for the differences in average number of antidepressants per prescription however indicated no practical significance seeing that the average number of antidepressants per prescription for the different years was approximately the same for the different years.

In **2005** the study period of May to August had the highest number of antidepressants. The total number of antidepressants prescribed for May to August 2005 was 35.98% (n = 86 521), of **the total number of antidepressants prescribed** for the year, this is only slightly higher than the other two periods. The usage of antidepressants for 2005 was mostly constant unlike in 2004 where the usage for September to December was substantially higher. The total number of antidepressants prescribed in 2005 was lower than in 2004, this may be attributable to the fact that the number of medical aids administrated by the medicine claims processing company decreased from 2004 to 2005 (refer to section 5.2). There was an increase of 12.90% in the total cost between study periods four and five and an overall reduction of 1.57% in the **total cost of antidepressants** from January 2005 to December 2005 (refer to table 5.5). The **average cost of antidepressants** decreased with R 5.94 ± R 6.31 between January 2005 and December 2005 but as indicated in table 5.6, this decrease in the average cost for the three study periods in 2005 was of no practical significance.

In **2006** the **prevalence** of antidepressants again peaked during May to August as was the case in 2005. This may be attributed to seasonal depression because these are the winter months in South Africa where the daylight times are shorter - causing seasonal depression (refer to section 2.4.2) (Gelder *et al.*, 1999:130). Although there was an increase in the prevalence of antidepressants between study periods seven (P7) and eight (P8), the **total cost** decreased continuously from period seven (P7) through to period nine (P9). The reduction in the **total cost** from January 2006 to December 2006 was 2.16%. However, the ***d*-values** calculated in table 5.6 indicated that the differences in the average cost per antidepressant between P7 and P9 was of no practically significance.

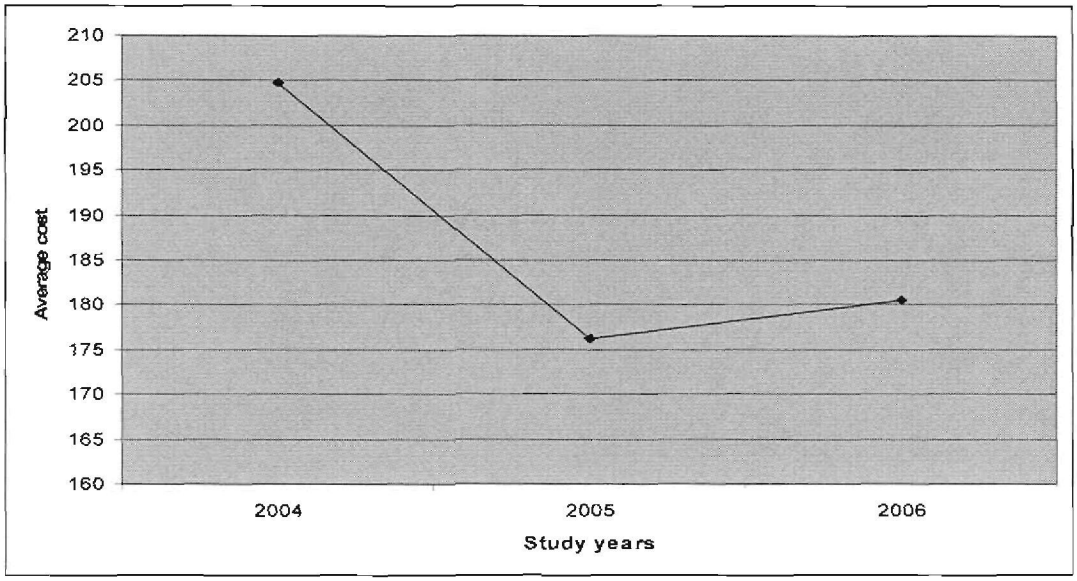


Figure 5.2: Average cost of antidepressants

It can be assumed from the data in table 5.5 that there was an average of just more than one antidepressant item on a prescription (average number of items per prescription = 1.1). Seeing that there is usually only one item per prescription there is only a slight difference between the cost per prescriptions and the cost per items. The **average cost per prescription** for 2004 was R 220.03 ± R 213.34. The **average cost per item** was R 204.82 ± R 186.89. Figure 5.2 points out the marked reduction in the average cost of antidepressant medicine in 2005 and 2006 compared to that of 2004 (a reduction of 11.90%). The average cost for an antidepressant item in 2004 was R 204.82 ± R 186.14 compared to R 176.21 ± R 178.81 in 2005 and R 180.45 ± R 204.20 in 2006. On average items were 14% cheaper in 2005 and 2006 compared to 2004. In table 5.7 the difference in the average cost of period P1 and each of the other study periods (P2 to P9) is reflected. There was an average cost decrease of 27.97 ± 1.9% between P1 and each of the other study periods (P2-P9) from 2004 to 2006 (refer to table 5.7). This may be an effect of the implementation and the debate around the single exit pricing system as noted earlier in this chapter (refer to section 3.6).

Table 5.6: Effect-size (*d*-values) for the differences in average cost per item

Period	Average Cost ± SD (R)	Effect-size (*d*-value)	Period	Average Cost ± SD (R)	Effect-size (*d*-value)
P1 and P2	P1 = 245.92±206.77	0.2	P3 and P9	P3 = 168.96±154.24	0.05
	P2 = 212.16±193.67			P9 = 179.93±203.12	
P1 and P3	P1 = 245.92±206.77	0.4	P4 and P5	P4 = 178.71±176.59	0.006
	P3 = 168.96±154.24			P5 = 177.58±179.13	
P1 and P4	P1 = 245.92±206.77	0.3	P4 and P6	P4 = 178.71±176.59	0.04
	P4 = 178.71±176.59			P6 = 172.24±180.57	
P1 and P5	P1 = 245.92±206.77	0.3	P4 and P7	P4 = 178.71±176.59	0.02
	P5 = 177.58±179.13			P7 = 183.89±212.02	
P1 and P6	P1 = 245.92±206.77	0.4	P4 and P8	P4 = 178.71±176.59	0.006
	P6 = 172.24±180.57			P8 = 177.62±197.36	
P1 and P7	P1 = 245.92±206.77	0.3	P4 and P9	P4 = 178.71±176.59	0.006
	P7 = 183.89±212.02			P9 = 179.93±203.12	
P1 and P8	P1 = 245.92±206.77	0.3	P5 and P6	P5 = 177.58±179.13	0.03
	P8 = 177.62±197.36			P6 = 172.24±180.57	
P1 and P9	P1 = 245.92±206.77	0.3	P5 and P7	P5 = 177.58±179.13	0.03
	P9 = 179.93±203.12			P7 = 183.89±212.02	
P2 and P3	P2 = 212.16±193.67	0.2	P5 and P8	P5 = 177.58±179.13	0.0002
	P3 = 168.96±154.24			P8 = 177.62±197.36	
P2 and P4	P2 = 212.16±193.67	0.2	P5 and P9	P5 = 177.58±179.13	0.01
	P4 = 178.71±176.59			P9 = 179.93±203.12	
P2 and P5	P2 = 212.16±193.67	0.2	P6 and P7	P6 = 172.24±180.57	0.05
	P5 = 177.58±179.13			P7 = 183.89±212.02	

Table 5.6: Effect-size (*d*-values) for the differences in average cost per item (continue)

Period	Average Cost ± SD (R)	Effect-size (*d*-value)	Period	Average Cost ± SD (R)	Effect-size (*d*-value)
P2 and P6	P2 = 212.16±193.67	0.2	P6 and P8	P6 = 172.24±180.57	0.03
	P6 = 172.24±180.57			P8 = 177.62±197.36	
P2 and P7	P2 = 212.16±193.67	0.1	P6 and P9	P6 = 172.24±180.57	0.04
	P7 = 183.89±212.02			P9 = 179.93±203.12	
P2 and P8	P2 = 212.16±193.67	0.2	P7 and P8	P7 = 183.89±212.02	0.03
	P8 = 177.62±197.36			P8 = 177.62±197.36	
P2 and P9	P2 = 212.16±193.67	0.2	P7 and P9	P7 = 183.89±212.02	0.02
	P9 = 179.93±203.12			P9 = 179.93±203.12	
P3 and P4	P3 = 168.96±154.24	0.1	P8 and P9	P8 = 177.62±197.36	0.01
	P4 = 178.71±176.59			P9 = 179.93±203.12	
P3 and P5	P3 = 168.96±154.24	0.05	-	-	-
	P5 = 177.58±179.13			-	
P3 and P6	P3 = 168.96±154.24	0.02	-	-	-
	P6 = 172.24±180.57			-	
P3 and P7	P3 = 168.96±154.24	0.07	-	-	-
	P7 = 183.89±212.02			-	
P3 and P8	P3 = 168.96±154.24	0.04	-	-	-
	P8 = 177.62±197.36			-	

Table 5.7: Percentage difference in average cost per item

Period	Average Cost ± SD (R)	Per centage difference (%)
P1 and P2	P1 = 245.92±206.77	13.73
	P2 = 212.16±193.67	
P1 and P3	P1 = 245.92±206.77	31.31
	P3 = 168.96±154.24	
P1 and P4	P1 = 245.92±206.77	27.33
	P4 = 178.71±176.59	
P1 and P5	P1 = 245.92±206.77	27.79
	P5 = 177.58±179.13	
P1 and P6	P1 = 245.92±206.77	29.96
	P6 = 172.24±180.57	
P1 and P7	P1 = 245.92±206.77	25.22
	P7 = 183.89±212.02	
P1 and P8	P1 = 245.92±206.77	27.77
	P8 = 177.62±197.36	
P1 and P9	P1 = 245.92±206.77	26.83
	P9 = 179.93±203.12	

5.3.2 Innovator *vs.* generic antidepressants

Table 5.8 shows the breakdown of the prevalence and medicine cost for generic and innovator antidepressants for each study period.

Table 5.8: The prescribing patterns and cost of innovator and generic antidepressant items

Period	Generic or innovator	Prevalence (%)*	Total Cost (R) (%)**	Average Cost ± SD (R)	CPI	Effect-size (*d*-value)
P1	Innovator	17 702 (40.60) *	6 940 351.89 (64.72)**	392.07 ±234.04	1.59	1.05
	Generic	25 904 (59.40) *	3 783 107.99 (35.28) **	146.04 ±99.84	0.59	
P2	Innovator	21 961 (41.17) *	7 779 946.09 (68.75) **	354.26 ±212.76	1.67	1.14
	Generic	31 379 (58.83) *	3 536 670.91 (31.25) **	112.71 ±89.73	0.53	
P3	Innovator	25 566 (42.01) *	7 413 456.55 (72.09) **	289.97 ±158.10	1.71	1.32
	Generic	35 298 (57.99) *	2 869 823.34 (27.91) **	81.30 ±68.03	0.48	
Total 2004	Innovator	**65 229 (41.33) ***	**22 133 754.53 (68.48) ** **	**339.32 ±204.17**	**1.66**	**1.12**
	Generic	**92 581 (58.67) ***	**10 189 602.24 (31.52) ** **	**110.06 ±89.23**	**0.54**	
P4	Innovator	12 332 (45.00) *	3 776 217.89 (77.11) **	306.21 ±185.92	1.71	1.25
	Generic	15 070 (55.00) *	1 120 760.42 (22.89) **	74.37 ±64.95	0.41	
P5	Innovator	14 144 (45.43) *	4 398 580.36 (79.56) **	310.99 ±184.69	1.75	1.32
	Generic	16 989 (54.57) *	1 129 916.85 (20.44) **	66.51 ±57.01	0.37	
P6	Innovator	11 505 (41.11) *	3 676 660.61 (76.27) **	319.61 ±193.79	1.86	1.29
	Generic	16 481 (58.89) *	1 143 573.72 (76.27) **	69.39 ±58.43	0.40	
Total 2005	Innovator	**37 981 (43.90) ***	**11 851 458.86 (77.74) ** **	**312.04 ±187.96**	**1.77**	**1.29**
	Generic	**48 540 (56.10) ***	**3 394 250.99 (22.26) ** **	**69.93 ±60.14**	**0.40**	
P7	Innovator	6 025 (38.26) *	2 202 338.67 (76.05) **	365.53 ±238.24	1.99	1.23
	Generic	9 724 (61.74) *	693 742.34 (23.95) **	71.34 ±67.32	0.39	
P8	Innovator	5 939 (36.56) *	2 123 802.90 (73.61) **	357.60 ±215.31	2.01	1.32
	Generic	10 304 (63.44) *	761 243.07 (26.39) **	73.88 ±72.43	0.42	
P9	Innovator	5 556 (35.28) *	2 038 026.65 (71.93) **	366.82 ±225.38	2.04	1.28
	Generic	10 192 (64.72) *	795 477.66 (28.07) **	78.05 ±81.48	0.43	
Total 2006	Innovator	**17 520 (36.70) ***	**6 364 168.22 (73.88) ** **	**363.25 ±226.61**	**2.01**	**1.27**
	Generic	**30 220 (63.30) ***	**2 250 463.07 (26.12) ** **	**74.47 ±74.11**	**0.41**	

**Prevalence % = Number of generic or innovator items for the specific study period divided by the total number of antidepressants claimed during the study period multiplied by a hundred (n1 = 43 606; n2 = 53 340; n3 = 60 864; n2004 = 157 810; n4 = 27 402; n5 = 31 133; n6 = 27 986; n2005 = 86 521; n7 = 15 749; n8 = 16 243; n9 = 15 748; n2006 = 47 740).*

***Total Cost % = Cost of generic or innovator items for the specific study period divided by the total cost of all antidepressants for that study period multiplied by a hundred (n1 = R 10 723 459.88; n2 = R 11 316 617.00; n3 = R 10 283 279.89; n2004 = R 32 323 356.77; n4 = R 4 896 978.31; n5 = R 5 528 497.21, n6*

= R 4 820 234.33; n2005 = R 15 245 709.85; n7 = R 2 896 081.01; n8 = R 2 885 045.97; n9 = R 2 833 504.31; n2006 = R 8 614 631.29).

Table 5.8 illustrates that generic antidepressants were consistently more prevalent than innovator antidepressants during the three study years.

Generic items constituted 58.99% (n = 157 810) of **all antidepressants** claimed during 2004, 56.49% (n = 86 521), during 2005 and 63.30% (n = 47 740) during 2006. The slight decrease in the number of generic items in 2005 compared to 2004, is explained by the increase in the number of innovator items in 2005. A possible reason for this may be that the prescriber and/or patients preferred the innovator product, such as Cipramil® instead of Cilift®, or Prothiaden® instead of Thaden®.

Table 5.8 also shows that there was a continuous decrease in the **average price** for innovator- and generic antidepressants over the three study periods in 2004. In 2005 the average cost per item of **generic medicine** items continued to decrease until the second period of 2005 (May to August). In contrast, the prices of **innovator medicines** started to increase steadily over the three study periods of 2005, to reach an average of R 319.61 + R 193.79 during the months September to December 2005. However, the **average cost for innovator medicine items** in 2005 was still less than the cost for these items in 2004, e.g. R 339.32 + R 204.17 (2004) *vs.* R 312.04 + R 187.96 in 2005 (a reduction of R 27.28 ± R 16.21 or 8.04%). The average cost of the innovator antidepressants increased further in 2006 to reach R 366.82 ± R 225.38 in September to December 2006 which was still 6.4% lower than the average cost in the first period of 2004.

The average cost for **generic antidepressants** in 2005 was also lower than that of generic items in 2004, with a reduction of 36.46%. The ***d*-value** calculated for this difference in average cost between these periods for generic antidepressants rendered a value of 0.45 (~0.5), which can be regarded as a "medium effect which may be significant" according to Steyn (1999:3). This decrease in average cost can be attributable to the fact that a number of new generic antidepressants entered the market in 2005 as can be seen in Appendix C, table 11c, causing an increase in competition between generic and innovator companies. There was an increase of 6.5% in the average cost for generic antidepressants in 2006 from 2005, but the **average cost for generic antidepressants** was still lower for 2006 than in 2004.

The **cost-prevalence index (CPI)** was calculated for every study period and in each case the CPI for the innovator antidepressants was higher than 1 which indicates that the innovator antidepressants were quite expensive compared to generic items. This corresponds with the

effect size (*d*-value) which was calculated between the average cost of the innovator and the generic antidepressants for each study period. In each study period the effect size was larger than 0.8, an indication that the innovator antidepressants were practically significantly more expensive than the generic antidepressants (refer to table 5.8).

In section 5.7 the possible cost savings that could be brought on by generic substitution of antidepressants will be calculated for each active ingredient according to strength.

5.3.3 The usage of antidepressants according to age and gender

In this section the prevalence of antidepressant usage in different age groups and gender groups will be discussed. The demographic information of age and gender was available only for 2006 data. Gender was divided into male (M) and female (F). The age of patients was divided into the following categories:

- 0≤9 – Between 0 and 9 years, including 0 and 9.
- >9 and ≤19 – Age larger than 9 and age 19 (including 19).
- >19 and ≤44 – Age larger than 19 and age 44 (including 44).
- >44 and ≤59 – Age larger than 44 and age 59 (including 59).
- >59 – Age larger than 59 (excluding 59).

In 2006 a total of 44 938 antidepressant prescriptions were claimed through the medicine claims processing company database (refer to table 5.2). The age of the patient was indicated on 44 915 prescriptions (99.95% of all antidepressant prescriptions in 2006) and the gender of the patient was indicated on 27 004 prescriptions (60.09% of all antidepressant prescriptions in 2006) (refer to table 5.9).

In table 5.9 the prevalence, average number of antidepressants per prescription, total cost and average cost per prescription are depicted for all age groups and the two gender categories for all age groups.

Table 5.9: The prescribing patterns and cost of antidepressants according to age and gender

Age and gender	Number of antidepressant prescriptions (%)*	Average number of antidepressants per prescription	Average cost per antidepressant prescription (R)	Total cost of antidepressant prescriptions (R) (%)**	CPI
0≤9 (years)	426 (0.95)	1.04±0.20	88.78±115.91	37 822.33 (0.44)	0.46
Female	96 (0.21)	1.00±0	57.45±46.43	5 515.38 (0.06)	0.30
Male	104 (0.23)	1.11±0.31	106.05±134.44	11 028.81 (0.13)	0.55
>9 and ≤19 (years)	1 762 (3.92)	1.05±0.25	141.22±164.55	248 832.65 (2.89)	0.74
Female	528 (1.18)	1.05±0.21	165.89±164.28	87 592 (1.02)	0.87
Male	446 (0.99)	1.06±0.31	130.06±141.02	58 005.67 (0.67)	0.68
>19 and ≤44 (years)	19 189 (42.72)	1.05±0.24	188.51±227.85	3 617 250.61 (42.01)	0.98
Female	8 141 (18.13)	1.06±0.25	196.93±236.19	1 603 250.77 (18.62)	1.03
Male	3 046 (6.78)	1.07±0.28	199.28±233.42	606 994.61 (7.05)	1.04
>44 and ≤59 (years)	15 747 (35.06)	1.07±0.27	205.25±245.58	3 232 108.98 (37.54)	1.07
Female	6 719 (14.96)	1.07±0.26	191.88±231.74	1 289 219.85 (14.97)	1.00
Male	2 842 (6.33)	1.05±0.23	219.74±240.94	624 507.68 (7.25)	1.15
>59 (years)	7 791 (17.35)	1.07±0.27	189.28±211.71	1 474 581.57 (17.13)	0.99
Female	3 496 (7.78)	1.08±0.28	189.38±206.94	662 072.04 (7.69)	0.99
Male	1 586 (3.53)	1.05±0.23	192.43±209.03	305 191.01 (3.54)	1.00
Total age (years)	44 915 (100)	-	-	8 610 596.14 (100)	1.00
Total female	18 980.00 (42.26)	-	-	3 647 650.04 (42.36)	1.00
Total male	8 024.00 (17.86)	-	-	1 605 727.78 (18.65)	1.04

**% of antidepressant prescriptions prescribed per age group = The number of prescriptions divided by the total number of prescriptions of all age groups multiplied by a hundred (n = 44 915).*

**% of antidepressant prescriptions prescribed per gender = The number of prescriptions in each age group according to gender divided by the total number of prescriptions of all age groups multiplied by a hundred. Some of the prescriptions in each age group was not classified by gender thus the number of prescriptions for both genders would not add up to get the number of prescriptions in the age group but the percentage of the two gender groups added together and subtracted from 100 indicated what percentage of age group prescriptions did not have gender indicated (n = 44 915).*

***% of total cost per age group = The total cost for each age group divided by the total cost of all age groups multiplied by a hundred (n = R 8 610 596.14).*

***% of total cost per gender = The total cost for each gender in each age group divided by the total cost of all age groups multiplied by a hundred (n = R 8 610 596.14).*

According to Ladikos (2003:4) the peak age of onset of major depressive disorder (MDD) in children is between 15 and 20 years of age (refer to section 2.3.3). Results in table 5.9 revealed that 3.92% of the prescriptions (n = 44 915) (where age was indicated) were for patients in the age group >9 and ≤19; compared to only 0.95% (n=44 915) in the age group 0≤9 years (refer to table 5.9).

Antidepressant prescriptions occurred more often for the age group **older than 19 and younger than 44** years of age with a percentage of 42.72% of all prescriptions (n = 44 915). Depression is not unrelated to the external environment (Eisendrath & Lichtmacher, 2004:1029) (refer to section 2.3.2). This percentage may be attributable to work stress, family stress and other environmental factors. The second highest number of antidepressant prescriptions was for the age group older than 44 and younger than 59 years of age with a percentage of 35.06% (n = 44 915). These two age groups accounted for 77.78% (n = 44 915) of all the antidepressant prescriptions that had age indicated on them.

Women have a higher risk of developing depression than men (Gelder *et al.* 1999:137) (refer to section 2.3.1). Similar results were found in this study (refer to table 5.9) except in the age group 0 to 9 years. The possible reasons for the higher incidence of depression in women may be because of different sociocultural roles or hormonal changes, amongst others (Meys, 1998:322; Piccinelli & Wilkinson, 2000:491)(refer to section 2.3.1).

The prevalence of antidepressant prescriptions is 96 prescriptions (22.54% of all prescriptions in this age group, n = 426) for girls in the age group **0 to 9** years compared to 104 prescriptions (24.41% of all the prescriptions in this age group, n = 426) for boys. Piccinelli and Wilkinson (2000:491) state that psychological attributes related to vulnerability to adverse life events and coping skills are likely to be factors associated with the difference in prevalence of depression between genders. The perspective of "cowboys don't cry" may be a possible reason for this phenomenon seeing that boys cannot express their emotions as freely as girls do and these unresolved feelings may lead to depression and because boys of this age have not developed the necessary coping skills yet.

The **cost-prevalence index (CPI)** for each age group and gender is depicted in table 5.9. In the age group **older than 19 and younger than 44** years of age the CPI for antidepressants for both male and female gender groups was higher than one, in the age group **older than 44 and younger than 59 years** of age the CPI was 1.07. This indicates that in these groups the cost of antidepressants was fairly expensive compared to the total cost of all the prescriptions that have age indicated on them. In all other cases the CPI was either equal to or smaller than 1, which indicates that the antidepressants in these groups were relatively inexpensive.

In table 5.10 the effect sizes for the average number of antidepressants per prescription and the average cost per antidepressant were calculated between each age group and each gender in every age group.

Table 5.10: Effect sizes (*d*-values) of the age and gender groups

Age	Average number of items per prescriptions ± SD	Effect size of average number of items per prescription.	Average cost ± SD (R)	Effect size of average cost
(0≤9) and (>9 and ≤19)	0≤9=1.04±0.20	0.04	0≤9=88.78±115.91	0.32
	>9 and ≤19=1.05±0.25		>9 and ≤19=141.22±164.55	
(0≤9) and (>19 and ≤44)	0≤9=1.04±0.20	0.04	0≤9=88.78±115.91	0.44
	>19 and ≤44=1.05±0.24		>19 and ≤44=188.51±227.85	
(0≤9) and (>44 and ≤59)	0≤9=1.04±0.20	0.1	0≤9=88.78±115.91	0.47
	>44 and ≤59=1.07±0.27		>44 and ≤59=205.25±245.58	
(0≤9) and (>59)	0≤9=1.04±0.20	0.1	0≤9=88.78±115.91	0.47
	>59=1.07±0.27		>59=189.28±211.71	
(>9 and ≤19) and (>19 and ≤44)	>9 and ≤19=1.05±0.25	0	>9 and ≤19=141.22±164.55	0.21
	>19 and ≤44=1.05±0.24		>19 and ≤44=188.51±227.85	
(>9 and ≤19) and (>44 and ≤59	>9 and ≤19=1.05±0.25	0.07	>9 and ≤19=141.22±164.55	0.26
	>44 and ≤59=1.07±0.27		>44 and ≤59=205.25±245.58	
(>9 and ≤19) and (>59)	>9 and ≤19=1.05±0.25	0.07	>9 and ≤19=141.22±164.55	0.23
	>59=1.07±0.27		>59=189.28±211.71	
(>19 and ≤44) and (>44 and ≤59)	>19 and ≤44=1.05±0.24	0.07	>19 and ≤44=188.51±227.85	007
	>44 and ≤59=1.07±0.27		>44 and ≤59=205.25±245.58	
(>19 and ≤44) and (>59)	>19 and ≤44=1.05±0.24	0.07	>19 and ≤44=188.51±227.85	0.003
	>59=1.07±0.27		>59=189.28±211.71	
(>44 and ≤59) and (>59)	>44 and ≤59=1.07±0.27	0	>44 and ≤59=205.25±245.58	0.07
	>59=1.07±0.27		>59=189.28±211.71	
Age and gender	**Average number of items per prescriptions ± SD**	**Effect size of Average number of items per prescription.**	**Average cost ± SD (R)**	**Effect size of Average cost**
0≤9 Female and Male	Female=1.00±0	0.35	Female=57.45±46.43	0.36
	Male=1.11±0.31		Male=106.05±134.44	
>9 and ≤19 Female and Male	Female=1.05±0.21	0.03	Female=165.89±164.28	0.22
	Male=1.06±0.31		Male=130.06±141.02	
>19 and ≤44 Female and Male	Female=1.06±0.25	0.04	Female=196.93±236.19	0.01
	Male=1.07±0.28		Male=199.28±233.42	
>44 and ≤59 Female and Male	Female=1.07±0.26	0.08	Female=191.88±231.74	0.12
	Male=1.05±0.23		Male=219.74±240.94	
>59 Female and Male	Female=1.08±0.28	0.12	Female=189.38±206.94	0.01
	Male=1.05±0.23		Male=192.43±209.03	

None of the ***d*-values** for either the average number of antidepressants per prescription or average cost per antidepressant was higher than 0.8. This indicates that the differences

between the average number of antidepressants per prescription as well as the average cost per antidepressant prescription between the age groups and genders were not of high practical significance (refer to table 5.10).

In table 5.11 it is indicated how many patients received a certain number of antidepressant prescriptions per year in each age group. (Take note that this number of antidepressant prescriptions includes repeat prescriptions).

Table 5.11: Number of prescriptions received by patients in each age group

Number of prescriptions	Number of patients per age group				
	0≤9 (%)*	>9 and ≤19 (%)*	>19 and ≤44 (%)*	>44 and ≤59 (%)*	>59 (%)*
1	159 (67.95)	465 (60.16)	4 696 (58.45)	2 367 (48.41)	624 (34.82)
2	37 (15.81)	113 (14.62)	1 221 (15.20)	704 (14.40)	227 (12.67)
3	15 (6.41)	66 (8.54)	605 (7.53)	389 (7.96)	155 (8.65)
4	7 (2.99)	30 (3.88)	385 (4.79)	233 (4.77)	123 (6.86)
5	2 (0.85)	20 (2.59)	248 (3.09)	215 (4.40)	90 (5.02)
6	4 (1.71)	22 (2.85)	211 (2.63)	179 (3.66)	96 (5.36)
7	4 (1.71)	11 (1.42)	175 (2.18)	179 (3.66)	81 (4.52)
8	1 (0.43)	13 (1.68)	126 (1.57)	144 (2.95)	78 (4.35)
9	3 (1.28)	12 (1.55)	102 (1.27)	103 (2.11)	74 (4.13)
10	0	10 (1.29)	88 (1.10)	111 (2.27)	61 (3.40)
11	1 (0.43)	5 (0.65)	80 (1.00)	93 (1.90)	62 (3.46)
12	1 (0.43)	4 (0.52)	50 (0.62)	102 (2.09)	79 (4.41)
More than 12 prescriptions	0	2	47 (0.59)	70 (1.43)	42 (2.34
Total	234 (100)	773 (100)	8 034 (100)	4 889 (100)	1 792 (100)
Average number of prescriptions per patient per year	1.82 ± 1.78	2.28 ± 2.34	2.39 ±2.49	3.22 ± 3.28	4.35 ± 3.88

**% of patients per age group = The number of patients who received antidepressants is divided by the total number of patients in the specific age group multiplied by a hundred (n 0≤9 = 234; n>9 and ≤19 = 773; n>19 and ≤44 = 8 034; n>44 and ≤59 = 4 889; n>59 = 1 792).*

In figure 2.2 it is stated that antidepressant therapy must be maintained for 4-6 months for the episodes to fully remit. In table 5.11 it is, however, indicated that between 67.95% and 34.82% patients from age group 0 to 9 to age group older than 59 years only receive **one prescription** per year. Only 2.99% to 6.86% receive **four** prescriptions for antidepressants per year and only 1.71% to 5.36% receive **six** antidepressant prescriptions per year (refer to table 5.11). It is, however, not indicated on the database whether these prescriptions are new prescriptions or repeat prescriptions. Although the diagnosis was not indicated on the database, it was assumed that all the antidepressants were prescribed for depression. However, it was not indicated whether the prescriptions were prescribed on an acute or chronic basis. These prescribing patterns can influence the efficacy of antidepressant therapy negatively.

In table 5.11 it can be seen that the average number of prescriptions that a patient receives per year increases as the age of the patient increases. Although the age group larger than 59 does

not have the highest prevalence for antidepressants they do have the highest average number of prescriptions per year. General practitioners explain that late-life depression may occur because of loneliness, lack of social network, and a reduction in functioning (Burroughs *et al.*, 2006:369). According to Hansen *et al.* (2007) antidepressants are used for relief of sadness and loneliness.

5.3.3.1 Top ten most prescribed active ingredients according to age group

In 2006, 47 740 antidepressant items were claimed through the medicine claims processing company, 99.95% of these items were classified into the different age groups as depicted in section 5.3.3. In Appendix C, table 2c all the active ingredients as prescribed in each age group are depicted. Figure 5.3 depicts the top ten prescribed active ingredients for each age group.

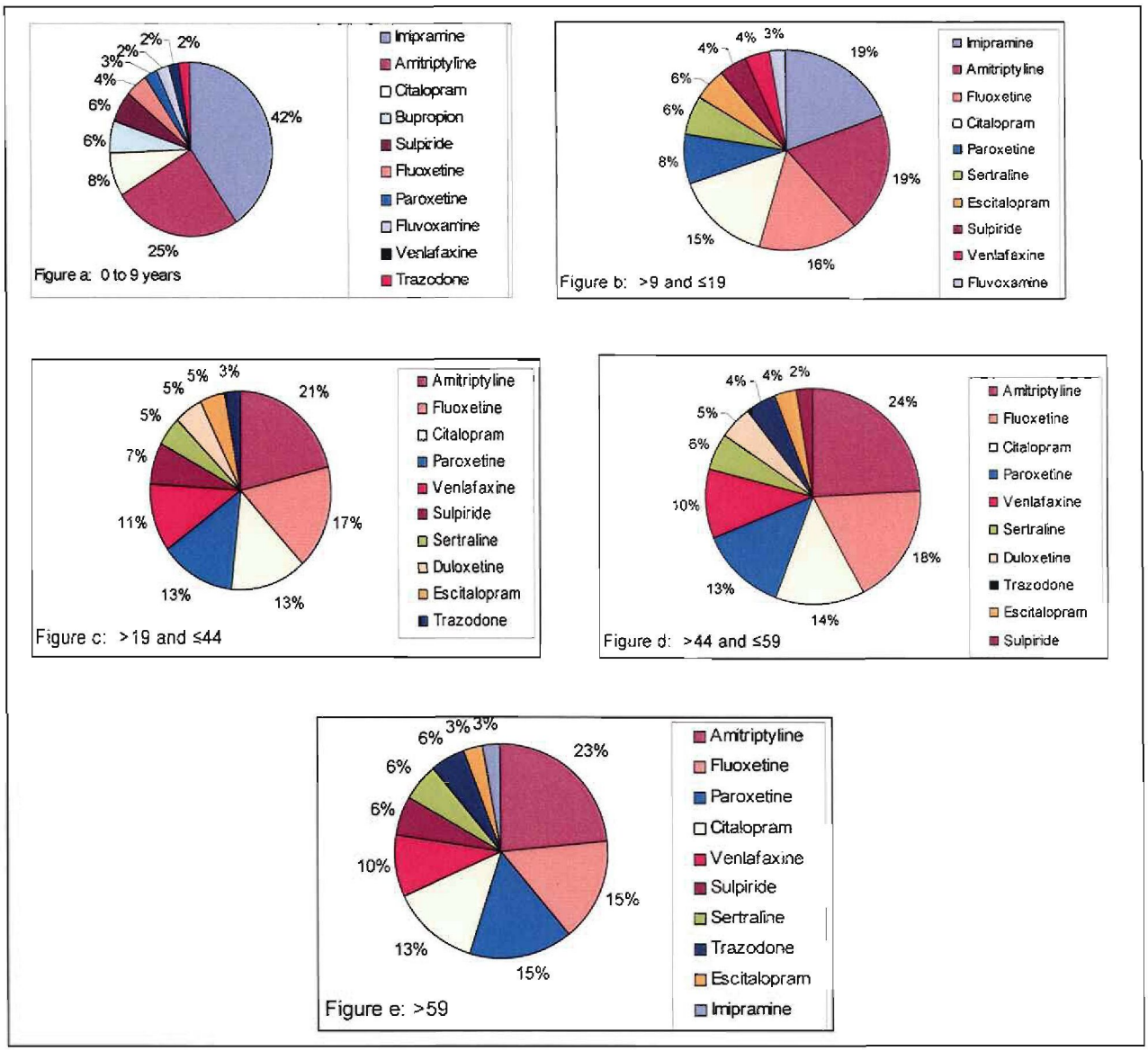


Figure 5.3: The top ten most prescribed antidepressant active ingredients in each age group (years)

In the age group **0 to 9 years** the most frequently prescribed antidepressant was imipramine (42%). Second to the antidepressant in this group was amitriptyline (refer to figure 5.3a). These two ingredients are classified as tricyclic antidepressants (TCA), and they account for 67% of the top ten most prescribed medicines in this age group. According to Drutz and Tu (2006) tricyclic antidepressants are sometimes used to manage nocturnal enuresis (bedwetting), this may explain the high prevalence of TCAs in this age group. Only 16% of the top ten most prescribed medicines in this group were selective serotonin reuptake inhibitors (SSRIs) (citalopram 8%, fluoxetine 4%, paroxetine 2% and fluvoxamine 2%) (refer to figure 5.3a).

In the age group **older than 9 and younger than 19 years** imipramine and amitriptyline accounted for the same percentage (19%) of the top ten most prescribed active ingredients. These two active ingredients were followed by fluoxetine (16%) (refer to figure 5.3b). Although imipramine and amitriptyline (both TCA) which were the most often prescribed active ingredients in this age group, TCA accounted for only 38% of the top ten active ingredients in this age group. SSRIs, which was also the most often prescribed antidepressant category (refer to section 5.4), accounted for 54% of the top ten active ingredients (citalopram 15%, fluoxetine 16%, paroxetine 8%, fluvoxamine 3%, sertraline 6%, and escitalopram 6%).

In the age group **older than 19 and younger than 44 years,** imipramine (that was the most prescribed active ingredient in the previous two age groups) was not among the top ten most prescribed active ingredients. Amitriptyline (TCA) was the most frequently prescribed active ingredient in this group and accounted for 21% of the top ten prescribed antidepressants (refer to figure 5.3c). Fluoxetine (an SSRI agent) was the second most prescribed antidepressant and accounted for 17% of the top ten active ingredients. SSRIs were also in this group, as in the previous group, the most often prescribed pharmacologic category and accounted for 53% of the top ten prescribed active ingredients while TCAs only accounted for 21%. The other pharmacological categories that were represented in the top ten active ingredients in this age group was serotonin and noradrenalin re-uptake inhibitors (SNRIs) (venlafaxine 11%, duloxetine 5%) and the pharmacological group classified as "others" (sulpiride 7%, trazodone 3%).

In a study conducted by Truter *et al.* (2006:301) [where the average age was 53 years in 1996 and 43 years (2002/2003)] the most frequently prescribed TCA were amitriptyline, dothiepin and imipramine. In this study the active ingredient appearing on prescriptions was amitriptyline in the age group **older than 44 and younger than 59 years**. Dothiepin and imipramine were not included in the top ten active ingredients in this study (refer to figure 5.3d). The second most prescribed active ingredient was fluoxetine and accounted for 18% of the top ten most prescribed active ingredients in this age group. SSRIs were also the most prevalent

pharmacological category in this age group and accounted for 55% of the top ten active ingredients. TCAs were the second most prescribed pharmacological category and accounted for 24% of the top ten active ingredients. Other pharmacological groups in this section were SNRIs (15%) and the pharmacological category "others" (15%) (refer to figure 5.3d).

In the age group **older than 59 years** the most prevalent active ingredient was amitriptyline (as was the case in the first three age groups) and accounted for 23% of the top ten active ingredients in this age group. The second most prevalent active ingredient was fluoxetine and accounted for 15% of the top ten active ingredients. SSRIs were the most prevalent pharmacological category (as were the case in the first three age groups) and accounted for 52% of the top ten active ingredients. TCAs were the second most prevalent active ingredient at 26%. The two pharmacological categories accounted for 78% of the top ten active ingredients in this age group. The other pharmacological categories in this age group were SNRIs (12%) and the category classified as "other" (10%) (refer to figure 5.3e).

In all the age groups, the most prevalent active ingredient claimed through the medicine claims processing company in 2006 was a TCA. However, only in the age groups 0 to 9 years the most prevalent pharmacological category was TCAs. SSRIs appeared as the most prevalent pharmacological category in age groups older than 9 and younger than 19 years, older than 19 and younger than 44 years, older than 44 and younger than 59 years and older than 59 years. This corresponds with the result that SSRIs were the most prevalent antidepressant in 2006 (refer to section 5.4).

5.4 PRESCRIPTION PATTERNS OF ANTIDEPRESSANTS ACCORDING TO PHARMACOLOGICAL CATEGORIES

Antidepressants are classified into seven categories according to the MIMS classification system (Snyman, 2007:15). The pharmacological classes, the number of items, average cost, total cost, as well as the percentage prevalence and the percentage cost of the different pharmacological categories are depicted in Appendix C, table 3c.

In this section the prescribing patterns and cost for these antidepressant categories will be discussed.

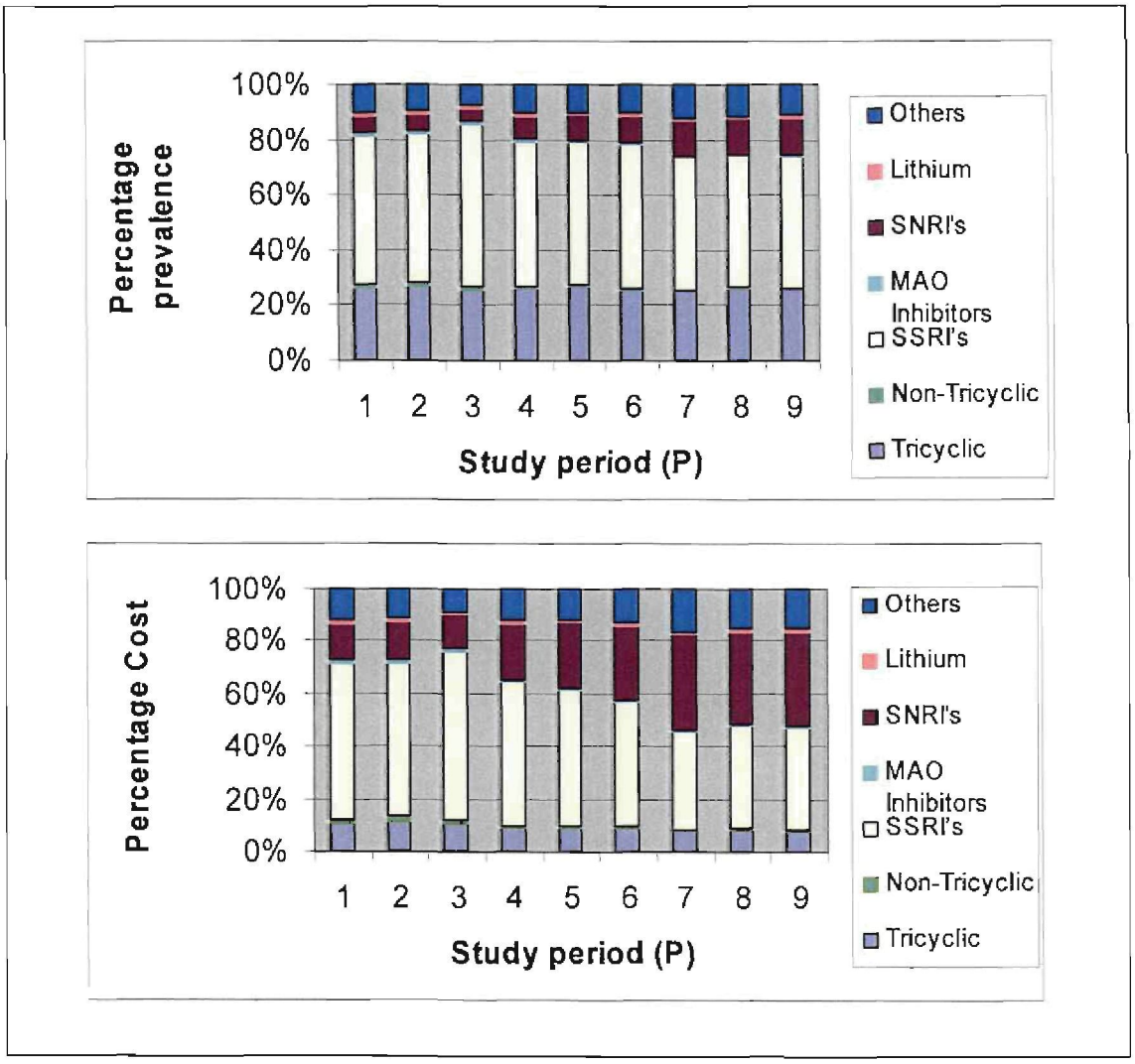


Figure 5.4: The prescribing patterns according to pharmacological class

Tricyclics antidepressants (TCAs) were more prevalent than SSRIs in South Africa *alias* a study published by Truter and Kotze (1997:1739). SSRIs have, however, become one of the first-line medicines in the treatment of depression (refer to section 2.8.2). A possible reason for this could be that SSRIs do not have anticholinergic and cardiac side-effects; do not cause weight gain and are safer in case of an overdose compared to other antidepressants (Potter & Hollister, 2001:505; Wells *et al.*, 2003:706). The **most prevalent** pharmacological category in this study was firstly SSRIs followed by tricyclic antidepressants and for **all nine study periods** (refer to figure 5.4).

In Appendix C, Table 3c it can be seen that the **average cost** of TCAs is lower than that of SSRIs and despite this SSRIs are still more prevalent than TCAs. SSRI's had the highest total cost except in January to March 2006 where serotonin and noradrenaline re-uptake inhibitors (SNRIs) had the highest total cost in correspondence with the prevalence of SSRIs. Although SNRIs were in some cases the third most prescribed medicine as indicated in figure 5.4, the

total cost was the second highest in most study periods and in January to March 2006 it was the highest. In most cases there was a continuous decrease in the average cost of the pharmacological categories from 2004 to 2006 (refer to Appendix C, table 3c), this can be attributed to the implementation of the transparent pricing system in May 2004 (refer to section 3.6).

The **cost-prevalence index (CPI)** for each pharmacological class for each study period was calculated and depicted in Appendix C, table 3c. The CPI for **TCAs** was below 1 in each study period which indicates that they are relatively inexpensive compared to the total cost of all antidepressants on the database. **SSRIs** were relatively inexpensive in period 1 (January to April 2004) and period 6-9 (September 2005 to December 2006) seeing that the CPI was below 0. In period 5 (May to August 2005) there was a good balance between the prevalence and the cost of antidepressants with a CPI = 0. **SNRIs** were particularly expensive in all study periods compared to the total antidepressant cost seeing that the CPI was above 2 in all cases. Non-tricyclics, MAO inhibitors, lithium and "others" are all relatively expensive compared to the total antidepressant cost seeing that the CPI was above 1 for all cases (refer to Appendix C, table 3c).

The **effect size** (*d*-values) for the difference in average cost between TCAs and all the other pharmacological classes was larger that 0.8 as depicted in Appendix C, table 4c; which indicates that the other pharmacological classes were all practical significantly more expensive than TCAs except the antidepressants classified as "others" in 2004. The effect sizes for the average cost between non-tricyclics and SSRIs were also higher than 0.8 for all three years which also indicates a practical significantly higher average cost for SSRIs compared to non-tricyclic agents. The average cost of SNRIs was significantly higher than that of all the other pharmacological classes and this corresponds with the high CPI value of SNRIs in each study period as well (refer to Appendix C, table 3c). The high cost of SNRIs is also illustrated in figure 5.4 seeing that it was only moderately prevalent but still had quite a high total cost compared to some of the other classes.

Each of these pharmacological classes consists of various active ingredients. The prescribing patterns and cost of these ingredients will be discussed in the following section.

5.5 PRESCRIBING PATTERNS AND COST OF ANTIDEPRESSANTS ACCORDING TO ACTIVE INGREDIENT

The prevalence, cost and the average cost per item for each antidepressant's active ingredient that was prescribed in 2004, 2005 and 2006 for each study period are indicated in Appendix C, table 5c and will be discussed in this section.

The **most common prescribed antidepressants** for 2004 on the database (in descending order) were as follows: fluoxetine (18.87%, n = 157 810), citalopram (17.77%, n = 157 810), amitriptyline (17.48%, n = 157 810), paroxetine (10.27%, n = 16 200) and venlafaxine (13.65%, n = 157 810). In 2005 and 2006 the five most prescribed active ingredients was the same as in 2004 but amitriptyline (2005 = 19.11%, n = 86 521; 2006 = 20.09%, n = 47 740) was the most prescribed followed by fluoxetine (2005 = 16.31%, n = 86 521; 2006 = 14.96%, n = 47 740), citalopram (2005 = 14.78%, n = 86 521; 2006 = 12.03%, n = 47 740), paroxetine (2005 = 9.64%, n = 86 521; 2006 = 11.84%, n = 47 740) and then venlafaxine (2005 = 7.12%, n = 86 521; 2006 = 9.04%, n = 47 740).

Escitalopram was only introduced in the South African market during May to August 2004 (refer to Appendix C, table 5c). Cipralex® (escitalopram 10mg) is the only antidepressant that contains escitalopram and was registered on 28 May 2004 (South Africa, 2004). There was a continuous increase in the **prevalence** of escitalopram from May to August 2004 where it accounted for 1.19% of all antidepressants prescribed; compared to May to August 2005 where it accounted for 6.45% of all antidepressants prescribed. In the period September to December 2005 the prevalence started to decrease and the prevalence was 6.14% during 2005 compared to 3.49% during 2006. The **cost-prevalence index (CPI)** for escitalopram was calculated for al nine study periods and in each case it was higher than 1 which indicates that it was fairly expensive compared to all antidepressants prescribed on the database during the study period.

The **CPI** was calculated for all antidepressant active ingredients as indicated in Appendix C, table 5c. The following active ingredients had a CPI of less than one for all nine study periods: fluoxetine, amitriptyline, sulpiride, imipramine, dothiepin and fluphenazine/nortriptyline which mean that these active ingredients are all relatively inexpensive compared to the number of items prescribed. Only **6 out of 29** active ingredients were relatively **inexpensive** for all nine study periods, and **14 out of 29** active ingredients had a CPI of higher than 1 for all nine study periods which indicates that these items were relatively **expensive**. This may cause some concern seeing that the aim of the National Drug Policy is to provide medicines at the lowest possible costs (South Africa, 1996).

In the following section the combinations of active ingredients that were prescribed for 2004 to 2006 and the associated medicine interactions will be discussed.

5.5.1 Combinations of antidepressants prescribed

In section 5.3.1 it is indicated that there was a general trend of only one antidepressant item on a prescription, in this section, however, the combinations that did occur in antidepressant

therapy on the database during the study period, will be discussed. The combinations that were prescribed for 2004 to 2006 are indicated in Appendix C (table 7-9c).

In 2004, 7.03% (n = 146 905) of all antidepressants prescribed were **combination therapy**, this number decreased to 5.5% (n = 81 830) in 2005 and in 2006 the combination antidepressant therapy was 5.93% (n = 44 938) of all antidepressants prescribed. In some cases there were two or three medicine items with the same active ingredient prescribed. Possible reasons for this may be the following:

- That the patient takes one strength of the antidepressant in the morning and another strength in the evening. Combinations may also be prescribed to simplify usage instructions.

- It may be that the strength that a patient is supposed to take is not on the market in one tablet and two or more strengths have to be combined to get the desired dosage. However, this aspect needs further investigation.

According to the treatment algorithm of depression illustrated in figure 2.2, the prescriber should consider switching the patient to alternative therapy or augmentation (lithium or TCA plus SSRI) if the patient shows only partial response to therapy. In table 2.6, however, it is indicated that there is a medicine interaction between TCAs and SSRIs.

There were various drug-drug interactions depicted in Appendix C (table 7-9c). In 2004, 50.75% (n = 10 339) of all combinations prescribed showed an interaction with a significance rating of between 1 and 5, in 2005 this number of drug-drug interactions increased to 53.64% (n = 4 502), and in 2006 the drug-drug interactions for combination therapy was 55.16% (n = 2 665) (refer to Appendix C, table 7-9c). The drug-drug interactions with a **significance rating of one and two** according to Tatro (2002: xiv), which is severe and well-documented interactions as indicated in section 2.9, was 79.45% (n = 5 247) of all drug-drug interactions in 2004, 65.76% (n = 2 415) in 2005 and 51.56% (n = 1 470) in 2006, such as the interaction between MAO inhibitors and SSRI's for example moclobemide and paroxetine, or MAO inhibitors and TCA's for example moclobemide and trimipramine or TCA's and SSRI's for example amitriptyline and sertraline .

The cause of this high incidence of drug-drug interactions may be due to the statement that the prescriber should consider switching the patient to alternative therapy or augmentation (lithium or TCA plus SSRI) if the patient shows only partial response to therapy (refer to figure 2.2). This number of drug-drug interactions may be a definite cause for concern seeing that drug-drug interactions with a significance rating of one and two may lead to hospitalisation (Tatro,

2002:xiv) (refer to section 2.9). The clinical implication of the interaction was, however, not determined in this study.

In the following section, expenditure of antidepressants according to trade name will be discussed. Only the top ten products according to expenditure will be discussed, seeing that these products influence the total antidepressant cost the most.

5.6 EXPENDITURE OF ANTIDEPRESSANTS ACCORDING TO TRADE NAME

In this section the expenditure of antidepressants according to trade name will be discussed. Only the **top ten products** according to expenditure will be discussed in this section. The statistics for this section were depicted in Appendix C, table 10c. These products accounted for 67.23% (n = R 32 323 356.78) in 2004, 67.12% (n = R 15 245 709.85) in 2005 and 55.63% (n = R 8 614 631.29) in 2006 of the total cost of all antidepressants prescribed. In figure 5.5 the top ten antidepressants according to expenditure for each year are illustrated.

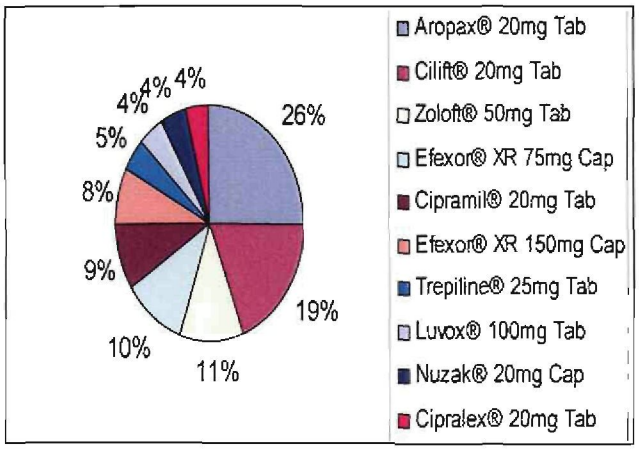


Figure 5.5a: Expenditure for 2004

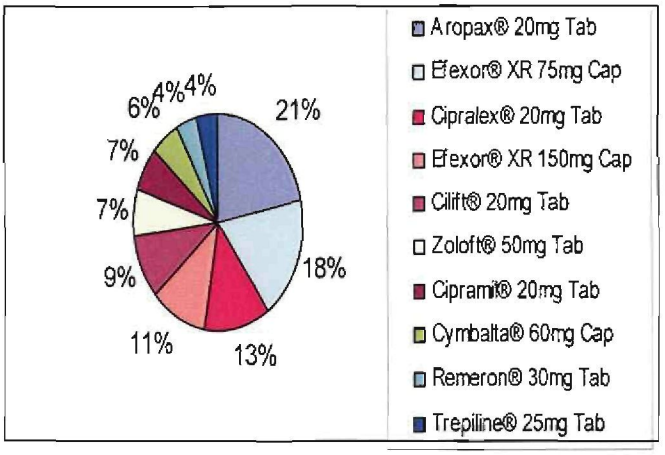


Figure 5.5b: Expenditure for 2005

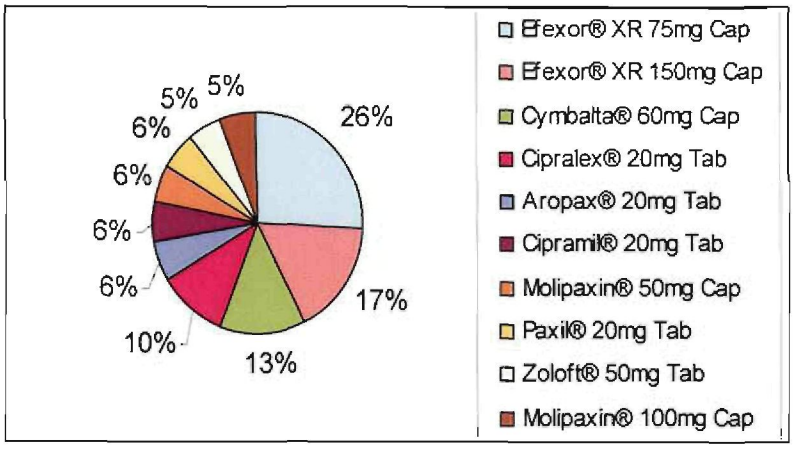


Figure 5.5c: Expenditure for 2006

Figure 5.5 Top ten antidepressants according to expenditure for 2004-2006

In 2004 and 2005 Aropax® (paroxetine 20mg) had the highest **total cost** and represented 26% in 2004 and 21% in 2005 of the total cost of all the top ten agents. Aropax® was the third most **prescribed** antidepressant in 2004 and accounted for 10.01% (n = 157 810) of all antidepressants prescribed, in 2005 it was the fourth most prescribed antidepressant accounting for 14.52% (n = 86 521) of all antidepressants prescribed (refer to Appendix C, table 10c). In 2006 Aropax® 20mg ranked fifth according to **total expenditure** as illustrated in figure 5.5c. This was due to a decrease in the number of Aropax® 20mg items prescribed in 2006 as illustrated in Appendix C, table 10c. The decrease in **prevalence** from 2005 to 2006 may be explained by the introduction of various generic products into the market in 2005 and 2006 as depicted in Appendix C, table 11c.

Cilift® (citalopram 20mg) was the **most frequently prescribed** antidepressant and accounted for 12.54% (n = 157 810) of all antidepressants prescribed in 2004 (refer to Appendix C, table 10c). The total cost of Cilift® ranked second and was 19% of the top ten antidepressants' total costs as illustrated in table 5.5a.

Trepiline® (amitriptyline 25mg) was the **second most prescribed** antidepressant in 2004 and represented 11.17% of all antidepressants prescribed as depicted in Appendix C, table 10c at an **average cost** of R 149.44 ± R 83.45. This made Trepiline® 25mg the seventh most cheapest antidepressant in 2004. Trepiline® 25mg was ranked seventh in the top ten antidepressants according **to expenditure** as indicated in figure 5.5a.

In **2005**, Efexor® XR (venlafaxine 75mg) was ranked **second** according to **total cost** as indicated in figure 5.5b and accounted for 18% (n = R 10 232 865.23) of the top ten antidepressant cost. Efexor® XR 75mg was the seventh most **prevalent** antidepressant with 5.18% (n = 86 521) of the all antidepressants prescribed; and the ninth most **expensive** antidepressant with an average cost of R 416.38 ± R 144.34 (refer to Appendix C, table 10c). In **2006**, Efexor® XR 75mg had the **highest total cost** and accounted for 26% of the top ten antidepressants according to total cost. Efexor® XR 75mg was the third most **prescribed** antidepressant in 2006 with a prevalence of 5.99% (n = 47 740) of all antidepressants prescribed. Efexor® XR 75mg was the tenth most **costly** antidepressant with an average cost of R 434.87 ± R 132.74.

Efexor® XR (venlafaxine 150mg) was the second most expensive antidepressant in 2005 with an average cost of R 742.40 ± R 246.72 and was ranked **fourth** among the **top ten antidepressants** according to expenditure. In 2006 Efexor® XR 150mg was ranked **second** (17% of the top ten antidepressants according to total expenditure) according to **total**

expenditure and this can be attributed to its high average cost of R 827.37 ± R 182.50 which made Efexor® XR 150mg the third most costly antidepressant in 2006.

The **prevalence percentage** of Cipralex® (escitalopram 20mg) increased from 2.14% (n = 157 810) in 2004 to 6.09% (n = 86 521) in 2005. This increase in prevalence cannot be attributable to a difference in average cost seeing that the effect size between these two was 0.02 and of no practical significance (refer to section 4.6.2.4). The **total cost** of Cipralex® was ranked third and accounted for 18% of the top ten total costs of antidepressants.

The **most expensive antidepressant** from 2004 to 2006 was Prozac® SI (fluoxetine 60mg) with an average cost of R 1 014.91 ± R 345.27 in 2004, compared to R 938.75 ± R 311.58 in 2005 and R 1 279.02 ± R 0.00 in 2006 (Appendix C, table 10c). The antidepressants with the **lowest cost** were Ethipramine® (imipramine 10mg) (R31.52 ± R 20.75) in 2004, Eglonyl® 2ml amps (sulpiride) (R 20.98 ± R 2.42) in 2005 and Noriline® tablets (amitriptyline 10mg) (R 18.36 ± R 0.00) in 2006 (Appendix C, table 10c). Interestingly, even though these agents had the lowest cost, their prevalence was never among the top 10 most prevalent.

In this section the total cost, average cost and prevalence of different antidepressants according to trade name was illustrated and summarised. In the following section the cost saving with generic substitution for each active ingredient according to strength and generic substitution will be calculated, using four hypothetical scenarios.

5.7 COST SAVINGS WITH GENERIC SUBSTITUTION

When an innovator medicine item is replaced with a generic medicine it is usually expected that some cost may be saved. In this section these cost savings will be investigated for antidepressants. Cost savings will be calculated by multiplying the average cost (refer to Appendix C, table 11c) of either the most expensive or least expensive generic item by the prevalence number of the innovator item, and then this cost will be subtracted from the total cost of the innovator item. This equation will be adapted to each scenario (refer to section 4.6.2.5).

Cost Saving = Total cost (innovator item) – [Average cost (generic item) x n (total number of innovator items)]

In Appendix C, Table 11c the average cost of all the innovator and generic antidepressants was depicted. The cost savings that are calculated in the following subsections were only calculated

for those innovator products that have generic equivalents and where the generic product is less expensive than the innovator product.

5.7.1 Amitriptyline

In table 5.12 and 5.13 the cost analysis of amitriptyline tablets are depicted to calculate the cost savings for amitriptyline tablets.

Table 5.12: Cost analysis of amitriptyline 10mg tablets

Innovator medicine item	Generic medicine item	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Tryptanol® 10mg Tab		2004	2	52.66±35.86	105.32
		2005	-	-	-
		2006	-	-	-
	Noriline® 10mg Tab	2004	66	64.42±31.08	4 251.79
		2005	17	39.92±14.70	678.65
		2006	1	18.36±0.00	18.36
	Trepiline® 10mg Tab	2004	8421	34.89±20.69	293 845.60
		2005	4852	30.77±21.17	149 304.43
		2006	2633	34.28±17.98	90 249.82

Tryptanol® 10mg tablets were only prescribed in 2004; thus in this case **only cost savings for 2004** can be calculated. Noriline® 10mg tablets were more expensive than the innovator and although they were more prevalent than Tryptanol® 10mg they were excluded from this analysis because there would be no possible cost saving.

Should all the Tryptanol® 10mg tablets for the year 2004, however, have been substituted with Trepiline® 10mg tablets (scenario 2) the cost savings would have been R 35.54. [A minimum of R 17.77 could have been saved based on scenario 1 if 50% of the Tryptanol® 10mg tablets had been substituted with Trepiline® 10 mg tablets].

Table 5.13: Cost analysis of amitriptyline 25mg tablets

Innovator medicine item	Generic medicine item	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Tryptanol® 25mg Tab		2004	448	163.46±117.19	73 231.34
		2005	210	97.08±103.85	20 387.56
		2006	89	88.29±81.82	7 857.51
	Rolab-Amitriptyline® 25mg Tab	2004	707	59.80±50.85	42 277.82
		2005	-	-	-
		2006	-	-	-
	Sandoz Amitriptyline® 25 mg Tab	2004	290	32.41±22.76	9 398.41
		2005	960	36.95±22.15	35 467.54
		2006	1 782	37.20±19.98	66 296.14
	Trepiline® 25mg Tab	2004	17 631	58.21±43.64	1 026 383.70
		2005	10 499	37.01±22.62	388 649.63
		2006	5 084	35.07±21.22	178 292.25

The most **expensive generic** for amitriptyline 25mg for **2004** was Rolab-Amitriptyline®. If only **50%** of the innovator items had been substituted by Rolab-Amitriptyline® (scenario 3) the cost saving would have been R 23 219.84. Should **100%** of the Tryptanol® 25mg tablets have been substituted with Rolab-Amitriptyline® (scenario 4) the cost saving for 2004 would have been R 46 440.94.

In **2005** the **most expensive** generic item was Trepiline® 25mg which could have generated a cost saving of R 6 287.40 if **50%** Tryptanol (scenario 3) had been substituted and R 12 615.46 if **100%** of the Tryptanol® items had been substituted with Trepiline® 25mg tablets (scenario 4).

The **least expensive** generic for **2004** and **2005** was Sandoz-Amitriptyline® that replaced Rolab-Amitriptyline® in 2003 (Sandoz, 2006). The cost saving would have been R 29 355.52 in **2004** if only **50%** of Tryptanol® 25mg (scenario 1) had been substituted. If **all** prescribed innovator items had been substituted with Sandoz Amitriptyline® the cost savings would have been R 58 711.65 for 2004 (scenario 2). If **50%** of all the Tryptanol® items prescribed for **2005** had been replaced with Sandoz Amitriptyline® the cost savings for 2005 would have been R 6 313.65 (scenario 1) and R 12 628.06 if **all** the Tryptanol® items had been substituted (scenario 2). The cost savings do not differ much from those of Trepiline® 25mg tablets; which were the most expensive generic. This can be ascribed to the fact that the prices are almost identical.

As was the case in 2005, the prices of the two available generics for Tryptanol® 25mg also did not differ much in 2006. Thus only the cost saving for the **least expensive** generic item, which was Trepiline®, was calculated.

If **50%** of the prescribed Tryptanol® 25mg tablet items for **2006** had been substituted with Trepiline® 25mg tablets the cost savings would have been R 1 112.85 (scenario 1) and if **all** Tryptanol® items had been substituted the cost savings would have been R 4 736.28 (scenario 2).

The highest possible cost savings for amitriptyline 25mg could have been R 58 711.65 in 2004, R 12 628.06 in 2005 and R4 736.28 in 2006. This decrease in cost saving is attributable to the decrease in prevalence of amitriptyline 25mg and medicine items in general.

Maximum cost savings for the years 2004 to 2006 were calculated by adding the cost savings for the least expensive generic item, if 100% of the innovator items were substituted, for the specific year. The maximum cost savings for generic substitution of amitriptyline 25mg for the years 2004 to 2006 could have been R 76 075.99.

5.7.2 Clomipramine

In table 5.14 and 5.15 the cost analysis of clomipramine tablets are depicted to calculate the possible cost savings for clomipramine tablets.

Table 5.14: Cost analysis of clomipramine 10mg tablets

Innovator medicine item	Generic medicine item	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Anafranil® 10mg Tab		2004	230	108.53±60.86	24 961.41
		2005	119	113.01±77.81	13 447.62
		2006	28	125.69±56.59	3 519.38
	Equinorm® 10mg Tab	2004	96	86.62±38.50	8 315.83
		2005	29	75.50±31.42	2 189.59
		2006	16	76.93±20.43	1230.80

The cost saving for clomipramine 10mg tablets in **2004** (if only **50%** of Anafranil® 10mg was replaced with Equinorm® 10mg) would have been R 2 519.65 (scenario 1) and if **all** Anafranil® 10mg items was replaced the cost savings would have been R 5 038.81 (scenario 2). In **2005** the cost saving, if only **50%** of the Anafranil 10mg was replaced, would have been R 2 250.60 (scenario 1) and if **all** Anafranil® 10mg was substituted the saving would have been R 4 463.12 (scenario 2). In **2006** the cost saving for **50%** Anafranil 10mg substituted by Equinorm® 10mg would have been R 682.64 (scenario1) and if **100%** of Anafranil® was substituted the cost saving would have been R 1 365.34 (scenario 2).

The maximum cost saving for clomipramine 10 mg tablets for the years 2004 to 2006 was R 10 867.27. The cost savings decreased from 2004 to 2006 due to the decrease in prevalence. Should the prevalence however have being constant, the cost savings would have increased seeing that the cost of Anafranil® 10mg had increased from 2004 to 2006 and the cost of Equinorm® 10 mg tablets had decreased from 2004 to 2005 and 2006.

Table 5.15: Cost analysis of clomipramine 25mg tablets

Innovator medicine item	Generic medicine item	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Anafranil® 25mg Tab		2004	567	268.42±225.02	152 196.02
		2005	240	256.70±235.40	61 607.38
		2006	130	314.74±201.67	40 915.94
	Clomidep® 25mg Tab	2004	4	103.22±63.98	412.89
		2005	22	185.41±156.72	4 079.03
		2006	30	290.16±105.81	8 704.77
	Equinorm® 25mg Tab	2004	360	193.28±174.96	69 581.69
		2005	175	190.37±168.11	33 314.35
		2006	46	254.70±209.00	11 716.09

The **most expensive generic** item for Anafranil® 25mg for **2004 and 2005** was Equinorm® 25 mg. If only **50%** of Anafranil® 25 mg had been substituted with Equinorm® 25 mg in **2004** the

cost saving would have been R 21 339.76 (scenario 3) and if **100%** of the innovator items had been substituted by Equinorm® 25mg the cost saving for clomipramine 25mg would have been R 42 606.26 (scenario 4). If **half** of all Anafranil® 25mg prescribed for **2005** had been replaced with Equinorm® 25mg the cost saving would have been R 7 959.60 (scenario 3) and the cost saving for **100%** Anafranil® substituted would have been R 15 918.58 (scenario 4).

The cost savings in **2004** for clomipramine 25mg would have been R 46 916.80 (scenario 1) if only **50%** of Anafranil® 25mg had been replaced with Clomidep® 25mg which was the **cheapest generic** for **2004** and **2005**. If all Anafranil® 25mg had been substituted with Clomidep® 25mg the cost saving would have been R93 670.28 (scenario 3) for **2004**. If Clomidep® 25mg had been substituted for **50%** of Anafranil® 25mg prescribed for 2005 the cost saving would have been R8 554.80 (scenario 1). If **100%** of all Anafranil® 25mg as prescribed for **2005** had been substituted with Clomidep® 25mg the cost saving would have been R17.108.98 (scenario 2). Clomidep® 25mg changed from being the least expensive in 2004 and 2005 to being the **most expensive generic** during 2006. If **50%** of Anafranil® 25mg had been substituted with Clomidep® 25mg the cost saving for 2006 would have been R 1 597.70 (scenario 3) and if **all** Anafranil® 25mg had been substituted the savings would have been R 3 195.14 (scenario 4).

In **2006** the **least expensive** generic item was Equinorm® 25mg tablets. If only **50% of all** Anafranil® 25mg prescribed for **2006** had been substituted by Equinorm® 25mg the cost saving would have been R3 902.60 (scenario 1) and if **100%** of Anafranil® 25 mg had been substituted the cost saving would have been R7 804.94 (scenario 2).

The cost saving if 100% of Anafranil® 25mg prescribed for 2004 to 2006 had been substituted by the least expensive generic item for each year would have been R 118 583.22.

5.7.3 Dothiepin

In tables 5.16 and 5.17 the cost analysis of dothiepin is depicted to calculate possible cost savings.

Table 5.16: Cost analysis of dothiepin 25mg capsules

Innovator medicine item	Generic medicine item	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Prothiaden® 25mg Cap		2004	586	129.22±83.10	75 725.72
		2005	185	105.72±43.73	19 558.38
		2006	40	115.10±49.33	4 604.06
	Sandoz-Dothiepin® 25mg Cap	2004	133	71.67±37.07	9 532.75
		2005	65	61.17±27.06	3 976.12
		2006	21	44.88±19.38	942.40
	Thaden® 25mg Cap	2004	1404	68.51±42.35	96 182.23
		2005	411	59.52±29.45	24 462.76
		2006	154	80.04±52.41	12 325.44

In **2004 and 2005** Sandoz-Dothiepin® 25mg was the **most expensive** generic item for dothiepin 25mg. In a scenario where only **50%** of the innovator Prothiaden® 25mg could be substituted with Sandoz-Dothiepin® 25mg the cost saving would have been R 16 862.15 (scenario 3) for **2004** and R 4 143.15 (scenario 3) in **2005**. In the case where **100%** of Prothiaden® 25mg had been substituted with Sandoz-Dothiepin® 25mg the cost saving for **2004** would have been R 33 727.10 (scenario 4) for 2004 and R 8 241.93 (scenario 4) for 2005.

In **2006** Thaden® 25mg which was the cheapest generic for 2004 and 2005 changed to be the **most expensive generic** item for dothiepin 25mg. If **50%** of Prothiaden® 25mg could be substituted with Thaden® 25mg the cost saving would have been R 701.20 (scenario 3) for 2006. If **all** the Prothiaden® 25mg which were prescribed for 2006 had been substituted with Thaden® 25mg the cost saving for 2006 would have been R 1 402.46 (scenario 4).

The **least expensive generic** item for **2004 and 2005** was Thaden® 25mg. In the case where only **half** of the Prothiaden were to be substituted with Thaden® 25mg the cost saving would have been R 17 788.03 (scenario 1) and if **all** the Prothiaden® 25mg which were prescribed for **2004** could be substituted with Thaden® 25mg the cost saving would have been R 35 578.86 (scenario 2). The cost saving for 2005 would have been R 4 296.60 (scenario 1) if only **half** of the Prothiaden® had been substituted and R 8 547.18 (scenario 2) if **100%** of the prescribed Prothiaden® had been substituted.

In **2006** the **least expensive** generic item was Sandoz-Dothiepin® 25mg with an average cost of almost half that of the most expensive generic (i.e. Thaden® 25mg). If **50%** of the Prothiaden® 25mg for 2006 had been substituted with Sandoz-Dothiepin® 25mg the cost saving would have been R 1 484.40 (scenario 1). If **all** of the prescribed Prothiaden® 25mg had been substituted the cost saving for 2006 would have been R 2 808.86 (scenario 2).

If all of the Prothiaden® 25mg that were prescribed from 2004 to 2006 had been substituted with the least expensive generic for each year; the maximum cost saving for dothiepin 25mg for the period 2004 to 2006 could amounted to R 46 934.90.

Table 5.17: Cost analysis of dothiepin 75mg tablets

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Prothiaden® 75mg Tab		2004	373	184.41±75.52	68 784.70
		2005	114	128.82±29.61	14 685.31
		2006	42	149.18±65.07	6265.63
	Sandoz Dothiepin® 75mg Tab	2004	412	143.50±56.70	59120.76
		2005	138	132.30±50.89	3 976.12
		2006	82	146.18±47.98	11 986.43
	Thaden® 75mg Tab	2004	1482	131.70±54.74	195 175.12
		2005	580	109.38±39.77	63 439.85
		2006	64	128.25±40.54	8 208.20

Sandoz-Dothiepin® 75mg was the **most expensive** generic item for dothiepin 75mg tablets for **2004 and 2006**. If only **half** of all Prothiaden® 75mg that was prescribed for 2004 was substituted with Sandoz-Dothiepin® 75mg, the cost saving would have been R 7 650.17 and R 63.00 for **2006** (scenario 3). If Prothiaden® 75mg was **100%** substituted with Sandoz-Dothiepin® 75mg the cost saving would have been R 15 259.20 for **2004** and R1 26.07 for **2006** (scenario 4). In **2005**, the average price of Sandoz-Dothiepin® 75mg was higher than that of the innovator and was therefore excluded from the analysis.

Thaden® 75mg was the **least expensive** generic for dothiepin 75mg tablets from **2004 to 2006**. If **50%** of Prothiaden® 75mg could be substituted with Thaden® 75mg the cost saving would have been R 9 856.77 for 2004, R 1 108.08 for 2005 and R 439.53 for 2006 (scenario 1). If **100%** of Prothiaden® 75mg could be substituted the cost saving would have been R 19 660.60 for 2004, R 2 215.99 for 2005 and R 879.13 for 2006 (scenario 2).

If the least expensive generic item for each year, in this case Thaden® 75mg, substituted all the prescribed Prothiaden® 75mg, the cost saving for 2004-2006 could have been R 22 755.72.

5.7.4 Imipramine

In table 5.18 and 5.19 the cost analysis of imipramine tablets is depicted to calculate the possible cost savings for imipramine.

Table 5.18: Cost analysis of imipramine 10mg tablets

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Tofranil® 10mg Tab		2004	784	73.40±52.40	57 545.52
		2005	301	46.09±24.66	46 112.98
		2006	92	42.44±25.21	3 904.43
	Ethipramine® 10mg Tab	2004	552	31.52±20.75	17 397.49
		2005	1640	53.43±38.95	19 403.28
		2006	418	33.30±23.13	13 917.72

Imipramine 10mg tablets had one generic item only i.e. Ethipramine® 10mg tablets. If only **50%** of Tofranil 10mg was substituted with Ethipramine® 10mg the cost saving for **2004** would have been R 16 416.96 and for **2006** the cost saving would have been R 420.44 (scenario 1). In the case of a **100%** substitution of Tofranil® 10mg the cost saving would have been R 32 833.84 for **2004** and R 807.53 for **2006** (scenario 2). In **2005**, Ethipramine® 10mg tablets had a higher average cost than the innovator item, and were thus excluded from this analysis.

Seeing that there was no cost saving for 2005 the maximum possible cost saving for 2004 and 2006 was R 33 641.37.

Table 5.19: Cost analysis of imipramine 25mg tablets

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Tofranil® 25mg Tab		2004	1331	136.71±90.62	181 967.33
		2005	485	95.08±53.71	46 112.98
		2006	138	81.69±48.21	11 272.75
	Ethipramine® 25mg Tab	2004	2374	54.69±40.89	129 838.07
		2005	1640	53.43±38.95	87 619.50
		2006	826	51.43±39.95	42 482.38

Ethipramine® 25mg tablets were the only generic item that could generate possible cost savings for imipramine 25mg. In the hypothetical situation where **50%** of Tofranil® 25mg was substituted with Ethipramine® 25mg the cost saving would have been R 54 625.32 for **2004**, R 10 120.95 for **2005** and R 2 087.94 for **2006** (scenario 1). The maximum cost saving for imipramine 25mg where 100% of the prescribed Tofranil® 10mg were substituted with Ethipramine® 25mg could be R 109 174.94 for 2004, R 20 199.43 for 2005 and R 4 175.41 for 2006 (scenario 2).

The maximum possible cost saving for imipramine 25 mg tablets for 2004 to 2006 could accumulate to R 133 549.82 if all the prescribed innovator items were to be substituted with the generic item.

5.7.5 Trimipramine

In table 5.20 the cost analysis of trimipramine is depicted to calculate the cost savings for trimipramine.

Table 5.20: Cost analysis of trimipramine 50mg capsules

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Surmontil® 50mg Cap		2004	180	358.66±161.18	64 558.49
		2005	67	198.45±60.26	13 295.86
		2006	58	188.54±33.10	10 935.45
	Tydamine® 50mg Cap	2004	1039	256.42±121.24	266.424.40
		2005	437	234.42±98.22	102 440.04
		2006	238	253.80±134.37	60 405.52

In the case where **50%** of Surmontil® 50mg had been substituted with Tydamine® 50mg the cost saving for **2004** was R 9 201.60 (scenario 1). If **all** the prescribed Surmontil® 50mg capsules had been substituted with Tydamine® 50mg the cost savings for **2004** could have been R 18 402.89 (scenario 2).

In **2005 and 2006** there could have been **no cost savings** for trimipramine 50mg capsules seeing that the average price of the innovator item decreased to be lower than that of Tydamine® 50mg.

5.7.6 Moclobemide

In table 5.21 and 5.22 the cost analysis of moclobemide is depicted to calculate the cost savings for moclobemide.

Table 5.21: Cost analysis of moclobemide 150mg tablets

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Aurorix® 150mg Tab		2004	177	349.18±192.83	61 805.33
		2005	67	304.67±125.35	20 413.14
		2006	28	320.57±116.04	8 976.07
	Clorix® 150mg Tab	2004	104	202.24±81.01	21 032.72
		2005	74	182.17±56.11	13 480.51
		2006	117	200.25±60.47	23 429.61
	Depnil® 150mg Tab	2004	1210	242.98±91.55	293 999.82
		2005	297	203.08±76.42	60 315.06
		2006	54	220.24±93.81	11 892.90

The **most expensive** generic medicine for moclobemide 150mg for **2004 to 2006** was Depnil® 150mg tablets. If only **half** of the Aurorix® 150mg tablets that were prescribed were substituted with Depnil® 150mg the cost savings could have been R 9 451.80 for **2004**, R 3 454.06 for **2005** and R 1 404.62 for **2006** (scenario 3). In the case where **100%** of the prescribed Aurorix®

150mg were substituted the following cost savings could have generated; R 18 797.87 for **2004**, R 6 806.78 for **2005** and R 2 809.35 for **2006** (scenario 4).

The **least expensive** generic item for moclobemide 150mg from 2004 to 2006 was Clorix® 150mg. In a scenario where **50%** of Aurorix® 150mg was substituted with Clorix® 150mg cost savings of R 13.074.10 for **2004,** R 4 165.00 for **2005** and R 1 684.48 for **2006** could have occurred (scenario 1). If **all** the prescribed Aurorix® 150mg were substituted with Clorix® 150mg, maximum cost savings of R 38 143.25 for **2004**, R 8 207.75 for **2005** and R 3 348.63 for **2006** could have been achieved (scenario 2).

The maximum cost saving for moclobemide 150mg tablets for 2004 to 2006 could have been R 49 699.63 if the innovator had been replaced with the cheapest generic item for each year.

Table 5.22: Cost analysis of moclobemide 300mg tablets

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Aurorix® 300mg Tab		2004	104	377.04±219.89	39 211.76
		2005	7	283.05±214.83	1 981.37
		2006	19	786.85±382.45	14 950.24
	Clorix® 300mg Tab	2004	161	263.69±83.79	42 454.82
		2005	31	207.18±76.51	6 422.47
		2006	37	203.88±42.73	7 543.54
	Depnil® 300mg Tab	2004	191	257.46±68.44	49 174.30
		2005	61	233.38±44.38	14 235.99
		2006	23	210.21±90.07	4 834.92

In **2004** the **most expensive generic** item for moclobemide 300mg was Clorix® 300mg. The cost saving could have been R 5 894.20 for **2004** if only **50%** of the Aurorix® 300mg had been substituted with Clorix 300mg (scenario 3). If **100%** of the prescribed Aurorix® 300mg had been substituted with Clorix® 300mg the cost saving could have been R 11 788.00 (scenario 4)

Depnil® 300mg was the **most expensive** generic item for moclobemide 300mg for **2005** and **2006.** If **50%** of the Aurorix® 300mg could be replaced with Depnil® 300mg the cost savings would have been R 198.68 for **2005** and R 5 766.40 for **2006** (scenario 3). If **all** the prescribed Aurorix® 300mg could be substituted with Depnil® 300mg there could have been cost savings of R 347.71 for **2005** and R 10 956.25 for **2006** (scenario 4).

In **2004**, Depnil® 300mg was the **least expensive** generic item for moclobemide 300mg tablets. If only **half** of the Aurorix® 300mg tablets that were prescribed for **2004** had been replaced with Depnil® 300mg the cost saving could have been R 6 218.16 (scenario 1). If **all** the Aurorix® 300mg had been replaced with Depnil® 300mg tablets, the cost savings for moclobemide 300mg in **2004** could have been R12 435.92 (scenario 2).

The average cost of Clorix® 300mg tablets decreased in 2005 and 2006 which resulted in Clorix® 300mg going from the most expensive generic item in 2004 to being the **least expensive** generic item for moclobemide 300mg during **2005 and 2006**. If only **50 %** of the Aurorix® 300mg had been substituted with Clorix® 300mg the cost savings would have been R 303.48 for **2005** and R 5 829.70 for **2006** (scenario 1). If **all** the prescribed Aurorix® 300mg had been replaced with Clorix® 300mg the cost savings could have been R 531.11 for **2005** and R 11 076.52 for **2006** (scenario 2).

The maximum potential cost saving for 2004 to 2006 for moclobemide 300mg could have been R 24 043.55.

5.7.7 Citalopram

In table 5.23 the cost analysis of citalopram is depicted to calculate the cost savings for citalopram.

Table 5.23: Cost analysis of citalopram 20mg tablets

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Cipramil® 20mg Tab		2004	6221	319.80±146.49	1 989 504.92
		2005	2605	262.02±150.39	682 599.61
		2006	867	317.13±215.31	274 951.91
	Cilift® 20mg Tab	2004	19796	206.18±83.13	4081450.35
		2005	7690	125.95±47.74	968 533.13
		2006	2973	78.21±19.47	232 528.34
	Citalohexal® 20mg Tab	2004	-	-	-
		2005	32	93.69±26.37	2 998.07
		2006	43	86.98±28.11	3 740.00
	Depramil® 20mg Tab	2004	-	-	-
		2005	105	94.38±26.13	9 910.25
		2006	36	64.11±41.77	2 307.91
	Sandoz Citalopram® 20mg Tab	2004	-	-	-
		2005	10	73.95±25.02	739.49
		2006	5	75.27±0.13	376.34
	Adco-Talomil® 20mg Tab	2004	2030	160.31±65.78	325 431.49
		2005	2346	106.70±52.72	250 303.45
		2006	1808	78.74±17.25	142 364.10

The **most expensive** generic item for citalopram 20mg was Cilift® 20mg in **2004 and 2005**. If only **half** of the Cipramil® 20mg had been substituted with Cilift® 20mg the cost saving would have been R 353 471.82 in **2004** and R 177 299.21 in **2005** (scenario 3). In scenario 4 where **100%** of Cipramil® 20mg could have been substituted with Cilift® 20mg the cost saving could have been R 706 859.14 for **2004** and R 354 499.86 for **2005**.

In **2006** the **most expensive** generic item for citalopram 20mg was Citalohexal® 20mg tablets. The cost saving for citalopram 20mg would have been R 99 885.10 in **2006** if only **half** of Cipramil® 20mg had been substituted with Citalohexal® 20mg (scenario 3). If **all** the prescribed Cipramil® 20mg had been substituted with Citalohexal® 20mg the cost saving for citalopram 20 mg for **2006** would have been R 199 540.25 (scenario 4).

The **least expensive** generic item for citalopram 20mg was Adco-Talomil® 20mg in **2004**. The cost saving for citalopram 20mg could have amounted to R 496 173.39 in **2004** if only **half** of the Cipramil® 20mg had been substituted with Adco-Talomil® 20mg (scenario 1). The maximum cost saving for citalopram 20mg that could gave occurred if **100%** of Cipramil® 20mg had been substituted with Adco-Talomil® 20mg could have been R 992 216.41 in 2004 (scenario 2).

In **2005** the **least expensive** generic product was Sandoz-Citalopram® 20mg. If only **50%** of Cipramil® 20mg had been substituted with Sandoz-Citalopram® the cost saving could have been R 245 055.21 (scenario 1). The cost savings could have been as much as R 489 959.86 for **2005** if **all** the prescribed Cipramil® 20 mg tablets had been substituted with Sandoz-Citalopram® (scenario 2).

Depramil® 20mg was the **least expensive** generic item for citalopram 20mg in **2006**. A cost saving of R 109 810.68 could have been achieved if **50%** of Cipramil® 20mg had been substituted with Depramil® 20mg (scenario 1). The cost saving for **2006** would have been R 219 368.54 if **100%** of Cipramil® 20mg had been substituted with Depramil® 20mg (scenario 2).

The maximum potential cost saving could have been R 1 681 716.52 for citalopram 20mg for 2004 to 2006 if all the prescribed innovator products had been substituted with the least expensive generic product for each year.

5.7.8 Fluoxetine

In table 5.24 and 5.25 the cost analysis of fluoxetine is depicted to calculate the cost savings for fluoxetine.

Table 5.24 Cost analysis of fluoxetine 20mg capsules

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Prozac® 20mg Cap		2004	285	488.95±219.39	139 351.14
		2005	219	497.90±260.51	109 040.81
		2006	116	649.02±611.11	75 286.24
	Apo-Fluoxetine® 20mg Cap	2004	11	131.48±27.62	1 446.23
		2005	-	-	-
		2006	-	-	-
	A-Lennon Fluoxetine® 20mg Cap	2004	-	-	-
		2005	64	29.59±10.08	1 893.45
		2006	28	25.20±0.66	705.67
	Deprozan® 20mg Cap	2004	114	64.91±39.59	7 399.30
		2005	35	31.48±13.84	1101.84
		2006	3	43.16±18.69	129.48
	Lilly-Fluoxetine® 20mg Cap	2004	5 347	132.23±57.68	707 054.62
		2005	2 305	96.42±59.24	222 242.12
		2006	873	102.05±63.18	89 089.27
	Lorien® 20mg Cap	2004	5 613	66.56±52.88	373 581.19
		2005	3 589	38.59±14.62	138 489.45
		2006	2 081	41.51±13.12	86 91.36
	Nuzak® 20mg Cap	2004	11 624	81.87±50.06	951 714.88
		2005	4 915	41.84±15.04	205 654.67
		2006	2 551	44.50±15.35	113 514.28
	Prohexal® 20mg Cap	2004	1 232	76.99±51.70	94 849.60
		2005	431	38.81±11.48	16 726.71
		2006	80	48.40±18.87	3 872.13
	Ranflocs® 20mg Cap	2004	619	45.89±40.63	28 408.73
		2005	384	25.25±9.00	9 696.23
		2006	214	26.27±6.16	5 621.25
	Sandoz-Fluoxetine® 20mg Cap	2004	2 516	75.45±52.41	189 823.97
		2005	1 273	45.43±15.59	57 829.34
		2006	887	45.20±11.02	40 091.35
	Sanzur® 20mg Cap	2004	3	114.35±86.37	343.04
		2005	-	-	-
		2006	-	-	-
	Trizac® 20mg Cap	2004	-	-	-
		2005	-	-	-
		2006	3	21.37±0.59	64.11

There were various generic items for fluoxetine 20mg capsules on the database. From **2004 to 2006**, the **most expensive** generic product for fluoxetine 20mg was Lilly-Fluoxetine® 20mg. If only **50%** of Prozac® 20mg had been substituted with Lilly-Fluoxetine® 20mg cost savings of R 51 010.96 in **2004**, R 44 162.80 in **2005** and R 31 724.26 in **2006** (scenario 3) could have been achieved. If **all** of the prescribed Prozac® 20mg capsules had been replaced with Lilly-Fluoxetine® cost savings would have amounted to R 101 665.59 in **2004**, R 87 924.83 in **2005** and R 63 448.44 in **2006** (scenario 4).

In **2004** and **2005**, Ranflocs 20mg capsules were the **least expensive** generic product for fluoxetine 20mg. The cost savings could have been R 63 357.58 for **2004** and R 51 991.50 in

2005 if only **50%** of Prozac® 20mg had been substituted with Ranflocs® 20mg (scenario 1). If **100%** of Prozac® 20mg had been substituted with Ranflocs® 20mg the cost savings would have been R 126 272.49 in **2004** and R 103 511.06 in **2005** (scenario 2).

In **2006** the **least expensive** generic product for fluoxetine 20mg was Trizac® 20mg capsules. In a scenario where only **50%** of Prozac® 20mg could have been substituted with Trizac® 20mg the cost saving for 2006 could have been R 36 403.70 (scenario 1). If **all** the prescribed Prozac® 20mg could have been substituted with Trizac® 20mg the cost saving in **2006** could have amounted to R 72 807.32 (scenario 2).

The maximum potential cost saving for 2004 to 2006 for Fluoxetine® 20mg capsules could have been R 302 590.87 had 100% of Prozac® 20mg been substituted with the least expensive generic (capsule) for each year.

Table 5.25: Cost analysis of fluoxetine 20mg tablets

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Prozac® 20mg Tab		2004	334	269.47±191.68	90 003.48
		2005	102	214.84±124.70	21 913.57
		2006	21	234.48±119.45	4 924.01
	Lorien® 20mg Tab	2004	956	90.82±46.35	86 821.79
		2005	355	62.06±24.68	22 031.75
		2006	146	56.36±23.87	8 229.22
	Prohexal® 20mg Dispers Tab	2004	663	86.41±36.91	57 291.26
		2005	234	60.96±27.28	14 264.10
		2006	70	77.66±22.82	5 435.95

The **most expensive generic** product for fluoxetine 20mg tablets in **2004** and **2005** was Lorien® 20mg tablets. Cost savings of R 29 834.55 in **2004** and R 7 791.78 in **2005** could have been generated if **50%** of the prescribed Prozac® 20mg tablets were substituted with Lorien® 20mg tablets (scenario 3). If **all** of the prescribed Prozac® 20mg tablets were substituted with Lorien® 20mg tablets the cost savings for fluoxetine 20mg tablets would have been R 59 669.60 in **2004** and R 15 583.45 in **2005** (scenario 4).

The **least expensive** generic product for fluoxetine 20mg tablets for **2004 and 2005** were Prohexal® 20mg dispersible tablets. If **50%** of Prozac® 20mg tablets were substituted with Prohexal® the cost savings could have been R 30 571.02 for **2004** and R 7 847.88 for **2005** (scenario 1). **Maximum cost savings** of R 61 142.54 for **2004** and R 15 695.65 for **2005** could have been achieved if all prescribed Prozac® 20mg tablets were substituted with Prohexal® 20mg tablets (scenario 2).

In **2006** Lorien® 20mg tablets changed from being the most expensive in 2004 and 2005 to being the **least expensive generic**. If **50%** of Prozac® 20mg tablets were replaced with Lorien® 20mg tablets the cost saving would have been R 1 959.32 (scenario 1) and if **100%** were substituted the cost saving could have been R 3 740.45 for **2006** (scenario 2). Prohexal® 20mg dispersible tablets were the **most expensive** generic product for fluoxetine 20mg in **2006**. If **50%** of the prescribed Prozac 20mg tablets were substituted with Prohexal® the cost saving for **2006** would have been R 1 725.02 (scenario 3) and if **all** the prescribed Prozac® 20 mg tablets were substituted the cost savings would have been R 3 293.15 (scenario 4).

The maximum possible savings for fluoxetine 20mg tablets for 2004 to 2006 could have been R 80 578.64 if 100% of Prozac® 20mg tablets had been substituted with the cheapest generic tablet in each year.

5.7.9 Paroxetine

In table 5.26 and 5.27 the cost analysis of paroxetine is depicted to calculate possible cost savings for paroxetine.

Table 5.26: Cost analysis of paroxetine 20mg tablets

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Aropax® 20mg Tab		2004	15 802	346.30±132.09	5 472 161.68
		2005	7 374	300.14±106.99	2 213 234.65
		2006	1 192	245.79±176.28	292 979.16
	Adco-Paroxetine® 20mg Tab	2004	-	-	-
		2005	306	150.94±89.88	46 186.95
		2006	1 817	66.63±94.23	121 064.95
	Deparoc® 20mg Tab	2004	-	-	-
		2005	89	142.11±66.63	12 647.85
		2006	130	142.74±56.78	18 556.74
	Paxil® 20mg Tab	2004	-	-	-
		2005	156	190.73±55.36	29 754.64
		2006	1 375	192.94±62.46	265 291.08
	Parax® 20mg Tab	2004	-	-	-
		2005	-	-	-
		2006	80	240.90±86.64	19 271.82
	Sanoz Paroxetine® 20mg Tab	2004	-	-	-
		2005	198	196.08±50.71	38 823.52
		2006	632	188.26±36.47	118 978.74
	Serrapress® 20mg Tab	2004	-	-	-
		2005	3	179.36±67.88	538.08
		2006	31	131.40±92.43	4 073.29

There were no generic products for paroxetine 20mg in 2004. In **2005** the **most expensive** generic product for paroxetine 20mg was Sandoz-Paroxetine® 20mg In the case where **50%** of

Aropax® 20mg could be substituted with Sandoz-Paroxetine® 20mg the cost saving could have been R 378 466.22 (scenario 3). If **100%** of the prescribed Aropax® 20mg could be substituted with Sandoz-Paroxetine® 20mg the cost saving could have been R 767 340.73 (scenario 4).

In **2006** the **most expensive** generic product for paroxetine 20mg was Parax® 20mg. The cost saving for paroxetine 20mg could have been R 2 914.44 in **2006** if half of the prescribed Aropax® 20mg had been substituted with Parax® 20mg (scenario 3). If **100%** of the Aropax® 20mg had been substituted with Parax® 20mg the cost saving would have been R 5 826.36 in **2006** (scenario 4).

The **least expensive generic** item for 2005 was Deparoc® 20mg. If **50%** of the prescribed Aropax® 20mg could be replaced with Deparoc 20mg the cost saving would have been R 574 755.11 (scenario 1) and if **100%** of Aropax® 20mg could be replaced the cost saving could have been R1 165 315.51 in **2005** (scenario 2).

Adco-Paroxetine® 20mg was the **least expensive** generic item for paroxetine 20mg in 2006. If **50%** of the prescribed Aropax® 20mg could be substituted with Adco-Paroxetine® 20mg the cost saving for **2006** would have been R 106 779.36 (scenario 1). Maximum cost saving of R 213 556.20 for **2006** could have been achieved if **all** prescribed Aropax 20mg had been substituted with Adco-Paroxetine® (scenario 2).

The maximum possible cost saving for 2005 to 2006 could have been R1 458 294.67 for paroxetine 20mg tablets in scenario 2 if 100% of the Aropax® 20mg tablets had been substituted with the cheapest generic for each year.

Table 5.27: Cost analysis of paroxetine 30mg tablets

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Aropax® 30mg Tab		2004	-	-	-
		2005	212	365.84±139.10	77 559.34
		2006	91	452.29±215.13	41 158.47
	Serrapress® 30mg Tab	2004	-	-	-
		2005	-	-	-
		2006	37	269.81± 34.79	9 983.06

There were **no generic products** for paroxetine 30mg prescribed in **2004 and 2005**. The only generic item for paroxetine could have brought on a cost saving of R8 394.08 in **2006** if **50%** of Aropax 30mg had been substituted with Serrapress® 30mg (scenario 1).

If **all** the prescribed Aropax® 30mg had been substituted with Serrapress® 30mg the cost saving could have amounted to R16 605.76 for paroxetine 30mg in **2006** (scenario 2).

5.7.10 Fluvoxamine

In table 5.28 the cost analysis of fluvoxamine is depicted to calculate the cost savings for fluvoxamine.

Table 5.28: Cost analysis of fluvoxamine 100mg tablets

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Luvox® 100mg Tab		2004	2 577	375.36±198.34	967 292.25
		2005	620	450.26±211.77	279 163.76
		2006	398	478.96±195.53	190 626.12
	Hexal-Fluvoxamine® 100mg Tab	2004	-	-	-
		2005	13	251.44±75.48	3 268.70
		2006	19	282.97±85.73	5 376.35

Hexal-Fluvoxamine® was the only generic for fluvoxamine 100mg in **2005 and 2006**. The cost savings could have been R 61 634.20 in **2005** and R 39 002.01 in **2006** if only **50%** of Luvox® 100mg could be substituted with Hexal-Fluvoxamine® 100mg (scenario 1).

If **100%** of Luvox® 100mg could be substituted with Hexal-Fluvoxamine® 100mg the cost savings could have been R 123 270.96 in **2005** and R 78 004.06 in **2006** (scenario 2).

5.7.11 Sertraline

In table 5.29 and 5.30 the cost analysis of sertraline is depicted to calculate possible cost savings for sertraline.

Table 5.29: Cost analysis of sertraline 50mg tablets

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Zoloft® 50mg Tab		2004	6 531	368.06±157.07	2 403 813.56
		2005	2 582	278.67±107.06	719 531.17
		2006	1 071	245.98±91.10	263 448.35
	Serlife® 50 mg Tab	2004	856	269.99±111.52	231 108.65
		2005	888	209.16±72.33	185 738.12
		2006	794	225.49±62.36	179 036.02
	Merck Sertraline® 50mg Tab	2004	-	-	-
		2005	-	-	-
		2006	20	245.37±103.45	4 907.46
	Serdep® 50mg Tab	2004	-	-	-
		2005	-	-	-
		2006	8	269.35±150.46	2 154.76
	Sertzof® 50mg Tab	2004	-	-	-
		2005	162	225.40±67.80	36 515.06
		2006	309	221.14±44.01	68 332.24

In **2004 and 2005** Serlife® 50mg tablets were the **cheapest generic** available for Sertraline 50mg tablets. In scenario 1 where **50%** of Zoloft® 50mg could be substituted with the **least**

expensive generic the cost savings could have amounted to R 320 296.62 in **2004** and R 89 737.41 in **2005.** In scenario 2 where **100%** of Zoloft® 50mg tablets could be substituted with Serlife® 50mg tablets the cost savings could have been R 640 508.87 in **2004** and R 179 480.05 in **2005**.

The **least expensive** generic product for sertraline 50mg in **2006**, i.e. Sertzol® 50mg, would have brought on a cost saving of R13 314.24 if only **50 %** of the prescribed Zoloft® 50mg had been substituted with Sertzol® 50mg (scenario 1) and R26 607.41 if **all** of the prescribed Zoloft® 50mg for 2006 had been substituted (scenario 2).

Sertzol® 50mg tablets however, were the **most expensive** generic item for sertraline 50mg tablets in **2005**. There would, however, still have been a cost saving of R 68 771.57 if **half** of the prescribed Zoloft® 50mg for **2005** had substituted with Sertzol® 50mg (scenario 3). If **all** the prescribed Zoloft® 50mg had been substituted with Sertzol® 50mg there could have been a cost saving of R 137 548.37 for **2005** (scenario 4).

In **2006** the **most expensive** generic product for sertraline 50mg was Serdep® 50mg but it was more expensive than Zoloft® 50mg thus it was **excluded** because there were no cost savings possible.

Table 5.30: Cost analysis of sertraline 100mg tablets

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Serlife® 100mg Tab		2004	-	-	-
		2005	58	263.00±54.43	15 253.95
		2006	18	304.17±122.12	5 474.98
	Sertzol® 100mg Tab	2004	-	-	-
		2005	26	424.85±172.03	11 046.06
		2006	7	359.02±80.58	2 513.14

In **2004** there were **no sertraline** 100mg prescribed. Seeing that the average cost of Sertzol® 100mg, which was the generic product for sertraline 100mg, was higher than that of Serlife® 100mg there would have been **no possible cost savings for 2005 and 2006**.

5.7.12 Venlafaxine

In table 5.31 and 5.32 the cost analysis of venlafaxine is depicted to calculate possible cost savings for venlafaxine.

Table 5.31: Cost analysis of venlafaxine XR 75mg capsules

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Efexor® XR 75mg Cap		2004	5 086	444.64±161.37	2 261 459.90
		2005	4 482	416.38±144.34	1 866 199.10
		2006	2 858	434.87±132.74	1 242 856.27
	Venlor® XR 75mg Cap	2004	-	-	-
		2005	-	-	-
		2006	295	283.32±106.89	83 578.82

A cost saving of R 216 564.95 could have occurred in **2006** if **50%** of Efexor® XR 75mg had been substituted with Venlor® XR 75mg (scenario 1). If **100%** of the prescribed Efexor® XR 75mg had been substituted with Venlor® XR 75mg the cost saving for venlafaxine XR 75mg could have been R 433 127.71 for **2006** (scenario 2).

Table 5.32: Cost analysis of venlafaxine XR 150mg capsules

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Efexor® XR 150mg Cap		2004	2 070	828.10±295.25	1 714 163.32
		2005	1 490	742.40±246.72	1 106 182.91
		2006	967	827.37±182.50	800 067.42
	Venlor® XR 150mg Cap	2004	-	-	-
		2005	-	-	-
		2006	115	409.90±171.92	47 138.56

The only generic product for venlafaxine XR 150mg was Venlor® XR 150mg which only entered the South African market in 2006. The cost saving would have been R 202 055.48 in **2006** if only **half** of the prescribed Efexor® XR 150 mg had been substituted with Venlor® XR 150mg (scenario 1) and R 403 694.12 based on scenario 2.

5.7.13 Sulpiride

In table 5.33 the cost analysis of sulpiride is depicted to calculate the cost savings for sulpiride.

Table 5.33: Cost analysis of sulpiride 50mg capsules

Innovator medicine items	Generic medicine items	Year	Prevalence (n)	Average cost (R)	Total cost (R)
Eglonyl® 50mg Cap		2004	1 199	145.79±100.92	174 798.08
		2005	465	113.18±73.74	52 627.84
		2006	205	120.41±85.55	24 684.25
	Depex® 50mg Cap	2004	966	104.89±62.82	101 324.80
		2005	-	-	-
		2006	-	-	-
	Espiride® 50mg Cap	2004	3 556	113.71±83.93	404 349.86
		2005	2 265	82.91±54.90	187 800.70
		2006	1 275	93.47±57.63	119 179.49
	Sandoz Sulpiride® 50mg Cap	2004	-	-	-
		2005	398	82.11±53.39	32 678.38
		2006	439	84.62±66.62	37 147.54

From **2004 to 2006**, the **most expensive** generic item for sulpiride 50mg capsules, was Espiride® 50mg capsules. The cost savings could have been R 19 248.00 for **2004**, R 7 052.91 for **2005** and R 2 774.82 for **2006** if only **50%** of the prescribed Eglonyl® 50mg had been replaced with Espiride® 50mg (scenario 3). In the case where **all** the Eglonyl® 50mg could be replaced with Espiride® cost savings of R 38 459.79 for **2004**, R 14 074.69 for **2005** and R 5 522.90 for **2006** could have occurred (scenario 4).

In **2004** the **least expensive** generic product for sulpiride 50mg was Depex® 50mg. If **50%** of the prescribed Eglonyl® 50mg had been substituted with Depex® 50mg the cost saving could have been R 24 540 (scenario 1) and if **all** the prescribed Eglonyl® 50mg had been replaced the cost saving for **2004** could have been R 49 034.97 (scenario 2).

In **2005 and 2006** the **least expensive** generic product was Sandoz Sulpiride® 50mg. The cost savings could have been R 7 239.31 for **2005** and R 3 686.37 for **2006** if only **50%** of Eglonyl® 50mg had been replaced with Sandoz Sulpiride® 50mg (scenario 1). If **all** the prescribed Eglonyl® 50mg had been replaced with Sandoz Sulpiride® the cost savings would have been R 14 446.69 for **2005** and R 7 337.15 for **2006** (scenario 2).

The maximum potential cost saving for sulpiride 50mg for 2004 to 2006 could have been R 70 818.81 if all the prescribed Eglonyl® 50mg had been substituted with the cheapest generic item for each year.

5.7.14 Summary on potential cost savings

From tables 5.34 and 5.35 the possible cost savings for each scenario according to active ingredient on the database are depicted. Table 5.34 summarises the cost savings for each

active ingredient if 100% of the innovator items were to be substituted with the least and most expensive generic products for each specific ingredient.

Table 5.34: Cost savings for antidepressants for 2004-2006 if 100% of innovator items are substituted with the most and least expensive generic items

Active Ingredient	Cost savings (R)					
	2004		2005		2006	
	Most expensive	Least Expensive	Most expensive	Least expensive	Most expensive	Least expensive
Amitriptyline 10mg tab	-	35.54	-	-	-	-
Amitriptyline 25mg tab	46 440.94	58 711.65	12 615.46	12 628.06	-	4 736.28
Clomipramine 10mg tab	-	5 038.81	-	4 463.12	-	1 365.34
Clomipramine 25mg Tab	42 606.26	93 670.28	15 918.58	17.108.98	3 195.14	7 804.94
Dothiepin 25mg Cap	33 727.10	35 578.86	8 241.93	8 547.18	1 402.46	2 808.86
Dothiepin 75mg Tab	15 259.20	19 660.60	-	2 215.99	126.07	879.13
Imipramine 10mg Tab	-	32 833.84	-	-	-	807.53
Imipramine 25mg Tab	-	109 174.94	-	20 199.43	-	4 175.41
Trimipramine 50mg Cap	-	18 402.89	-	-	-	-
Moclobemide 150mg Tab	18 797.87	38 143.25	6 806.78	8 207.75	2 809.35	3 348.63
Moclobemide 300mg Tab	11 788.00	12 435.92	347.71	531.11	10 956.25	11 076.52
Citalopram 20mg Tab	706 859.14	992 216.41	354 499.86	489 959.86	199 540.25	219 368.54
Fluoxetine 20mg Cap	101 665.59	126 272.49	87 924.83	103 511.06	63 448.44	72 807.32
Fluoxetine 20mg Tab	59 669.60	61 142.54	15 583.45	15 695.65	3 293.15	3 740.45
Paroxetine 20mg Tab	-	-	767 340.73	1 165 315.51	5 826.36	213 556.20
Paroxetine 30mg Tab	-	-	-	-	-	16 605.76
Fluvoxamine 100mg Tab	-	-	-	123 270.96	-	78 004.06
Sertraline 50mg Tab	-	640 508.87	137 548.37	179 480.05	-	26 607.41
Sertraline 100mg Tab	-	-	-	-	-	-
Venlafaxine XR 75mg Cap	-	-	-	-	-	433 127.71
Venlafaxine XR 150mg Cap	-	-	-	-	-	403 694.12
Sulpiride 50mg Cap	38 459.79	49 034.97	14 074.69	14 446.69	5 522.90	7 337.15
Total cost savings	**1 075 273.49**	**2 292 861.86**	**1 420 902.39**	**2 303 129.71**	**296 120.37**	**1 511 043.83**

The **maximum cost saving** could occur when 100% of all innovator items are substituted with the cheapest generic. This could give an estimated cost saving of R 6 107 035.40 for 2004 to 2006, which is 10.87% (n = R 56 183 697.91) of the actual antidepressant cost on the database for 2004 to 2006. The individual cost savings for each year and each active ingredient are depicted in table 5.34.

The **lowest cost saving** could occur if 100% of innovator items are substituted with the most expensive generic items and the cost savings for the three study years could have been estimated at R 2 792 296.25, which is 4.97% (n = R 56 183 697.91) of the actual antidepressant cost on the database.

These cost savings are, however, difficult to achieve in practice seeing that there will always be patients and prescribers who will prefer the innovator product. Table 5.35 depicts a more realistic scenario where only 50% of the innovator items of each active ingredient are substituted.

Table 5.35: Cost savings for antidepressants for 2004-2006 if 50% of innovator items are substituted with the most and least expensive generic items

Active Ingredient	Cost savings (R)					
	2004		2005		2006	
	Most expensive	Least expensive	Most expensive	Least expensive	Most expensive	Least expensive
Amitriptyline 10mg tab	-	17.77	-	-	-	-
Amitriptyline 25mg tab	23 219.84	29 355.52	6 287.40	6 313.65	-	1 112.85
Clomipramine 10mg tab	-	2 519.65	-	2 250.60	-	682.64
Clomipramine 25mg Tab	21 339.76	46 916.80	7 959.60	8 554.80	1 597.70	3 902.60
Dothiepin 25mg Cap	16 862.15	17 788.03	4 143.15	4 296.60	701.20	1 484.40
Dothiepin 75mg Tab	7 650.17	9 856.77	-	1 108.08	63.00	439.53
Imipramine 10mg Tab	-	16 416.96	-	-	-	420.44
Imipramine 25mg Tab	-	54 625.32		10 120.95	-	2 087.94
Trimipramine 50mg Cap	-	9 201.60	-	-	-	-
Moclobemide 150mg Tab	9 451.80	13.074.10	3 454.06	4 165.00	1 404.62	1 684.48
Moclobemide 300mg Tab	5 894.20	6 218.16	198.68	303.48	5 766.40	5 829.70
Citalopram 20mg Tab	353 471.82	496 173.39	177 299.21	245 055.21	99 885.10	109 810.68
Fluoxetine 20mg Cap	51 010.96	63 357.58	44 162.80	51 991.50	31 724.26	36 403.70
Fluoxetine 20mg Tab	29 834.55	30 571.02	7 791.78	7 847.88	1 725.02	1 959.32
Paroxetine 20mg Tab	-	-	378 466.22	574 755.11	2 914.44	106 779.36
Paroxetine 30mg Tab	-	-	-	-	-	8 394.08
Fluvoxamine 100mg Tab	-	-	-	61 634.20	-	39 002.01
Sertraline 50mg Tab	-	320 296.62	68 771.57	89 737.41	-	13 314.24
Sertraline 100mg Tab	-	-	-	-	-	-
Venlafaxine XR 75mg Cap	-	-	-	-	-	216 564.95
Venlafaxine XR 150mg Cap	-	-	-	-	-	202 055.48
Sulpiride 50mg Cap	19 248.00	24 540.00	7 052.91	7 239.31	2 774.82	3 686.37
Total cost savings	**537 983.22**	**1 187 845.95**	**705 587.38**	**1 144 145.35**	**148 556.56**	**755 614.77**

A more **realistic cost saving** occurs where 50% of all innovator items are substituted with the cheapest generic and could have been R 3 087 606.07 for 2004 to 2006, which is 5.50% (n = R 56 183 697.91) of the actual antidepressant cost on the database for 2004 to 2006.

The **lowest cost saving of the four hypothetical** scenarios occurred if 50% of the innovator medicines were substituted with the most expensive generic antidepressant and this cost saving was R1 392 127.16 from 2004 to 2006, which is 2.48% (n = R 56 183 697.91) of the actual antidepressants cost on the database for 2004 to 2006.

In this section the cost savings for each antidepressant active ingredient in four hypothetical scenarios were calculated for the three study years except where there was no generic product available or where the generic product was more expensive than the innovator product. These scenarios indicate that the medicine claims processing company could have saved up to 10.87% on mental health care cost in 2004 to 2006, thus the total cost of antidepressants could have been R 50 076 662.51 instead of R 56 183 697.91. These estimated cost savings

correspond with the estimated cost savings of the study conducted by Karim *et al.* (1996:198) (refer to section 3.5).

5.8 CHAPTER SUMMARY

In this chapter the prescribing patterns and cost of all the medicine claimed through the medicine claims processing company, CNS agents and antidepressants for 2004 to 2006 were discussed. Various variables such as age, gender and potential drug-drug interactions and combinations were brought into consideration. Finally cost savings for four hypothetical scenarios for each active ingredient according to strength was calculated and discussed.

In the following chapter conclusions regarding the results that were found in this chapter will be discussed, and the research questions that were stated in paragraph 4.3 will be answered.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

6.1 INTRODUCTION

In this chapter the limitations for this study will be stated. Conclusions for the literature review as well as the empirical investigation research questions as stated in chapter four will be discussed. Recommendations for future studies will be made according to results and conclusions from this study.

6.2 LIMITATIONS

There were various limitations for this study that could have influenced the accuracy and the scope of this study. The following limitations should be taken into account when interpreting this study:

- The data used in this study were obtained from one South African medicine claims processing company (pharmaceutical benefit management company or PBM), thus no direct manipulation of data was possible by the researcher and the results can only be generalised to the specific database used, and to the specific study population.
- The datasets were verified by testing for outlying data, as well as by performing random data checks.
- Data were analysed from the perspective that the information was exact and accurate on the PBM database.
- Numerical values were mostly rounded off to two decimal places. It may thus happen in some cases that the percentages do not add up to a hundred per cent.
- Demographic information, such as age and gender, was available for 2006 only and it was not indicated on all prescriptions (as stated in chapter five). Demographic information related to race was not available on the database.
- It is not indicated on the database whether these prescriptions were new prescriptions or repeat prescriptions. The diagnosis was also not indicated on the database; therefore it could not be determined whether the prescription was for an acute or chronic condition or specific treatment option. Assumptions of treatments according to age due to the nature

of treatments were made. Thus patient compliance and the success of the antidepressant therapy could not be determined. It was assumed that if a patient received an antidepressant it was prescribed for depression.

- Clinical implications of interactions were not determined in this study.

6.3 CONCLUSIONS

The following conclusions were made for the specific research questions that were stated in sections 1.4 (and 4.3):

- The **fist specific research objective** was to *review depression as an illness and its treatment from the literature.*

This objective was achieved through a literature investigation of various aspects of depression in chapter two. These aspects included the definition of the different types of depression, the pathophysiology, aetiology, measurement of the severity of depression and the diagnosis of depression. Furthermore, the management of depression, drug interactions of antidepressants with other medication, patient compliance and risk of suicide and toxicity were discussed.

It was found that there are various types of depression and it was stated in chapter two that depression is best treated with a combination of cognitive therapy and medicine treatment.

According to Taylor (2002) bipolar mood disorder must be treated with lithium salt or carbamazepine, but usually after the manic episode has been controlled with an antipsychotic such as haloperidol. The maintenance therapy for bipolar mood disorder is lithium, taken orally in divided doses. Another alternative for maintenance therapy is carbamazepine orally two to three times per day or sodium valproate orally three times per day as a mood stabiliser (Taylor, 2002). Taylor (2002) states that major depressive disorder must be treated with tricyclic antidepressants (TCAs) except in patients with cardiac conduction disturbances or high suicide risk and seeing that it is lethal in overdose the dosage must be started at lower than therapeutic doses and titrated up to therapeutic dosage within seven days. Selective serotonin re-uptake inhibitors (SSRIs) should be used for patients with contra-indications to TCAs but must only be prescribed by a psychiatrist. Major depressive disorder must be treated for duration of at least six months (Taylor, 2002).

According to the algorithm for the treatment of depression, treatment must be continued for at least 4-6 months after a recovery has been made. It can be concluded that depression is a

complex disease because the physical signs are sometimes difficult to observe and this may influence the successful diagnosis and treatment of depression.

❖ The **second specific research objective** was to *discuss managed care, drug utilisation studies, pharmacoeconomic analysis and generic substitution as related to antidepressants.*

This objective was achieved through a literature review of the above-mentioned aspects. These terms were defined and discussed in chapter three. Managed care was discussed as related to the South African setting. The aspects of drug utilisation studies, pharmacoeconomic analysis and generic substitution were illustrated by means of examples of antidepressant studies.

Managed care, drug utilisation studies, pharmacoeconomic studies and generic substitution are all techniques that are used to reduce medicine costs. The examples of drug utilisation studies, pharmacoeconomic studies and generic substitution that were discussed in chapter three were done to determine the prescribing patterns of antidepressants and the effectiveness of antidepressants as related to costs (refer to section 3.3-3.5)

The economic burden of health care in South Africa may be reduced if methods of cost saving are practised to their full potential.

❖ The **third specific research objective** was to *determine the prescribing patterns and cost of antidepressants relevant to other central nervous system stimulants (CNS) and all medicines claimed through the medicine claims processing company for 2004 to 2006.*

In section 5.2.1, the following results regarding an analysis on all medicine items, CNS items and antidepressants claimed through the PBM were obtained:

The total number of medicine items prescribed decreased from 5 305 846 in 2004 to 3 606 992 in 2005 and 2 370 572 in 2006 (55.32%). CNS medicine items accounted for 8.6% of the total number of medicines (n = 5 305 846) prescribed in 2004. In 2005 the number of CNS medicine items declined to 7.4% of all medicine items prescribed (n = 3 606 992) in 2005, compared to only 6.45% of all medicine items (n = 2 370 572) in 2006. In 2004, antidepressants accounted for 2.97% (n = 5 305 846) of all medicine items prescribed. Antidepressant represented 2.40% (n = 3 606 992) of all items prescribed in 2005 and 2.01% (n = 2 370 572) of that in 2006. Antidepressants, however, represented 34.72% (n = 454 551), 32.50% (n = 266 228) and 31.25% (n = 152 787) of all CNS medicines during 2004, 2005 and 2006 respectively (refer to section 5.2.1).

The average cost for all medicines claimed through the database decreased with 9.7% from R 124.62 ± R 228.55 per item during 2004 to R 112.51 ± R 226.99 per item during 2005 and increased slightly during 2006 with 4.67% to R 117.76 ± R 237.81 per item. The average cost of CNS agents was R 163.54 ± R 197.91 in 2004; it decreased to R 144.30 ± R 192.12 in 2005 and increased in 2006 to R 154.41 ± R 224.46. The average cost in 2006 was, however, still lower than the average cost of a CNS agent in 2004. The average cost for an antidepressant medicine item also decreased from R 204.82 ± R 186.14 per item in 2004 to R 180.45 ± R 204.20 during 2006. The cost-prevalence index (CPI) for CNS agents as well as antidepressants was calculated for each year and this indicated that the cost of CNS agents as well as antidepressants was both relatively expensive compared to the total medicine expenditure on the database as the cost-prevalence index was higher than 1 in all cases (refer to section 5.2.1).

From these results it can be concluded that the prevalence of all medicine items claimed, CNS items and antidepressants all decreased from 2004 to 2006. This may be attributable to the decline of 56% in the number of medical schemes administrated by the medicine claims processing company from 2004 to 2006 (refer to section 5.2.1). The average cost of all medicine items claimed through the PBM, CNS items and antidepressants also decreased from 2004 to 2006. The decrease in the average cost of all medicine items may be mainly attributable to the implementation of the single exit pricing system on the 2nd of May 2004 (Tshabalala-Msimang, 2004) (refer to section 3.6).

❖ The **fourth specific research objective** was to *compare the prescribing patterns and cost of generic and innovator medicine items for all medicines claimed through the database, CNS medicine items and antidepressants.*

In section 5.2.2 it was found that the total percentage of innovator items on the database declined by 6.7% between 2004 and 2006, and a total cost percentage decrease of 5.95% was observed. CNS innovator medicine items remained relatively stable during the study period with a relatively steady change of 2.58% from January 2004 to December 2006. This decrease in innovator items can be directly linked to the 2.58% increase in generic CNS agents. However, a decrease of 3.24% was documented in the total cost percentage of CNS generic items from 2004 to 2006. The prevalence of antidepressant generic items increased by 4.63% from 2004 to 2006, while the total cost percentage of innovator antidepressants increased with 5.4% during the study period, thus indicating that innovator items still have a substantial impact on the mental health care costs (refer to section 5.2.2).

The effect sizes (*d*-value) for the difference between the average cost of the innovator and generic items were calculated for the total database, CNS agents and antidepressants for each study year. The antidepressants constituted the only group where the effect size for each year was higher than 0.8, an indication that the innovator products were practical significantly more expensive than the generic product (refer to table 5.3).

❖ The **fifth specific research objective** was to *determine the general prescribing patterns and cost of the antidepressants claimed through the medicine claims processing company for 2004 to 2006.*

In table 5.4. it is depicted that the usage of antidepressants varied between 5.31% and 5.95% of the total number of prescriptions claimed during each study period for 2004. In 2005 the usage of antidepressants varied between 4.84% and 5.34% of the total number of prescriptions claimed through the medicine claims processing company only slightly lower than 2005. The usage of antidepressants in 2006 was between 4.40% and 4.64% of the total number of prescriptions claimed. This indicated that the usage of antidepressants remained relatively constant for 2004 to 2006.

It can be assumed from the data in table 5.5 that there was an average of just more than one antidepressant item on a prescription (average number of items per prescription = 1.1).

The total cost of these items increased from the first time-period (January-April 2004) to the second period (May-August 2004), where after a decline in total cost was observed during the last period of 2004, to a value below that of the initial first period (a total reduction of 4.2%). There was an increase of 12.90% in the total cost from January 2005 to August 2005 as well as an overall reduction of 1.57% in the total cost of antidepressants from January 2005 to December 2005. The total cost decreased consecutively from January 2006 to December 2006. The reduction in the total cost from January 2006 to December 2006 was 2.16%. The average cost for an antidepressant item in 2004 was R 204.82 ± R 186.14 compared to R 176.21 ± R 178.81 in 2005 and R 180.45 ± R 204.20 in 2006. On average, medicine items were 14% cheaper in 2005 and 2006 compared to 2004. There was an average cost decrease of R27.97 ± 1.9% between P1 and each of the other study periods (P2-P9) from 2004 to 2006 (refer to section 5.3.1).

❖ The **sixth specific research objective** was to *determine the possible influence of generic substitution on the prescribing patterns and cost of antidepressants claimed through the medicine claims processing company.*

Generic items constituted 58.99% (n = 157 810) of all antidepressants claimed during 2004, 56.49% (n = 86 521) during 2005 and 63.30% (n = 47 740) during 2006 (refer to section 5.3.2).

There was a consecutive decrease in the average cost for generic antidepressants over the three study periods in 2004 (refer to table 5.8). In 2005 the average cost per item of generic medicine items continued to decrease from 2004 until the second period of 2005 (May to August). The average cost for generic antidepressants in 2005 was lower than that of generic items in 2004, with a reduction of R 40.13 ± R 29.09 (36.46%). There was an increase of 6.5% in the average cost for generic antidepressants in 2006 from 2005, but the average cost for generic antidepressants was still lower for 2006 than in 2004 (refer to section 5.3.2).

The cost-prevalence index (CPI) was calculated for innovator and generic medicine items for each study period and indicated that innovator antidepressants were relatively expensive compared to the generic items (refer to section 5.3.2).

❖ The **seventh specific research objective** was to *analyse the prescribing patterns of antidepressants according to age and gender for 2006.*

In 2006 a total of 44 938 antidepressant prescriptions were claimed (refer to table 5.2). The age of the patient was indicated on 44 915 prescriptions (99.95% of all antidepressant prescriptions in 2006) and the gender of the patient was indicated on 27 004 prescriptions (60.09% of all antidepressant prescriptions in 2006) (refer to table 5.9).

Results of table 5.9 revealed that 3.92% of the prescriptions (n = 44 915) (where the age was indicated and who received antidepressant therapy) were for patients in the age group between 10 and 19 years of age; compared to 0.95% (n=44 915) in the age group 9 years or younger. Antidepressant prescriptions was the highest in the age group older than 19 to 43 years of age with a percentage of 42.72% (n = 44 915). The second highest number of antidepressant prescriptions was for the age group of older than 43 to the age of 58 years with a percentage of 35.06% (n = 44 915). These two age groups account for 77.78% (n = 44 915) of all the antidepressant prescriptions that had age indicated on them.

In all the age groups the most prevalent active ingredient claimed in 2006 was tricyclic antidepressants (TCAs). In children (defined as patients with an age younger than 19 years), the most prescribed ingredient from the tricyclic antidepressant group was imipramine. According to Drutz and Tu (2006) tricyclic antidepressants are sometimes used to manage nocturnal enuresis (bedwetting), this may explain the high prevalence of TCAs in this age group. Amitriptyline was the active ingredient from the tricyclic antidepressant group that was

mostly prescribed to those older than 19 years. SSRIs was the most prevalent pharmacological category in patients above the age of 9 years.

Prescriptions of antidepressants to female patients represented 42.26% (n = 44 915) compared to 17.86% prescribed to male patients (refer to table 5.9). These results may be a confirmation of the statement in section 2.3.1 that women have a higher risk of developing depression than men (Gelder *et al.,* 1999:137).

According to the literature (refer to figure 2.2) antidepressant therapy must be maintained for 4-6 months for an episode to fully remit. Results of this study (refer to table 5.11) indicated that 67.95% of children below the age of 10 and 34.82% of adults above the age of 59 years only receive one prescription per year. Only 2.99% to 6.86% of all patients receive four prescriptions for antidepressants per year and only 1.71% to 5.36% receive six prescriptions per year. These prescribing patterns can influence the efficacy of antidepressant therapy negatively.

In table 5.11 it can be seen that the average number of prescriptions that a patient receives per year increases as the age of the patient increases. Although the age group larger than 59 does not have the highest prevalence for antidepressants they do have the highest average number of prescriptions per year. General practitioners explain that late-life depression may occur because of loneliness, lack of social network, and a reduction in functioning (Burroughs *et al.*, 2006:369). According to Hansen *et al.* (2007) antidepressants are used for relief of this sadness and loneliness.

The cost-prevalence index (CPIs) for each age group and gender is depicted in table 5.9. In the age group older than 19 and younger than 44 years of age the CPI for both male and female gender groups was higher than one, in the age group older than 44 and younger than 59 years of age the CPI was 1.07. This indicates that in these groups the cost of antidepressants was fairly expensive compared to the total cost of all the prescriptions that had an age indicated on them.

❖ The **eighth specific research objective** was to *compare the prescribing patterns of different classes of antidepressants according to the Monthly Index of Medical Specialities (MIMS)-classification system.*

Antidepressants are classified into seven categories according to the MIMS classification system (Snyman, 2007:15). The most prevalent pharmacological category in this study was firstly SSRIs followed by tricyclic antidepressants for all nine study periods (refer to figure 5.4).

The average costs of tricyclics (TCAs) were much lower than those of selective serotonin re-uptake inhibitors (SSRIs), with a difference of between R 87.03 and R 137.48 from 2004 to 2006 (refer to Appendix C, table 3c). Despite these statistics, SSRIs were more prevalent than TCAs on the database (refer to Appendix C, table 3c). SSRIs had the highest total cost of all antidepressants prescribed on the database except during the time period January to March 2006; when serotonin and noradrenaline re-uptake inhibitors (SNRIs) had the highest total cost. The high cost of SNRIs is also illustrated in figure 5.4 seeing that it was not that prevalent but still had quite a high total cost compared to some of the other classes (refer to section 5.4).

The effect size (*d*-values) for the difference in average cost between TCAs and all the other pharmacological classes was larger than 0.8 (refer to Appendix C, table 4c) indicating that these differences in average cost was of high practical significance. The effect sizes for the average cost between non-tricyclics and SSRIs were also higher than 0.8 for all three years, which indicates that the difference between the average cost of SSRIs and non-tricyclics antidepressants was also of practical significance.

❖ The **ninth specific research objective** was to *investigate the prescribing patterns and cost of antidepressants based on active ingredients.*

The most common prescribed antidepressants for 2004 on the database (in descending order) were as follows: fluoxetine (18.87%), citalopram (17.77%), amitriptyline (17.48%), paroxetine (10.27%) and venlafaxine (13.65%) (refer to section 5.5). In 2005 and 2006 the five most prescribed active ingredients was the same as in 2004 but amitriptyline (2005 = 19.11%; 2006 = 20.09%) was the most prevalent followed by fluoxetine (2005 = 16.31%; 2006 = 14.96%), citalopram (2005 = 14.78%; 2006 = 12.03%), paroxetine (2005 = 9.64%; 2006 = 11.84%) and then venlafaxine (2005 = 7.12%; 2006 = 9.04%).

The CPI was calculated for all antidepressant active ingredients (refer to Appendix C, table 5c). Only 6 of the 29 active ingredients were relatively inexpensive for all nine study periods; i.e.: fluoxetine, amitriptyline, sulpiride, imipramine, dothiepin and fluphenazine/nortriptyline. The majority of active ingredients (14 of 29) however, had a CPI of higher than 1 for all nine study periods which indicates that these items were relatively expensive. This may cause some concern seeing that the aim of the National Drug Policy is to provide medicines at the lowest possible costs (South Africa, 1996) (refer to section 5.5).

❖ The **tenth specific research objective** was to *examine the drug interactions that may occur with antidepressant medicine therapy.*

In 2004, 7.03% (n = 146 905) of all antidepressants prescribed on the database were combination therapy prescriptions. This number decreased to 5.5% in 2005 to rise to 5.93% of all antidepressants prescribed in 2006.

In 2004, 50.75% (n = 146 905) of all combinations prescribed on the database showed a drug-drug interaction with a significance rating of between 1 and 5. In 2005 the number of drug-drug interactions increased to 53.64% (n = 4 502), and in 2006 the medication interaction for combination therapy was 55.16% (n = 2 665) (refer to Appendix C, table 7-9c). The drug-drug interactions with a significance rating of one and two according to Tatro (2002: xiv), which are severe and well-documented interactions as indicated in section 2.9, were respectively 79.45% (n = 5 247) in 2004, 65.76% (n = 2 415) in 2005 and 51.56% (n = 1 470) in 2006 of all interactions that occurred on the database during the study period (refer to section 5.5.1). The interactions that occurred with combination therapy were indicated in Appendix A, table 7-9c. This number of drug-drug interactions may be a definite cause for concern seeing that interactions with a significance rating of one and two may lead to hospitalisation (Tatro, 2002:xiv) (refer to section 2.9). The clinical implications of these interactions, however, fall outside the scope of this study and were therefore not determined.

❖ The **eleventh specific research objective** was to *examine the prevalence and cost of the top ten antidepressants according to trade name.*

The top ten antidepressant products accounted for 67.23% (n = R 32 323 356.78), 67.12% (n = R 15 245 709.85) and 55.63% (n = R 8 614 631.29) of the total cost of all antidepressants prescribed in 2004, 2005 and 2006 respectively. In 2004 and 2005, Aropax® (paroxetine 20mg) had the highest total cost and represented 26% and 21% of the top ten agents respectively in 2004 and 2005. The total cost of Cilift® was ranked second in 2004 and was 19% of the top ten antidepressant total costs as illustrated in figure 5.5a. In 2005 Efexor® XR (venlafaxine 75mg) was ranked second according to total cost as indicated in figure 5.5b and accounted for 18% of the top ten antidepressant cost. Efexor® XR 150mg was ranked second (17% of the top ten antidepressants according to total expenditure) according to total expenditure and this can be attributed to its high average of R 827.37 ± R 182.50 which made Efexor® XR 150mg the third most costly antidepressant in 2006. In 2006 Efexor® XR 75mg had the highest total cost, accounting for 26% of the top ten antidepressants. The most expensive antidepressant from 2004 to 2006 was Prozac® SI (fluoxetine 60mg) with an average cost of R 1 014.91 ± R 345.27 in 2004, R 938.75 ± R 311.58 in 2005 and R 1 279.02 ± R 0.00 in 2006 (Appendix C, table 10c) (refer to section 5.6).

❖ The **twelfth specific research objective** was to *determine the cost savings that can be achieved with generic substitution by conducting hypothetical scenarios.*

The maximum possible cost saving occurs when 100% of all innovator items are substituted with the cheapest generic. Results of this study indicated an estimated maximum saving of R 6 107 035.40 for the total study period, which is 10.87% (n = R 56 183 697.91) of the actual cost of antidepressants on the database. The lowest possible cost saving occurs when 100% of all innovator items are substituted with the most expensive generic items. The minimum possible cost saving calculated for this study was R 2 792 296.25, which represented 4.97% (n = R 56 183 697.91) of the actual cost of antidepressants on the database (refer to section 5.7). These cost savings are, however, difficult to achieve in practice seeing that there will always be patients and prescribers who will prefer the innovator product.

A more realistic cost saving occurs where 50% of all innovator items are substituted with the cheapest generic. Results of this study indicated a saving of R 3 087 606.07 for the total study period, representing 5.50% (n = R 56 183 697.91) of the actual cost of antidepressants on the database for 2004 to 2006.

These scenarios indicate that the PBM company could have saved up to R 6 107 035.40 or 10.87% of its costs on mental health care during the time period January 2004 to December 2006 (refer to section 5.7). These cost savings correspond with a study conducted by Karim *et al* (1996:198) who concluded that generic prescribing and substitution have the potential to reduce medicine costs by nearly 10 % if it is practised to the maximum capacity (refer to section 3.5).

6.4 RECOMMENDATIONS

The following recommendations can be made at the completion of this study:

- The indirect cost of depression, such as the cost due to loss of productivity, should be further investigated.
- Hospitalisation costs due to antidepressant overdose or drug-drug interactions should be investigated.
- The clinical diagnosis must be identified on prescriptions via an acceptable classification system such as the ICD-10 codes to determine whether the prescription was for an acute or chronic condition. This can be used to determine patient compliance and antidepressant therapy effectiveness.

- Patient compliance should be examined to determine the success of antidepressant therapy.
- The cost savings for all medicines claimed through the PBM should be estimated to determine the impact of generic substitution on the health care budget.

6.5 CHAPTER SUMMARY

In this chapter the limitations of this study were noted, the concluding remarks on all research questions were made and discussed and recommendations for future studies were made.

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APPENDIX A

The Hamilton rating scale for depression (HRSD) (Hamilton, 1979: 6)

1. Depressed mood

   0=Absent

   1=These feelings states indicated only on questioning

   2=These feelings states spontaneously reported verbally

   3=Communicates feeling states non-verbally – i.e. Through facial expression, posture, voice, and tendency to weep

   4=Patient reports virtually only these feeling states in his spontaneous verbal and non-verbal communication

2. Feelings of guilt

   0=Absent

   1=Self reproach, feels he has let people down

   2=Ideas of guilt or rumination over past errors or sinful deeds

   3=Present illness is a punishment. Delusions of guilt

   4=Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. Suicide

   0=Absent

   1=Feels life is not worth living

   2=Wishes he were dead or any thoughts of possible death to self

   3=Suicidal ideas or gesture

   4=Attempts at suicide (any serious attempt rates 4)

4. Insomnia Early

0=No difficulty falling asleep

1=Complains of occasional difficulty falling asleep – i.e. more than half hour

2=Complains of nightly difficulty falling asleep.

5. Insomnia middle

0=No difficulty

1=Patient complains of being restless and disturbed during the night

2=Waking during the night – any getting out of bed rates 2 (except for the purpose of voiding)

6. Insomnia late

0=No difficulty

1=Waking in early hours of the morning but goes back to sleep

2=Unable to fall asleep again if he gets out of bed

7. Work and activities

0=No difficulty

1=Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies

2=Loss of interest in activity; hobbies or work –either directly reported by patient, or indirect in listlessness, indecision and vacillation 9feels he has to push self to work or activities)

3=Decrease in actual time spent in activities or decrease in productivity

4=Stopped working because of present illness

8. *Retardation: Psychomotor (slowness of thought and speech; impaired ability to concentrate; decreased motor activity)*

0=Normal speech and thought

1=Slight retardation at interview

2=Obvious retardation at interview

3=Interview difficult

4=Complete stupor

9. Agitation

0=None

1=Fidgetiness

2=Playing with hands, hair, etc

3=Moving about, can't sit still

4=Hand wringing, nail biting, hair-pulling, biting of lips

10. Anxiety

0=No difficulty

1=Subjective tension and irritability

2=Worrying about minor matters

3=Apprehensive attitude apparent in face or speech

4=Fears expressed without questioning

11. Anxiety Somatic: Physiological concomitants of anxiety, (i.e., effects of autonomic over activity, "Butterflies", indigestion, stomach cramps, blenching, diarrhoea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e. dry mouth, constipation)

0=Absent

1=Mild

2=Moderate

3=Severe

4=Incapacitating

12. Somatic symptoms (gastrointestinal)

0=None

1=Loss of appetite but eating without encouragement from others. Food intake about normal

2=Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. Somatic Symptoms General

0=None

1=Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability.

2=Any clear-cut symptom rates 2

14. Genital symptoms (symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

0=Absent

1=Mild

2=Severe

15. Hypochondriasis

0=Not present

1=Self-absorption (bodily)

2=Preoccupation with health

3=Frequent complaints, requests for help, etc.

4=Hypochondriacal delusions

16. Loss of weight

A. When rating by history:

0=No weight loss associated with present illness

2=Definite (according to patient) weight loss

3=Not assessed

17. Insight

0=Acknowledges being depressed and ill

1=Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.

2=Denies being ill at all

18. Diurnal variation

A. Note whether symptoms are worse in morning or evening. If No diurnal variation, mark none

0=No variation

1=Worse in A.M.

2=Worse in P.M.

B. When present, mark the severity of the variation. Mark "None" if No variation

0=None

1=Mild

2=Severe

19. Depersonalization and derealization (Such as: Feelings of unreality; Nihilistic ideas)

0=Absent

1=Mild

2=Moderate

3=Severe

4=Incapacitating

20. Paranoid Symptoms

0=None

1=Suspicious

2=Ideas of reference

3=Delusions of reference and persecution

21. Obsessional and compulsive symptoms

0=Absent

1=Mild

2=Severe

APPENDIX B

Table 1b: Montgomery-Asberg Depression rating scale (Montgomery & Åsberg, 1979: 134)

Purpose: To evaluate a person for depression using the Montgomery and Asberg Depression Rating Scale (MADRS).								Citations with documentation. 18.04.10	Medal Project 2001. See disclaimer.
data	**enter**								
Are you evaluating a person for depression? (Y or N)	Y								
enter an "x" in the appropriate column for each item (give only 1 answer per row)									
	None 0	1	looks dispirited but brightens up 2	3	sad and unhappy most of the time 4	5	looks miserable all of the time 6		
apparent sadness						x		Yes	5
	occasional sadness		sad or low but brightens up		pervasive sadness or gloominess		continuous sadness or despondency		
reported sadness						x		Yes	5
	placid		occasional edginess or discomfort		continuous tension but can master		unrelenting dread, panic or anguish		
inner tension						x		Yes	5
	sleeps as usual		slight difficulty		reduced or broken up		less than 2-3 hours of sleep		
reduced sleep						x		Yes	5
	not reduced (may be increased)		slightly reduced		no appetite and finds food tasteless		needs persuasion to eat at all		

Table 1b: Montgomery-Asberg Depression rating scale (continue) (Montgomery & Åsberg, 1979: 134)

enter an "x" in the appropriate column for each item (give only 1 answer per row)									
reduced appetite						x		Yes	5
	none		occasional		difficult, with reduced abilities		only with great difficulty		
concentration difficulties						x		Yes	5
	no sluggishness		finds it hard to start tasks		simple tasks take effort		unable to do anything without help		
lassitude						x		Yes	5
	normal interests		reduced ability to enjoy		loss of interests and feelings		emotionally paralyzed		
inability to feel						x		Yes	5
	none		fluctuating		persistent guilt		delusions of ruin and sin		
pessimistic thoughts						x		Yes	5
	none; enjoys life		weary of life		common but no plans		explicit plans		
suicidal thoughts						x		Yes	5
calculate	**result**								
data complete?	Yes								
evaluation appropriate?	Yes								
total rating scale	50	out of 60, or	83%	of maximal depression					
number of near-normal measures	0	out of 10							
number of more severe findings	10	out of 10							

APPENDIX C

Table 1c: The prevalence and cost of the top eleven pharmacological groups

Year	Name of the class	Items prescribed	Per cent (%)	Ranking according to items	Total cost (R)	Ranking according to cost
2004	Antihypertensives	441 032	8.31	1	81 408 951.38	1
	Cough and cold medicine	421 117	7.94	2	18 163 193.83	9
	Combination Analgesics	381 809	7.20	3	21 288 560.33	7
	Antimicrobial Beta-lactams	288 259	5.43	4	29 224 922.32	5
	Non-steroidal anti-inflammatory agents	239 938	4.52	5	25 942 986.82	6
	Hypolipidaemic agents	162 550	3.06	6	33 336 343.13	2
	Antidepressants	157 810	2.97	7	32 323 356.77	3
	Anti-diabetic agents	143 447	2.70	8	29 734 655.19	4
	Sex-hormones	139 207	2.62	9	20 910 396.77	8
	Antihistamines	137 351	2.59	10	14 657 519.53	10
	Diuretics	137 090	2.58	11	8 767 278.98	11
2005	Cough and cold medicine	239 137	8.13	1	10 767 482.55	9
	Combination Analgesics	281 590	7.81	2	14 265 812.95	7
	Antihypertensives	260 062	7.21	3	43 854 683.29	1
	Antimicrobial Beta-lactams	207 037	5.74	4	19 155 485.91	3
	Non-steroidal anti-inflammatory agents	157 975	4.38	5	11 649 351.11	8
	Antimicrobial Erythromycin and other macrolides	134 121	3.72	6	40 628 640.32	2
	Antihistamines	106 328	2.95	7	10 704 174.29	10
	Hypolipidaemic agents	89 901	2.49	8	17 506 957.70	4
	Acid reducers	89 532	2.48	9	16 505 869.14	5
	Topical nasal preparations	87 594	2.43	10	9 230 588.54	11
	Antidepressants	86 521	2.40	11	15 245 709.85	6
2006	Combination Analgesics	187 745	7.92	1	8 791 228.57	10
	Cough and cold medicine	184 755	7.79	2	7 355 424.01	9
	Antihypertensives	150 938	6.37	3	28 533 467.15	2
	Antimicrobial Beta-lactams	130 649	5.51	4	13 613 079.96	3
	Antimicrobial Erythromycin and other macrolides	119 937	5.06	5	37 118 476.26	1
	Non-steroidal anti-inflammatory agents	112 541	4.75	6	8 073 034.74	8
	Antihistamines	81 676	3.45	7	8 910 622.73	5
	Not otherwise classified	71 249	3.01	8	6 896 392.82	10
	Acid reducers	59 059	2.49	9	10 378 358.78	4
	Topical nasal preparations	53 594	2.26	10	6 066 656.50	11
	Antidepressants	47 740	2.01	11	8 614 631.29	7

Table 2c: Number of antidepressant active ingredient prescribed according to age group

Active ingredient	Number of items prescribed per age group in years				
	0≤9 (%)*	>9 and ≤19 (%)*	>19 and ≤44 (%)*	>44 and ≤59 (%)*	>59 (%)*
Amitriptyline	109 (0.23)	327 (0.68)	3837 (8.04)	3 577 (7.49)	1 731 (3.63)
Amitriptyline/ Chlordiazepoxide	0 (0.00)	0 (0.00)	6 (0.01)	39 (0.08)	22 (0.05)
Bupropion	26 (0.05)	8 (0.02)	278 (0.58)	258 (0.54)	36 (0.08)
Citalopram	35 (0.07)	261 (0.55)	2450 (5.13)	2 024 (4.24)	970 (2.03)
Clomipramine	2 (0.00)	18 (0.04)	97 (0.20)	101 (0.21)	59 (0.12)
Dothiepin	0 (0.00)	11 (0.02)	89 (0.19)	165 (0.35)	138 (0.29)
Duloxetine	1 (0.00)	41 (0.09)	880 (1.84)	726 (1.52)	139 (0.29)
Escitalopram	2 (0.00)	94 (0.20)	836 (1.75)	518 (1.09)	218 (0.46)
Fluoxetine	19 (0.04)	266 (0.56)	3 086 (6.46)	2 626 (5.50)	1 141 (2.39)
Flupenthixol	0 (0.00)	15 (0.03)	131 (0.27)	93 (0.19)	14 (0.03)
Fluphenazine/ Nortriptyline	1 (0.00)	0 (0.00)	46 (0.10)	122 (0.26)	100 (0.21)
Fluvoxamine	10 (0.02)	43 (0.09)	160 (0.34)	162 (0.34)	42 (0.09)
Imipramine	174 (0.36)	333 (0.70)	462 (0.97)	311 (0.65)	194 (0.41)
Lithium	7 (0.01)	1 (0.0)	282 (0.59)	191 (0.40)	40 (0.08)
Lofepramine	0 (0.00)	7 (0.01)	21 (0.04)	74 (0.16)	5 (0.01)
Maprotiline	0 (0.00)	0 (0.00)	0 (0.00)	9 (0.02)	1 (0.00)
Mianserin	0 (0.00)	0 (0.00)	24 (0.05)	34 (0.07)	76 (0.16)
Mirtazapine	0 (0.00)	17 (0.04)	211 (0.44)	288 (0.60)	140 (0.29)
Moclobemide	0 (0.00)	5 (0.01)	105 (0.22)	119 (0.25)	49 (0.10)
Paroxetine	13 (0.03)	139 (0.29)	2 442 (5.12)	1 935 (4.05)	1 122 (2.35)
Reboxetine	0 (0.00)	1 (0.00)	15 (0.03)	18 (0.04)	1 (0.00)
Sertraline	2 (0.00)	105 (0.22)	896 (1.88)	814 (1.71)	408 (0.85)
Sulpiride	24 (0.05)	75 (0.16)	1 231 (2.58)	353 (0.74)	419 (0.88)
Trazodone	9 (0.02)	23 (0.05)	498 (1.04)	644 (1.35)	402 (0.84)
Trimipramine	1 (0.00)	1 (0.00)	110 (0.23)	135 (0.28)	179 (0.37)
Venlafaxine	9 (0.02)	65 (0.14)	2 019 (4.23)	1 520 (3.18)	702 (1.47)
Total	**444 (0.93)**	**1 856 (3.89)**	**20 212 (42.34)**	**16 856 (35.31)**	**8 348 (17.49)**

**Prevalence % = Number of active ingredients for each age group divided by the total number of antidepressants claimed during 2006 multiplied by a hundred (n2006 = 47 740).*

Table 3c: The utilisation patterns and cost of the antidepressant classes

Time		Tricyclic	Non-Tricyclic	MAO Inhibitors	SSRI's	SNRI's	Lithium	Others
P1	Items (%)*	11 388 (26.12)	682 (1.56)	653 (1.50)	23 241 (53.30)	2 516 (5.77)	584 (1.34)	4 542 (10.42)
	Average Cost (R)	99.88± 108.76	286.79± 190.58	287.97± 145.16	270.23± 165.07	592.54±302.07	248.19± 120.20	283.17± 235.82
	Total Cost (R) (%)**	1 137 435.79 (10.61)	195 593.72 (1.82)	188 045.16 (1.75)	6 280 482.91 (58.57)	1 490 820.85 (13.90)	144 943.17 (1.35)	1 286 138.28 (11.99)
	CPI	0.41	1.17	1.17	0.54	2.41	1.01	1.15
P2	Items (%)*	14 374 (26.95)	844 (1.58)	652 (1.22)	28 601 (53.62)	3 153 (5.91)	701 (1.30)	5 015 (9.40)
	Average Cost (R)	88.25 ±109.43	281.42± 192.60	265.02± 120.41	228.11± 160.16	531.66±272.00	216.11± 113.15	256.40± 221.68
	Total Cost (R) (%)**	1 268 434.90 (11.21)	237 514.53 (2.10)	172 790.03 (1.53)	6 524 216.32 (57.62)	1 676 323.88 (14.81)	151 496.32 (1.34)	1 285 841.03 (11.36)
	CPI	0.42	1.33	1.25	1.08	2.51	1.03	1.21
P3	Items (%)*	15 465 (25.41)	987 (1.62)	720 (1.18)	35 523 (58.36)	2 895 (4.76)	764 (1.26)	4 345 (7.41)
	Average Cost (R)	68.05± 91.62	215.49± 143.00	220.36± 77.33	183.95± 131.40	440.69±211.27	173.16± 82.82	206.26± 188.84
	Total Cost (R) (%)**	1 052 434.04 (10.23)	212 690.49 (2.07)	158 659.14 (1.54)	6 534 627.82 (63.55)	1 275 804.11 (12.41)	132 295.50 (1.29)	916 768.79 (8.92)
	CPI	0.40	1.28	1.31	1.09	2.61	1.02	1.20
Total for 2004	Items (%)*	41 227 (26.12)	2 513 (1.59)	2 025 (1.28)	87 365 (55.36)	8 564 (5.43)	2 049 (1.30)	14 067 (8.91)
	Average Cost (R)	83.88 ±103.74	256.98 ±177.31	256.54 ±119.93	221.36 ±154.55	518.79 ±269.89	209.24 ±109.45	248.01 ±218.47
	Total Cost (R) (%)**	3 458 304.73 (10.78)	645 798.74 (2.00)	519 494.32 (1.61)	19 339 327.05 (59.83)	4 442 948.84 (13.75)	428 734.99 (1.33)	3 488 748.10 (10.79)
	CPI	0.41	1.26	1.26	1.08	2.53	1.02	1.21

Table 3c: The utilisation patterns and cost of the antidepressant classes (continue)

Time		Tricyclic	Non-Tricyclic	MAO Inhibitors	SSRI's	Serotonin and Noradrenalin re-uptake inhibitors	Lithium	Others
P4	Items (%)*	7 212 (26.32)	200 (0.73)	212 (0.77)	14 327 (52.28)	2 242 (8.18)	348 (1.27)	2 861 (10.44)
	Average Cost (R)	60.99± 87.97	208.16± 144.36	203.86± 78.94	185.65± 141.29	465.11±221.20	185.15± 81.12	211.57± 193.63
	Total Cost (R) (%)**	439 847.95 (8.98)	41 632.23 (0.85)	43 219.16 (0.88)	2 659 758.32 (54.31)	1 042 784.77 (21.29)	64 430.55 (1.32)	605 305.33 (12.36)
	CPI	0.34	1.16	1.14	1.04	2.60	1.04	1.18
P5	Items (%)*	8 387 (26.94)	212 (0.68)	199 (0.64)	15 926 (51.15)	2 927 (9.40)	371 (1.19)	3 111 (9.99)
	Average Cost (R)	58.67± 90.22	221.68± 149.06	216.36± 86.81	178.00± 138.36	471.98±208.32	182.82± 87.42	212.84± 190.57
	Total Cost (R) (%)**	492 092.81 (8.90)	46 995.40 (0.85)	43 056.61 (0.78)	2 834 897.84 (51.28)	1 381 478.77 (25.00)	67 825.89 (1.23)	662 149.89 (11.25)
	CPI	0.33	1.25	1.22	1.00	2.66	0.65	1.13
P6	Items (%)*	7 169 (25.62)	187 (0.67)	161 (0.58)	14 608 (52.20)	2 709 (1.20)	337 (1.20)	2 815 (10.06)
	Average Cost (R)	58.75± 85.10	194.51± 140.14	221.15± 104.74	157.14± 132.26	490.32±207.44	195.82± 91.11	226.38± 190.01
	Total Cost (R) (%)**	421 213.71 (8.74)	36 374.24 (0.75)	35 605.85 (0.74)	2 295 520.57 (47.62)	1 328 277.25 (27.56)	65 992.21 (1.37)	637 250.50 (13.22)
	CPI	0.34	1.12	1.28	0.91	2.85	1.14	1.31
Total for 2005	Items (%)*	22 768 (26.31)	599 (0.69)	572 (0.66)	44 861 (51.85)	7 878 (9.11)	1 056 (1.22)	8 787 (10.16)
	Average Cost (R)	59.43 ±87.92	208.68 ±114.93	213.08 ±89.69	173.65 ±137.87	467.33 ±212.00	187.74 ±86.72	216.76 ±191.49
	Total Cost (R) (%)**	1 353 154.47 (8.88)	125 001.87 (0.82)	121 881.62 (0.80)	7 790 176.73 (51.10)	3 752 540.79 (24.61)	198 248.65 (1.30)	1 904 705.72 (12.49)
	CPI	0.34	1.19	1.21	0.99	2.70	1.07	1.23

Table 3c: The utilisation patterns and cost of the antidepressant classes (continue)

Time		Tricyclic	Non-Tricyclic	MAO Inhibitors	SSRI's	Serotonin and Noradrenalin re-uptake inhibitors	Lithium	Others
P7	Items (%)*	3 998 (73.27)	52 (0.33)	77 (0.49)	7 541 (47.88)	1 980 (12.57)	157 (1.00)	1 944 (12.34)
	Average Cost (R)	61.25 ±104.38	261.31 ±218.90	273.93 ±127.45	142.29 ±154.87	523.88 ±203.64	225.16 ±93.24	242.22 ±211.07
	Total Cost (R) (%)**	244 875.82 (8.45)	13 587.98 (0.47)	21 092.87 (0.73)	1 073 017.17 (37.05)	1 037 282.75 (35.82)	35 349.57 (1.22)	470 874.85 (16.26)
	CPI	0.12	1.42	1.49	0.77	2.85	1.22	1.32
P8	Items (%)*	4 250 (74.04)	48 (0.30)	107 (0.66)	7 776 (47.87)	2 047 (12.60)	188 (1.16)	1 827 (11.25)
	Average Cost (R)	56.90 ±86.51	266.06 ±237.14	247.74 ±157.17	143.18 ±141.15	495.43 ±196.13	213.83 ±98.05	238.75 ±204.57
	Total Cost (R) (%)**	241 833.27 (8.38)	12 770.64 (0.44)	26 508.02 (0.92)	1 113 388.80 (38.59)	1 014 156.97 (35.15)	40 200.62 (1.39)	436 187.65 (15.12)
	CPI	0.11	1.47	1.39	0.81	2.79	1.20	1.34
P9	Items (%)*	4 097 (26.02)	44 (0.28)	94 (0.60)	7 531 (47.82)	2 077 (13.19)	178 (1.13)	1 727 (10.97)
	Average Cost (R)	52.67 ±77.43	253.14 ±182.00	255.60 ±260.24	146.36 ±147.70	490.44 ±214.92	218.81 ±88.13	244.76 ±204.90
	Total Cost (R) (%)**	215 799.70 (7.62)	11 138.34 (0.39)	24 026.39 (0.85)	1 102 244.19 (38.90)	1 018 644.56 (35.95)	38.948.71 (1.37)	422 702.42 (14.92)
	CPI	0.29	1.39	1.42	0.81	2.37	1.21	1.36
Total for 2006	Items (%)*	12 345 (25.86)	144 (0.30)	278 (0.58)	22 848 (47.86)	6 104 (12.79)	523 (1.10)	5 498 (11.52)
	Average Cost (R)	56.91 ±89.05	260.40 ±213.45	257.65 ±191.73	143.94 ±147.95	502.96 ±205.59	218.93 ±93.26	241.86 ±206.97
	Total Cost (R) (%)**	702 508.79 (8.15)	37 496.96 (0.44)	71 627.28 (0.83)	3 288 650.16 (38.18)	3 070 084.28 (35.64)	114 498.90 (1.33)	1 329 764.92 (15.44)
	CPI	0.32	1.47	1.43	0.80	2.79	1.21	1.34

SSRI's = Selective serotonin re-uptake inhibitors; SNRI's = Serotonin and noradrenaline re-uptake inhibitors

**Prevalence % = Number of items in the pharmacologic group for a specific study period divided by the total number of antidepressants claimed during the same period multiplied by a hundred. (n1 = 43 606; n2 = 53 340; n3 = 60 864; n2004 = 157 810; n4 = 27 402; n5 = 31 133; n6 = 2 7986; n2005 = 86 521; n7 = 15 749; n8=16 243; n9 = 15 748; n2006 = 47 740).*

***Cost % = Cost of the items in a pharmacologic group for a specific study period divided by the total cost of antidepressants for that study period multiplied by a hundred. (n1 = R 10723459.88; n2 = R 11 316 617.00; n3 = R 10 283 279.87; n2004 = R 32 323 356.77; n4 = R 4 896 978.31; n5 = R 552 849.88; n6 = R 4 820 234.33; n2005 = R 15 245 709.85; n7 = R 2 896 081.01; n8 = R 2 885 045.97; n9 = R 2 833 504.31; n2006 = R 8 614 631.29).*

CPI=Cost Prevalence Index

Table 4c: Effect sizes (*d*-values) of the different pharmacologic groups

Active ingredient	Compared to	Average Cost (R)			Effect-size (d)		
		2004	2005	2006	2004	2005	2006
Tricyclic Average Cost (R) 2004 = 83.88±103.74 2005 = 59.43±87.92 2006 = 56.91±89.05	Non-Tricyclic	256.98 ±177.31	208.68 ±114.93	260.40 ±213.45	0.98	1.30	0.95
	MAO-Inhibitors	256.54 ±119.93	213.08 ±89.69	257.65 ±191.73	1.44	1.71	1.05
	SSRI's	221.36 ±154.55	173.65 ±137.87	143.94 ±147.95	0.89	0.83	0.59
	SNRI's	518.79 ±269.89	467.33 ±212.00	502.96 ±205.59	1.61	1.92	2.17
	Lithium	209.24 ±109.45	187.74 ±86.72	218.93 ±93.26	1.15	1.46	1.74
	Others	248.01 ±218.47	216.76 ±191.49	241.86 ±206.97	0.75	0.82	0.89
Non-Tricyclic Average Cost (R) 2004 = 256.98±177.31 2005 = 208.68±114.93 2006 = 260.40±213.45	MAO-Inhibitors	256.54 ±119.93	213.08 ±89.69	257.65 ±191.73	0.002	0.04	0.01
	SSRI's	221.36 ±154.55	173.65 ±137.87	143.94 ±147.95	0.2	0.25	0.55
	SNRI's	518.79 ±269.89	467.33 ±212.00	502.96 ±205.59	0.97	1.22	1.14
	Lithium	209.24 ±109.45	187.74 ±86.72	218.93 ±93.26	0.27	0.18	0.19
	Others	248.01 ±218.47	216.76 ±191.49	241.86 ±206.97	0.04	0.04	0.09
MAO-Inhibitors Average Cost (R) 2004 = 256.54±119.93 2005 = 213.08±89.69 2006 = 257.65±191.73	SSRI's	221.36 ±154.55	173.65 ±137.87	143.94 ±147.95	0.23	0.29	0.59
	SNRI's	518.79 ±269.89	467.33 ±212.00	502.96 ±205.59	0.97	1.20	1.19
	Lithium	209.24 ±109.45	187.74 ±86.72	218.93 ±93.26	0.39	0.28	0.20
	Others	248.01 ±218.47	216.76 ±191.49	241.86 ±206.97	0.04	0.02	0.08
SSRI's Average Cost (R) 2004 = 221.36±154.55 2005 = 173.65±137.87 2006 = 143.94±147.95	SNRI's	518.79 ±269.89	467.33 ±212.00	502.96 ±205.59	1.10	1.39	1.75
	Lithium	209.24 ±109.45	187.74 ±86.72	218.93 ±93.26	0.08	0.10	0.51
	Others	248.01 ±218.47	216.76 ±191.49	241.86 ±206.97	0.12	0.23	0.47
SNRI's Average Cost (R) 2004 = 518.79±269.89 2005 = 467.33±212.00 2006 = 502.96±205.59	Lithium	209.24 ±109.45	187.74 ±86.72	218.93 ±93.26	1.15	1.32	1.38
	Others	248.01 ±218.47	216.76 ±191.49	241.86 ±206.97	1.00	1.18	1.26
Lithium Average Cost (R) 2004 = 209.24±109.45 2005 = 187.74±86.72 2006 = 218.93±93.26	Others	248.01 ±218.47	216.76 ±191.49	241.86 ±206.97	0.18	0.15	0.11

SSRI'S = SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS; SNRI'S = SEROTONIN AND NORADRENALINE RE-UPTAKE INHIBITORS; MAO-INHIBITORS = MONO-AMINE OXIDASE INHIBITORS

Table 5c: The prevalence and cost of antidepressants according to active ingredient

Active Ingredient	Variable	P1	P2	P3	Total 2004	P4	P5	P6	Total 2005	P7	P8	P9	Total 2006
Amitriptyline	Prevalence (%)*	7 613 (17.46)	9 552 (17.91)	10 413 (17.11)	27 578 (17.48)	5 185 (18.92)	6 062 (19.47)	5 291 (18.91)	16 538 (19.11)	3 032 (19.25)	3 264 (20.09)	3 293 (20.91)	9 589 (20.09)
	Cost (%)**	540 121.23 (5.04)	525 424.63 (4.64)	386 656.87 (3.76)	1 452 202.73 (4.49)	191052.48 (3.90)	211401.21 (4.04)	192036.12 (3.98)	594489.81 (3.90)	108 700.72 (3.75)	115 308.58 (4.00)	118 704.78 (4.19)	342 714.08 (3.98)
	CPI	0.29	0.26	0.22	0.26	0.21	0.21	0.21	0.20	0.19	0.20	0.20	0.20
Amitriptyline/ Chlordiazepoxide	Prevalence (%)*	39 (0.09)	45 (0.08)	57 (0.09)	141 (0.09)	34 (0.12)	31 (0.10)	22 (0.08)	87 (0.10)	22 (0.14)	24 (0.15)	21 (0.13)	67 (0.14)
	Cost (%)**	6 832.73 (0.06)	8 250.03 (0.07)	8 888.75 (0.09)	23 971.51 (0.07)	6 322.43 (0.13)	5 558.44 (0.10)	3 446.07 (0.07)	15 326.94 (0.10)	3 184.46 (0.11)	3 495.16 (0.12)	3 083.75 (0.11)	9 763.37 (0.11)
	CPI	0.67	0.88	1.00	0.78	1.08	1.00	0.88	1.00	0.79	0.80	0.85	0.79
Clomipramine	Prevalence (%)*	420 (0.96)	594 (1.11)	688 (1.13)	1 702 (1.08)	247 (0.90)	273 (0.88)	189 (0.68)	709 (0.82)	95 (0.60)	99 (0.61)	83 (0.53)	277 (0.58)
	Cost (%)**	110 397.98 (1.30)	187 550.42 (1.66)	189 393.81 (1.84)	487 342.21 (1.51)	67 152.45 (1.37)	78 306.79 (1.42)	54 453.25 (1.13)	199 912.49 (1.31)	39 526.79 (1.36)	29 362.23 (1.02)	23 560.02 (0.83)	92 449.04 (1.07)
	CPI	1.07	1.50	1.63	1.40	1.52	1.61	1.66	0.72	2.27	1.67	1.57	1.84
Dothiepin	Prevalence (%)*	1 259 (2.89)	1 483 (2.78)	1 648 (2.71)	4 390 (2.78)	437 (1.59)	532 (1.71)	524 (1.87)	1 493 (1.73)	127 (0.81)	134 (0.82)	142 (0.90)	403 (0.84)
	Cost (%)**	168 254.58 (1.57)	175 935.95 (1.55)	160 330.75 (1.56)	504 521.28 (1.56)	43214.73 (0.88)	50924.28 (0.92)	50239.84 (1.04)	144378.85 (0.95)	14 534.43 (0.50)	14 501.87 (0.53)	15 295.86 (0.54)	44 332.16 (0.51)
	CPI	0.54	0.56	0.58	0.56	0.55	0.54	0.56	0.55	0.62	0.65	0.60	0.61

Table 5c: The prevalence and cost of antidepressants according to active ingredient (continue)

Active Ingredient	Variable	P1	P2	P3	Total 2004	P4	P5	P6	Total 2005	P7	P8	P9	Total 2006
Imipramine	Prevalence (%)*	1 318 (3.02)	1 905 (3.57)	1 818 (2.99)	5 041(3.19)	978 (3.57)	1 159 (3.72)	839 (3.00)	2 976 (3.44)	536 (3.40)	536 (3.30)	402 (2.55)	1 474 (3.09)
	Cost (%)**	111 321.81 (1.04)	158 424.50 (1.40)	117 002.10 (1.14)	386 748.41 (1.20)	55724.67 (1.14)	65385.47 (1.18)	45897.89 (0.95)	167008.03 (1.10)	28 712.65 (0.99)	26 501.80 (0.92)	16 362.83 (0.58)	71 577.28 (0.83)
	CPI	0.34	0.39	0.38	0.38	0.32	0.32	0.32	0.32	0.29	0.28	0.23	0.27
Lofepramine	Prevalence (%)*	182 (0.42)	159 (0.30)	154 (0.25)	495 (0.31)	69 (0.25)	83 (0.27)	79 (0.28)	231 (0.27)	36 (0.23)	44 (0.27)	27 (0.17)	107 (0.22)
	Cost (%)**	67 867.92 (0.63)	56 498.16 (0.50)	47 297.00 (0.46)	171 633.08 (0.53)	23 932.52 (0.49)	29 765.75 (0.54)	30 024.28 (0.62)	83 722.55 (0.55)	17 355.56 (0.60)	19 232.62 (0.67)	10 202.06 (0.36)	46 790.24 (0.54)
	CPI	1.5	1.67	1.84	1.71	1.96	2.00	2.21	2.04	2.61	2.48	2.12	2.45
Perphenazine /Amitriptyline	Prevalence (%)*	7 (0.02)	1 (0)	2 (0)	10 (0.01)	1 (0)	0	0	1 (0)	0	0	0	0
	Cost (%)**	2 794.33 (0.03)	102.96 (0.09)	686.60 (067)	3 583.89 (0.01)	194.99 (0.004)	0	0	194.99 (0.001)	0	0	0	0
	CPI	1.5	0	0	1.00	0	0	0	0	0	0	0	0
Reboxetine	Prevalence (%)*	97 (0.22)	68 (0.13)	38 (0.06)	203 (0.13)	32 (0.12)	34 (0.11)	37 (0.13)	103 (0.12)	5 (0.03)	6 (0.04)	24 (0.15)	35 (0.07)
	Cost (%)**	39 756.38 (0.37)	25 097.23 (0.22)	11 668.32 (0.11)	76 521.93 (0.24)	10 315.16 (0.21)	9 013.10 (0.16)	10 300.63 (0.21)	29 628.89 (0.19)	1 163.20 (0.04)	1 488.12 (0.05)	7 572.78 (0.27)	10 224.10 (0.12)
	CPI	1.68	1.69	1.83	1.85	1.75	1.45	1.62	1.58	1.33	1.25	1.80	1.71

Table 5c: The prevalence and cost of antidepressants according to active ingredient (continue)

Active Ingredient	Variable	P1	P2	P3	Total 2004	P4	P5	P6	Total 2005	P7	P8	P9	Total 2006
Trimipramine	Prevalence (%)*	550 (1.26)	635 (1.19)	685 (1.13)	1 870 (1.18)	261 (0.95)	247 (0.79)	225 (0.80)	733 (0.85)	150 (0.95)	149 (0.92)	129 (0.82)	428 (0.90)
	Cost (%)**	129 845.21 (1.21)	156 248.25 (1.38)	142 178.16 (1.38)	428 271.62 (1.32)	52 253.68 (1.07)	50 750.87 (0.92)	45 116.26 (0.94)	148 120.81 (0.97)	32 861.21 (1.13)	33 431.01 (1.16)	28 590.40 (1.18)	94 882.62 (1.10)
	CPI	0.96	1.16	1.22	1.12	1.13	1.16	1.18	1.14	1.19	1.26	1.44	1.22
Maprotiline	Prevalence (%)*	106 (0.24)	109 (0.20)	112 (0.18)	327 (0.21)	35 (0.13)	32 (0.10)	25 (0.09)	92 (0.11)	5 (0.03)	2 (0.01)	3 (0.02)	10 (0.02)
	Cost (%)**	43 335.32 (0.40)	37 683.24 (0.33)	31 681.86 (0.31)	112 700.42 (0.35)	11 406.70 (0.23)	9 896.04 (0.18)	7 185.12 (0.15)	28 487.86 (0.19)	2 280.75 (0.08)	912.30 (0.03)	1 236.88 (0.04)	4 429.93 (0.05)
	CPI	1.67	1.65	1.72	1.67	1.77	1.8	1.67	1.73	2.67	3.00	2.00	2.5
Mianserin	Prevalence (%)*	576 (1.32)	735 (1.38)	875 (1.44)	2 186 (1.39)	165 (0.60)	180 (0.58)	162 (0.58)	507 (0.59)	47 (0.30)	46 (0.28)	41 (0.26)	134 (0.28)
	Cost (%)**	152 258.40 (1.42)	199 831.29 (1.69)	181 008.63 (1.76)	533 098.32 (1.65)	30 225.53 (0.62)	37 099.36 (0.67)	29 189.12 (0.61)	96 514.01 (0.63)	11 307.23 (0.39)	11 858.34 (0.41)	9 901.46 (0.35)	33 067.03 (0.38)
	CPI	1.06	1.22	1.22	1.19	1.03	1.16	1.05	1.07	1.30	1.46	1.35	1.36
Moclobemide	Prevalence (%)*	630 (1.44)	625 (1.17)	692 (1.14)	1 947 (1.23)	192 (0.70)	191 (0.61)	154 (0.55)	537 (0.62)	77 (0.49)	107 (0.66)	94 (0.60)	278 (0.58)
	Cost (%)**	184 387.55 (1.72)	168 455.12 (1.49)	154 836.11 (1.51)	507 678.78 (1.57)	40 565.14 (0.83)	41 406.13 (0.75)	34 877.27 (0.72)	116 848.54 (0.77)	21 092.87 (0.73)	26 508.02 (0.92)	24 026.39 (0.85)	71 627.28 (0.83)
	CPI	1.19	1.27	1.31	1.28	1.19	1.23	1.31	1.24	1.49	1.39	1.42	1.43

Table 5c: The prevalence and cost of antidepressants according to active ingredient (continue)

Active ingredient	Variable	P1	P2	P3	Total 2004	P4	P5	P6	Total 2005	P7	P8	P9	Total 2006
Tranylcypromine	Prevalence (%)*	23 (0.05)	27 (0.05)	28 (0.05)	78 (0.05)	20 (0.07)	8 (0.03)	7 (0.03)	35 (0.04)	0	0	0	0
	Cost (%)**	3 657.61 (0.03)	4 334.90 (0.04)	3 823.03 (0.04)	11 815.54 (0.04)	2 654.02 (0.05)	1 650.48 (0.03)	728.58 (0.02)	5 033.08 (0.03)	0	0	0	0
	CPI	0.6	0.8	0.8	0.8	0.71	1.00	0.67	0.75	0	0	0	0
Escitalopram	Prevalence (%)*	0	636 (1.19)	2 736 (4.50)	3 372 (2.14)	1 558 (5.69)	2 009 (6.45)	1 706 (6.10)	5 273 (6.14)	500 (3.17)	595 (3.66)	573 (3.64)	1 668 (3.49)
	Cost (%)**	0	172 593.90 (1.53)	656 861.29 (6.39)	829 455.19 (2.57)	367 569.58 (7.51)	497 651.28 (9.00)	442 136.80 (9.17)	1 307 357.66 (8.58)	142 879.57 (4.93)	174 999.92 (6.07)	181 986.98 (6.42)	499 866.47 (5.80)
	CPI	0	1.29	1.42	1.20	1.32	1.40	1.50	1.41	1.56	1.66	1.76	1.66
Citalopram	Prevalence (%)*	8 003 (18.35)	9 591 (17.98)	10 453 (17.17)	28 047 (17.77)	4 061 (14.82)	4 578 (14.70)	4 151 (14.83)	12 790 (14.78)	1 904 (12.09)	1 934 (11.91)	1 903 (12.08)	5 741 (12.03)
	Cost (%)**	2 264 587.76 (21.12)	2 281 267.97 (20.16)	1 850 531.03 (18.00)	6 396 386.76 (19.79)	692 341.14 (14.14))	695 843.00 (12.59)	527047.82 (10.93)	1 915 231.96 (12.56)	217 913.85 (7.52)	215 881.20 (7.48)	223 136.43 (7.87)	656 931.48 (7.63)
	CPI	1.15	1.12	1.05	1.11	0.95	0.86	0.74	0.85	0.62	0.63	0.65	0.63
Fluoxetine	Prevalence (%)*	8 398 (19.25)	10 030 (18.80)	11 354 (19.65)	29 782 (18.87)	4 626 (16.88)	4 861 (15.61)	4 624 (16.52)	14 111 (16.31)	2 427 (15.41)	2 372 (14.60)	2 342 (14.87)	7 141 (14.96)
	Cost (%)**	1 178 212.08 (10.99)	1 021 798.55 (9.02)	706 026.82 (6.87)	2 906 037.45 (9.00)	327075.65 (6.68)	299033.73 (5.41)	272215.88 (5.65)	898325.26 (5.89)	159 742.47 (5.52)	151 409.91 (5.25)	146 175.65 (5.16)	457 318.03 (5.31)
	CPI	0.57	0.48	0.35	0.48	0.40	0.35	0.34	0.36	0.36	0.36	0.35	0.35

Table 5c: The prevalence and cost of antidepressants according to active ingredient (continue)

Active ingredient	Variable	P1	P2	P3	Total 2004	P4	P5	P6	Total 2005	P7	P8	P9	Total 2006
Fluvoxamine	Prevalence (%)*	511 (1.17)	649 (1.22)	1417 (2.33)	2577 (1.63)	210 (0.77)	221 (0.71)	202 (0.72)	633 (0.73)	147 (0.93)	148 (0.91)	122 (0.77)	417 (0.87)
	Cost (%)**	227 874.44 (2.13)	218 451.65 (1.93)	520 966.16 (5.07)	967 292.25 (3.00)	959 952.96 (1.96)	99 353.16 (1.80)	87 126.34 (1.81)	282 432.46 (1.85)	69 133.63 (2.39)	68 892.65 (2.39)	57 976.19 (2.05)	196 002.47 (2.28)
	CPI	1.82	1.58	2.18	1.84	2.55	2.54	2.51	2.53	2.57	2.63	2.66	2.62
Paroxetine	Prevalence (%)*	4401 (10.09)	5388 (10.10)	6411 (10.53)	16 200 (10.27)	2 685 (9.80)	2 945 (9.56)	2 708 (9.68)	8 338 (9.64)	1 794 (11.39)	1 953 (12.02)	1 907 (12.11)	5 654 (11.84)
	Cost (%)**	1 761 026.78 (16.42)	1 964 220.68 (17.36)	1 879 985.73 (18.29)	5 605 233.19 (17.34)	821621.68 (16.78)	912779.77 (16.51)	684343.58 (14.20)	2 418 745.03 (15.87)	301 876.22 (10.42)	319 695.16 (11.08)	331 093.38 (11.68)	952 664.76 (11.06)
	CPI	1.63	1.72	1.74	1.69	1.71	1.73	1.47	1.65	0.91	0.92	0.96	0.93
Sertraline	Prevalence (%)*	1 928 (4.42)	2 307 (4.33)	3 152 (5.18)	7 387 (4.68)	1 187 (4.33)	1 312 (4.21)	1 217 (4.35)	3 716 (4.29)	769 (4.88)	774 (4.77)	684 (4.34)	2 227 (4.66)
	Cost (%)**	848 781.85 (7.92)	865 883.57 (7.65)	920 256.79 (8.95)	2 634 922.21 (8.15)	355197.31 (7.25)	330236.90 (5.97)	282650.15 (5.86)	968084.36 (6.35)	181 481.43 (6.27)	182 509.96 (6.33)	161 875.56 (5.71)	525 866.95 (6.10)
	CPI	1.79	1.77	1.73	1.74	1.67	1.42	1.35	1.48	1.28	1.33	1.32	1.31
Duloxetine	Prevalence (%)*	0	0	87 (0.14)	87 (0.06)	267 (0.97)	730 (2.34)	717 (2.56)	1 714 (1.98)	495 (3.14)	643 (3.96)	650 (4.13)	1 788 (3.75)
	Cost (%)**	0	0	29 794.80 (0.29)	29 794.80 (0.09)	97 909.04 (2.00)	298 089.66 (5.39)	309 879.75 (6.43)	705 878.45 (4.63)	232 268.53 (8.02)	312 390.89 (10.83)	319 836.51 (11.29)	864 495.93 (10.04)
	CPI	0	0	2.07	1.5	2.06	2.30	2.51	2.34	2.55	2.73	2.73	2.68

Table 5c: The prevalence and cost of antidepressants according to active ingredient (continue)

Active ingredient	Variable	P1	P2	P3	Total 2004	P4	P5	P6	Total 2005	P7	P8	P9	Total 2006
Venlafaxine	Prevalence (%)*	2 516 (5.77)	3 153 (5.91)	2 808 (4.61)	8 477 (5.37)	1 975 (7.21)	2 197 (7.06)	1 992 (7.12)	6 164 (7.12)	1 485 (9.43)	1 404 (8.64)	1 427 (9.06)	4 316 (9.04)
	Cost (%)**	1 490 820.85 (13.90)	1 676 323.88 (14.81)	1 246 009.31 (12.12)	4 413 154.04 (13.65)	944875.73 (18.30)	1083389.11 (19.60)	1018397.5 0 (20.80)	3046662.34 (19.98)	805 014.22 (27.80)	701 766.08 (24.32)	698 808.05 (24.66)	2 205 588.35 (25.60)
	CPI	2.41	2.51	2.63	2.54	2.54	2.78	2.92	2.81	2.95	2.81	2.72	2.83
Lithium	Prevalence (%)*	584 (1.34)	701 (1.31)	764 (1.26)	2049 (1.30)	348 (1.27)	371 (1.19)	337 (1.20)	1056 (1.23)	157 (1.00)	188 (1.16)	178 (1.13)	523 (1.10)
	Cost (%)**	144 943.17 (1.35)	151 496.32 (1.34)	132 295.50 (1.29)	428 734.99 (1.33)	64 430.55 (1.32)	67 825.89 (1.23)	65 992.21 (1.37)	198 248.65 (1.30)	35 349.57 (1.22)	40 200.62 (1.39)	38 948.71 (1.37)	114 498.90 (1.33)
	CPI	1.01	1.02	1.02	1.02	1.04	1.03	1.14	1.07	1.22	1.20	1.21	1.21
Bupropion	Prevalence (%)*	303 (0.69)	393 (0.74)	165 (0.27)	861 (0.55)	203 (0.74)	351 (1.13)	351 (1.25)	905 (1.05)	220 (1.40)	185 (1.14)	201 (1.28)	606 (1.27)
	Cost (%)**	50 705.01 (0.47)	52 921.91 (0.47)	20 564.76 (0.20)	124 191.68 (0.38)	25 154.22 (0.51)	45 661.37 (0.83)	62 421.24 (1.30)	133 236.83 (0.87)	48 782.90 (1.68)	41 825.87 (1.45)	49 860.10 (1.76)	140 468.87 (1.63)
	CPI	0.68	0.64	0.74	0.68	0.69	0.73	1.01	0.83	1.20	1.27	1.38	1.28
Flupenthixol	Prevalence (%)*	612 (1.40)	654 (1.23)	675 (1.11)	1 941 (1.23)	207 (0.76)	198 (0.64)	176 (0.63)	581 (0.67)	95 (0.60)	75 (0.46)	83 (0.53)	253 (0.53)
	Cost (%)**	203 365.14 (1.90)	211 357.90 (1.87)	173 864.21 (1.69)	588 587.25 (1.82)	56897.13 (1.16)	59840.38 (1.08)	52754.91 (1.09)	169492.42 (1.11)	31 683.30 (1.09)	21 486.92 (0.74)	23 843.55 (0.84)	77 013.77 (0.89)
	CPI	1.36	1.52	1.52	1.48	1.53	1.69	1.73	1.66	1.82	1.61	1.58	1.68

Table 5c: The prevalence and cost of antidepressants according to active ingredient (continue)

Active ingredient	Variable	P1	P2	P3	Total 2004	P4	P5	P6	Total 2005	P7	P8	P9	Total 2006
Fluphenazine/ Nortriptyline	Prevalence (%)*	214 (0.49)	205 (0.38)	231 (0.38)	650 (0.41)	152 (0.55)	146 (0.47)	143 (0.51)	441 (0.51)	104 (0.66)	95 (0.58)	70 (0.44)	269 (0.56)
	Cost (%)**	22 261.61 (0.21)	21 106.56 (0.19)	22 536.07 (0.22)	65 904.24 (0.20)	16 255.23 (0.33)	15 315.41 (0.28)	15 174.64 (0.31)	46 745.28 (0.31)	11 589.58 (0.40)	10 852.90 (0.38)	7 308.58 (0.26)	29 751.06 (0.35)
	CPI	0.43	0.5	0.58	0.49	0.6	0.60	0.61	0.61	0.61	0.66	0.59	0.63
Mirtazapine	Prevalence (%)*	686 (1.57)	772 (1.45)	700 (1.15)	2 158 (1.37)	497 (1.81)	506 (1.63)	422 (1.51)	1 425 (1.65)	233 (1.48)	215 (1.32)	208 (1.32)	656 (1.37)
	Cost (%)**	350 999.33 (3.27)	370 768.44 (3.28)	271 050.91 (2.64)	992 818.68 (3.07)	185896.72 (3.80)	197778.49 (3.58)	179416.77 (3.72)	563091.98 (3.69)	112 399.59 (3.88)	107 395.38 (3.72)	104 525.35 (3.69)	324 320.32 (3.76)
	CPI	2.08	2.26	2.30	2.24	2.10	2.20	2.46	2.24	2.62	2.82	2.80	2.74
Sulpiride	Prevalence (%)*	2 030 (4.66)	2 152 (4.03)	1 977 (3.25)	6 159 (3.90)	1 181 (4.31)	1 224 (3.93)	1 031 (3.68)	3 436 (3.97)	739 (4.69)	714 (4.40)	650 (4.13)	2 103 (4.41)
	Cost (%)**	315 275.73 (2.94)	289 232.34 (2.56)	181 830.56 (1.77)	786 338.63 (2.43)	115446.33 (2.36)	114981.60 (2.08)	107235.33 (2.22)	337663.26 (2.21)	71 513.63 (2.47)	76 834.60 (2.66)	69 900.52 (2.47)	218 248.75 (2.53)
	CPI	0.63	0.64	0.54	0.62	0.55	0.53	0.60	0.56	0.53	0.60	0.60	0.57
Trazodone	Prevalence (%)*	583 (1.34)	765 (1.43)	715 (1.17)	2 063 (1.31)	589 (2.15)	652 (2.09)	655 (2.34)	1 896 (2.19)	548 (3.48)	537 (3.31)	491 (3.12)	1576 (3.30)
	Cost (%)**	297 471.10 (2.77)	312 506.39 (2.76)	231 313.94 (2.25)	841 291.43 (2.60)	195 340.54 (3.99)	219 559.54 (3.97)	209 946.98 (4.36)	624 847.06 (4.10)	193 742.65 (6.69)	176 303.86 (6.11)	159 691.54 (5.64)	529 738.05 (6.15)
	CPI	2.07	1.93	1.92	1.98	1.86	1.90	1.86	1.87	1.92	1.85	1.81	1.86
Nefazodone	Prevalence (%)*	17 (0.04)	6 (0.01)	9 (0.01)	32 (0.02)	0	0	0	0	0	0	0	0
	Cost (%)**	6 303.98 (0.06)	2 850.26 (0.03)	3 940.02 (0.04)	13 094.26 (0.04)	0	0	0	0	0	0	0	0
	CPI	1.5	3	4	2	0	0	0	0	0	0	0	0

**Prevalence % = Number of items in the pharmacologic group for a specific study period divided by the total number of antidepressants for the same period multiplied by a hundred. (n1 = 43 606; n2 = 53 340; n3 = 60 864; n2004 = 157 810; n4 = 27 402; n5 = 31 133; n6 = 27 986; n2005 = 86 521; n7 = 15 749; n8 = 16 243; n9 = 15 748; n2006 = 47 740)*

***Cost % = Cost of the items in a pharmacologic group for a specific study period divided by the total cost of antidepressants for that study period multiplied by a hundred. (n1 = R 10 723 459.88; n2 = R 11 316 617.00; n3 = R 10 283 279.87; n2004 = R 32 323 356.77; n4 = R 4 896 978.31; n5 = R 552 849.88; n6 = R 4 820 234.33; n2005 = R 15 245 709.85; n7 = R 2 896 081.01; n8 = R 2 885 045.97; n9 = R 2 833 504.31; n2006 = R 8 614 631.29).*

Table 6c: Number of prescriptions with only one antidepressant prescribed for each active ingredient

	2004			2005			2006		
Active ingredient	**Prevalence (%)***	**Total cost (R) (%)****	**CPI**	**Prevalence (%)***	**Total cost (R) (%)****	**CPI**	**Prevalence (%)***	**Total cost (R) (%)****	**CPI**
Amitriptyline	23 960 (16.31)	1 234 907.22 (3.82)	0.23	14 939 (18.26)	525 420.67 (3.45)	0.19	8 752 (19.48)	311 615.45 (3.62)	0.19
Amitriptyline/ Chlordiasepoxide	105 (0.07)	17 308.94 (0.05)	0.75	71 (0.09)	13 207.36 (0.09)	1.00	66 (0.15)	9 626.84 (0.11)	0.76
Bupropion	858 (0.58)	123 670.78 (0.38)	0.66	843 (1.03)	121 810.67 (0.80)	0.78	511 (1.14)	118 016.08 (1.37)	1.20
Citalopram	26 101 (17.77)	5 939 115.66 (18.37)	1.03	12 144 (14.84)	1 816 957.74 (11.92)	0.80	5 340 (11.88)	608 505.91 (7.06)	0.59
Clomipramine	1 476 (1.00)	403 566.60 (1.25)	1.24	622 (0.76)	165 081.08 (1.08)	1.42	238 (0.53)	75 342.12 (0.87)	1.65
Dothiepin	3 276 (2.23)	385 725.23 (1.19)	0.54	1 210 (1.48)	118 258.99 (0.78)	0.52	299 (0.67)	34 517.33 (0.40)	0.60
Duloxetine	84 (0.06)	28 717.66 (0.09)	1.55	1 412 (1.73)	592 651.28 (3.89)	2.25	1 516 (3.37)	734 705.76 (8.53)	2.53
Escitalopram	2 988 (2.03)	731 647.02 (2.26)	1.11	4 980 (6.09)	1 231 490.22 (8.08)	1.33	1 524 (3.39)	456 768.77 (5.30)	1.56
Fluoxetine	27 262 (18.56)	2 665 901.34 (8.25)	0.44	13 167(16.09)	843 448.71 (5.53)	0.34	6 737 (14.99)	431 348.21 (5.01)	0.33
Flupentixol	1 116 (0.76)	316 302.36 (0.98)	1.29	319 (0.39)	91 421.47 (0.60)	1.54	119 (0.26)	31 659.70 (0.37)	1.39
Fluphenazine/ Nortriptyline	605 (0.41)	62 546.20 (0.19)	0.47	422 (0.52)	44 556.77 (0.29)	0.57	258 (0.57)	28 562.84 (0.33)	0.58
Fluvoxamine	2 053 (1.40)	793 142.50 (2.45)	1.76	587 (0.72)	259 428.34 (1.70)	2.37	381 (0.85)	183 383.06 (2.13)	2.51
Imipramine	4 577 (3.12)	351 752.12 (1.09)	0.35	2 712 (3.31)	149 584.60 (0.98)	0.30	1 304 (2.90)	60 825.98 (0.71)	0.24
Lithium	1 156 (0.79)	259 522.00 (0.80)	1.02	711 (0.87)	137 282.40 (0.90)	1.04	357 (0.79)	76 011.12 (0.88)	1.11
Lofepramine	359 (0.24)	121 281.05 (0.38)	1.54	158 (0.19)	53 499.47 (0.35)	1.82	65 (0.14)	26 976.13 (0.31)	2.16
Maproteline	212 (0.14)	74 500.73 (0.23)	1.60	54 (0.07)	17 294.66 (0.11)	1.72	3 (0.01)	1 236.88 (0.01)	2.15
Mainserin	1 313 (0.89)	307 070.58 (0.95)	1.06	357 (0.44)	66 538.21 (0.44)	1.00	111 (0.25)	26 560.74 (0.31)	1.25
Mirtazapine	1 623 (1.10)	752 930.14 (2.33)	2.11	1 039 (1.27)	417 129.26 (2.74)	2.15	488 (1.09)	247 917.66 (2.88)	2.65
Moclobemide	1 699 (1.16)	437 360.06 (1.35)	1.17	467 (0.57)	100 586.34 (0.66)	1.16	191 (0.43)	54 123.82 (0.63)	1.48
Nefazodone	27 (0.02)	11 531.39 (0.04)	1.94	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Paroxetine	14 623 (9.95)	4 992 686.42 (15.45)	1.55	7 729 (9.45)	2 227 159.95 (14.61)	1.55	5 270 (11.73)	877 563.58 (10.19)	0.87
Perphenazine/ Amitriptyline	9 (0.01)	3 246.36 (0.01)	1.64	1 (0.00)	195 (0.00)	1.05	0 (0.00)	0 (0.00)	0.00
Reboxetine	107 (0.07)	44 211.89 (0.14)	1.88	60 (0.07)	17 621.39 (0.12)	1.58	21 (0.05)	6 303.23 (0.07)	1.57
Sertraline	6 411 (4.36)	2 281 677.63 (7.06)	1.62	3 314 (4.05)	856 716.05 (5.62)	1.39	1 972 (4.39)	461 407.73 (5.36)	1.22

Table 6c: Number of prescriptions with only one antidepressant prescribed for each active ingredient (continue)

	2004			2005			2006		
Active ingredient	**Prevalence (%)**	**Total cost (R) (%)**	**CPI**	**Prevalence (%)**	**Total (R) cost (%)**	**CPI**	**Prevalence (%)**	**Total cost (R) (%)**	**CPI**
Sulpiride	5 355 (3.65)	674 418.69 (2.09)	0.57	3 060 (3.74)	291 264.18 (1.91)	0.51	1 880 (4.18)	188 109.69 (2.18)	0.52
Tranylcypromine	74 (0.05)	11 156.72 (0.03)	0.69	33 (0.04)	4 761.37 (0.03)	0.77	0 (0.00)	0 (0.00)	0.00
Trazodone	1 192 (0.81)	502 763.99 (1.56)	1.92	989 (1.21)	335 553.08 (2.20)	1.82	714 (1.59)	248 578.54 (2.89)	1.82
Trimipramine	1 156 (0.79)	236 568.85 (0.73)	0.93	599 (0.73)	117 140.01 (0.77)	1.05	365 (0.81)	77 260.87 (0.90)	1.10
Venlafaxine	6 782 (4.62)	3 484 873.82 (10.78)	2.34	5 331 (6.51)	2 605 156.41 (17.09)	2.62	3 791 (8.44)	1 898 701.35 (22.04)	2.61
Total	136 559 (92.96)	27 250 103.95 (84.30)	34.99	77 330 (94.50)	13 221 215.68 (86.72)	34.63	42 273 (94.07)	7 275 629.39 (84.46)	

**% Prevalence = The prevalence for the active ingredient divided by the total number of all antidepressant prescriptions for the specific year multiplied by hundred. (n 2004 = 146 905; n 2005 = 81 830, n2006 = 44 938).*

***% Cost = The total cost for each active ingredient divided by the total cost of all the prescriptions prescribed for a specific year multiplied by hundred. (n2004 = R32 323 356.77, n2005 = R 15 245 709.85, n2006 = R 8 614 631.29).*

Table 7c: Number of prescriptions with two antidepressants prescribed for each active ingredient as well as drug-drug interactions

Active ingredient		2004			2005			2006		
		Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)	CPI
Amitriptyline	Amitriptyline	199 (0.14)	17 438.09 (0.05)	0.40	80 (0.10)	5 056.60 (0.03)	0.34	43 (0.10)	2 036.51 (0.02)	0.25
	Bupropion ☺	0 (0.00)	0.00 (0.00)	0.00	6 (0.01)	1 148.36 (0.01)	1.03	10 (0.02)	3 117.76 (0.04)	1.63
	Amitriptyline/ Chlordiazepoxide	3 (0.00)	355.04 (0.00)	0.54	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Citalopram ●	655 (0.45)	184 202.65 (0.57)	1.28	276 (0.34)	43 335.56 (0.28)	0.84	137 (0.30)	16 558.35 (0.19)	0.63
	Clomipramine	10 (0.01)	1 282.53 (0.00)	0.58	8 (0.01)	1 740.08 (0.01)	1.17	9 (0.02)	1 666.5 (0.02)	0.97
	Dothiepin	25 (0.02)	3 458.76 (0.01)	0.63	1 (0.00)	135.54 (0.00)	0.73	0 (0.00)	0 (0.00)	0.00
	Duloxetine	1 (0.00)	401.26 (0.00)	1.82	21 (0.03)	8 153.07 (0.05)	2.08	12 (0.03)	6 562.13 (0.08)	2.85
	Escitalopram ●	104 (0.07)	29 462.19 (0.09)	1.29	89 (0.11)	25 538.34 (0.17)	1.54	35 (0.08)	11 157.68 (0.13)	1.66
	Fluoxetine ●	1 107 (0.75)	167 329.56 (0.52)	0.69	466 (0.57)	44 146.74 (0.29)	0.51	187 (0.42)	18 863.82 (0.22)	0.53
	Flupenthixol	115 (0.08)	50 891.24 (0.16)	2.01	40 (0.05)	15 706.94 (0.10)	2.11	11 (0.02)	3 906.15 (0.05)	1.85
	Fluphenazine/ Nortriptyline ☺	4 (0.00)	558.42 (0.00)	0.63	5 (0.01)	692.05 (0.00)	0.74	3 (0.01)	555.46 (0.01)	0.97
	Fluvoxamine ●	25 (0.02)	10 351.24 (0.03)	1.88	13 (0.02)	7 451.72 (0.05)	3.08	0 (0.00)	0 (0.00)	0.00
	Imipramine	19 (0.01)	2 616.44 (0.01)	0.63	2 (0.00)	169.37 (0.00)	0.45	1 (0.00)	24.48 (0.00)	0.13
	Lithium ☺	26 (0.02)	5 830.88 (0.02)	1.02	4 (0.00)	1 218.22 (0.01)	1.63	2 (0.00)	800.58 (0.01)	2.09
	Lofepramine	9 (0.01)	4 947.92 (0.02)	2.50	13 (0.02)	5 525.55 (0.04)	2.28	5 (0.01)	2 642.23 (0.03)	2.76
	Mianserin	7 (0.00)	3 577.60 (0.01)	2.32	5 (0.01)	1 405.24 (0.01)	1.51	1 (0.00)	235.86 (0.00)	1.23
	Mirtazapine	12 (0.01)	6 445.06 (0.02)	2.44	20 (0.02)	10 078.17 (0.07)	2.70	12 (0.03)	6 741.14 (0.08)	2.93
	Moclobemide ●	63 (0.04)	18 874.82 (0.06)	1.36	14 (0.02)	3 245.72 (0.02)	1.24	70 (0.16)	15 209.72 (0.18)	1.13
	Nefazodone	1 (0.00)	346.91 (0.00)	1.58	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Paroxetine ●	395 (0.27)	170 236.32 (0.53)	1.96	205 (0.25)	74 012.70 (0.49)	1.94	108 (0.24)	22 818.29 (0.26)	1.10
	Reboxetine	1 (0.00)	760.47 (0.00)	3.46	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00

Table 7c: Number of prescriptions with two antidepressants prescribed for each active as well as drug-drug interactions ingredient (continue)

Active ingredient		2004			2005			2006		
		Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
Amitriptyline	Sertraline ●	233 (0.16)	110 902.34 (0.34)	2.16	70 (0.09)	22 348.64 (0.15)	1.71	28 (0.06)	7 929.72 (0.09)	1.48
	Sulpiride	107 (0.07)	16 760.93 (0.05)	0.71	62 (0.08)	7 667.01 (0.05)	0.66	23 (0.05)	3 571.79 (0.04)	0.81
	Tranylcypromine ●	3 (0.00)	655.24 (0.00)	0.99	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Trazodone	19 (0.01)	7 563.30 (0.02)	1.81	14 (0.02)	3 275.25 (0.02)	1.26	8 (0.02)	3 697.71 (0.04)	2.41
	Trimipramine	33 (0.02)	11 089.53 (0.03)	1.53	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Venlafaxine ☺	101 (0.07)	55 022.78 (0.17)	2.48	53 (0.06)	29 285.92 (0.19)	2.97	56 (0.12)	33 888.73 (0.39)	3.16
Amitriptyline/ Chlordiazepoxide	Citalopram ●	12 (0.01)	6 025.73 (0.02)	2.28	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Escitalopram ●	1 (0.00)	318.84 (0.00)	1.45	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Fluoxetine ●	0 (0.00)	0.00 (0.00)	0.00	4 (0.00)	954.29 (0.01)	1.28	0 (0.00)	0 (0.00)	0.00
	Paroxetine ●	17 (0.01)	8 514.35 (0.03)	2.28	12 (0.01)	6 971.07 (0.05)	3.12	1 (0.00)	424.35 (0.00)	2.21
Bupropion	Citalopram	1 (0.00)	234.72 (0.00)	0.00	2 (0.00)	796.82 (0.01)	2.14	4 (0.01)	1 843.57 (0.02)	2.40
	Dothiepin ☺	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	98.98 (0.00)	0.53	1 (0.00)	192.64 (0.00)	1.00
	Duloxetine	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	1 340.52 (0.01)	3.60	12 (0.03)	7 765.90 (0.09)	3.38
	Escitalopram	0 (0.00)	0.00 (0.00)	0.00	9 (0.01)	3 313.62 (0.02)	1.98	8 (0.02)	3 655.26 (0.04)	2.38
	Fluoxetine	1 (0.00)	263.45 (0.00)	1.20	4 (0.00)	1 189.62 (0.01)	1.60	1 (0.00)	381.49 (0.00)	1.99
	Flupenthixol	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	516.58 (0.00)	2.77	1 (0.00)	516.58 (0.01)	2.69
	Fluvoxamine	0 (0.00)	0.00 (0.00)	0.00	3 (0.00)	1 862.58 (0.01)	3.33	5 (0.01)	2 973.26 (0.03)	3.10
	Lithium ☺	0 (0.00)	0.00 (0.00)	0.00	9 (0.01)	4 469.53 (0.03)	2.67	3 (0.01)	903.58 (0.01)	1.57
	Mirtazapine	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	417.52 (0.00)	2.24	3 (0.01)	1 672.55 (0.02)	2.91
	Reboxetine	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	450.27 (0.00)	2.42	0 (0.00)	0 (0.00)	0.00
	Paroxetine	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0.00 (0.00)	0.00	4 (0.01)	1 522.95 (0.02)	1.99
	Sertraline	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	25.39 (0.00)	0.14	0 (0.00)	0 (0.00)	0.00
	Sulpiride	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	108.70 (0.00)	0.58	1 (0.00)	835.56 (0.01)	4.36
	Trazodone	0 (0.00)	0.00 (0.00)	0.00	11 (0.01)	4 985.52 (0.03)	2.43	24 (0.05)	11 340.03 (0.13)	2.46
	Trimipramine ☺	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	261.99 (0.00)	1.41	0 (0.00)	0 (0.00)	0.00
	Paroxetine	1 (0.00)	719.98 (0.00)	3.27	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Venlafaxine	0 (0.00)	0.00 (0.00)	0.00	3 (0.00)	1 411.01 (0.01)	2.52	9 (0.02)	9 086.12 (0.11)	5.27

Table 7c: Number of prescriptions with two antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient		2004			2005			2006		
		Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
Citalopram	Citalopram	8 (0.01)	3 991.84 (0.01)	2.27	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Clomipramine ●	20 (0.01)	10 641.82 (0.03)	2.42	9 (0.01)	3 234.55 (0.02)	1.93	0 (0.00)	0 (0.00)	0.00
	Dothiepin ●	215 (0.15)	70 656.45 (0.22)	1.49	30 (0.04)	6 378.44 (0.04)	1.14	20 (0.04)	3 120.64 (0.04)	0.81
	Duloxetine	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	1 257.42 (0.01)	3.37	1 (0.00)	567.42 (0.01)	2.96
	Escitalopram	1 (0.00)	485.63 (0.00)	2.21	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Fluoxetine	36 (0.02)	11 355.65 (0.04)	1.43	6 (0.01)	858.35 (0.01)	0.77	3 (0.01)	308.63 (0.00)	0.54
	Flupenthixol	93 (0.06)	44 398.28 (0.14)	2.17	12 (0.01)	4 381.80 (0.03)	1.96	5 (0.01)	2 003.49 (0.02)	2.09
	Fluphenazine/ Nortriptyline	6 (0.00)	1 392.71 (0.00)	1.05	1 (0.00)	266.67 (0.00)	1.43	1 (0.00)	213.96 (0.00)	1.12
	Fluvoxamine	6 (0.00)	2 901.58 (0.01)	2.20	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Imipramine ●	54 (0.04)	16 294.69 (0.05)	1.37	49 (0.06)	9 435.95 (0.06)	1.03	1 (0.00)	189.06 (0.00)	0.99
	Lithium	109 (0.07)	60 749.56 (0.19)	2.53	26 (0.03)	21 854.58 (0.14)	4.51	25 (0.06)	20 532.94 (0.24)	4.28
	Lofepramine ●	2 (0.00)	755.61 (0.00)	1.72	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Maprotiline	0 (0.00)	0.00 (0.00)	0.00	4 (0.00)	2 529.82 (0.02)	3.39	0 (0.00)	0 (0.00)	0.00
	Mianserin	177 (0.12)	77 671.26 (0.24)	1.99	21 (0.03)	10 898.84 (0.07)	2.79	1 (0.00)	141.30 (0.00)	0.74
	Mirtazapine	29 (0.02)	21 160.01 (0.07)	3.32	15 (0.02)	6 979.30 (0.05)	2.50	18 (0.04)	12 944.12 (0.15)	3.75
	Moclobemide ●	14 (0.01)	4 603.57 (0.01)	1.49	4 (0.00)	1 314.92 (0.01)	1.76	0 (0.00)	0 (0.00)	0.00
	Nefazodone	2 (0.00)	1 242.60 (0.00)	2.82	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Paroxetine	14 (0.01)	7 238.76 (0.02)	2.35	0 (0.00)	0.00 (0.00)	0.00	8 (0.02)	2 795.54 (0.03)	1.82
	Reboxetine	17 (0.01)	10 138.05 (0.03)	2.71	1 (0.00)	283.47 (0.00)	1.52	1 (0.00)	547.61 (0.01)	2.86
	Sertraline	20 (0.01)	9 439.09 (0.03)	2.14	5 (0.01)	2 080.96 (0.01)	2.23	0 (0.00)	0 (0.00)	0.00
	Sulpiride	126 (0.09)	41 172.08 (0.13)	1.49	41 (0.05)	9 765.58 (0.06)	1.28	21 (0.05)	3 645.51 (0.04)	0.91
Citalopram	Trazodone ☺	106 (0.07)	65 778.77 (0.20)	2.82	107 (0.13)	50 522.36 (0.33)	2.53	126 (0.28)	42 968.73 (0.50)	1.78

Table 7c: Number of prescriptions with two antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient		2004			2005			2006		
		Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
	Trimipramine ●	78 (0.05)	33 145.62 (0.10)	1.93	13 (0.02)	7 516.72 (0.05)	3.10	12 (0.03)	7 082.47 (0.08)	3.08
	Venlafaxine	40 (0.03)	27 843.50 (0.09)	3.16	5 (0.01)	2 782.77 (0.02)	2.99	1 (0.00)	913.22 (0.01)	4.76
Clomipramine	Clomipramine	13 (0.01)	6 432.27 (0.02)	2.25	12 (0.01)	5 387.36 (0.04)	2.41	0 (0.00)	0 (0.00)	0.00
	Duloxetine	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0.00 (0.00)	0.00	6 (0.01)	4 249.04 (0.05)	3.69
	Escitalopram ●	6 0.00 ()	3 056.77 (0.01)	2.32	3 (0.00)	644.49 (0.00)	1.15	0 (0.00)	0 (0.00)	0.00
	Fluoxetine ●	25 (0.02)	15 309.33 (0.05)	2.78	1 (0.00)	486.32 (0.00)	2.61	6 (0.01)	3 531.14 (0.04)	3.07
	Flupenthixol	11 (0.01)	4 928.76 (0.02)	2.04	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Imipramine	8 (0.01)	2 192.25 (0.01)	1.25	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Lithium ☺	20 (0.01)	16 277.47 (0.05)	3.70	11 (0.01)	12 429.32(0.08)	6.06	6 (0.01)	11 004.21 (0.13)	9.57
	Maprotiline	43 (0.03)	35 730.37 (0.11)	3.78	13 (0.02)	15 343.95 (0.10)	6.34	0 (0.00)	0 (0.00)	0.00
	Mianserin	1 (0.00)	209.00 (0.00)	0.95	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Mirtazapine	1 (0.00)	907.73 (0.00)	4.13	9 (0.01)	7 745.53 (0.05)	4.62	0 (0.00)	0 (0.00)	0.00
	Paroxetine ●	5 (0.00)	1 981.44 (0.01)	1.80	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	935.20 (0.01)	2.44
	Reboxetine	7 (0.00)	2 392.11 (0.01)	1.55	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Sertraline ●	11 (0.01)	9 421.89 (0.03)	3.89	1 (0.00)	262.74 (0.00)	1.41	0 (0.00)	0 (0.00)	0.00
	Sulpiride	1 (0.00)	821.40 (0.00)	3.73	3 (0.00)	1 165.40 (0.01)	2.09	3 (0.01)	1 282.44 (0.01)	2.23
	Trazodone	16 (0.01)	10 019.38 (0.03)	2.85	1 (0.00)	193.49 (0.00)	1.04	0 (0.00)	0 (0.00)	0.00
	Venlafaxine ☺	5 (0.00)	4 004.17 (0.01)	3.64	1 (0.00)	757.82 (0.00)	4.07	0 (0.00)	0 (0.00)	0.00
Dothiepin	Dothiepin	119 (0.08)	24 129.10 (0.07)	0.92	26 (0.03)	4 168.73 (0.03)	0.86	7 (0.02)	1 134.96 (0.01)	0.85
	Duloxetine	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	955.83 (0.01)	2.57	0 (0.00)	0 (0.00)	0.00
	Escitalopram ●	39 (0.03)	11 794.80 (0.04)	1.37	8 (0.01)	2 684.17 (0.02)	1.80	17 (0.04)	6 049.94 (0.07)	1.86
Dothiepin	Fluoxetine ●	226 (0.15)	40 192.37 (0.12)	0.81	56 (0.07)	5 846.39 (0.04)	0.56	3 (0.01)	223.53 (0.00)	0.39

Table 7c: Number of prescriptions with two antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient		2004			2005			2006		
		Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
	Flupenthixol	14 (0.01)	6 791.79 (0.02)	2.20	4 (0.00)	864.48 (0.01)	1.16	0 (0.00)	0 (0.00)	0.00
	Fluphenazine/ Nortriptyline	8 (0.01)	946.90 (0.00)	0.54	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	179.07 (0.00)	0.93
	Fluvoxamine ●	14 (0.01)	5 424.84 (0.02)	1.76	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	721.56 (0.01)	1.88
	Lithium ☺	25 (0.02)	9 064.70 (0.03)	1.65	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Lofepramine	1 ()0.00	388.48 (0.00)	1.77	2 (0.00)	371.80 (0.00)	1.00	1 (0.00)	743.36 (0.01)	3.88
	Mirtazapine	1 (0.00)	743.39 (0.00)	3.38	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Moclobemide ●	6 (0.00)	1 628.23 (0.01)	1.23	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Nefazodone	1 (0.00)	348.00 (0.00)	1.58	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Paroxetine ●	108 (0.07)	46 992.06 (0.15)	1.98	37 (0.05)	13 811.70 (0.09)	2.00	2 (0.00)	639.66 (0.01)	1.67
	Reboxetine	9 (0.01)	4 897.92 (0.02)	2.47	13 (0.02)	5 992.46 (0.04)	2.47	1 (0.00)	302.51 (0.00)	1.58
	Sertraline ●	41 (0.03)	27 863.43 (0.09)	3.09	38 (0.05)	16 991.77 (0.11)	2.40	22 (0.05)	11 161.88 (0.13)	2.65
	Sulpiride	39 (0.03)	12 287.17 (0.04)	1.43	19 (0.02)	4 362.69 (0.03)	1.23	3 (0.01)	453.70 (0.01)	0.79
	Trazodone	0 (0.00)	0.00 (0.00)	0.00	3 (0.00)	1 206.59 (0.01)	2.16	7 (0.02)	4 437.35 (0.05)	3.31
	Trimipramine	6 (0.00)	1 439.21 (0.00)	1.09	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Venlafaxine ☺	23 (0.02)	14 797.60 (0.05)	2.92	11 (0.01)	7 267.05 (0.05)	3.55	9 (0.02)	5 246.08 (0.06)	3.04
Duloxetine	Duloxetine	0 (0.00)	0.00 (0.00)	0.00	86 (0.11)	57 945.25 (0.38)	3.62	53 (0.12)	45 584.50 (0.53)	4.49
	Escitalopram	0 (0.00)	0.00 (0.00)	0.00	6 (0.01)	3 327.63 (0.02)	2.98	4 (0.01)	3 500.16 (0.04)	4.56
	Fluoxetine	1 (0.00)	368.84 0.00 ()	1.68	3 (0.00)	955.33 (0.01)	1.71	4 (0.01)	2 032.63 (0.02)	2.65
	Flupenthixol	0 (0.00)	0.00 (0.00)	0.00	3 (0.00)	1 708.49 (0.01)	3.06	1 (0.00)	713.97 (0.01)	3.72
	Imipramine	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	350.46 (0.00)	1.88	4 (0.01)	2 317.44 (0.03)	3.02
	Lithium	0 (0.00)	0.00 (0.00)	0.00	14 (0.02)	11 944.55 (0.08)	4.58	2 (0.00)	2 507.38 (0.03)	6.54
	Maprotiline	0 (0.00)	0.00 (0.00)	0.00	3 (0.00)	2 836.53 (0.02)	5.07	7 (0.02)	6 618.57 (0.08)	4.93
	Mianserin	0 (0.00)	0.00 ()0.00	0.00	16 (0.02)	10 487.65 (0.07)	3.52	2 (0.00)	1 671.63 (0.02)	4.36

Table 7c: Number of prescriptions with two antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient		2004			2005			2006		
		Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
Duloxetine	Mirtazapine	0 (0.00)	0.00 (0.00)	0.00	18 (0.02)	12 017.81 (0.08)	3.58	15 (0.03)	18 222.41 (0.21)	6.34
	Sertraline	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	1 201.11 (0.01)	6.45	5 (0.01)	3 306.53 (0.04)	3.45
	Sulpiride	1 (0.00)	495.67 (0.00)	2.25	1 (0.00)	520.09 (0.00)	2.79	1 (0.00)	165.60 (0.00)	0.86
	Trazodone	0 (0.00)	0.00 (0.00)	0.00	18 (0.02)	10 917.07 (0.07)	3.26	72 (0.16)	57 908.74 (0.67)	4.20
	Venlafaxine	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	1 735.61 (0.01)	4.66	0 (0.00)	0 (0.00)	0.00
Escitalopram	Fluoxetine	3 (0.00)	915.12 (0.00)	1.39	7 (0.01)	2 050.69 (0.01)	1.57	1 (0.00)	453.85 (0.01)	2.37
	Flupenthixol	16 (0.01)	6 091.84 (0.02)	1.73	27 (0.03)	11 362.60 (0.07)	2.26	3 (0.01)	969.35 (0.01)	1.69
	Fluphenazine/ Nortriptyline	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	351.21 (0.00)	1.83
	Fluvoxamine	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	533.45 (0.00)	2.86	0 (0.00)	0 (0.00)	0.00
	Imipramine ●	3 (0.00)	878.79 (0.00)	1.33	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Lithium	26 (0.02)	10 751.84 (0.03)	1.88	23 (0.03)	10 082.78 (0.07)	2.35	7 (0.02)	3 569.36 (0.04)	2.66
	Mianserin	130 (0.09)	54 379.26 (0.17)	1.90	25 (0.03)	6 621.76 (0.04)	1.42	2 (0.00)	536.29 (0.01)	1.40
	Mirtazapine	24 (0.02)	17 887.59 (0.06)	3.39	37 (0.05)	21 736.02 (0.14)	3.15	8 (0.02)	3 866.14 (0.04)	2.52
	Paroxetine	1 (0.00)	489.96 (0.00)	2.23	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Reboxetine	0 (0.00)	0.00 (0.00)	0.00	6 (0.01)	3 468.53 (0.02)	3.10	3 (0.01)	2 160.33 (0.03)	3.76
	Sulpiride	7 (0.00)	1 990.66 (0.01)	1.29	18 (0.02)	6 215.76 (0.04)	1.85	6 (0.01)	2 044.52 (0.02)	1.78
	Trazodone	2 (0.00)	1 288.78 (0.00)	2.93	19 (0.02)	9 864.77 (0.06)	2.79	44 (0.10)	26 706.62 (0.31)	3.17
	Trimipramine ●	7 (0.00)	2 502.85 (0.01)	1.63	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Venlafaxine	2 (0.00)	1 078.94 (0.00)	2.45	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Fluoxetine	Fluoxetine	45 (0.03)	12 479.47 (0.04)	1.26	9 (0.01)	1 358.16 (0.01)	0.81	8 (0.02)	1 584.07 (0.02)	1.03
	Flupenthixol	125 (0.09)	50 506.40 (0.16)	1.84	16 (0.02)	6 493.60 (0.04)	2.18	4 (0.01)	1 844.57 (0.02)	2.41
	Fluphenazine/ Nortriptyline	5 (0.00)	755.54 (0.00)	0.69	6 (0.01)	692.69 (0.00)	0.62	1 (0.00)	210.11 (0.00)	1.10
Fluoxetine	Fluvoxamine	1 (0.00)	213.29 (0.00)	0.97	1 (0.00)	600.67 (0.00)	3.22	7 (0.02)	1 190.86 (0.01)	0.89

Table 7c: Number of prescriptions with two antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient		2004			2005			2006		
		Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
	Imipramine ●	55 (0.04)	7 665.75 (0.02)	0.63	43 (0.05)	4 486.42 (0.03)	0.56	13 (0.03)	1 738.87 (0.02)	0.70
	Lithium ☺	111 (0.08)	32 666.85 (0.10)	1.34	40 (0.05)	8 621.95 (0.06)	1.16	20 (0.04)	6 795.63 (0.08)	1.77
	Lofepramine ●	11 (0.01)	5 135.35 (0.02)	2.12	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Maprotiline	27 (0.02)	12 038.64 (0.04)	2.03	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Mianserin	130 (0.09)	38 857.83 (0.12)	1.36	25 (0.03)	6 807.32 (0.04)	1.46	0 (0.00)	0 (0.00)	0.00
	Mirtazapine	33 (0.02)	18 033.01 (0.06)	2.48	16 (0.02)	6 043.83 (0.04)	2.03	4 (0.01)	2 385.38 (0.03)	3.11
	Moclobemide ●	9 (0.01)	4 116.51 (0.01)	2.08	2 (0.00)	529.48 (0.00)	1.42	0 (0.00)	0 (0.00)	0.00
	Paroxetine	14 (0.01)	5 573.32 (0.02)	1.81	9 (0.01)	2 764.30 (0.02)	1.65	1 (0.00)	44.50 (0.00)	0.23
	Reboxetine	17 (0.01)	9 833.54 (0.03)	2.63	5 (0.01)	1 567.79 (0.01)	1.68	3 (0.01)	500.73 (0.01)	0.87
	Sertraline	1 (0.00)	439.80 (0.00)	2.00	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Sulpiride	166 (0.11)	33 350.07 (0.10)	0.91	67 (0.08)	8 853.32 (0.06)	0.71	32 (0.07)	4 575.82 (0.05)	0.75
	Trazodone ☺	77 (0.05)	40 783.92 (0.13)	2.41	84 (0.10)	32 409.01 (0.21)	2.07	73 (0.16)	31 146.04 (0.36)	2.23
	Trimipramine ●	100 (0.07)	32 315.37 (0.10)	1.47	34 (0.04)	7 421.24 (0.05)	1.17	14 (0.03)	3 299.33 (0.04)	1.23
	Venlafaxine	39 (0.03)	32 484.74 (0.10)	3.79	13 (0.02)	13 233.00 (0.09)	5.46	7 (0.02)	6 359.51 (0.07)	4.74
Flupenthixol	Flupenthixol	5 (0.00)	1 655.84 (0.01)	1.51	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Fluphenazine/ Nortriptyline	2 (0.00)	280.02 (0.00)	0.64	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Fluvoxamine	15 (0.01)	9 769.97 (0.03)	2.96	2 (0.00)	3 013.42 (0.02)	8.09	0 (0.00)	0 (0.00)	0.00
	Imipramine	19 (0.01)	11 638.02 (0.04)	2.78	14 (0.02)	8 265.80 (0.05)	3.17	12 (0.03)	8 215.54 (0.10)	3.57
Flupenthixol	Lithium	7 (0.00)	4 286.12 (0.01)	2.78	5 (0.01)	4 705.22 (0.03)	5.05	3 (0.01)	3 497.34 (0.04)	6.08

Table 7c: Number of prescriptions with two antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient		2004			2005			2006		
		Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
	Lofepramine	10 (0.01)	7 720.60 (0.02)	3.51	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Mianserin	26 (0.02)	16 241.80 (0.05)	2.84	1 (0.00)	326.68 (0.00)	1.75	0 (0.00)	0 (0.00)	0.00
	Mirtazapine	1 (0.00)	763.77 (0.00)	3.47	10 (0.01)	7 868.54 (0.05)	4.22	16 (0.04)	13 729.25 (0.16)	4.48
	Moclobemide	19 (0.01)	9 130.69 (0.03)	2.18	12 (0.01)	5 554.03 (0.04)	2.48	7 (0.02)	3 434.64 (0.04)	2.56
	Paroxetine	54 (0.04)	50 798.45 (0.16)	4.28	18 (0.02)	9 038.72 (0.06)	2.70	10 (0.02)	2 998.08 (0.03)	1.56
	Sertraline	60 (0.04)	38 128.45 (0.12)	2.89	16 (0.02)	8 643.81 (0.06)	2.90	11 (0.02)	5 788.11 (0.07)	2.74
	Trazodone	4 (0.00)	4 691.49 (0.01)	5.33	5 (0.01)	5 209.29 (0.03)	5.59	8 (0.02)	4 528.04 (0.05)	2.95
	Trimipramine	9 (0.01)	3 661.11 (0.01)	1.85	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Venlafaxine	46 (0.03)	50 748.84 (0.16)	5.01	22 (0.03)	23 705.07 (0.16)	5.78	19 (0.04)	16 632.18 (0.19)	4.57
Fluphenazine/ Nortriptyline	Imipramine ☺	1 (0.00)	252.57 (0.00)	1.15	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Mianserin	3 (0.00)	996.10 (0.00)	1.51	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Paroxetine ☺	7 0.00 ()	3 297.45 (0.01)	2.14	6 (0.01)	3 096.18 (0.02)	2.77	3 (0.01)	774.91 (0.01)	1.35
	Reboxetine	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	387.90 (0.00)	2.08	0 (0.00)	0 (0.00)	0.00
	Sertraline	3 (0.00)	1 742.48 (0.01)	2.64	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Sulpiride	5 (0.00)	1 748.05 (0.01)	1.59	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Trazodone ☺	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	360.65 (0.00)	1.88
	Venlafaxine	1 (0.00)	498.28 (0.00)	2.26	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Fluvoxamine	Imipramine ●	15 (0.01)	8 780.94 (0.03)	2.66	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Lithium ☺	18 (0.01)	8 812.97 (0.03)	2.23	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	555.62 (0.01)	2.90
	Lofepramine ●	7 (0.00)	7 182.95 (0.02)	4.66	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Fluvoxamine	Mianserin	4 (0.00)	2 088.14 (0.01)	2.37	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Mirtazapine ☺	6 (0.00)	3 187.77 (0.01)	2.41	2 (0.00)	1 177.58 (0.01)	3.16	0 (0.00)	0 (0.00)	0.00

Table 7c: Number of prescriptions with two antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient		2004			2005			2006		
		Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
	Moclobemide ●	1 (0.00)	615.79 (0.00)	2.80	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Paroxetine	126 (0.09)	79 024.40 (0.24)	2.85	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Reboxetine	0 (0.00)	0.00 (0.00)	0.00	6 (0.01)	5 382.22 (0.04)	4.81	0 (0.00)	0 (0.00)	0.00
	Sertraline	203 (0.14)	114 993.03 (0.36)	2.57	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Sulpiride	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	1 080.04 (0.01)	2.90	0 (0.00)	0 (0.00)	0.00
	Trazodone	20 (0.01)	21 358.34 (0.07)	4.85	16 (0.02)	12 770.46 (0.08)	4.28	20 (0.04)	14 758.7 (0.17)	3.85
	Trimipramine ●	27 (0.02)	16 654.28 (0.05)	2.80	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Venlafaxine	11 (0.01)	13 743.80 (0.04)	5.68	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Imipramine	Imipramine	68 (0.05)	5 594.97 (0.02)	0.37	22(0.03)	1 310.80 (0.01)	0.32	17 (0.04)	838.32 (0.01)	0.26
	Lithium ☺	15 (0.01)	3 799.64 (0.01)	1.15	11 (0.01)	1 433.34 (0.01)	0.70	10 (0.02)	1 280.07 (0.01)	0.67
	Mianserin	3 (0.00)	75.51 (0.00)	0.11	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Mirtazapine	3 (0.00)	1 920.12 (0.01)	2.91	10 (0.01)	11 678.73 (0.08)	6.27	0 (0.00)	0 (0.00)	0.00
	Moclobemide ●	8 (0.01)	2 867.46 (0.01)	1.63	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Paroxetine ●	19 (0.01)	6 946.54 (0.02)	1.66	13 (0.02)	4 229.27 (0.03)	1.75	19 (0.04)	8 198.83 (0.10)	2.25
	Sertraline ●	9 (0.01)	5 134.71 (0.02)	2.59	8 (0.01)	3 936.62 (0.03)	2.64	3 (0.01)	1 861.14 (0.02)	3.24
	Sulpiride	51 (0.03)	19 025.45 (0.06)	1.70	39 (0.05)	13 165.72 (0.09)	1.81	35 (0.08)	8 382.53 (0.10)	1.25
	Venlafaxine	16 (0.01)	14 709.39 (0.05)	4.18	16(0.02)	11 883.75 (0.08)	3.99	2 (0.00)	1 327.57 (0.02)	3.46
Lithium	Lithium	21 (0.01)	4 087.18 (0.01)	0.88	10 (0.01)	1 676.89 (0.01)	0.90	2 (0.00)	600.15 (0.01)	1.57
	Lofepramine	5 (0.00)	2 450.52 (0.01)	2.23	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	1 448.28 (0.02)	3.78
Lithium	Maprotiline	9 (0.01)	4 882.51 (0.02)	2.47	11 (0.01)	5 009.94 (0.03)	2.44	0 (0.00)	0 (0.00)	0.00
	Mianserin	20 (0.01)	12 352.29 (0.04)	2.81	0(0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00

Table 7c: Number of prescriptions with two antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient		2004			2005			2006		
		Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
	Mirtazapine	19 (0.01)	17 982.01 (0.06)	4.30	2 (0.00)	1 176.00 (0.01)	3.16	0 (0.00)	0 (0.00)	0.00
	Moclobemide	51 (0.03)	27 056.86 (0.08)	2.41	13 (0.02)	6 137.34 (0.04)	2.53	4 (0.01)	1 642.52 (0.02)	2.14
	Paroxetine	61 (0.04)	35 657.49 (0.11)	2.66	22 (0.03)	10 927.13 (0.07)	2.67	16 (0.04)	6 028.97 (0.07)	1.97
	Sertraline	39 (0.03)	26 375.71 (0.08)	3.07	12 (0.01)	7 833.21 (0.05)	3.50	13 (0.03)	7 459.65 (0.09)	2.99
	Sulpiride	9 (0.01)	2 252.47 (0.01)	1.14	1 (0.00)	645.90 (0.00)	3.47	7 (0.02)	3 813.39 (0.04)	2.84
	Tranylcypromine	1 (0.00)	472.83 (0.00)	2.15	2 (0.00)	464.26 (0.00)	1.25	0 (0.00)	0 (0.00)	0.00
	Trazodone	0 (0.00)	0.00 (0.00)	0.00	9 (0.01)	5 543.21 (0.04)	3.31	8 (0.02)	4 601.60 (0.05)	3.00
	Trimipramine	3 (0.00)	2 603.70 (0.01)	3.94	1(0.00)	601.55 (0.00)	3.23	0 (0.00)	0 (0.00)	0.00
	Venlafaxine ☺	111 (0.08)	97 374.53 (0.30)	3.99	53 (0.06)	46 393.48 (0.30)	4.70	13 (0.03)	11 701.9 (0.14)	4.70
Lofepramine	Paroxetine ●	6 (0.00)	3 326.64 (0.01)	2.52	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Sertraline ●	11 (0.01)	10 444.28 (0.03)	4.32	11 (0.01)	6 743.43 (0.04)	3.29	0 (0.00)	0 (0.00)	0.00
	Sulpiride	21 (0.01)	12 686.74 (0.04)	2.75	3 (0.00)	3 128.22 (0.02)	5.60	4 (0.01)	3 422.99 (0.04)	4.46
	Trazodone	32 (0.02)	22 177.66 (0.07)	3.15	42 (0.05)	32 016.12 (0.21)	4.09	30 (0.07)	24 395.03 (0.28)	4.24
	Trimipramine	3 (0.00)	1 922.67 (0.01)	2.91	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Maprotiline	Maprotiline	11 (0.01)	8 300.81 (0.03)	3.43	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Sertraline	7 (0.00)	4 151.67 (0.01)	2.70	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Trimipramine	0 (0.00)	0.00 (0.00)	0.00	6 (0.01)	1 454.52 (0.01)	1.30	0 (0.00)	0 (0.00)	0.00
	Venlafaxine	7 (0.00)	6 535.06 (0.02)	4.24	1 (0.00)	885.08 (0.01)	4.75	0 (0.00)	0 (0.00)	0.00
Mianserin	Mianserin	21 (0.01)	6 208.40 (0.02)	1.34	9 (0.01)	2 218.20 (0.01)	1.32	1 (0.00)	463.46 (0.01)	2.42
Mianserin	Moclobemide	8 (0.01)	3 626.23 (0.01)	2.06	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Paroxetine	145 (0.10)	140 964.99 (0.44)	4.42	17 (0.02)	11 505.23 (0.08)	3.63	11 (0.02)	5 720.88 (0.07)	2.71

Table 7c: Number of prescriptions with two antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient		2004			2005			2006		
		Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
	Sertraline	18 (0.01)	11 172.80 (0.03)	2.82	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Sulpiride	23 (0.02)	8 860.93 (0.03)	1.75	11 (0.01)	5 104.66 (0.03)	2.49	2 (0.00)	1 270.50 (0.01)	3.31
	Trazodone	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	2 215.43 (0.01)	5.95	2 (0.00)	2 177.93 (0.03)	5.68
	Venlafaxine	20 (0.01)	12 886.99 (0.04)	2.93	1 (0.00)	531.24 (0.00)	2.85	0 (0.00)	0 (0.00)	0.00
Mirtazapine	Mirtazapine	49 (0.03)	44 022.40 (0.14)	4.08	46 (0.06)	32 628.78 (0.21)	3.81	15 (0.03)	12 902.29 (0.15)	4.49
	Moclobemide	7 (0.00)	6 451.64 (0.02)	4.19	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Paroxetine	30 (0.02)	28 507.77 (0.09)	4.32	21 (0.03)	19 424.51 (0.13)	4.96	2 (0.00)	1 110.80 (0.01)	2.90
	Reboxetine	15 (0.01)	14 153.08 (0.04)	4.29	5 (0.01)	3 790.50 (0.02)	4.07	0 (0.00)	0 (0.00)	0.00
	Sertraline	33 (0.02)	25 313.78 (0.08)	3.49	38 (0.05)	23 422.28 (0.15)	3.31	15 (0.03)	9 183.06 (0.11)	3.19
	Sulpiride	15 (0.01)	11 891.30 (0.04)	3.60	1 (0.00)	469.80 (0.00)	2.52	1 (0.00)	444.72 (0.01)	2.32
	Trazodone	23 (0.02)	24 626.99 (0.08)	4.87	1 (0.00)	553.57 (0.00)	2.97	0 (0.00)	0 (0.00)	0.00
	Trimipramine	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	547.03 (0.00)	2.94	0 (0.00)	0 (0.00)	0.00
	Venlafaxine	112 (0.08)	96 849.69 (0.30)	3.93	56 (0.07)	48 202.76 (0.32)	4.62	22 (0.05)	20 613.51 (0.24)	4.89
Moclobemide	Moclobemide	12 (0.01)	6 122.61 (0.02)	2.32	2 (0.00)	562.47 (0.00)	1.51	1 (0.00)	516.27 (0.01)	2.69
	Paroxetine ●	3 (0.00)	1 282.15 (0.00)	1.94	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Sulpiride	9 (0.01)	4 383.38 (0.01)	2.21	4 (0.00)	1 476.44 (0.01)	1.98	0 (0.00)	0 (0.00)	0.00
	Trazodone	2 (0.00)	1 135.00 (0.00)	2.58	1 (0.00)	127.25 (0.00)	0.68	0 (0.00)	0 (0.00)	0.00
	Trimipramine ●	15 (0.01)	15 599.88 (0.05)	4.73	14 (0.02)	10 841.85 (0.07)	4.16	4 (0.01)	3 459.88 (0.04)	4.51
	Venlafaxine	1 (0.00)	553.37 (0.00)	2.51	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Nefazodone	Sertraline	1 (0.00)	494.15 (0.00)	2.25	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Paroxetine	Paroxetine	1 (0.00)	587.97 (0.00)	2.67	10(0.01)	5 879.73 (0.04)	3.16	3 (0.01)	791.69 (0.01)	1.38
	Reboxetine	4 (0.00)	3 519.61 (0.01)	4.00	2 (0.00)	1 005.34 (0.01)	2.70	0 (0.00)	0 (0.00)	0.00

Table 7c: Number of prescriptions with two antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient		2004			2005			2006		
		Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
	Sertraline	47 (0.03)	28 374.28 (0.09)	2.74	2 (0.00)	743.14 (0.00)	1.99	1 (0.00)	500.17 (0.01)	2.61
	Sulpiride	54 (0.04)	28 711.52 (0.09)	2.42	27 (0.03)	10 891.93 (0.07)	2.17	23 (0.05)	6 596.19 (0.08)	1.50
	Trazodone ☺	108 (0.07)	80 714.36 (0.25)	3.40	130 (0.16)	85 011.74 (0.56)	3.51	123 (0.27)	64 709.65 (0.75)	2.74
	Trimipramine ●	218 (0.15)	127 213.90 (0.39)	2.65	36 (0.04)	16 469.29 (0.11)	2.46	11 (0.02)	3 706.50 (0.04)	1.76
	Venlafaxine	46 (0.03)	45 450.24 (0.14)	4.49	29 (0.04)	21 052.50 (0.14)	3.90	6 (0.01)	4 569.99 (0.05)	3.97
Reboxetine	Sertraline	1 (0.00)	728.51 (0.00)	3.31	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Trazodone	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	323.72 (0.00)	1.69
	Trimipramine	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	648.73 (0.01)	3.38
	Venlafaxine	6 (0.00)	6 311.15 (0.02)	4.78	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Sertraline	Sertraline	1 (0.00)	645.77 (0.00)	2.93	2 (0.00)	1 265.33 (0.01)	3.40	2 (0.00)	863.10 (0.01)	2.25
	Sulpiride	14 (0.01)	7 475.63 (0.02)	2.43	16 (0.02)	6 209.30 (0.04)	2.08	13 (0.03)	5 288.98 (0.06)	2.12
	Trazodone ☺	136 (0.09)	93 876.30 (0.29)	3.14	159 (0.19)	86 989.55 (0.57)	2.94	131 (0.29)	65 291.86 (0.76)	2.60
	Trimipramine ●	32 (0.02)	26 196.31 (0.08)	3.72	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	669.04 (0.01)	3.49
	Venlafaxine	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	1 162.72 (0.01)	3.12	0 (0.00)	0 (0.00)	0.00
Sulpiride	Sulpiride	10 (0.01)	3 665.34 (0.01)	1.67	7 (0.01)	3 190.34 (0.02)	2.45	3 (0.01)	1 187.24 (0.01)	2.06
	Trazodone	39 (0.03)	18 254.34 (0.06)	2.13	12 (0.01)	2 769.21 (0.02)	1.24	1 (0.00)	255.12 (0.00)	1.33
	Trimipramine	24 (0.02)	7 419.96 (0.02)	1.41	1 (0.00)	517.66 (0.00)	2.78	0 (0.00)	0 (0.00)	0.00
	Venlafaxine	18 (0.01)	9 805.46 (0.03)	2.48	10 (0.01)	8 667.14 (0.06)	4.65	9 (0.02)	6 575.31 (0.08)	3.81
Trazodone	Trazodone	35 (0.02)	23 274.22 (0.07)	3.02	53 (0.06)	31 739.11 (0.21)	3.21	31 (0.07)	25 538.38 (0.30)	4.30
	Trimipramine	20 (0.01)	11 767.76 (0.04)	2.67	1 (0.00)	586.86 (0.00)	3.15	0 (0.00)	0 (0.00)	0.00
Trazodone	Venlafaxine ☺	109 (0.07)	104 016.44 (0.32)	4.34	110 (0.13)	99 047.85 (0.65)	4.83	82 (0.18)	71 738.25 (0.83)	4.56

Table 7c: Number of prescriptions with two antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient		2004			2005			2006		
		Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
Trimipramine	Trimipramine	19 (0.01)	6 390.01 (0.02)	1.53	2 (0.00)	669.63 (0.00)	1.80	2 (0.00)	736.85 (0.01)	1.92
	Venlafaxine ☺	35 (0.02)	25 185.73 (0.08)	3.27	16 (0.02)	10 374.57 (0.07)	3.48	16 (0.04)	11 136.97 (0.13)	3.63
Venlafaxine	Venlafaxine	376 (0.26)	402 447.81 (1.25)	4.86	147 (0.18)	145 179.07 (0.95)	5.30	84 (0.19)	95 015.28 (1.10)	5.90
Total		9814.00 (6.68)	4 565 079.67 (14.12)	525.25	4 323 (5.28)	1 863 103.58 (12.22)	0	2528.00 (5.63)	1 188 533.69 (13.80)	0.25

**% Prevalence=The prevalence for the active ingredient divided by the total number of all antidepressant prescriptions for the specific year multiplied by hundred. (n 2004 = 146 905; n 2005 = 81 830, n2006 = 44 938).*

***% Cost=The total cost for each active ingredient divided by the total cost of all the prescriptions prescribed for a specific year multiplied by hundred. (n2004 = R 32 323 356.77, n2005 = R 15 245 709.85, n2006 = R 8 614 631.29).*

● *= Drug interaction with a significance rating of 1 or 2*

☺ *= Drug interaction with a significance rating of between 3 and 5.*

Table 8c: Number of prescriptions with three antidepressants prescribed for each active ingredient as well as drug-drug interactions

Active ingredient			2004			2005			2006		
			Prevalence (%) *	Total cost (R) (%) **	CPI	Prevalence (%) *	Total cost (R) (%) **	CPI	Prevalence (%) *	Total cost (R) (%) **	CPI
Amitriptyline	Amitriptyline	Amitriptyline/ Chlordiasepoxide	3 (0.00)	434.95 (0.00)	0.66	0 (0.00)	0 (0)	0.00	0 (0.00)	0 (0.00)	0.00
		Fluoxetine ●	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	133.70 (0.00)	0.17	0 (0.00)	0 (0.00)	0.00
		Escitalopram ●	1 (0.00)	303.51 (0.00)	1.38	0 (0.00)	0 (0.00)	0.00	1 (0.00)	275.73 (0.00)	1.44
		Paroxetine ●	2 (0.00)	932.33 (0.00)	2.12	0 (0.00)	0 (0.00)	0.00	1 (0.00)	39.03 (0.00)	0.20
		Sertraline ●	1 (0.00)	291.64 (0.00)	1.33	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Venlafaxine ☺	1 (0.00)	525.26 (0.00)	2.39	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Citalopram	Flupenthixol ●	2 (0.00)	897.42 (0.00)	2.04	2 (0.00)	453.42 (0.00)	0.28	0 (0.00)	0 (0.00)	0.00
		Trazodone ●	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	338.45 (0.00)	0.42	0 (0.00)	0 (0.00)	0.00
		Trimipramine ●	10 (0.01)	4 917.39 (0.02)	2.23	0 (0.01)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Venlafaxine ●	1 (0.00)	1 004.18 (0.00)	4.56	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Clomipramine	Escitalopram ●	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	363.55 (0.00)	0.45	0 (0.00)	0 (0.00)	0.00
		Paroxetine ●	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	7 (0.02)	5512.57 (0.06)	4.11
	Dothiepin	Dothiepin ●	1 (0.00)	176.92 (0.00)	0.80	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Perphenazine/ Amitriptyline ☺	1 (0.00)	602.42 (0.00)	2.74	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Duloxetine	Paroxetine ●	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	2406.84 (0.02)	1.49	0 (0.00)	0 (0.00)	0.00
		Sertraline ●	0 (0.00)	0.00 (0.00)	0.00	4 (0.00)	2 527.83 (0.02)	0.78	5 (0.01)	3 055.00 (0.04)	3.19
	Escitalopram	Fluoxetine ●	2 (0.00)	747.94 (0.00)	1.70	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Lithium ☺	4 (0.00)	2 947.50 (0.01)	3.35	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Sulpiride	0 (0.00)	0.00 (0.00)	0.00	12 (0.00)	3 987.70 (0.03)	0.41	0 (0.00)	0 (0.00)	0.00
	Fluoxetine	Flupenthixol ●	6 (0.00)	2 291.29 (0.01)	1.74	4 (0.00)	1 014.06 (0.01)	0.31	0 (0.00)	0 (0.00)	0.00
		Fluvoxamine ●	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	124.46 (0.00)	0.65
Amitriptyline	Fluoxetine	Imipramine ●	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	173.46 (0.00)	0.21	0 (0.00)	0 (0.00)	0.00
		Lithium ●	7 (0.00)	2 005.17 (0.01)	1.30	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Mianserin ●	6 (0.00)	2 094.69 (0.01)	1.59	5 (0.00)	1 483.95 (0.01)	0.37	0 (0.00)	0 (0.00)	0.00

Table 8c: Number of prescriptions with three antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient			2004			2005			2006		
			Prevalence (%) *	Total cost (R) (%) **	CPI	Prevalence (%) *	Total cost (R) (%) **	CPI	Prevalence (%) *	Total cost (R) (%) **	CPI
		Reboxetine ●	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	273.17 (0.00)	0.34	0 (0.00)	0 (0.00)	0.00
		Sertraline ●	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	254.48 (0.00)	1.33
		Sulpiride ●	3 (0.00)	1 456.17 (0.00)	2.21	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Trimipramine ●	14 (0.01)	4 670.32 (0.01)	1.52	0 (0.01)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Amitriptyline	Flupenthixol	Fluvoxamine ●	3 (0.00)	3 708.00 (0.01)	5.62	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Paroxetine ●	1 (0.00)	844.87 (0.00)	3.84	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Sertraline ●	2 (0.00)	1 749.53 (0.01)	3.98	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Trazodone	3 (0.00)	2 874.58 (0.01)	4.35	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Venlafaxine ☺	9 (0.01)	7 737.92 (0.02)	3.91	3 (0.01)	3 301.56 (0.02)	1.36	0 (0.00)	0 (0.00)	0.00
Amitriptyline	Imipramine	Mianserin	7 (0.00)	1 987.36 (0.01)	1.29	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Lithium	Moclobemide ●	1 (0.00)	450.80 (0.00)	2.05	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Sertraline ●	6 (0.00)	4 587.66 (0.01)	3.48	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Lofepramine	Sulpiride	7 (0.00)	3 364.85 (0.01)	2.18	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Mianserin	Sertraline ●	1 (0.00)	1 059.68 (0.00)	4.82	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Paroxetine	Sulpiride ●	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	8 (0.02)	2 735.04 (0.03)	1.78
Amitriptyline	Paroxetine	Trazodone ●	0 (0.00)	0.00 (0.00)	0.00	0 ()0.00	0 (0.00)	0.00	5 (0.01)	3 576.94 (0.04)	3.73
	Sertraline	Trazodone ●	2 (0.00)	1 378.97 (0.00)	3.13	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Sulpiride	Trazodone	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	162.93 (0.00)	0.20	0 (0.00)	0 ()0.00	0.00
		Venlafaxine ☺	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	1 213.36 (0.01)	1.50	0 (0.00)	0 ()0.00	0.00
	Trimipramine	Venlafaxine ☺	2 (0.00)	1 184.39 (0.00)	2.69	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Trazodone	Venlafaxine ☺	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	1 296.04 (0.02)	6.76

Table 8c: Number of prescriptions with three antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient			2004			2005			2006		
			Prevalence (%) *	Total cost (R) (%) **	CPI	Prevalence (%) *	Total cost (R) (%) **	CPI	Prevalence (%) *	Total cost (R) (%) **	CPI
	Venlafaxine	Venlafaxine ☺	13 (0.01)	16 618.89 (0.05)	5.81	3 (0.01)	2 836.60 (0.02)	1.17	1 (0.00)	1 030.21 (0.01)	5.37
Bupropion	Duloxetine	Lithium	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	614.54 (0.00)	0.76	0 (0.00)	0 (0.00)	0.00
		Escitalopram	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	804.05 (0.01)	4.19
	Flupenthixol	Trazodone	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	378.55 (0.00)	0.47	0 (0.00)	0 (0.00)	0.00
	Fluoxetine	Trazodone ☺	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	576.62 (0.01)	3.01
	Lithium	Venlafaxine	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	3 (0.01)	3 511.95 (0.04)	6.11
	Trazodone	Trazodone	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	791.91 (0.01)	4.13
	Venlafaxine	Venlafaxine	0 (0.00)	0.00 (0.00)	0.00	4 (0.00)	4 858.20 (0.03)	1.50	3 (0.01)	6 004.42 (0.07)	10.44
Citalopram	Clomipramine	Lithium ●	6 (0.00)	5 575.75 (0.02)	4.22	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Dothiepin	Reboxetine ●	7 (0.00)	3 735.05 (0.01)	2.43	0 (0.00)	0 ( )	0.00	0 (0.00)	0 (0.00)	0.00
		Sertraline ●	1 ()0.00	588.60 (0.00)	2.68	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Sulpiride ●	5 ()0.00	1 146.49 (0.00)	1.04	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Citalopram	Dothiepin	Trimipramine ●	2 (0.00)	831.86 (0.00)	1.89	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Duloxetine	Duloxetine	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	906.57 (0.01)	1.12	0 (0.00)	0 (0.00)	0.00
	Escitalopram	Imipramine ●	1 (0.00)	631.49 (0.00)	2.87	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Flupenthixol	Lithium	4 (0.00)	4 682.98 (0.01)	5.32	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Mianserin	13 (0.01)	10 392.49 (0.03)	3.63	0 (0.01)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Trazodone ☺	1 (0.00)	785.51 (0.00)	3.57	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Fluoxetine	Trazodone ☺	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	327.78 (0.00)	1.71
	Imipramine	Moclobemide ●	3 (0.00)	1 388.37 (0.00)	2.10	2 (0.00)	819.72 (0.01)	0.51	0 (0.00)	0 (0.00)	0.00

Table 8c: Number of prescriptions with three antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient			2004			2005			2006		
			Prevalence (%) *	Total cost (R) (%) **	CPI	Prevalence (%) *	Total cost (R) (%) **	CPI	Prevalence (%) *	Total cost (R) (%) **	CPI
		Sulpiride ●	1 (0.00)	104.17 (0.00)	0.47	0 (0.00)	0 (0.00)	0.00	6 (0.01)	1 197.06 (0.01)	1.04
	Lithium	Mianserin	1 (0.00)	631.59 (0.00)	2.87	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Sulpiride	1 (0.00)	598.15 (0.00)	2.72	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Venlafaxine	8 (0.01)	7 320.89 (0.02)	4.16	0 (0.01)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Lofepramine	Trazodone ●	1 (0.00)	542.17 (0.00)	2.46	0 ()0.00	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Trimipramine ●	5 (0.00)	3 776.68 (0.01)	3.43	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Mianserin	Sulpiride	1 (0.00)	474.46 (0.00)	2.16	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Paroxetine	Trimipramine ●	4 (0.00)	2 634.79 (0.01)	2.99	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Sulpiride	Trazodone ☺	3 (0.00)	3 450.30 (0.01)	5.23	4 (0.00)	3 528.97 (0.02)	1.09	9 (0.02)	8 113.29 (0.09)	4.70
	Trazodone	Trazodone ☺	5 (0.00)	5 841.96 (0.02)	5.31	7 (0.00)	7 933.61 (0.05)	1.40	0 (0.00)	0 (0.00)	0.00
	Venlafaxine	Venlafaxine	1 (0.00)	1 507.68 (0.00)	6.85	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Clomipramine	Lithium	Lithium ☺	3 (0.00)	2 032.73 (0.01)	3.08	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Mirtazapine	Mirtazapine	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	2 722.24 (0.02)	1.68	0 (0.00)	0 (0.00)	0.00
	Mirtazapine	Trazodone	1 (0.00)	1 983.65 (0.01)	9.02	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Dothiepin	Dothiepin	Lithium ☺	2 (0.00)	687.58 (0.00)	1.56	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Escitalopram ●	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	779.50 (0.01)	0.48	0 (0.00)	0 (0.00)	0.00
		Sertraline ●	7 (0.00)	4 971.50 (0.02)	3.23	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Venlafaxine ☺	1 (0.00)	495.72 (0.00)	2.25	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Fluoxetine	Flupenthixol ●	3 (0.00)	2 155.43 (0.01)	3.27	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Trimipramine ●	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	597.54 (0.00)	0.37	0 (0.00)	0 (0.00)	0.00

Table 8c: Number of prescriptions with three antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient			2004			2005			2006		
			Prevalence (%) *	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
	Flupenthixol	Trimipramine	2 (0.00)	476.68 (0.00)	1.08	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Lithium	Mirtazapine ☺	1 (0.00)	863.72 (0.00)	3.93	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Sulpiride ☺	11 (0.01)	7 622.52 (0.02)	3.15	0 (0.01)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Sertraline	Sulpiride ●	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	944.01 (0.01)	4.92
Duloxetine	Duloxetine	Lithium	0 (0.00)	0.00 (0.00)	0.00	3 (0.00)	2 666.58 (0.02)	1.10	0 (0.00)	0 (0.00)	0.00
		Escitalopram	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	476.44 (0.01)	2.49
	Flupenthixol	Mirtazapine	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	2 631.19 (0.03)	13.73
		Trazodone	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	1 585.67 (0.02)	8.27
	Mirtazapine	Mirtazapine	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	6 (0.01)	7 061.51 (0.08)	6.14
Duloxetine	Trazodone	Trazodone	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	2 449.00 (0.02)	1.51	2 (0.00)	2 213.30 (0.03)	5.77
Escitalopram	Flupenthixol	Mianserin	1 (0.00)	828.04 (0.00)	3.76	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Lithium	Trazodone	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	973.18 (0.01)	5.08
	Mianserin	Mianserin	2 (0.00)	986.96 (0.00)	2.24	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Paroxetine	1 (0.00)	679.44 (0.00)	3.09	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Trazodone	Trazodone	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	598.23 (0.01)	3.12
Fluoxetine	Fluoxetine	Imipramine ●	4 (0.00)	1 441.48 (0.00)	1.64	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Reboxetine	2 (0.00)	1 309.92 (0.00)	2.98	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Flupenthixol	Imipramine ●	1 (0.00)	305.39 (0.00)	1.39	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Lithium ☺	4 (0.00)	3 303.12 (0.01)	3.75	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Mianserin	20 (0.01)	16 969.10 (0.05)	3.86	2 (0.01)	590.39 (0.00)	0.36	0 (0.00)	0 (0.00)	0.00

Table 8c: Number of prescriptions with three antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient			2004			2005			2006		
			Prevalence (%) *	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
		Reboxetine	1 (0.00)	635.73 (0.00)	2.89	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Trazodone ☺	4 (0.00)	3 222.91 (0.01)	3.66	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Trimipramine ●	4 (0.00)	631.64 (0.00)	0.72	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Venlafaxine	1 (0.00)	1 473.57 (0.00)	6.70	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Lithium	Lithium ☺	1 (0.00)	220.75 (0.00)	1.00	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Mianserin ☺	1 (0.00)	858.43 (0.00)	3.90	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Mirtazapine ☺	6 (0.00)	3 578.53 (0.01)	2.71	2 (0.00)	1 157.58 (0.01)	0.71	0 (0.00)	0 (0.00)	0.00
		Paroxetine ☺	4 (0.00)	2 252.67 (0.01)	2.56	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Mianserin	Mianserin	2 (0.00)	440.12 (0.00)	1.00	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Mirtazapine	Mirtazapine	2 (0.00)	2 062.47 (0.01)	4.69	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 ()0.00	0.00
	Trazodone	Trazodone ☺	6 (0.00)	5 213.45 (0.02)	3.95	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Trimipramine	Trimipramine ●	1 (0.00)	1 052.11 (0.00)	4.78	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Fluphenthixol	Imipramine	Lithium	9 (0.01)	5 967.53 (0.02)	3.01	8 (0.01)	6 137.57 (0.04)	0.95	9 (0.02)	4 538.34 (0.05)	2.63
		Venlafaxine	1 (0.00)	3 274.46 (0.01)	14.88	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Lithium	Sertraline	4 (0.00)	4 744.17 (0.01)	5.39	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Lithium	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	533.30 (0.00)	0.33	0 (0.00)	0 (0.00)	0.00
	Mianserin	Paroxetine	35 (0.02)	57 364.88 (0.18)	7.45	1 (0.02)	862.65 (0.01)	1.07	0 (0.00)	0 (0.00)	0.00
		Sertraline	3 (0.00)	4 318.93 (0.01)	6.54	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Mirtazapine	Trazodone	1 (0.00)	758.00 (0.00)	3.45	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Paroxetine	Venlafaxine	1 (0.00)	1 870.23 (0.01)	8.50	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00

Table 8c: Number of prescriptions with three antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient			2004			2005			2006		
			Prevalence (%) *	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
		Trazodone ☺	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	2 (0.00)	1 312.67 (0.02)	3.42
	Trazodone	Venlafaxine ☺	1 (0.00)	1 950.88 (0.01)	8.87	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Venlafaxine	Venlafaxine	5 (0.00)	7 093.35 (0.02)	6.45	22 (0.00)	29 824.37 (0.20)	1.67	10 (0.02)	16 202.28 (0.19)	8.45
Fluvoxamine	Paroxetine	Sertraline	22 (0.01)	19 516.58 (0.06)	4.03	0 (0.01)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Imipramine	Imipramine	Mianserin	1 (0.00)	191.92 (0.00)	0.87	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Paroxetine	Reboxetine ●	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	4 (0.01)	4 259.01 (0.05)	5.55
	Venlafaxine	Venlafaxine ☺	1 (0.00)	1 563.22 (0.00)	7.10	3 (0.00)	4 823.17 (0.03)	1.99	17 (0.04)	26 750.53 (0.31)	8.21
Lithium	Lithium	Moclobemide	1 (0.00)	585.62 (0.00)	2.66	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Venlafaxine	7 (0.00)	7 450.66 (0.02)	4.84	8 (0.00)	8 401.16 (0.06)	1.30	0 (0.00)	0 (0.00)	0.00
	Lofepramine	Sulpiride	2 (0.00)	392.74 (0.00)	0.89	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Mirtazapine	Mirtazapine	2 (0.00)	2 737.80 (0.01)	6.22	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Paroxetine	0 (0.00)	0.00 (0.00)	0.00	1 (0.00)	641.09 (0.00)	0.79	0 (0.00)	0 (0.00)	0.00
		Trazodone	2 (0.00)	6 299.64 (0.02)	14.32	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Venlafaxine	12 (0.01)	18 508.36 (0.06)	7.01	19 (0.01)	14 879.55 (0.10)	0.97	0 (0.00)	0 (0.00)	0.00
	Moclobemide	Sulpiride	1 (0.00)	677.30 (0.00)	3.08	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Paroxetine	Sulpiride	11 (0.01)	8 822.97 (0.03)	3.65	0 (0.01)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Trazodone	Trazodone	3 (0.00)	5 449.10 (0.02)	8.26	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Trimipramine	5 (0.00)	10 515.54 (0.03)	9.56	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Venlafaxine	Venlafaxine	0 (0.00)	0.00 (0.00)	0.00	2 (0.00)	1 492.16 (0.01)	0.92	7 (0.02)	7 848.39 (0.09)	5.85
Lofepramine	Mianserin	Mianserin	1 ()0.00	209.80 (0.00)	0.95	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00

Table 8c: Number of prescriptions with three antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient			2004			2005			2006		
			Prevalence (%) *	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
	Trazodone	Venlafaxine ☺	1 (0.00)	992.61 (0.00)	4.51	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
		Trimipramine	0 (0.00)	0.00 (0.00)	0.00	1 (0.01)	1 351.10 (0.01)	1.67	0 (0.00)	0 (0.00)	0.00
	Trimipramine	Venlafaxine ☺	1 (0.00)	1 253.22 (0.00)	5.70	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Mianserin	Paroxetine	Paroxetine	1 (0.00)	494.32 (0.00)	2.25	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Trimipramine	Venlafaxine ☺	10 (0.01)	12 864.11 (0.04)	5.85	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Mirtazapine	Mirtazapine	Moclobemide	1 (0.00)	1 275.42 (0.00)	5.80	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Mirtazapine	Mirtazapine	Venlafaxine	0 (0.00)	0.00 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00	1 (0.00)	1040.65 (0.01)	5.43
	Sertraline	Sertraline	0 (0.00)	0.00 (0.00)	0.00	1 (0.01)	788.58 (0.01)	0.97	0 (0.00)	0 (0.00)	0.00
	Trimipramine	Venlafaxine ☺	1 (0.00)	1 013.95 (0.00)	4.61	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Venlafaxine	Venlafaxine	17 (0.01)	29 482.81 (0.09)	7.88	4 (0.02)	4 969.16 (0.03)	1.53	7 (0.02)	20 534.26 (0.24)	15.30
Moclobemide	Sulpiride	Venlafaxine	1 (0.00)	977.16 (0.00)	4.44	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Paroxetine	Sulpiride	Trimipramine ●	5 (0.00)	3 723.04 (0.01)	3.38	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Trazodone	Trazodone ☺	1 (0.00)	1 219.04 (0.00)	5.54	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
	Trimipramine	Trimipramine ●	0 (0.00)	0.00 (0.00)	0.00	1 (0.01)	522.90 (0.00)	0.65	0 (0.00)	0 (0.00)	0.00
	Venlafaxine	Venlafaxine	1 (0.00)	1 308.59 (0.00)	5.95	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Reboxetine	Venlafaxine	Venlafaxine	9 (0.01)	10 257.12 (0.03)	5.18	2 (0.01)	2 321.30 (0.02)	1.43	0 (0.00)	0 (0.00)	0.00
Sertraline	Trazodone	Trazodone ☺	4 (0.00)	4 177.30 (0.01)	4.75	12 (0.06)	10 875.83 (0.07)	1.12	1 (0.00)	869.98 (0.01)	4.54
Sulpiride	Trazodone	Venlafaxine	1 (0.00)	1 423.46 (0.00)	6.47	4 (0.02)	6 400.42 (0.04)	1.98	7 (0.02)	9451.88 (0.11)	7.04
	Venlafaxine	Venlafaxine	2 (0.00)	1866.18 (0.01)	4.24	1 (0.01)	1564.19 (0.01)	1.93	1 (0.00)	1 564.19 (0.02)	8.16
Trazodone	Venlafaxine	Venlafaxine ☺	2 (0.00)	3 114.62 (0.01)	7.08	0 (0.00)	0 (0.00)	0.00	1 (0.00)	385.92 (0.00)	2.01

Table 8c: Number of prescriptions with three antidepressants prescribed for each active ingredient as well as drug-drug interactions (continue)

Active ingredient			2004			2005			2006		
			Prevalence (%) *	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI	Prevalence (%)*	Total cost (R) (%)**	CPI
Trimipramine	Trimipramine	Venlafaxine ☺	1 (0.00)	1 784.18 (0.01)	8.11	0 (0.00)	0 (0.00)	0.00	0 (0.00)	0 (0.00)	0.00
Venlafaxine	Venlafaxine	Venlafaxine	3 (0.00)	3 298.43 (0.01)	5.00	0 (0.00)	0 (0)	0.00	0 (0.00)	0 (0.00)	0.00
Total			488 (0.33)	450 032.63 (1.39)		169 (0.90)	147 062.07 (0.96)	43.78	137 (0.30)	150 468.21 (1.75)	190.02

**% Prevalence = The prevalence for the active ingredient divided by the total number of all antidepressant prescriptions for the specific year multiplied by hundred. (n 2004 = 146 905; n 2005 = 81 830, n2006 = 44 938).*

***% Cost = The total cost for each active ingredient divided by the total cost of all the prescriptions prescribed for a specific year multiplied by hundred. (n2004 = R 32 323 356.77, n2005 = R 15 245 709.85, n2006 = R 8 614 631.29).*

● *= Drug interaction with a significance rating of 1 or 2*

☺ *= Drug interaction with a significance rating of between 3 and 5.*

Table 9c: Number of prescriptions with four antidepressants prescribed for each active ingredient as well as drug-drug interactions

Active ingredient				2004			2005			2006		
				Prevalence (%)	Total cost (R) (%)	CPI	Prevalence (%)	Total cost (R) (%)	CPI	Prevalence (%)	Total cost (R) (%)	CPI
Amitriptyline	Flupenthixol	Mirtazapine	Mirtasapine	1 (0.00)	1 543.50 (0.00)	7.01	0 (0.00)	0 (0.00)	0	0	0	0
		Venlafaxine	Venlafaxine ☺	11 (0.01)	19 499.84 (0.06)	8.06	9 (0.01)	12 569.31 (0.08)	7.50	0	0	0
Citalopram	Flupenthixol	Mirtazapine	Trazodone ☺	10 (0.01)	10 865.13 (0.03)	4.94	0 (0.00)	0 (0.00)	0	0	0	0
Dothiepin	Dothiepin	Lithium	Mirtasapine	10 (0.01)	8 290.82 (0.03)	3.77	0 (0.00)	0 (0.00)	0	0	0	0
Fluoxetine	Flupenthixol	Lithium	Mianserin ☺	1 (0.00)	1 533.55 (0.00)	6.97	0 (0.00)	0 (0.00)	0	0	0	0
		Trazodone	Trazodone ☺	1 (0.00)	1 248.82 (0.00)	5.68	0 (0.00)	0 (0.00)	0	0	0	0
Flupenthixol	Lithium	Mianserin	Paroxetine	2 (0.00)	4 891.38 (0.02)	11.12	0 (0.00)	0 (0.00)	0	0	0	0
			Sertraline	1 (0.00)	1 523.27 (0.00)	6.92	0 (0.00)	0 (0.00)	0	0	0	0
Lofepramine	Trazodone	Trazodone	Trimipramine	0 (0.00)	0.00 (0.00)	0	1 (0.00)	1 759.23 ()0.01	9.44	0	0	0
Total				**37 (0.03)**	**49 396.31 (0.15)**	**54.46**	**10.00 (0.01)**	**14 328.54 (0.09)**	**0**	**0**	**0**	**0**

% Prevalence = The prevalence for the active ingredient divided by the total number of all antidepressant prescriptions for the specific year multiplied by hundred. (n 2004 = 146 905; n 2005 = 81 830, n2006 = 44 938).

% Cost = The total cost for each active ingredient divided by the total cost of all the prescriptions prescribed for a specific year multiplied by hundred. (n2004 = R 32 323 356.77, n2005 = R 15 245 709.85, n2006 = R 8 614 631.29).

● *= Drug interaction with a significance rating of 1 or 2*

☺ *= Drug interaction with a significance rating of between 3 and 5.*

Table 10c: Expenditure of antidepressants according to trade name.

Antidepressants	2004			2005			2006		
	Prevalence (%)*	Total Cost (R) (%)*	Average Cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)
Adco-Paroxetine® 20mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	306 (0.35)	46 186.95 (0.30)	150.94±89.88	1 817 (3.81)	121 064.95 (1.41)	66.63±94.23
Adco-Talomil® 20mg Tab	2 030 (1.29)	325 431.49 (1.01)	160.31±65.78	2 346 (2.71)	250 303.45 (1.64)	106.69±52.69	1 808 (3.79)	142 364.10 (1.65)	78.74±17.25
A-Lennon Fluoxetine® 20mg Cap	0 (0.00)	0.00 (0.00)	0.00±0	64 (0.07)	1 893.45 (0.01)	29.59±10.10	28 (0.06)	705.67 (0.01)	25.20±0.65
Anafranil SR 75mg Tab	444 (0.28)	231 750.09 (0.72)	521.96±289.89	124 (0.14)	85 274.52 (0.56)	687.70±319.36	27 (0.06)	26 362.06 (0.31)	976.37±412.67
Anafranil® 10mg Tab	230 (0.15)	24 961.41 (0.08)	108.52±60.86	119 (0.14)	13 447.62 (0.09)	113.01±77.81	28 (0.06)	3 519.38 (0.04)	125.69±56.59
Anafranil® 25/2ml Amp	1 (0.00)	124.28 (0.00)	124.28±0	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Anafranil® 25mg Tab	567 (0.36)	152 196.02 (0.47)	268.42±225.02	240 (0.28)	61 607.38 (0.40)	256.70±235.40	130 (0.27)	40 915.94 (0.47)	314.74±201.67
Apo-Fluoxetine® 20mg	11 (0.01)	1 446.23 (0.00)	131.48±27.62	(0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Aropax® 20mg Tab	15 802 (10.01)	5 472 161.68 (16.93)	346.30±132.09	7 374 (8.52)	2 213 234.65 (14.52)	300.14±106.99	1 192 (2.50)	292 979.16 (3.40)	245.79±176.28
Aropax® 30mg Tab	398 (0.25)	133 071.51 (0.41)	334.35±54.69	212 (0.25)	77 559.34 (0.51)	365.85±139.10	91 (0.19)	41 158.47 (0.48)	452.29±215.13
Aropax® CR 12.5mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	152 (0.32)	32 056.38 (0.37)	210.9±33.14
Aropax® CR 25mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	88 (0.18)	24 107.99 (0.28)	273.95±22.66
Aurorix® 150mg Tab	177 (0.11)	61 805.33 (0.19)	349.18±192.83	67 (0.08)	20 413.14 (0.13)	304.67±125.35	28 (0.06)	8 976.07 (0.10)	320.57±116.04
Aurorix® 300mg Tab	104 (0.07)	39 211.76 (0.12)	377.04±219.89	7 (0.01)	1 981.37 (0.01)	283.05±214.82	19 (0.04)	14 950.24 (0.17)	786.85±382.45
Camcolit® 250mg Tab	696 (0.44)	167 222.94 (0.52)	240.26±126.98	347 (0.40)	71 682.65 (0.47)	206.58±102.84	153 (0.32)	35 570.70 (0.41)	232.49±120.37

Table 10c: Expenditure of antidepressants according to trade name (continue)

Antidepressants	2004			2005			2006		
	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)
Camcolit® 400mg Tab	1 042 (0.66)	191 874.70 (0.59)	184.14±84.58	578 (0.67)	104 265.07 (0.68)	180.39±74.95	321 (0.67)	67 397.40 (0.78)	209.96±77.47
Cilift® 20mg Tab	19 796 (12.54)	4 081 450.36 (12.63)	206.18±83.13	7 690 (8.89)	968 533.13 (6.35)	125.95±47.74	2 973 (6.23)	232 528.34 (2.70)	78.21±19.47
Cipralex® 20mg Tab	3 372 (2.14)	829 455.19 (2.57)	245.98±76.30	5 273 (6.09)	1 307 357.66 (8.58)	247.93±82.18	1 668 (3.49)	499 866.47 (5.80)	299.68±120.89
Cipramil® 20mg Tab	6 221 (3.94)	1 989 504.92 (6.16)	319.80±146.80	2 605 (3.01)	682 559.61 (4.48)	262.02±150.02	867 (1.82)	274 951.91 (3.19)	317.13±215.31
Citalohexal® 20mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	32 (0.04)	2 998.07 (0.02)	93.69±26.37	43 (0.09)	3 740.00 (0.04)	86.98±28.11
Clomidep® 25mg Tab	4(0.00)	412.89 (0.00)	103.22±63.98	22 (0.03)	4 079.03 (0.03)	185.41±156.72	30 (0.06)	8 704.77 (0.10)	290.16±105.81
Clorix® 150mg Tab	104(0.07)	21 032.72 (0.07)	202.24±81.01	74 (0.09)	13 480.51 (0.09)	182.17±56.11	117 (0.25)	23 429.61 (0.27)	200.25±60.47
Clorix® 300mg Tab	161(0.10)	42 454.85 (0.13)	263.69±83.79	31 (0.04)	6 422.47 (0.04)	207.18±76.51	37 (0.08)	7 543.54 (0.09)	203.88±42.73
Cymbalta® 30mg Cap	9 (0.01)	3 162.51 (0.01)	351.39±0	348 (0.40)	133 565.24 (0.88)	383.81±167.40	513 (1.07)	241 584.53 (2.80)	470.93±141.27
Cymbalta® 60mg Cap	78 (0.05)	26 632.29 (0.08)	341.44±51.20	1 366 (1.58)	572 313.21 (3.75)	418.97±134.04	1 275 (2.67)	622 911.40 (7.23)	488.56±139.57
Deparoc® 20mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	89 (0.10)	12 647.85 (0.08)	142.11±66.63	130 (0.27)	18 556.74 (0.22)	142.74±56.78
Depex® 50mg Cap	966 (0.61)	101 324.80 (0.31)	104.89±62.82	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Depnil® 150mg Tab	1 210 (0.77)	293 999.82 (0.91)	242.98±91.55	297 (0.34)	60 315.06 (0.40)	203.08±76.42	54 (0.11)	11 892.90 (0.14)	220.24±93.81
Depnil® 300mg Tab	191 (0.12)	49 174.30 (0.15)	257.46±68.44	61 (0.07)	14 235.99 (0.09)	233.38±44.38	23 (0.05)	4 834.92 (0.06)	210.21±90.07

Table 10c: Expenditure of antidepressants according to trade name (continue)

Antidepressants	2004			2005			2006		
	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)
Depramil® 20mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	105 (0.12)	9 910.25 (0.07)	94.38±26.13	36 (0.08)	2 307.91 (0.03)	64.11±41.77
Depramil® 40mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	3 (0.01)	310.50 (0.00)	103.5±0
Deprozan® 20mg Cap	114 (0.07)	7 399.30 (0.02)	64.91±39.91	35 (0.04)	1 101.87 (0.01)	31.48±13.84	3 (0.01)	129.48 (0.00)	43.16±18.69
Edronax® 4mg Tab	203 (0.13)	76 521.93 (0.24)	376.96±174.40	103 (0.12)	29 628.89 (0.19)	287.66±101.38	35 (0.07)	10 224.10 (0.12)	292.12±130.25
Efexor® 37.5mg Tab	1 185 (0.75)	373 802.20 (1.16)	315.44±152.83	62 (0.07)	17 210.30 (0.11)	277.59±95.53	2 (0.00)	296.15 (0.00)	148.08±127.03
Efexor® 50mg Tab	2 (0.00)	550.16 (0.00)	275.08±70.13	1 (0.00)	126.05 (0.00)	126.05±0	0 (0.00)	0.00 (0.00)	0.00±0
Efexor® 75mg Tab	134 (0.08)	63 178.46 (0.20)	471.48±193.26	129 (0.15)	56 943.98 (0.37)	441.43±163.85	61 (0.13)	28 930.44 (0.34)	474.27±38.52
Efexor® XR 150mg Cap	2 070 (1.31)	1 714 163.32 (5.30)	828.10±295.25	1 490 (1.72)	1 106 182.91 (7.26)	742.40±246.72	967 (2.03)	800 067.42 (9.29)	827.37±182.50
Efexor® XR 75mg Cap	5 086 (3.22)	2 261 459.90 (7.00)	444.64±161.37	4 482 (5.18)	1 866 199.10 (12.24)	416.38±144.34	2 858 (5.99)	1 242 856.27 (14.43)	434.87±132.74
Eglonyl® 2ml Amp	18 (0.01)	1 173.55 (0.00)	65.19±180.80	24 (0.03)	503.40 (0.00)	20.98±2.42	18 (0.04)	497.46 (0.01)	27.64±14.22
Eglonyl® 50mg Cap	1 199 (0.76)	174 798.08 (0.54)	145.79±100.92	465 (0.54)	52 627.84 (0.35)	113.18±73.74	205 (0.43)	24 684.25 (0.29)	120.41±85.55
Eglonyl® Elix 25mg/5ml	130 (0.08)	16 364.37 (0.05)	125.88±108.13	90 (0.10)	10 474.27 (0.07)	116.38±57.14	75 (0.16)	7 377.37 (0.09)	98.36±44.80
Eglonyl® Forte 200mg Tab	290 (0.18)	88 327.97 (0.27)	304.58±140.11	194 (0.22)	53 578.67 (0.35)	276.18±106.12	91 (0.19)	29 362.64 (0.34)	322.67±92.40

Table 10c: Expenditure of antidepressants according to trade name (continue)

Antidepressants	2004			2005			2006		
	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)
Emdalen® 70mg Tab	495 (0.31)	171 663.08 (0.53)	346.79±184.54	231 (0.27)	83 722.55 (0.55)	362.44±166.60	107 (0.22)	46 790.24 (0.54)	437.29±172.23
Equinorm® 10mg Tab	96 (0.06)	8 315.83 (0.03)	86.62±38.50	29 (0.03)	2 189.59 (0.01)	75.50±31.42	16 (0.03)	1 230.80 (0.01)	76.93±20.43
Equinorm® 25mg Tab	360 (0.23)	69 581.69 (0.22)	193.28±174.96	175 (0.20)	33 314.35 (0.22)	190.37±168.11	46 (0.10)	11 716.09 (0.14)	254.70±209.00
Espiride® 50mg Cap	3 556 (2.25)	404 349.86 (1.25)	113.71±83.93	2 265 (2.62)	187 800.70 (1.23)	82.91±54.89	1 275 (2.67)	119 179.49 (1.38)	93.47±57.63
Ethipramine® 10mg Tab	552 (0.35)	17 397.49 (0.05)	31.52±20.75	550 (0.64)	19 403.28 (0.13)	35.28±27.14	418 (0.88)	13 917.72 (0.16)	33.30±23.13
Ethipramine® 25mg Tab	2 374 (1.50)	129838.07 (0.40)	54.69±40.89	1 640 (1.90)	87 619.50 (0.57)	53.43±38.95	826 (1.73)	42 482.38 (0.49)	51.43±39.95
Etrafon A® Tab	3 (0.00)	1 369.73 (0.00)	456.57±157.47	1 (0.00)	194.99 (0.00)	194.99±0	0 (0.00)	0.00 (0.00)	0.00±0
Etrafon D® Tab	3 (0.00)	944.08 (0.00)	314.69±257.80	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Etrafon F® Tab	3 (0.00)	1 013.39 (0.00)	337.80±91.98	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Etrafon M® Tab	1 (0.00)	256.69 (0.00)	256.69±0	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Fluanxol® 0.25mg Tab	395 (0.25)	95 197.90 (0.29)	241.01±148.56	122 (0.14)	28 209.89 (0.19)	231.23±142.75	32 (0.07)	6 564.15 (0.08)	205.13±72.71
Fluanxol® 0.5mg Tab	779 (0.49)	202 465.84 (0.63)	259.90±147.83	221 (0.26)	52 857.79 (0.35)	239.18±163.28	107 (0.22)	29 746.16 (0.35)	278.00±157.58
Fluanxol® 1.0mg Tab	767 (0.49)	290 923.51 (0.90)	379.30±201.01	238 (0.28)	88 424.74 (0.58)	371.53±188.54	114 (0.24)	40 703.46 (0.47)	357.05±144.42
Flutinol® 20mg Cap	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0

Table 10c: Expenditure of antidepressants according to trade name (continue)

Antidepressants	2004			2005			2006		
	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)
Hexal Fluvoxamine® 100mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	13 (0.02)	3 268.70 (0.02)	251.44±75.48	19 (0.04)	5 376.35 (0.06)	282.97±85.73
Lantanon® 10mg Tab	822 (0.52)	102 174.05 (0.32)	124.30±69.40	246 (0.28)	28 460.71 (0.19)	115.69±73.07	59 (0.12)	8 223.28 (0.10)	139.38±75.29
Lantanon® 30mg Tab	1 364 (0.86)	430 924.27 (1.33)	315.93±182.09	261 (0.30)	68 053.30 (0.45)	260.74±157.70	75 (0.16)	24 843.75 (0.29)	331.25±249.23
Lentolith® 400mg Cap	169 (0.11)	47 188.84 (0.15)	279.22±126.50	2 (0.00)	309.48 (0.00)	154.74±0	0 (0.00)	0.00 (0.00)	0.00±0
Lilly-Fluoxetine® 20mg Cap	5 347 (3.39)	707 054.62 (2.19)	132.23±57.68	2 305 (2.66)	222 242.13 (1.46)	96.42±59.24	873 (1.83)	89 089.27 (1.03)	102.05±63.18
Limbitrol® 12.5/5mg Cap	141 (0.09)	23 971.51 (0.07)	170.01±92.48	87 (0.10)	15 326.94 (0.10)	176.16±71.16	67 (0.14)	9 763.37 (0.11)	145.72±36.14
Lorien® 20mg Cap	5 613 (3.56)	373581.19 (1.16)	66.57±52.88	3 589 (4.15)	138 489.45 (0.91)	38.59±14.62	2 081 (4.36)	86 391.36 (1.00)	41.51±13.12
Lorien® 20mg Tab	956 (0.61)	86 821.79 (0.27)	90.82±46.35	355 (0.41)	22 031.75 (0.14)	62.06±24.68	146 (0.31)	8 229.22 (0.10)	56.36±23.87
Ludiomil® 25mg Tab	207 (0.13)	62 913.13 (0.19)	303.93±150.19	58 (0.07)	14 752.52 (0.10)	254.35±84.05	1 (0.00)	324.58 (0.00)	324.58±0
Ludiomil® 75mg Tab	120 (0.08)	49 787.29 (0.15)	414.89±145.65	34 (0.04)	13 735.34 (0.09)	403.98±63.29	9 (0.02)	4 105.35 (0.05)	456.15±0
Luvox® 100mg Tab	2 577 (1.63)	967 292.25 (2.99)	375.36±198.34	620 (0.72)	279 163.76 (1.83)	450.26±211.77	398 (0.83)	190 626.12 (2.21)	478.96±195.53
Merck® Sertraline 50mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	20 (0.04)	4 907.46 (0.06)	245.37±103.45
Merck-Citalopram® 20mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Motipaxin® 100mg Cap	863 (0.55)	509 888.96 (1.58)	590.83±295.97	708 (0.82)	340 838.01 (2.24)	481.41±247.54	501 (1.05)	263 270.23 (3.06)	525.49±260.73

Table 10c: Expenditure of antidepressants according to trade name (continue)

Antidepressants	2004			2005			2006		
	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)
Molipaxin® 50mg Cap	1 200 (0.76)	331 402.47 (1.03)	276.17±141.49	1 188 (1.37)	284 009.05 (1.86)	239.06±116.78	1 075 (2.25)	266 467.82 (3.09)	247.88±110.59
Motival® Tab 0.5/10mg	650 (0.41)	65 904.24 (0.20)	101.39±48.00	441 (0.51)	46 745.28 (0.31)	106.00±50.82	269 (0.56)	29 751.06 (0.35)	110.6±47.28
Noriline® 10mg Tab	66 (0.04)	4 251.79 (0.01)	64.42±31.08	17 (0.02)	678.65 (0.00)	39.92±14.70	1 (0.00)	18.36 (0.00)	18.36±0
Nuzak® 20mg Cap	11 624 (7.37)	951 714.88 (2.94)	81.87±50.06	4 915 (5.68)	205 654.67 (1.35)	41.84±15.04	2 551 (5.34)	113 514.28 (1.32)	44.50±15.35
Parax® 20mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	80 (0.17)	19 271.82 (0.22)	240.90±86.64
Parax® 40mg Tab	0 (0.00)	0.00(0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	4 (0.01)	642.22 (0.01)	160.55±65.71
Parnate® 10mg Tab	78 (0.05)	11 815.54 (0.04)	151.48±66.13	35 (0.04)	5 033.08 (0.03)	143.80±63.26	0 (0.00)	0.00 (0.00)	0.00±0
Paxil® 20mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	156 (0.18)	29 754.64 (0.20)	190.73±55.36	1 375 (2.88)	265 291.08 (3.08)	192.94±62.46
Prohexal® 20mg Cap	1 232(0.78)	94 849.60 (0.29)	76.98±51.70	431 (0.50)	16 726.71 (0.11)	38.81±11.48	80 (0.17)	3 872.13 (0.04)	48.40±18.87
Prohexal® Dispers 20mg Tab	663 (0.42)	57 291.26 (0.18)	86.41±36.90	234 (0.27)	14 264.10 (0.09)	60.96±27.28	70 (0.15)	5 435.95 (0.06)	77.66±22.82
Prohexal® Dispers 40 mg Tab	247 (0.16)	46 222.16 (0.14)	187.13±68.44	89 (0.10)	12 454.82 (0.08)	139.94±20.39	16 (0.03)	1 908.68 (0.02)	119.29±41.50
Prothiaden® 25mg Cap	586 (0.37)	75 725.72 (0.23)	129.22±83.10	185 (0.21)	19 558.38 (0.13)	105.72±43.73	40 (0.08)	4 604.06 (0.05)	115.10±49.33
Prothiaden® 75mg Tab	373 (0.24)	68 784.70 (0.21)	184.41±74.52	114 (0.13)	14 685.31 (0.10)	128.82±29.61	42 (0.09)	6 265.63 (0.07)	149.18±65.07
Prozac® 20mg Cap	285 (0.18)	139 351.14 (0.43)	488.95±219.39	219 (0.25)	109 040.81 (0.72)	497.90±260.51	116 (0.24)	75 286.24 (0.87)	649.02±611.11

Table 10c: Expenditure of antidepressants according to trade name (continue)

Antidepressants	2004			2005			2006		
	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)
Prozac® 20mg Tab	334 (0.21)	90 003.48 (0.28)	269.47±191.68	102 (0.12)	21 913.57 (0.14)	214.84±124.70	21 (0.04)	4 924.01 (0.06)	234.48±119.45
Prozac® 20mg/5ml Liq	45 (0.03)	15 366.25 (0.05)	341.47±127.38	69 (0.08)	26 278.82 (0.17)	380.85±205.57	45 (0.09)	19 128.14 (0.22)	425.07±243.38
Prozac® 40 Sl Cap	135 (0.09)	77 793.23 (0.24)	576.25±155.72	11 (0.01)	4 912.66 (0.03)	446.61±301.67	6 (0.01)	1 647.87 (0.02)	274.65±251.72
Prozac® 60 Sl Cap	38 (0.02)	38 566.58 (0.12)	1014.91±345.27	36 (0.04)	33 794.88 (0.22)	938.75±311.58	1 (0.00)	1 279.02 (0.01)	1279.02±0
Quilonum® Retard Tab	142 (0.09)	22 448.51 (0.07)	158.09±68.63	129 (0.15)	21 991.45 (0.14)	170.48±80.91	49 (0.10)	11 530.80 (0.13)	235.32±87.43
Ran-Citalopram® 20mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	6 (0.01)	352.38 (0.00)	58.73±7.16
Ran-Citalopram® 40mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Ranflocs® 20mg Cap	619 (0.39)	28 408.73 (0.09)	45.89±40.63	384 (0.44)	9 696.23 (0.06)	25.25±9.00	214 (0.45)	5 621.25 (0.07)	26.27±6.16
Remeron® 15mg Tab	745 (0.47)	235 630.74 (0.73)	316.28±99.12	532 (0.61)	154 787.82 (1.02)	290.95±129.02	249 (0.52)	89 541.92 (1.04)	359.61±139.15
Remeron® 30mg Tab	1 413 (0.90)	757 187.94 (2.34)	535.87±233.10	893 (1.03)	408 304.16 (2.68)	457.23±204.63	407 (0.85)	234 778.40 (2.73)	576.85±232.79
Rolab-Amitriptyline® 25mg Tab	707 (0.45)	42 277.82 (0.13)	59.80±50.85	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Sandoz Amitriptyline® 25mg Tab	290 (0.18)	9 398.41 (0.03)	32.41±22.76	960 (1.11)	35 469.54 (0.23)	36.95±22.15	1 782 (3.73)	66 296.14 (0.77)	37.20±19.98
Sandoz Citalopram® 20mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	10 (0.01)	739.49 (0.00)	73.95±25.02	5 (0.01)	376.34 (0.00)	75.27±0.13
Sandoz Citalopram® 40mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	2 (0.00)	187.96 (0.00)	93.98±0	0 (0.00)	0.00 (0.00)	0.00±0
Sandoz Dothiepin® 25mg Cap	133 (0.08)	9 532.75 (0.03)	71.67±37.07	65 (0.08)	3 976.12 (0.03)	61.17±27.06	21 (0.04)	942.40 (0.01)	44.88±19.38

Table 10c: Expenditure of antidepressants according to trade name (continue)

Antidepressants	2004			2005			2006		
	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)
Sandoz Dothiepin® 75mg Tab	412 (0.26)	59 120.76 (0.18)	143.50±56.70	138 (0.16)	18 256.43 (0.12)	132.29±50.89	82 (0.17)	11 986.43 (0.14)	146.18±47.98
Sandoz Paroxetine® 20mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	198 (0.23)	38 823.52 (0.25)	196.08±50.71	632 (1.32)	118 978.74 (1.38)	188.26±36.47
Sandoz Sulpiride® 50mg Caps	0 (0.00)	0.00 (0.00)	0.00±0	398 (0.46)	32 678.38 (0.21)	82.11±53.39	439 (0.92)	37 147.54 (0.43)	84.62±66.62
Sandoz-Fluoxetine® 20mg Cap	2 516 (1.59)	189 823.97 (0.59)	75.45±52.41	1 273 (1.47)	57 829.34 (0.38)	45.43±15.59	887 (1.86)	40 091.35 (0.47)	45.20±11.02
Sanzur® 20mg Cap	*3 (0.00)*	*343.04 (0.00)*	*114.35±86.37*	*0 (0.00)*	*0.00 (0.00)*	*0.00±0*	*0 (0.00)*	*0.00 (0.00)*	*0.00±0*
Saroten® Ret 25mg Cap	11 (0.01)	2 166.33 (0.01)	196.94±48.92	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Saroten® Ret 50mg Cap	2 (0.00)	542.42 (0.00)	271.21±0	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Sedarin® 20mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	25 (0.05)	4 500.86 (0.05)	180.03±22.71
Serdep® 50mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	8 (0.02)	2 154.76 (0.03)	269.35±150.46
Serlife® 100mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	58 (0.07)	15 253.95 (0.10)	263.00±54.43	18 (0.04)	5 474.98 (0.06)	304.17±122.12
Serlife® 50mg Tab	856 (0.54)	231 108.65 (0.71)	269.98±111.52	888 (1.03)	185 738.12 (1.22)	209.16±72.33	794 (1.66)	179 036.02 (2.08)	225.49±62.36
Serrapress® 20mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	3 (0.00)	538.08 (0.00)	179.36±67.88	31 (0.06)	4 073.29 (0.05)	131.4±92.43
Serrapress® 30mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	37 (0.08)	9 983.06 (0.12)	269.81±34.79
Sertzol® 100mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	26 (0.03)	11 046.06 (0.07)	424.85±172.03	7 (0.01)	2 513.14 (0.03)	359.02±80.58

Table 10c: Expenditure of antidepressants according to trade name (continue)

Antidepressants	2004			2005			2006		
	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)
Sertzol® 50mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	162 (0.19)	36 515.06 (0.24)	225.40±67.80	309 (0.65)	68 332.24 (0.79)	221.14±44.01
Serzone® 100mg Tab	5 (0.00)	1 399.11 (0.00)	279.82±89.91	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Serzone® 200mg Tab	27 (0.02)	11 695.15 (0.04)	433.15±136.48	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Surmontil® 25mg Tab	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Surmontil® 50mg Cap	180 (0.11)	64 558.49 (0.20)	358.66±161.18	67 (0.08)	13 295.86 (0.09)	198.45±60.26	58 (0.12)	10 935.45 (0.13)	188.54±33.10
Thaden® 25mg Cap	1 404 (0.89)	96 182.23 (0.30)	68.51±42.35	411 (0.48)	24 462.76 (0.16)	59.52±29.45	154 (0.32)	12 325.44 (0.14)	80.04±52.41
Thaden® 75mg Tab	1 482 (0.94)	195 175.12 (0.60)	131.70±54.74	580 (0.67)	63 439.85 (0.42)	109.38±39.77	64 (0.13)	8 208.20 (0.10)	128.25±40.54
Tofranil® 10mg Tab	784 (0.50)	57 545.52 (0.18)	73.40±52.40	301 (0.35)	13 872.27 (0.09)	46.09±24.66	92 (0.19)	3 904.43 (0.05)	42.44±25.21
Tofranil® 25mg Tab	1 331 (0.84)	181 967.33 (0.56)	136.71±90.62	485 (0.56)	46 112.98 (0.30)	95.08±53.71	138 (0.29)	11 272.75 (0.13)	81.69±48.21
Trepiline® 10mg Tab	8 421 (5.34)	293 845.60 (0.91)	34.89±20.69	4 852 (5.61)	149 304.43 (0.98)	30.77±21.17	2 633 (5.52)	90 249.82 (1.05)	34.28±18.98
Trepiline® 25mg Tab	17 631 (11.17)	1 026 383.70 (3.18)	58.21±43.64	10 499 (12.13)	388 649.63 (2.55)	37.02±22.62	5 084 (10.65)	178 292.25 (2.07)	35.07±21.22
Trizac® 20mg Cap	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	3 (0.01)	64.11 (0.00)	21.37±0.59
Tryptanol® 10mg Tab	2(0.00)	105.32 (0.00)	52.66±35.86	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0
Tryptanol® 25mg Tab	448(0.28)	73 231.34 (0.23)	163.46±117.19	210 (0.24)	20 387.56 (0.13)	97.08±103.85	89 (0.19)	7 857.51 (0.09)	88.29±81.82

Table 10c: Expenditure of antidepressants according to trade name (continue)

Antidepressants	2004			2005			2006		
	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average cost (R)	Prevalence (%)*	Total Cost (R) (%)**	Average Cost (R)
Tydamine® 25mg Tab	651(0.41)	97 288.73 (0.30)	149.45±83.46	229 (0.26)	32 384.91 (0.21)	141.42±68.55	132 (0.28)	23 541.65 (0.27)	178.35±92.15
Tydamine® 50mg Cap	1 039(0.66)	266 424.40 (0.82)	256.42±121.24	437 (0.51)	102 440.04 (0.67)	234.42±98.22	238 (0.50)	60 405.52 (0.70)	253.80±134.37
Venlor® XR 150 mg Cap	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	115 (0.24)	47 138.56 (0.55)	409.90±171.92
Venlor® XR 37.5 mg Cap	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	18 (0.04)	2 720.69 (0.03)	151.15±32.30
Venlor® XR 75 mg Cap	0 (0.00)	0.00 (0.00)	0.00±0	0 (0.00)	0.00 (0.00)	0.00±0	295 (0.62)	83 578.82 (0.97)	283.32±283.32
Wellbutrin® SR 150mg Tab	861 (0.55)	124 191.68 (0.38)	144.24±110.13	905 (1.05)	133 236.83 (0.87)	147.22±96.40	606 (1.27)	140 468.87 (1.63)	231.80±97.66
Zoloft® 50mg Tab	6 531 (4.14)	2 403 813.56 (7.44)	368.06±157.07	2 582 (2.98)	719 531.17 (4.72)	278.67±107.06	1 071 (2.24)	263 448.35 (3.06)	245.98±91.10
Total	157 810 (100)	32 323 356.78 (100)		86 521 (100)	15 245 709.85 (100.00)		47 740 (100)	8 614 631.29 (100)	

**Prevalence % = Number of antidepressant products claimed through the PBM for a specific study period divided by the total number of antidepressants for the same period multiplied by a hundred. (n2004 = 157 810; n2005 = 86 521; n2006 = 47 740).*

***Cost % = Cost of the antidepressant products claimed through the PBM for a specific study period divided by the total cost of antidepressants for that study period multiplied by a hundred. (n2004 = R 32 323 356.77; n2005 = R 15 245 709.85; n2006 = R 8 614 631.29).*

Table 11c: The average cost of antidepressants according to trade name

Mims classification	Active ingredient	Trade name and dosage form	Innovator or generic	Average cost 2004 (R)	Average cost 2005 (R)	Average cost 2006 (R)
Tricyclic agents	Amitriptyline	Saroten® Ret 25mg Cap	Innovator	196.93 ±48.92	0	0
		Saroten® Ret 50mg Cap	Innovator	271.21 ±0.00	0	0
		Tryptanol® 10mg Tab	Innovator	52.66 ±35.86	0	0
		Tryptanol® 25mg Tab	Innovator	163.46 ±117.18	97.08 ±103.85	88.29 ±81.82
		Noriline® 10mg Tab	Generic	64.42 ±31.08	39.92 ±14.70	18.36 ±0.00
		Rolab-Amitriptyline® 25mg Tab	Generic	59.80 ±50.84	0	0
		Sandoz Amitriptyline® 25mg Tab	Generic	32.40 ±22.76	36.95 ±22.15	37.20 ±19.98
		Trepiline® 10mg Tab	Generic	34.89 ±20.69	30.77 ±21.17	34.28 ±18.98
		Trepiline® 25mg Tab	Generic	58.21 ±43.64	37.02 ±22.62	35.07 ±21.22
	Amitriptyline/ Chlordiazepoxide	Limbitrol® 12.5/5mg Cap	Innovator	170.01 ±92.48	176.71 ±71.16	145.72 ±36.14
	Clomipramine	Anafranil® 25mg Tab	Innovator	268.42 ±225.02	256.70 ±235.40	314.74 ±201.67
		Anafranil SR 75mg Tab	Innovator	521.96 ±289.89	687.70 ±319.36	976.37 ±412.67
		Anafranil® 10mg Tab	Innovator	108.53 ±60.86	113.01 ±77.81	125.69 ±56.59
		Anafranil® 25/2ml Amp	Innovator	124.28 ±0	0	0

Table 11c: The average cost of antidepressants according to trade name (continue)

MIMS classification	Active ingredient	Trade name and dosage form	Innovator or generic	Average cost 2004 (R)	Average cost 2005 (R)	Average cost 2006 (R)
		Clomidep® 25mg Tab	Generic	103.22 ±63.98	185.41 ±156.72	290.16 ±105.81
		Equinorm® 25mg Tab	Generic	193.28 ±174.96	190.37 ±168.11	254.70 ±209.00
		Equinorm® 10mg Tab	Generic	86.62 ±38.50	75.50 ±31.42	76.93 ±20.43
	Dothiepin	Prothiaden® 25mg Cap	Innovator	129.22 ±83.10	105.72 ±43.73	115.10 ±49.33
		Prothiaden® 75mg Tab	Innovator	184.41 ±74.52	128.82 ±29.61	149.18 ±65.07
		Sandoz Dothiepin® 25mg Cap	Generic	71.67 ±37.07	61.17 ±27.06	44.88 ±19.38
		Sandoz Dothiepin® 75mg Tab	Generic	143.50 ±56.70	132.29 ±50.89	146.18 ±47.98
		Thaden® 25mg Cap	Generic	68.50 ±42.35	59.52 ±29.45	80.04 ±52.41
		Thaden® 75mg Tab	Generic	131.70 ±54.74	109.38 ±39.77	128.25 ±40.54
	Imipramine	Tofranil® 10mg Tab	Innovator	73.40 ±52.40	46.09 ±24.66	42.44 ±25.21
		Tofranil® 25mg Tab	Innovator	136.71 ±90.62	95.08 ±53.71	81.69 ±48.21
		Ethipramine® 10mg Tab	Generic	31.52 ±20.75	35.28 ±27.14	33.30 ±23.13
		Ethipramine® 25mg Tab	Generic	54.69 ±40.89	53.43 ±38.95	51.43 ±39.95
	Lofepramine	Emdalen® 70mg Tab	Innovator	346.79 ±184.54	362.44 ±166.60	437.29 ±172.23

Table 11c: The average cost of antidepressants according to trade name (continue)

Mims classification	Active ingredient	Trade name and dosage form	Innovator or generic	Average cost 2004 (R)	Average cost 2005 (R)	Average cost 2006 (R)
	Perphenazine/ amitriptyline	Etrafon A® Tab	Innovator	456.58 ±157.47	194.99 ±0	0
		Etrafon D® Tab	Innovator	314.69 ±257.80	0	0
		Etrafon F® Tab	Innovator	337.79 ±91.98	0	0
		Etrafon M® Tab	Innovator	256.69 ±0	0	0
	Trimipramine	Surmontil® 50mg Cap	Innovator	358.66 ±161.18	198.45 ±60.26	188.54 ±33.10
		Surmontil® 25mg Tab	Innovator	0	0	0
		Tydamine® 50mg Cap	Generic	256.42 ±121.24	234.42 ±98.22	253.80 ±134.37
		Tydamine® 25mg Tab	Generic	149.45 ±83.46	141.42 ±68.55	178.35 ±92.15
Non-Tricyclic agents	Maprotiline	Ludiomil® 25mg Tab	Innovator	303.93 ±150.19	254.36 ±84.05	324.58 ±0.00
		Ludiomil® 75mg Tab	Innovator	414.89 ±145.65	403.98 ±63.29	456.15 ±0.00
	Mianserin	Lantanon® 30mg Tab	Innovator	124.30 ±69.40	260.74 ±157.70	331.25 ±249.23
		Lantanon® 10mg Tab	Innovator	315.93 ±182.09	115.69 ±73.07	139.38 ±75.29
MAO inhibitors	Moclobemide	Aurorix® 150mg Tab	Innovator	349.18 ±192.83	304.67 ±125.35	320.57 ±116.04
		Aurorix® 300mg Tab	Innovator	377.04 ±219.89	283.05 ±214.83	786.85 ±382.45
		Clorix® 150mg Tab	Generic	202.24 ±81.00	182.17 ±56.11	200.25 ±60.47

Table 11c: The average cost of antidepressants according to trade name (continue)

Mims classification	Active ingredient	Trade name and dosage form	Innovator or generic	Average cost 2004 (R)	Average cost 2005 (R)	Average cost 2006 (R)
		Clorix® 300mg Tab	Generic	263.69 ±83.79	207.18 ±76.51	203.88 ±42.73
		Depnil® 150mg Tab	Generic	242.98 ±91.55	203.08 ±76.42	220.24 ±93.81
		Depnil® 300mg Tab	Generic	257.46 ±68.44	233.38 ±44.38	210.21 ±90.07
	Tranylcypromine	Parnate® 10mg Tab	Innovator	151.48 ±66.13	143.80 ±63.28	0
SSRI's	Citalopram	Cipramil® 20mg Tab	Innovator	319.80 ±146.49	262.02 ±150.39	317.13 ±215.31
		Cilift® 20mg Tab	Generic	206.18 ±83.13	125.95 ±47.74	78.21 ±19.47
		Citalohexal® 20mg Tab	Generic	0	93.69 ±26.37	86.98 ±28.11
		Depramil® 20mg Tab	Generic	0	94.38 ±26.13	64.11 ±41.77
		Depramil® 40mg Tab	Generic	0	0	103.50 ±0.00
		Merck-Citalopram® 20mg Tab	Generic	0	0	0
		Ran-Citalopram® 20mg Tab	Generic	0	0	58.73 ±7.16
		Ran-Citalopram® 40mg Tab	Generic	0	0	0
		Sandoz Citalopram® 20mg Tab	Generic	0	73.95 ±25.02	75.27 ±0.13
		Sandoz Citalopram® 40mg Tab	Generic	0	93.98 ±0	0
		Adco-Talomil® 20mg Tab	Generic	160.31 ±65.78	106.69 ±52.72	78.74 ±17.25

Table 11c: The average cost of antidepressants according to trade name (continue)

Mims classification	Active ingredient	Trade name and dosage form	Innovator or generic	Average cost 2004 (R)	Average cost 2005 (R)	Average cost 2006 (R)
	Escitalopram	Cipralex® 20mg Tab	Innovator	245.98 ±76.30	247.93 ±82.18	299.68 ±120.8
	Fluoxetine	Prozac® 20mg Cap	Innovator	488.95 ±219.39	497.90 ±260.51	649.02 ±611.11
		Prozac® 20mg Tab	Innovator	269.47 ±191.68	214.84 ±124.70	234.48 ±119.45
		Prozac® 20mg/5ml Liq	Innovator	341.47 ±127.38	380.85 ±205.57	425.07 ±243.39
		Prozac® 40 SI Cap	Innovator	576.25 ±155.72	446.61 ±301.67	274.65 ±251.72
		Proza®c 60 SI Cap	Innovator	1014.91 ±345.27	938.75 ±311.58	1279.02 ±0.00
		Apo-Fluoxetine® 20mg	Generic	131.48 ±27.62	0	0
		A-Lennon Fluoxetine® 20mg Cap	Generic	0	29.59 ±10.08	25.20 ±0.66
		Deprozan® 20mg Cap	Generic	64.91 ±39.59	31.48 ±13.84	43.16 ±18.69
		Flutinol® 20mg Cap	Generic	0	0	0
		Lilly-Fluoxetine® 20mg Cap	Generic	132.23 ±57.69	96.42 ±59.24	102.05 ±63.18
		Lorien® 20mg Cap	Generic	66.56 ±52.88	38.59 ±14.62	41.51 ±13.12
		Lorien® 20mg Tab	Generic	90.82 ±46.35	62.06 ±24.68	56.36 ±23.87
		Nuzak® 20mg Cap	Generic	81.87 ±50.06	41.84 ±15.04	44.50 ±15.35

Table 11c: The average cost of antidepressants according to trade name (continue)

Mims classification	Active ingredient	Trade name and dosage form	Innovator or generic	Average cost 2004 (R)	Average cost 2005 (R)	Average cost 2006 (R)
		Prohexal® 20mg Cap	Generic	76.98 ±51.70	38.80 ±11.48	48.40 ±18.87
		Prohexal® Dispers 20mg Tab	Generic	86.41 ±36.91	60.96 ±27.28	77.66 ±22.82
		Prohexal® Dispers 40 mg Tab	Generic	187.13 ±68.44	139.94 ±20.39	119.29 ±41.50
		Ranflocs® 20mg Cap	Generic	45.89 ±40.63	25.25 ±9.00	26.27 ±6.16
		Sandoz-Fluoxetine® 20mg Cap	Generic	75.45 ±52.41	45.43 ±15.59	45.20 ±11.02
		Sanzur® 20mg Cap	Generic	114.35 ±86.37	0	0
		Trizac® 20mg Cap	Generic	0	0	21.37 ±0.59
	Paroxetine	Aropax® 20mg Tab	Innovator	346.30 ±132.09	300.14 ±106.99	245.79 ±176.28
		Aropax® 30mg Tab	Innovator	334.35 ±54.69	365.85 ±139.10	452.29 ±215.13
		Aropax® CR 12.5mg Tab	Innovator	0	0	210.90 ±33.14
		Aropax® CR 25mg Tab	Innovator	0	0	273.95 ±22.66
		Adco-Paroxetine® 20mg Tab	Generic	0	150.94 ±89.88	66.63 ±94.23
		Deparoc® 20mg Tab	Generic	0	142.11 ±66.63	142.74 ±56.78
		Paxil® 20mg Tab	Generic	0	190.73 ±55.36	192.94 ±62.46

Table 11c: The average cost of antidepressants according to trade name (continue)

Mims classification	Active ingredient	Trade name and dosage form	Innovator or generic	Average cost 2004 (R)	Average cost 2005 (R)	Average cost 2006 (R)
		Parax® 20mg Tab	Generic	0	0	240.90 ±86.64
		Parax® 40mg Tab	Generic	0	0	160.56 ±65.71
		Sandoz Paroxetine® 20mg Tab	Generic	0	196.08 ±50.71	188.26 ±36.47
		Sedarin® 20mg Tab	Generic	0	0	180.03 ±22.71
		Serrapress® 20mg Tab	Generic	0	179.36 ±67.88	131.40 ±92.43
		Serrapress® 30mg Tab	Generic	0	0	269.81 ±34.79
		XET® 20mg Tab	Generic	0	0	0
	Fluvoxamine	Luvox® 100mg Tab	Innovator	375.36 ±198.34	450.26 ±211.77	478.96 ±195.53
		Hexal Fluvoxamine® 100mg Tab	Generic	0	251.44 ±75.48	282.97 ±85.73
	Sertraline	Serlife® 100mg Tab	Innovator	0	263.00 ±54.43	304.17 ±122.12
		Zoloft® 50mg Tab	Innovator	368.06 ±157.07	278.67 ±107.06	245.98 ±91.10
		Serlife® 50mg Tab	Generic	269.99 ±111.52	209.16 ±72.33	225.49 ±62.36
		Merck® Sertraline 50mg Tab	Generic	0	0	245.37 ±103.45
		Serdep® 50mg Tab	Generic	0	0	269.35 ±150.46

Table 11c: The average cost of antidepressants according to trade name (continue)

Mims classification	Active ingredient	Trade name and dosage form	Innovator or generic	Average cost 2004 (R)	Average cost 2005 (R)	Average cost 2006 (R)
		Sertzol® 100mg Tab	Generic	0	424.85 ±172.03	359.02 ±80.58
		Sertzol® 50mg Tab	Generic	0	225.40 ±67.80	221.14 ±44.01
Serotonin and noradrenaline re-uptake inhibitor	Venlafaxine	Efexor® XR 75mg Cap	Innovator	444.64 ±161.37	416.38 ±144.34	434.87 ±132.74
		Efexor® XR 150mg Cap	Innovator	828.10 ±295.25	742.40 ±246.72	827.37 ±182.50
		Efexor® 37.5mg Tab	Innovator	315.44 ±152.83	277.59 ±95.53	148.08 ±127.03
		Efexor® 75mg Tab	Innovator	471.48 ±193.26	441.43 ±163.85	474.27 ±38.52
		Efexor® 50mg Tab	Innovator	275.08 ±70.13	126.05 ±0	0
		Venlor® XR 37.5 mg Cap	Generic	0	0	151.15 ±32.30
		Venlor® XR 75 mg Cap	Generic	0	0	283.32 ±106.89
		Venlor® XR 150 mg Cap	Generic	0	0	
	Duloxetine	Cymbalta® 30mg Cap	Innovator	351.39 ±0	383.81 ±167.39	470.93 ±141.27
		Cymbalta® 60mg Cap	Innovator	341.44 ±51.20	418.97 ±134.04	488.56 ±139.57
	Lithium	Camcolit® 400mg Tab	Innovator	184.14 ±84.58	108.39 ±74.95	209.96 ±77.12
		Camcolit® 250mg Tab	Innovator	240.26 ±126.98	206.58 ±102.84	232.49 ±120.37

Table 11c: The average cost of antidepressants according to trade name (continue)

Mims classification	Active ingredient	Trade name and dosage form	Innovator or generic	Average cost 2004 (R)	Average cost 2005 (R)	Average cost 2006 (R)
Lithium		Lentolith® 400mg Cap	Innovator	279.22 ± 126.50	154.74 ±0	0
		Quilonum® Retard Tab	Innovator	158.09 ±68.63	170.48 ±80.91	235.32 ±87.43
Others	Bupropion	Wellbutrin® SR 150mg Tab	Innovator	144.24 ±110.13	212.09 ±86.85	231.80 ±97.66
	Fluphenazine/ Nortriptyline	Motival® Tab 0.5/10mg	Innovator	101.39 ±48.00	106.00 ±50.81	110.60 ±47.28
	Flupenthixol	Fluanxol® 1.0mg Tab	Innovator	379.30 ±201.01	371.53 ±188.54	357.05 ±144.42
		Fluanxol® 0.5mg Tab	Innovator	259.90 ±147.83	239.18 ±163.28	278.00 ±157.58
		Fluanxol® 0.25mg Tab	Innovator	241.01 ±148.56	231.23 ±142.75	205.13 ±72.71
	Mirtazapine	Remeron® 30mg Tab	Innovator	535.87 ±233.10	457.23 ±204.63	576.85 ±232.79
		Remeron® 15mg Tab	Innovator	316.28 ±99.12	290.95 ±129.02	359.61 ±139.15
	Nefazodone	Serzone® 200mg Tab	Innovator	433.15 ±136.48	0	0
		Serzone® 100mg Tab	Innovator	279.82 ±89.91	0	0
	Reboxetine	Edronax® 4mg Tab	Innovator	376.96 ±174.40	287.66 ±101.38	292.12 ±130.25
	Sulpiride	Eglonyl® 2ml Amp	Innovator	65.20 ±180.80	20.98 ±2.42	27.64 ±14.22
		Eglonyl® 50mg Cap	Innovator	145.79 ±100.92	113.18 ±73.74	120.41 ±85.55

Table 11c: The average cost of antidepressants according to trade name (continue)

Mims classification	Active ingredient	Trade name and dosage form	Innovator or generic	Average cost 2004 (R)	Average cost 2005 (R)	Average cost 2006 (R)
		Eglonyl® Elix 25mg/5ml	Innovator	125.88 ±108.13	116.38 ±57.14	98.36 ±44.80
		Eglonyl® Forte 200mg Tab	Innovator	304.58 ±140.11	276.18 ±106.12	322.67 ±92.40
		Depex® 50mg Cap	Generic	104.89 ±62.82	0	0
		Espiride® 50mg Cap	Generic	113.71 ±83.93	82.91 ±54.90	93.47 ±57.63
		Sandoz Sulpiride® 50mg Caps	Generic	0	82.11 ±53.39	84.62 ±66.62
	Trazodone	Molipaxin® 50mg Cap	Innovator	590.83 ±295.97	239.06 ±116.78	247.88 ±110.59
		Molipaxin® 100mg Cap	Innovator	276.19 ±141.49	481.41 ±247.54	525.49 ±260.73

APPENDIX D

Potential Cost Savings for Antidepressants Brought on by Generic Substitution

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Purpose:

The aim of the National Drug Policy (NDP) regarding drug pricing is to promote the availability of safe and effective medicines at the lowest possible cost. One of the methods to achieve this is by generic substitution (South Africa, 1996). The Medicines and Related Substance Control Act 101 of 1965 as amended in 1997 states that pharmacists, *inter alia*, have to inform any patient of the benefits of generic substitution and dispense generic medicine items with certain exceptions. The purpose of this study was to determine cost savings attributable to generic substitution with regard to antidepressants by using data from a medicine claims database.

Methods:

Data from a medical claims database were analysed by means of a retrospective drug utilisation review (DUR) study for the years 2004, 2005, 2006. The SAS 9.1 programme (2001-2002) was used for the statistical analysis of the data. The potential cost savings were calculated by creating certain hypothetical scenarios. Innovator items were substituted with 50% of the least and most expensive generic items and 100% of the least and most expensive generic.

Results:

In 2004, 58.67% (n = 157 810) of all antidepressants prescribed on the database were generic medicine items; compared to 56.49% (n = 86 521) in 2005 , and 63.30% (n= 47 470) during 2006. The average cost for generic antidepressants was

R110.06±89.23 in 2004, compared to R69.96±60.14 in 2005 and R74.47 ±74.11 in 2006. The effect sizes calculated between the average cost of antidepressants during 2004 and 2005 were of practical significance (d=0.8). A potential R2 292 861.86 could have been saved during 2004 had all the items been substituted with the cheapest generic item. A further R2 303 129.71 and R1 511 043.83 could have been saved during 2005 and 2006 respectively.

Conclusion:

In South-Africa, where the aim of the NDP is to promote the lowest possible medicine price, generic substitution can play a vital role. Generic substitution could have decreased mental health care costs in 2004 to 2006 with 10.87 %. Pharmacists can play an important role in promoting generic substitution and providing education regarding generic substitution.