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Antidepressant prescribing in Gauteng: a public sector drug utilization review

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Antidepressant prescribing in Gauteng:

A public sector drug utilization review



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Declaration

I, Nirvana Bagwathpersad, declare that this is a dissertation of my own research. It is submitted for a degree of Master of Science in Medicine in the University of the Witwatersrand, Johannesburg. It had not been submitted previously for any other degree or examination at this or any other university.



Nirvana Bagwathpersad

Abstract

Introduction: In South Africa, neuropsychiatric conditions rank third in its contribution to the burden of disease, after AIDS and other infectious diseases. Within the past two decades, the prescribing and subsequent use of antidepressants has become increasingly common, even among children and adolescents. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are widely prescribed by doctors for depression, panic, anxiety, pain and stress disorders. The aim of this study was to conduct a retrospective drug utilisation review on the prescribing of antidepressant drugs in a public health sector outpatient psychiatric clinic and to calculate the drug cost associated with treating depression in this study. The study was conducted on records over a period from January 2011 to September 2014.

Methods: Following ethical approval for the study, out-patient prescription records are obtained from the Charlotte Maxeke Johannesburg Academic hospitals psychiatric clinic. This information was then recorded on case report forms and later transferred to a purpose designed spread sheet using Microsoft Excel 2010. Descriptive statistics were used to chart the use of specific antidepressants, the patient demographics and the indications for antidepressant use. Inferential statistics were used to document correlations and drug use.

Results: The patient population consisted of 41 male (30.30%) and 94 female patients (69.70%). The population consisted of various ethnicities of which 35.70% (n=48) were Black, 10.30% (n=14) were colored, 13.30% (n=18) were Indian and 40.70% (n=55) were White. The average age of all the patients was 50.16 years (SD= 16.32). Unemployed patients consisted of 50.40% of the patient population whilst only 23.70% of patients were employed and the remainders were pensioners (25.90%). Married patients consisted of 54.81% of the sample whilst single, widowed or divorced patients comprised 45.19%. More than half of the patients had been diagnosed with major depressive disorder or MDD (56.30%). Patients who had also been receiving treatment for a bipolar mood disorder had also been receiving antidepressant therapy (10.37%). Mild depression and MDD with psychotic features were the least present diagnosis (0.74% and 4.44% respectively). Of the total patient population, almost half had been prescribed citalopram as their antidepressant (51.61%), followed by venlafaxine (30.33%) then fluoxetine (18.03%). The patient race has been shown to influence the type of antidepressant chosen ($p< 0.0001$). There were correlations between the antidepressant chosen and patient race as well as marital status ($p<0.0001$). As shown in a number of other studies, there are more female patients receiving antidepressant therapy than males. In this study the amount of black male and female patients had been nearly equal with white patients having been

composed of more females than males. For coloured and Indian patients, there had been more males than female patients. As expected, the diagnosis of a patient, which had been noted using the ICD 10 codes, had a great influence on the type of antidepressant chosen ($p<0.000$). The ICD codes used were for the range of depressive disorders from F32 to F42 (Appendix D). .The antidepressant with the most amounts of repeat prescriptions was venlafaxine with an average of 15.13 repeats followed by fluoxetine with 11.77 repeats and citalopram with 10.67 repeats. As shown previously with the total patient population, most males and females had been prescribed citalopram, although it had been prescribed to 12.33% more of the female patients. Fluoxetine was however prescribed to a slightly greater extent to males than females. Fluoxetine was however prescribed to a slightly greater extent to males than females. Citalopram had been the preferred antidepressant in Black, Coloured and White patients (57.14%; 58.30% and 44.00% respectively). Venlafaxine had been prescribed to a much greater extent in the Indian population (55.60%). Fluoxetine had been prescribed more to Black patients than other race group with the same group having venlafaxine prescribed to the least amount of patients. With employed patients, citalopram had been the most frequently prescribed (52.40%) followed by fluoxetine (26.66%) then Venlafaxine (20.94%). In the unemployed group of patients, the second most frequently prescribed drug was venlafaxine (26.96%) followed by fluoxetine (15.19%). The type of antidepressant chosen was shown to be influenced by the marital status of the patient ($p= 0.048$). The most expensive antidepressant used had been venlafaxine with an average cost per patient of R144.12 per month. Fluoxetine had been the cheapest antidepressant with only a small difference, of between R1.02 and R3.00, as compared to the slightly more expensive citalopram.

Conclusion: The data correlates with a number of international DURs and has provided valuable insight into the use of antidepressants in the public sector.

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Abbreviations

APA	American Psychiatric Association
DDD	Defined Daily dose
DSM-V	Diagnostic and statistical manual of mental disorder (5)
DUR	Drug utilization review
GAD	Generalized anxiety disorder
ECT	Electroconvulsive therapy
EDL	Essential drug list
ICD-10	International Classification of disease
ICER	Increment cost effectiveness ratio
MDD	Major Depressive Disorder
OR	Odds ratio
P	Probability
PDD	Prescribed daily dose
SEP	Single exit price
SSRI	Selective serotonin re-uptake inhibitor
SNRI	Serotonin Noradrenaline re-uptake inhibitor
TCA	Tricyclic antidepressant
US	United states
UK	United Kingdom
WHO	World Health Organisation

Chapter One: Rationale for this study

The use of antidepressants has increased within the last two decades (Aarts *et al,* 2014; Vetulani and Nalepa 2000; Courtet *et al,* 2014). As a result of the increased prescribing and use of antidepressants, the need for information regarding the actual prescribing practices has become vitally important in order to maintain patient safety as well as to ensure that the optimal therapeutic outcome is achieved, especially when the nature of the side effects of these drugs are considered (Artigas, 2015). Within the past decade, there has been a considerable amount of drug utilization reviews on antidepressants that have been conducted as the use of these drugs gained the interest of many researchers. The results of these DURs do vary slightly however all do provide vital information that can help to improve the prescribing process of antidepressants (Bauer *et al,* 2008; Gondalez *et al,* 2010; Serna *et al,* 2010).

A retrospective DUR involves reviewing therapy after the patient has received treatment. A retrospective review may detect patterns in prescribing, dispensing, or administering drugs to prevent recurrence of inappropriate use of drugs (Hess, 2004). In this study, patient records were reviewed and information such as age, sex, race and area of residence were recorded to chart differences in patient demographics. Information about antidepressant drugs as well as dose, frequency of dosing and dosing instructions were collated and analysed to infer patterns of prescribing of these drugs.

Most of the South African published drug utilisation reviews on antidepressants records that were reviewed are from a decade ago and were from a private medical scheme (Truter and Kotze 2007, 1997), the results showed a deviation of actual prescribing practices from the recommended guidelines. This proposed study differs from the previous DURs in that it will be the first to be conducted in the state health facilities. The study results could inform antidepressant prescribing in the public sector and contribute to improved patient care.

1.1 Aim

The aim of this study was to conduct a drug utilisation review and identify the costs directly associated with antidepressant prescribing in an outpatient psychiatric clinic at a Gauteng Academic hospital.

1.2 Study Objectives

- To determine which antidepressants are prescribed
- To determine the frequency of antidepressant drugs prescribed as well as their doses
- To quantify the patient return-rate through repeat prescriptions
- To investigate whether patient demographics vary with prescribed antidepressant
- To investigate whether patient diagnosis varies with antidepressant prescribed
- To compare drug use in the public sector with EDL recommendations and standard treatment guidelines (STGs).
- To calculate the costs associated with antidepressant prescriptions in the out-patient clinic.

Chapter Two: Literature review

2.1 Retrospective drug utilization reviews

A retrospective review utilizes existing data that have been collected for reasons other than research, these data are best represented as prescriptions and patient records (Hess, 2004). A retrospective review can find patterns in prescribing, dispensing, or administering drugs, helps to prevent occurrence of inappropriate medicine use and serves as a platform for developing prospective recommendations and target interventions. In this kind of drug utilization review (DUR), patient medical records are analysed to detect whether the drug therapy has met the approved criteria and aids prescribers' in improving care for their patients, individually and within groups of patients, such as those with psychiatric disorders.

One of the most important aspects to measure, when conducting a retrospective review, is the amount of drug prescribed which is then compared to a recommended dose. Antidepressant medication should be prescribed in the correct doses in order to achieve the desired therapeutic effect and avoid toxicity (Truter and Kotze, 2007). A drug utilisation research method that is used for the analysis of data is the Defined Daily Dose (DDD) method. DDD is known as the dose which corresponds to the average dose per day for a drug, when used for the main indication in adults (WHO, 2003). There are limitations to the use of the DDD because a large percentage of drugs are used for off –label indications, therefore are used at different dosages. The DDD is a technical unit of measurement, and is not necessarily equivalent to the average doses actually prescribed. Therefore, the prescribed daily dose (PDD) is used to overcome the limitations of the DDD. The PDD is the actual prescribed dose of the drug and is obtained by the dosing instructions in prescriptions (Truter and Kotze, 1997). By using the dosing instructions it is seen how many times per day the drug would be taken, this helps to enable calculation of the total daily dose. An example of the use of this method is a study that had been conducted in 2000, which focused on a sample of 98 adolescents and young adults in South Africa and investigated the prescribing patterns of TCAs and SSRIs, the found that the SSRIs were more likely to be prescribed within a close range of the DDD than the TCAs (Kairuz *et al,* 2003).

2.2. Antidepressant prescribing across various countries

A study by Bauer and other researchers conducted in 2008 aimed at describing the prescribing patterns as well as any factors that influence the choice on antidepressant by prescriber in the Factors Influencing Depression Endpoints Research (FINDER) study that involved 3468 patients in 12 European countries. This study had been done as a result of growing curiosity among researchers in Europe after it had been shown by surveys that there were differences between European countries in the prescribing of antidepressants where TCAs were favored more in some countries but SSRIs more frequently prescribed in others (Tylee *et al.*, 1999). This variation is evident even though other studies had shown that there had been a shift from the prescribing of TCAs (Tricyclic antidepressants) to the better tolerated SSRIs (Selective serotonin re-uptake inhibitors) (Guaiana *et al,* 2005; Lawrenson *et al,* 2000; Van Marwijk *et al,* 2001). FINDER was an observational study that involved 12 European countries namely: Austria, Belgium, France, Germany, Ireland, Italy, the Netherlands, Norway, Portugal, Sweden, Switzerland and the UK (Garcia- Cebrian *et al,* 2008). This study had been designed to help understand the types of factors that can affect the health-related quality of life (HRQoL) outcomes for patients undergoing treatment for depression. This study had been used by the researchers to determine the physician and patient characteristics that influence the type of antidepressant that will be initially selected (Bauer *et al,* 2008). All the patients who participated in this study were adults over the age of 18.

The results of the study showed that the most commonly prescribed antidepressants were SSRIs (63.3% of all patients) followed by SNRIs (Serotonin and noradrenalin re-uptake inhibitors) (13.6% of all patients) (Bauer *et al.,* 2008). The prescribing of different antidepressant groups varied between countries; SSRIs prescribed ranged from 31.7% in Germany to 81.5% in France. TCAs were prescribed for only 1.5% of patients in the Netherlands and 8.6% in Austria but accounted for 26.5% of antidepressants prescribed in Germany. Combinations of antidepressants were prescribed more frequently in Austria (24. 5% of patients) whilst no combinations at all were used in the Netherlands and Ireland. The mean dose of amitriptyline (55.6mg/day) is considerably lower than the recommended dose (75mg/day). Interestingly, it also had been shown that primary care physicians prescribed higher mean dosed for duloxetine and trazodone but lower mean doses for amitriptyline and venlafaxine.

A study in the United States aimed at investigating the utilization, price and spending patterns of antidepressants during the period from January 1991 to December 2005 (Chen *et al,* 2008). This study had used information from a Medicaid program in which a descriptive time series had been conducted to assess the trends of expenditure, utilization, market shares and prices during the specified time for SSRIs, TCAs and other antidepressants. The study had found that during the 1990's, antidepressants were the most widely prescribed medication in the US. The study showed that the amount of antidepressant prescriptions had increased drastically from 6.8 million in 1991 to 35.0 million in 2004 but then decreased to 32.7 million prescriptions in 2005. The way in which the prescribing of SSRIs had come to dominate was shown in the study by the increase in the number of prescription from 1.0 million in 1991 to 20.8 million in 2005 (Chen *et al,* 2008). The amount of prescriptions for TCAs increased steadily from 1991 in which it was 4.7 million to 6.4 million in 2001. It then showed a slight decrease in 2002 to 6.0 million but then proceeded to drastically decline to 3.7 million in 2005. The use of other antidepressants had shown the greatest amount of growth from being less than 1 million prescriptions in 1991 to 9.9 million prescriptions in 2005.

2.2.1 Decline in the use of TCAs

There was found to be an increase in the overall use of antidepressants in a middle-aged and elderly population from 3.9% in 1991 to 8.3% in 2011 (Aarts *et al,* 2014), this study had showed the fluctuation in the prescribing of TCAs.

Amitriptyline and Paroxetine were the most commonly prescribed antidepressants with mirtazapine and venlafaxine being the other antidepressants that were also commonly prescribed, but to a lesser extent (Aarts *et al,* 2014). The study confirms the increased use of SSRIs in the elderly and middle-aged population, this is most likely due to the low toxicity, mild adverse drug reaction profile and no need for plasma monitoring (Parabiaghi *et al,* 2011). The relatively stable prevalence and slight decrease in the use of TCAs was shown to be consistent with the other literature (Parabiaghi *et al,* 2011) eventhough the researchers expected to see a greater decline in the use of these drugs due to their poor tolerability and not being the first choice of antidepressant drug in the elderly population (Aarts *et al,* 2014). The high incidence in the use of TCAs might be explained by the numerous indications for which these drugs are also prescribed; this includes neuropathic pain (Raymond *et al,* 2007). The increase in

antidepressant use in the elderly age groups could also be related to increasing loneliness, physical health problems and other disabilities as well as the worsening of chronic diseases (Aarts *et al,* 2014; Parabiaghi *et al,* 2011).

In contrast, a study in Spain showed that the antidepressant that was most frequently prescribed was SSRIs at 63.8% followed by TCAs at 18.2% (Serna *et al,* 2010). This had been confirmed in a US based study which showed that SSRI/SNRI type antidepressants were prescribed to 71% of the patients in contrast to the 3% of patients that were prescribed older antidepressants such as TCAs (Lin *et al,* 2011). The amount of prescriptions for TCAs increased steadily from 1991 in which it was 4.7 million to 6.4 million in 2001, it then showed a slight decrease in 2002 to 6.0 million but then proceeded to drastically decline to 3.7 million in 2005 (Chen *et al,* 2008).This finding has been mirrored in other studies, one that had been conducted over various countries in Europe. TCAs were prescribed for only 1.5% of patients in the Netherlands and 8.6% in Austria but accounted for 26.5% of antidepressants prescribed in Germany (Bauer *et al,* 2008). The way in which the prescribing of SSRIs had come to dominate was shown in the study by the increase in the number of prescription from 1.0 million in 1991 to 20.8 million in 2005 (Chen *et al,* 2008). Of all the 16,886 antidepressants prescribed, 7,044 (41.72%) were SSRIs, 5,739 (33.99%) were TCAs (Bauer *et al,* 2008).

In South Africa, older studies have shown a similar pattern with the most frequently prescribed antidepressant, as shown in a study conducted on medical aid data, was TCAs which accounted for 40.9% of all antidepressant prescriptions, followed by SSRIs at 34.5% (Truter and Kotze, 1997). The prescribing patterns of TCAs were studied using patients who are on a private medical aid scheme, data from 1996 (1982 patients) and 2002/2003 (2345 patients) were used (Truter and Kotze, 2007). Almost two-thirds of these patients were female (67.41% in 1996 and 57.53% in 2002/2003) (Truter and Kotze, 2007). Interestingly, TCAs were more frequently prescribed to males than females in the younger age groups in 1996 but in the older age groups in 2002/2003 (Truter and Kotze, 2006).

Although the potency of SSRIs are often debated upon, with their efficacy being compared to TCAs and other older antidepressants, most psychiatrists and other health professionals agree that they should be used as the first choice of drugs because of their less serious side effect profile. An older drug utilization review conducted in Denmark showed that approximately 75% of had TCAs prescribed to patients, whilst SSRIs were only used by 10% of the population

(Rosholm *et al,* 1993). This shows the way in which the use of antidepressants has changed over the years.

2.2.2 Prescribing patterns

Antidepressants are often used to treat a number of anxiety related conditions (Gondalez *et al,* 2010). They can be used alone or in combination with anxiolytics. In South Africa, one study showed that anxiolytics contributed to the second largest amount of nervous system drugs prescribed (Truter and Kotze, 1997).

In South Africa, of all the SSRIs prescribed, Fluoxetine had been the most frequently prescribed with it accounting for 63.3% of all prescriptions, the second most commonly prescribed of which was Paroxetine with 28.5% (Truter and Kotze, 1997). In another South African study, female patients (62.33%) were more frequently prescribed SSRIs and SNRIs than males (Van Schalwyk and Truter, 2010). In terms of factors influencing the type of antidepressant prescribed, there were some socio-demographic factors that had been shown to be associated with the type of antidepressant prescribed at the baseline visit. For example, non-smokers, younger patients and patients with a higher level of education were more likely to have a SSRI prescribed as opposed to any other antidepressant. Interestingly, the researchers had found that the type of antidepressant prescribed was not influenced by factors such as severity of anxiety, current patient functioning or co-morbidity.

In South Africa, the health sector is divided into the private and public sector. The private sector provides health care to patients who have a medical aid fund which allows access to private (non-government owned) hospitals and other health care services. Within this sector, prescribing is not limited to a list of drugs however it is controlled by the availability of that drug in South Africa as a whole. Within the public health sector, which is state controlled, prescribing is controlled by a list of approved drugs known as the Essential Drug List (EDL). The purpose of such a list is to ensure adequate and safe supply of effective and safe medicines in the most cost-effective manner to all citizens of South Africa.

The criteria for the selection of essential drugs for Primary Health Care in South Africa were based on the WHO guidelines for drawing up a national EDL. They include the following:
• any drug included must meet the needs of the majority of the population

• sufficient proven scientific data regarding effectiveness must be available
• any drug included in the EDL should have a substantial safety and risk/benefit ratio
• all products must be of an acceptable quality, and must be tested on a continuous basis
• the aim, as a rule, is to include only products containing single pharmacologically active ingredients
• combination products, as an exception, will be included where patient compliance becomes an important factor, or two pharmacologically active ingredients are synergistically active in a product
• products will be listed according to their generic names only• a request for a new product to be included on the EDL must be supported by
scientific data and appropriate references on its advantages and benefits over an existing product.

The standard treatment guidelines characterize depression as a depressed mood (sadness) accompanied by loss of interest and decreased experiencing of pleasure as well as social withdrawal. With regards to prescribing, the choice of antidepressant is guided by the comorbid conditions eg cardiovascular disease and in the elderly. TCAs are avoided in cardiovascular disease and SSRIs are used with caution in the elderly. According to the EDL, the first line for treatment of MDD are the TCAs amitriptyline and impramine. The second line treatment is the SSRIs citalopram and fluoxetine (Department of Health, 2012). In the private sector, there is a larger variety of antidepressants available which does not limit prescribing to just two classes, as with the public sector.

2.2.3 Antidepressant use in patients under 20 years of age

A study to show the prescribing patterns in patients younger than 18 showed that SSRIs accounted for 55.91% of antidepressant prescriptions which was ahead only of TCAs which contributed to 32.32% of prescriptions. These two antidepressants accounted for 79.49% of the antidepressant cost (Truter, 2010). Another study which had aimed at investigating the prescribing patterns of SSRIs and SNRIs in patients 19 and younger showed that 440 patients

younger than 19 years receiving antidepressant therapy which had accounted for 6.20% of patients of any age receiving antidepressants (Van Schalwyk and Truter, 2010). The average age of these patients was 14.21 (SD=3.05) years with the majority of patients being older than 12 years old (77.13%) (Van Schalwyk and Truter, 2010). Antidepressants prescribed to patients 18 and younger, from a private medical scheme database, 12549 antidepressant prescriptions were made to this patient population out of the total of 814540 antidepressant prescriptions in the year 2009 (Truter, 2010). Another study which had been done in the US had shown that younger patients were more likely than older patients to receive an SSRI (Bartels *et al,* 1997).

A study in Germany aimed at describing the antidepressant drug use and off-label prescribing of antidepressants in the child and adolescent population. The SSRI fluoxetine and only a few TCAs as well as the herbal treatment for depression, St John's Wort, had been licensed for the treatment of depression in children and adolescents in Germany (Dorks *et al,* 2013). The study revealed that the prevalence of antidepressant use was 1.84 per 1000 children in 2004, 1.57 in 2005 and 1.66 in 2006 (Dorks *et al,* 2013). From the children treated with antidepressants, 56.30% had been diagnosed with a depressive disorder. From these patients, 43.14% received one prescription, 18.36% received two, 10.88% received three and 27.62% received more than three antidepressant prescriptions. Of all the 16,886 antidepressants prescribed, 7,044 (41.72%) were SSRIs, 5,739 (33.99%) were TCAs, 2656 (15.73%) were St John's Wort and 1,447 (8.57%) were other types of antidepressants. Of all the antidepressants prescribed, 13,035 (49.11%) were for off-label antidepressant use, meaning it had been prescribed for conditions other than its registered indications. The researchers also found that the off-label use by age (40.18%) was more common than the off label use by indication (16.63%) which showed that younger patients would be more likely to be prescribed an antidepressant for indications other than depression. This appears to be a trend even though the use of antidepressants is not recommended in children and adolescents because of an increase in the risk of suicide as shown with the black box warning. Regulatory bodies have warned about the use of antidepressants particularly in the first few weeks, the use of antidepressants remain prevalent regardless of risk of suicide associated with these drugs (Courtet *et al,* 2014).

The results of the study showed clearly that the prevalence of antidepressant use did not vary much over the study period from 2004 to 2006. From all the patients treated with antidepressants, most of the patients received single prescriptions and TCAs accounted for a majority of all antidepressants prescribed. The proportion of SSRIs, mainly fluoxetine, use increased during the study period while the proportion of use of St John's wort decreased (Dorks *et al,* 2013).

2.3 Gender in antidepressant studies

Through a number of studies, the prevalence of depression had been shown to be higher in women than in men. Studies done in both Europe and South Africa have showed the same findings. A Danish study showed that among a group of patients diagnosed with depression over a long period of time, 59.69% were female (Grasse *et al,* 2013). This finding is confirmed by other studies which show that depression is treated and diagnosed half as frequently in male than in female patients (Truter and Kotze, 2006).

Often the question is raised as to whether depression is more prevalent in women or whether women seek treatment more frequently than men.

Another European based study which had showed statistics, from a sample of people whom come from various countries, which further encouraged the theory that depression is more prevalent in women (Bauer *et al,* 2008; Aarts *et al,* 2014; Serna *et al,* 2010). In the United States, similar findings were reported with 70% of the population who were receiving antidepressant therapy being women (Lin *et al,* 2011). A study in Spain showed that 67.1% were female and the average age of the patients was 51 (Serna *et al,* 2010). A study in the US showed that of the 2 111 615 patients, all of whom were adults that have been diagnosed with MDD, 70% were female (Lin *et al,* 2011). The same findings were shown here in South Africa. A South African study conducted on 2117 patients showed that 72.8% of the patients were female with the remainder 27.2% being male (Truter and Kotze, 1997). In 2009, results from a private medical aid scheme in South Africa showed that of these patients, on antidepressants, 53.74% were female (Truter, 2010). The results from the South African mental health and stress study shows that there were more females than males who had received treatment or sought medical attentions because the group consisted mostly of females (53.7%) (Tomlinson *et al,* 2009).

Another South African study on mental health patterns had shown that women were more likely to seek treatment overall however, among 12-month cases there had been no significant gender differences for mood disorders, this difference could be because women more of a tendency to recognize symptoms of affective distress than men over a long term period (Seedat *et al,* 2009). There have been deviations in the proportion of male to female when younger age groups of children and adolescents had been studied for the off-label use of antidepressants, where the proportions are almost equal (Dorks *et al,* 2013). Depression is more prevalent in women than in men, therefore when antidepressants are prescribed for off-label conditions, the gender differences is minimal. This is mainly due to the fact that the off-label conditions, for which antidepressants are prescribed, are found in near equal proportions in both males and females.

The manners in which antidepressants are prescribed differ between the two gender groups as well. Female patients (62.33%) were more frequently prescribed SSRIs and SNRIs than males (Van Schalwyk and Truter, 2010). In 1995, of a total of 2117 patients on fluoxetine, 72.8% were female and 27.2% were male (Truter and Kotze, 1997). TCAs were more frequently prescribed to males than females in the younger age groups in 1996 but in the older age groups in 2002/2003 (Truter and Kotze, 2006). This could be largely due to the fact that TCAs are now being used more for their off-label uses such as neuropathic pain.

2.4 Patient Ethnicity in relation to antidepressant prescribing

Differences in depressive symptoms as well as the prevalence of depression are found to vary among various ethnic groups. There have been a number of studies to show which ethnic groups are affected most by depression. An American based study, which aimed to show the prevalence of depression among the minority groups, showed that the prevalence is higher in Puerto Rican patients, with the lowest being among Chinese and Filipino groups (Gondalez *et al* 2010). Another similar study showed that there is also a difference in the types of symptoms reported among ethnic groups with Latino patients reporting more symptoms than White or African-American groups (Kemp *et al,* 1999). The finding that patients of a Hispanic origin exhibit more depressive symptoms than any other ethnic group in America had been confirmed in a previous study which showed that Mexican Americans showed higher levels of depression than White and African-American patients (Neff and Hope, 1993). On the opposing end of the

spectrum, a more recent study showed that African-Americans and Hispanics showed lower rates of depression when compared to Caucasian patients (Williams and Sternthal, 2010) Studies have shown the varied beliefs of depression and its treatment between different ethnic groups with ethnic minority groups being less likely to believe that the cause of depression is a biological change (Givens *et al,* 2007). These same minority groups had also less faith in using antidepressants in the treatment of depression, they had been more likely to believe in non pharmacological treatment such as counseling and prayer as these patients felt that antidepressants were addictive (Givens *et al,* 2007).

In South Africa, there had not been many studies done to show which of the ethnic groups have been most affected by depression. Results from the South African stress and health study analysed 4351 adult South Africans of all ages and all racial groups. The sample of patients had been diagnosed with either a 12 month or lifetime major depression (Tomlinson *et al,* 2009). The group consisted mostly black patients (76.2%) followed by coloureds (10.4%), white (3.4%) and Indian/Asian (3.4%) (Tomlinson *et al,* 2009). The prevalence of depression in this study group was proportionally consistent with the demographic of our country which consists of 76.4% Black, 9.1% White, 8.9% Coloureds and 2.5% Indian or Asian, with the exception of white and coloured patients (STATS SA, 2012).

With regard to the type of antidepressant chosen for each group, one study that had been conducted using Medicaid patient information in the US had shown that the patient's race had an influence on the type of antidepressant prescribed (Melfi *et al,* 2000). The study had shown that of all those patients receiving antidepressant therapy, whites were found to be more likely than patients of an African descent to have been given SSRIs.

2.5 Age groups that were frequently prescribed antidepressants

Age is one of the most important patient factors to consider when conducting any drug utilization review (Worster, 2004). With regards to an antidepressant drug utilization review, it not only provides information on the type of antidepressants prescribed to each group but also on the age groups which are more likely to be affected by depression. The results of a stress related study in South Africa showed that the average age of patients diagnosed with depression was 37.0 years (Tomlinson, *et al,* 2009) whilst another South African study showed a much different result with the average age of patients in that study on antidepressants was 53.4 (SD= 14.5 years), the average age of the male participants was 54.0 (SD=15.4 years) and the average of

the female patients were 53.2 (SD=14.2 years) (Truter and Kotze, 1997). A study in Spain showed that the average age of the patients was 51 (Serna *et al,* 2010). In certain European countries the average age of patients receiving antidepressant therapy had been slightly lower than shown here at 46.8 (SD=14.7) (Bauer *et al,* 2008). In the Netherlands, researchers had used a patient population consisted of 14,926 patients who were receiving antidepressant therapy, which had shown that this group presented with the average age of 65.5 years (SD=10.5) (Aarts *et al,* 2014). In contrast, one US based study showed that elderly patients were less likely to spend on MDD drugs as compared to patients aged between 18 and 25 years (Lin *et al,* 2011).

Over the progression of the past two decades, the use of antidepressants in adolescents, children and young adults has increased tremendously (Zito *et al,* 2006). This study showed that TCA were the most frequently prescribed antidepressant in 1988 but this had shifted to SSRIs by the year 1994. A commission on safety of these drugs in 2003 reviewed results from antidepressant drug trials in the United Kingdom which showed that venlafaxine, should not be used because of its lack of efficacy in treating depressive disorders and the increased risk of harmful results such as suicidal ideation and hostility in children aged 6-17 (Vitiello and Swedo, 2004). A year after that result, the UK had extended that warning to include SSRIs as well, soon after the United States Food and Drug Administration (FDA) issued a black box warning for all SSRIs and SNRIs due to the increased risk of suicidal ideation in studies with children who have been diagnosed with major depression (Kennedy, 2006).

2.6 Depression has an effect on work productivity

A decreased amount of productivity as well as absenteeism at work are both factors that have been associated with depression (Gasse *et al,* 2013). Financial burdens, increased work stress as well as the ever present threat of recession are all factors that can contribute to the deterioration of an individuals mental state. A high rate of unemployment is often shown in patient groups who are undergoing treatment for depression. There is speculation as to what causes this trend with some researchers investigating the effects of depressed patients taking sick leave for longer than 8 weeks , this high rate of sick leave can be associated to the job losses because of depression (Bratberg *et al,* 2009; Lund *et al,* 2008). In South Africa, a study of a sample population of depressed patients showed that 69.2% of the patients had been

unemployed at the time of the study (Tomlinson *et al,* 2009). There has been much debate as to the relationship between work productivity, employment status and depression. One study has shown that there is a clear association between mental health and unemployment where there is an improvement in a patients mental health when they make a move from unemployment to employment whilst those who lose their jobs have been shown to be more likely to develop symptoms associated with depression (Murphy and Athanasou*,* 1999). This shows that depression leads to a decrease in productivity which increases the cost to a company. A review of the cost associated with a diagnosis of depression showed that depression was associated with a large increase in direct and indirect cost, this referred not only to the cost of the drug itself but also to costs associated with sick leave and hospitalization (Luppa *et al,* 2007). Patients with depression and anxiety had sought medical treatment from health care facilities more than the general population (Wittchen, 2002), as a result this contributed to an increase in the health care related cost. Another US based study showed that depressive disorders contributed to $ 2.1 billion for direct costs (health and social services), $10 billion for loss of productivity and $4.2 billion as a result of increased mortality (Stewart, 1998).

2.7 Marital status and depression

The link between marital status and mental health has often been a topic of interest among researchers. Some have shown that those who are married or living with a partner have been shown to enjoy longer lives because of an improved physical and mental health compared to those individuals who were non-married or single (Earle *et al,* 1998; Ross 1995). Conversely, the effects of being married can have a negative effect on an individual's mental well-being with some studies showing that there is a clear relationship between marital dissatisfaction and depression (Whisman *et al,* 2004; Coyne *et al,* 2002). The rates of divorce are found to be greater in patients with a history of a mental disorder, and divorced patients were more likely to develop a psychiatric condition (Merikangas *et al,* 1985; Krohnmuller *et al.,* 2011. The adherence to treatment can also be affected by marital status with married men shown to be less likely to adhere to antidepressant treatment because of the common side effect of sexual dysfunction (Segrave and Balon, 2014).There is evidence of an association between marital status, divorce rate and depression. Studies have reported that rates of depression are higher among married women than non-married women (Gove, 1972). Some studies have found that

there is an association between marital status and the types of antidepressant prescribed with people who are married being more likely to be prescribed an SSRI (Bauer *et al,* 2008; Serna *et al,* 2010).

2.8 Antidepressant costing

The cost involved in treating depression has often been a topic of interest among researchers as well (Pan *et al,* 2014; Sado *et al,* 2009; Greenberg *et al,* 2003) . There has been considerable debate, since the introduction of SSRIs as first-line treatment for depression, regarding the cost-effectiveness of SSRIs and TCAs (Kennedy, 2006). Even though SSRIs are considered as a major innovation in psychopharmacology with improved safety, there are still on-going investigations comparing the current treatment to the older and cheaper TCAs. These investigations have an impact on clinical practice as well as the way in which antidepressants are prescribed.

A study conducted in 2009 aimed at comparing the cost effectiveness of a combination of cognitive behavioural therapy and antidepressant therapy versus antidepressant therapy alone (Sado *et al,* 2009). The cost effectiveness had been assessed by determining the incremental cost-effectiveness ratio (ICER) per successfully treated patient and then the ICER per quality-adjusted life years (QALYs). The study had found that the combined therapy had led to an increase in the rate of successfully treated patients, QALY of severe depression and QALY of moderate depression by 0.15, 0.08 and 0.04 respectively. The ICER per successfully treated patient was JPY (Japanese Yen) 140 418, the ICER per QALY of severe depression was JPY 268 550 and the ICER per QALY of moderate depression was JPY 537 100 (Sado *et al,* 2009).

A study conducted in the Netherlands aimed at determining the cost-effectiveness of escitalopram in major depressive disorder. This study found that escitalopram is associated with a cost saving of €263 per patient when compared with venlafaxine (Nuijten *et al,* 2012). A recent study in Taiwan aimed at determining which of the antidepressant drug groups were more cost effective at treating depression as well as the impact of comorbid cardiovascular disease on the economic evaluations of antidepressants. The study had found that compared to TCAs and SNRIs, SSRIs were the most cost-effective option as shown by the incremental cost-effectiveness ratios (Pan *et al,* 2014). Although TCAs are relatively cheaper, one study has

shown that the total health care costs for patients on antidepressants were lower or the same for patients on SSRIs as compared to the cheaper antidepressants (Frank *et al,* 2001).

Thus far, there have been no studies conducted in the public health sector of South Africa that reveal the cost of treating a patient with antidepressants, neither as recent study which compare the cost effectiveness of antidepressant therapy. A US based study showed that the amount of money spent on SSRIs increased as well from $ 64,444,222 in 1991 to 1,502,742,579 in 2005. This could be due to an increase in the population however an exponential increase such as that could mostly be attributed to an increase in antidepressant prescribing as well as the shift from older TCA prescribing to increased use in SSRIs. The expenditure on TCAs increased from $ 77,747,994 in 1991 to $ 188,851,359 in 2001 but then decreased to $ 46,237,742 in 2005. In accordance with the drastic increase in the use of other antidepressants as shown with the number of prescriptions, the expenditure increased from $ 17,184,228 in 1991 to $ 688,814,186 in 2005 (Chen *et al,* 2008).

The cost of depression spans to much more than just the direct cost associated with medication but also include the cost of hospitalization, counseling and loss of productivity at work. The direct and indirect costs in the US have risen from $77.4 billion in 1990 to $83.1 billion in 2000 (Greenberg *et al,* 2003). Thought the initial costs do seem substantial, the increase within that time period can also be attributed to the growth of the population which therefore reflects as an increase in the number of people using the antidepressants. In Europe costs related to mood disorders (including depression) have been estimated at €114.4 billion, half of which is attributed to the indirect cost, with sick leave contributing for a large amount of these (Gustavsson *et al,* 2011).

Chapter Summary

The burden of depression is prevalent not only in the US and Europe but also in South Africa. The prescribing of antidepressant has changed over time, with some antidepressants now being favored more than others. Drug utilization reviews have been done worldwide to measure the extent to which these antidepressants are prescribed as well as the patient demographics to which these drugs are frequently prescribed to. Health care in South Africa is divided into two sectors, namely the private and public sector. To measure the way in which antidepressants are prescribed, a retrospective drug utilization review had been done using data from the public sector.

Chapter Three: More about depression and its treatment (Background Information)

3.1 Depression

Depression is a psychiatric disorder that has become increasingly common in South Africa (Van Schalwyk and Truter, 2010). In terms of years lost to disability, depression is described as the most disabling medical condition, and it has been projected that by 2030, depression will become the highest contributor to the worldwide burden of disease (WHO, 2008). The characteristics of depression in a patient are a profoundly negative view of the future, themselves and the world as well as a decreased response to previously pleasurable events; it is this negative view of the world that has been related to negative effects in interpretation, memory and attention (Mathews and MacLeod, 2005). The typical symptoms of depression include anhedonia, constant depressed mood, slowed reaction time, poor concentration and memory, appetite disturbance which can result in weight change, loss of libido, sexual dysfunction, non-localized pain, low energy, inappropriate guilt, worthlessness, suicidal ideation, , altered sleep patterns and daytime fatigue (Naismith *et al,* 2012). The average suicide attempts among depressed patients is shown to be 180 – 400 per 100 000 as opposed to the 10 – 25 per 100 000 average among non-depressed patients (Unverir *et al,* 2006). Depression is regarded as a very serious condition, it is not to be underestimated with an estimated lifetime prevalence of 20% and large amount of patients (30%) who do not show any kind of response to treatment (Pederson *et al,* 2008).

3.1.1 Prevalence of depression

The burden of mental disorders is one that is ever increasing in all regions of the world, neuropsychiatric disorders now contribute around 14% of the global burden of disease (Prince *et al,* 2007). Within the coming decades, depression has been projected to become the second leading cause of disability worldwide and the leading cause of disability in first world countries such as the US (Mathers and Loncar, 2006). In New Zealand, the prevalence of depression increased 35% over a period of 5 years (Read *et al,* 2015). In the UK prescriptions for antidepressants increased by 10% each year between 1998 and 2010 (Illyas and Moncrieff, 2012). The World Health Organisation study of the Global Burden of Disease estimates that by the year 2020, the resultant disability from depressive illness will be second only to

cardiovascular disease (Murray and Lopez, 1997). In a European study which surveyed data for the European union plus Iceland, Norway and Switzerland showed that depression has been estimated to affect 6.99% of the population 14 years and older therefore affecring 30.3 million people per year, making depression rank number 1 for Disability Adjusted Life years lost (Wittchen *et al,* 2011). Depression is also found to be present in children with a prevalence of 0.4% to 2.5% in primary school children, and from 0.4% to 8.3% in adolescents (Birmaher *et al,* 1996). In line with the international patterns of depression, the lifetime prevalence of major depression in South Africa is estimated at 9.7% (Tomlinson *et al,* 2009). With regard to the disease burden in South Africa, neuropsychiatric conditions rank third in their contribution to the burden of disease, after human immunodeficiency virus/ acquired immune deficiency syndrome (HIV/AIDS) and other infectious diseases (Lund *et al,* 2010).

An epidemiological study conducted between 2002 and 2004 revealed that the prevalence of a major depressive episode in South Africans was 9.8% for a lifetime and 4.9% for within the past 12 months (Tomlinson *et al,* 2009). It has also been shown that 16.5% of South Africans suffer from either severe anxiety or depression and 43% of people with HIV across provinces presented with a mental disorder (Williams et al, 2007). Studies that have been conducted in rural areas have found a prevalence rate of the symptoms of depression to be 18% and a rate of depression of 27% whilst urban areas are found to have a prevalence of depression of 25.2% (Tomlinson et al, 2009).

Depression has been shown to be twice as likely to occur in women as in men (Rihmer and Angst, 2008). As shown in a number of other studies, there are more female patients receiving antidepressant therapy than males. Other antidepressant drug utilization reviews that have used patient information from countries in Europe have reported the same findings where there had been more than 65% of the entire patient population consisting of females (Bauer *et al,* 2008) (Aarts *et al,* 2014) (Serna *et al,* 2010). The same has been shown in the United States, only more so, with a 70% of the patient population on antidepressant therapy being females (Lin *et al,* 2011). The higher prevalence of depression in females than males can be directly linked to this as it is known that depression has been shown to be twice as likely to occur in women as in men (Rihmer and Angst, 2008). This is largely so when the patient population has a variation of age ranges. There have been deviations in the proportion of male to female when younger age groups of children and adolescents had been studied for the off-label use of antidepressants, where the proportions are almost equal (Dorks *et al,* 2013).

3.1.2 Psychobiology of depression

Stress has often been associated with the onset of depression. The vulnerability of individuals to psychiatric disorders such as depression varies greatly. The diathesis/stress model helps to understand this variability by considering issues such as vulnerability (the diathesis) and precipitation (the stress) (Monroe and Simons, 1991). This model shows that as an increase in the diathesis occurs, there is a lower level of stress needed to precipitate an episode of depression and the occurrence of an episode of depression itself increases the diathesis for episodes that may occur in the future (Willner *et al,* 2012).

The diathesis can occur in numerous different ways and at a variety of stages within the life cycle that can render an individual more likely to have a depressive episode. Many adverse early life experiences have been shown to cause an increase in the risk of depression (Slavich *et al*, 2011). Psychological, psychosocial and biological processes contribute to the mechanism by which these early life experiences increase the risk of developing depression through conversion of these traumatic experiences into long-term vulnerabilities (Slavich *et al*, 2011). This is shown as absent or poor care by parents or loss of a parent which leads to lowered self-esteem and emotional instability, this in turn leads to a lowered ability to form close relationships, thereby minimizing the quality of social support available, a factor that is considered a vulnerability to depression (Schoenfelder *et al*, 2011).

Methods of processing information are also determined by these early life experiences for example, the negative thinking pattern that is always found in depressed patients often reflects a negative cognitive system that is acquired through adverse experiences in childhood such as criticism, having a depressed parent and rejection (Willner *et al,* 2012). There is also an increased potential for beginning a depressive episode among individuals who have experienced a major adverse life event such as bereavement or it can also be attributed to a combination minor events such as poverty, family conflict, unemployment, chronic illness or even unwanted pregnancies (Farmer and McGuffin, 2003).

Another factor which reflects early life experiences but is also inheritable is personality factors that combines with both social and cognitive factors to contribute to the development of depression (Compass *et al*, 2004). Neuroticism, a personality factor, is the strongest risk factor

for depression and greatly influences the effect of genetics and early life experiences on chronic depressive symptoms (Kendler and Gardner, 2011).

3.1.3 Effect of stress

The hypothalamic pituitary adrenal (HPA) axis is a major physiological system that is activated as a result of stress. This physiological system involves the release of corticotropin releasing hormone (CRH) from the paraventricular nucleus within the hypothalamus which causes the production of adrenocorticotrophic hormone (ACTH) from the pituitary gland, this stimulates the release of the glucocorticoid, cortisol, from the adrenal cortex into circulation (Holsboer and Ising, 2010). The release of cortisol has a negative feedback effect on the hypothalamus that helps to control the activation of the HPA axis. The amygdala as well as descending pathways from the forebrain relays emotional stimuli to the HPA axis, as a result this has a stimulatory effect (Willner *et al,* 2012). An inhibitory control of the HPA axis is exerted by the hippocampus through a negative feedback loop whereby cortisol is used to inhibit the HPA axis (Holsboer and Ising, 2010).

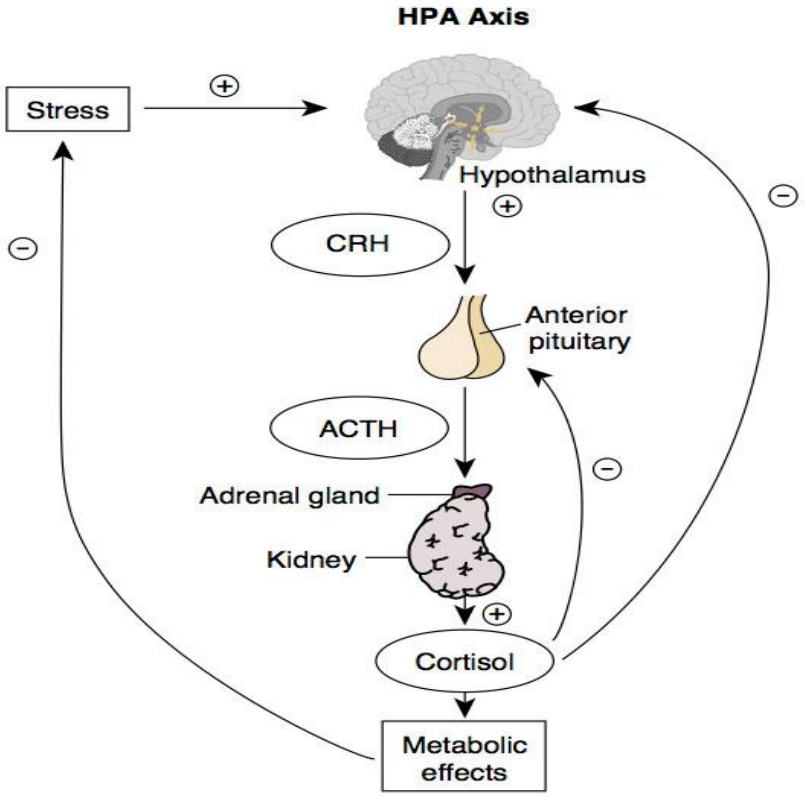


Fig 3.1: The effect of stress on the HPA axis is shown as it stimulates the release of CRH from the hypothalamus. As a result, ACTH is released from the anterior pituitary which causes the adrenal gland to secrete cortisol, the release of which has its own metabolic effects and has a negative feedback effect to inhibit the release of CRH (Holsboer and Ising, 2010).

As a result of persistent stress, chronic exposure to cortisol can be neurotoxic, this is because it leads to a loss of sensitivity of the glucocorticoid receptor (GR) which further causes increases in cortisol through the lack of an inhibitory effect on the HPA axis (Willner *et al,* 2012). If the loss of GR sensitivity persists, the hyper-stimulatory effects on the HPA axis can have severe effects such as production of neurotoxic free radicals as a result of hyperactivity of calcium-dependant enzymes, decreased production of brain derived neurotrophic factor (BDNF) and a lowered transport of glucose into the cell which results in a loss of energy capacity (Willner et al, 2012). The evidence of a decrease in BDNF levels during chronic exposure to stress is shown by a study which found decreased BDNF in the hippocampus of patients who had committed suicide (Karege *et al,* 2005).

One of the main effects that chronic exposure to cortisol had been found to cause is an increase in the activity of MOA-A, an enzyme which causes the breakdown of the monoamines NA and 5HT, thereby causing a decrease in these neurotransmitters (Willner et al, 2012). This is further proven by neuroimaging studies which found an increased MAO-A activity in the brains of

depressed patients (Meyer, 2012). These findings help to further augment the theory of decreased levels of 5HT and NA in depressed patients. Among these changes caused by chronic exposure to glucocorticoids are the neurochemical and structural changes that occur in the hippocampus and closely resemble that of depressed patients (Willner et al, 2012). Chronic exposure to high levels of glucocorticoids can also cause damage to other areas of the brain such as the prefrontal cortex in addition to the damage caused to the hippocampus (Willner et al, 2012).

Prolonged exposure to stress and elevated levels of cortisol has also been linked to the anhedonia that depressed patients' experience. Anhedonia is the inability to experience pleasure and is a core symptom of depression. This symptom has been associated with a lowered activity in the mesolimbic dopamine (DA) projection from projection from the ventral tegmental area (VTA) of the midbrain to the nucleus accumbens (Treadway and Zald, 2011).

CRH has been shown in a recent study to cause a release of DA from the nucleus accumbens which results in a rewarding effect however, after exposure to severe stress, CRH can no longer cause the release of DA instead now has an aversive effect (Lemos et al, 2012). In a similar manner to the other symptoms of depression, anhedonia may also be linked to a decrease in the hippocampal activity.

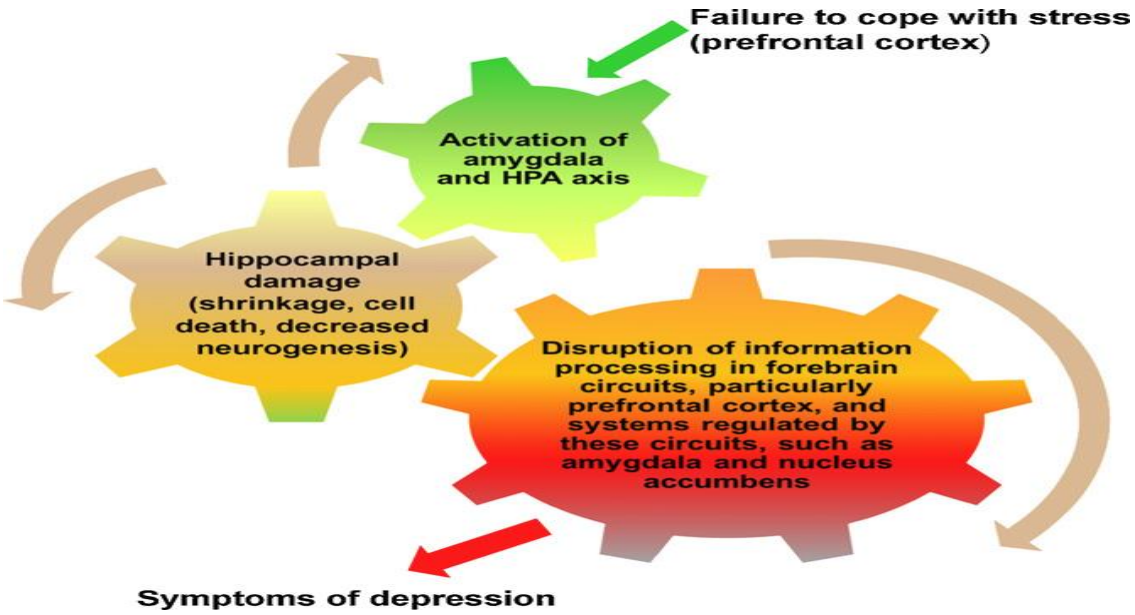


Fig 3.2: Stress plays a role in the aetiology of depression through the effects of HPA axis hyperactivity which leads to hippocampal damage. This damage further leads to a disruption in the manner in which information is processed in the forebrain, these disruptions leads to the types of symptoms that are then displayed (Willner *et al,* 2013).

3.1.4 Adverse events in childhood related to depression

There has been a large amount of research which has shown that adverse events during childhood such as sexual, physical and verbal abuse as well as exposure to foster care are major factors that can contribute to the aetiology of depression in individuals later in life (Mersky *et al,* 2013; Widom *et al,* 2007; Dube *et al,* 2010). Within this theory of depression which focuses on early childhood stressors, there are two hypotheses which are used to explain the variation of depression within these patients (Riolo *et al,* 2005). The first is the differential exposure hypothesis which states that the variation in mental health outcomes is due to the different types of exposure to stressors. This model of stress means that women have more symptoms of depression than men because they experience more stressful events and of a different kind than that of men (Turner and Avison, 2003). The differential vulnerability hypothesis states that at the same amount of exposure there is a variation between individuals in the impact of exposure in depression which is largely due to factors of the individual which

renders them more or less vulnerable (Turner and Avison, 2003). This basically means that women may be more depressed than men because the same type of events has a greater effect on women and are more potent stressors for women.

The effects of physical assault and physical abuse in childhood on the well-being of an adult has been well documented with these studies showing that this form of abuse has been associated with increased risk of anxiety, substance abuse, depression and mental illness with a greater likelihood for the conviction of violent offenses (Roxburgh and MacArthur, 2014). With regard to foster care, there is less known about the relation between depression and the lack of a stable parenting system. There are theories which suggest that the best way to understand the effect that foster care has on an individual in later life is due to factors such as neglect, parental substance abuse, unstable living arrangement and multiple transitions between care takers which thereby increase the likelihood of poor outcomes in later life such as depression (Herrenkohl *et al,* 2013). This kind of finding has also been supported by another study which had shown that for over 60% of eighteen year old individuals who had been transitioning from foster homes to adulthood had been exposed to at least one traumatic event, the most common of which had been sexual abuse (Courtney *et al,* 2011). These traumatic events contributes to the increasing vulnerability of a patient to depression (Turner and Avison, 2003).

3.1.5 Neurobiology of depression

The monoamine neurotransmitters noradrenalin (NA), serotonin (5-HT) and dopamine (DA) facilitate transmission in neural pathways that originate in the brainstem have numerous ascending projections to the limbic system and cortex as well as descending projections to the autonomic nervous system (Nutt, 2002). Aspects of behavioural function which includes mood and anxiety are controlled by these pathways. A deficiency of monoamines has been implicated by early theories in the physiology of depression This is largely evident because drugs that facilitate the release of monoamine (e.g. amphetamine) had been found to be show antidepressant action , while drugs that inhibit the release of monoamine (e.g. reserpine) show depressive symptoms in patients after administration (Nash and Nutt, 2007).

Post-mortem evidence in which neuroendocrine and neuroimaging studies have been conducted showed that depression is associated with abnormalities of postsynaptic monoamine

receptor function; some antidepressants have direct actions on these receptors (Nutt, 2002). Numerous clinical and preclinical studies indicate that a disturbance in serotonergic activity may be associated with major depression. Noradrenergic and dopaminergic neurotransmission has also been implicated (Artigas, 2015).

3.1.6 Monoaminergic role in depression

Throughout the years of investigation about the root cause of major depression, it is still believed that a lack of function and hypo activity of the monoaminergic system have been assumed to be the cause of the symptoms of depression. This assumption had mainly been based on the observation that antidepressant drugs increase the activity and thus the function of monoaminergic systems, in particular serotonin and norepinephrine (Artigas, 2015). One common charactersitic of these ascending monoaminergic systems is that their cell bodies are found in the brainstem and that their activity is strictly regulated by the prefrontal cortex (PFC), a cortical area where metabolic abnormalities have been reported in depressive patients.

Therefore, the locus coeruleus, the raphe nuclei and the ventral tegmental area, where the cell bodies of ascending noradrenergic, serotonergic and dopaminergic neurons are found, respectively, receive dense afferents from dorsal and ventral parts of the medial prefrontal cortex in rodents, which are equivalent to dorsal and ventral cingulate areas in primate and human brain (Groenewegen and Uylings, 2000).

Electrophysiological studies have shown that the activity of monoaminergic neurons is tightly regulated by these descending afferents via direct (e.g., monosynaptic) or indirect (via local interneurons) inputs (Jodo *et al,* 1998). Therefore, metabolic changes in the anterior subgenual cingulate can affect the functional relationships between limbic and cortical areas, a change that has been shown to lead to the depressive illness (Seminowicz *et al*, 2004). The metabolic changes in ventral cingulate areas can often cause a functional hypoactivity of the ascending monoamine systems that can as well add to the depressive symptoms, given the involvement of monoamines in mood, anxiety, affect, cognition, sexual drive, sleep. The treatment with antidepressant drugs would restore monoamine function in cortical and limbic areas, thus improving depressive symptoms.

3.1.7 Serotonin relation in depression and treatment

Physiological and anatomical characteristics of 5-HT neurons are relevant for the action of antidepressants; the same points of action are often shared with noradrenergic neurons. The release of serotonin and serotonergic activity in the forebrain is a very strictly controlled process, which is regulated by a number of pre-synaptic and post synaptic mechanisms which have been refined through the years of human development to keep a tonic and regular activity of the serotonin neurons (Artigas, 2015). This demonstrates that when antidepressants aim at increasing the amount of serotonin released, it interferes with the homeostasis of the serotonergic system thus activating self-adaptive systems and mechanisms that limit the full working potential of the antidepressant (Wong *et al,* 2008).

Extensive research has been dedicated to the investigation of the way in which different 5-HT receptors can have an influence in the treatment and pathophysiology of major depression. There has been interest into this particular receptor as researchers are trying to find novel ways in which antidepressant treatment can be enhanced by bypassing or breaking the adaptive mechanisms to cause a greater and increase in extracellular serotonin. Among all the serotonin receptors that have been studied, the one that is shown to be of most interest is the 5-HT1A receptor. This is mainly because the 5-HT1A receptor abnormalities have been found in patients with major depression thus have been a target for numerous antidepressants. With this in mind, it is then clear to understand why many post-mortem and genetic studies have revealed that patients with a higher level or activity of the 5-HT1A autoreceptors are much more susceptible to mood disorders and also have displayed a poor response to antidepressant treatment (Lemonde *et al,* 2003). To support this finding, it has been proven that a lowered 5-HT1A receptor binding potential has been found in patients with major depression that have recovered compared to control subjects, this has in turn caused the belief that suggests that low 5-HT1A receptor density may give rise to vulnerability to major depression (Bhagwagar *et al*, 2004).

When an SSRI or SNRI is administered, the excess serotonin activates somatodendritic 5-HT1A autoreceptors and hyperpolarizes 5-HT neurons which therefore oppose the incoming excitatory inputs (Artigas, 2015). In this way, antidepressants cause an over-activation of this physiological feedback mechanism by having a greatly increased extracellular amount of serotonin in the

raphe nuclei, which is the region that contains the greatest amount of serotonin transport systems in the brain, therefore this causes a decrease in serotonergic activity and release of serotonin in the forebrain. With this finding, there are currently numerous researchers that are investigating ways in which the autoreceptor can be antagonised so that antidepressant effect can be enhanced.

Another serotonergic receptor that has become of great interest to researcher is the 5-HT2A receptor. It has been widely documented that a number of antidepressants and antipsychotic drugs bind with a high affinity to this receptor, thus showing the potential that this receptor has to play an important role in depression (Artigas, 2015). There have been numerous clinical studies which suggest that atypical antipsychotic drugs have increased the clinical response to SSRIs in treatment resistant patients (Carvalho *et al,* 2009). As a new discovery, it has been made known that 5-HT3 receptor antagonism or receptor blockage had the ability to potentiate the increase of extracellular serotonin produced by the SSRI citalopram in the rat (Mork *et al,* 2012). Also, it has been shown that administration of an agonist of serotonin in the rat brain modifies key markers that are considered to be important in depression which enhanced phosphorylation of CREB protein and neurogenesis in the hippocampus (Lucas *et al,* 2007).

3.1.8 Use of antipsychotics in the treatment of depression

There have been a number of studies which have shown that there is a beneficial effect to adding on an atypical antipsychotic drug to current treatment with an antidepressant. This is particularly evident in treatment with SSRIs that is found in drug resistant depression. Although antidepressant therapy is found to initially alleviate and decrease the symptoms of depression in many patients, only 50 to 60% of patients with major depression show a positive response to antidepressant treatment (Rogoz, 2013). These atypical antipsychotics are olanzapine, ariprizole, ziprasidone, quetiapine and risperidone. These are agents that have been found to potentiate the effects of antidepressants (Wright *et al,* 2013). Atypical antipsychotics have the potentiating effect on antidepressants by binding to serotonin receptors with a greater affinity than dopamine receptors; they also bind to histamine receptors and adrenergic ones as well with ariprazole showing an strong tendency to show activity at 5-HT1A receptors (Jordan *et al,* 2002).

3.1.9 Social opinions on depression

The common belief among the public regarding mental health problems have often being a subject of interest. This is largely because of the relationship to stigma about recovery. Mental disorders such as psychosis, schizophrenia and depression have often been related to increased stigma in the community as well as the decreased expectation of recovery (Read *et al,* 2014). The common view of the public, which has proven to be quite resilient, is that the treatment of depression should rather consist of a psycho-social treatment over a bio-genetic or pharmacological treatment approach (Hughes *et al,* 2011). In Germany, it has been a common belief that “brain disease” as a cause of depression increased from 25% to 38% between 1993 to 2001, with a slight increase from 37% to 40% for “hereditary” causes, “partnership problems” and “work stress” had been identified far more frequently recognised with increases of 73% to 81% and 75% to 80% respectively (Angermeyer *et al,* 2013). A study in Sweden had shown that 69% of depressed patients recognised current life stressors, mostly from work and family, and life events of the past (32%) as the main cause of their depression (Hannsson *et al,* 2010). A similar study in Austria has shown the belief in “inherited or genetic” increased from 49% in 1995 to 65% in 2011, where they had regarded “day to day problems” and “death of a close friend and relative” and “problems in childhood” as one of the greatest causes for depression (Pilkington *et al,* 2013). Studies have shown that depressed patients were much likely to label psychosocial stress as the cause of depression compared to the opinion of non-depressed patients and that patients who had received treatment for depression had a greater likelihood than non-depressed patients to label conditions of socialisation such as adverse childhood occurrences and less likely to label biological factors as the cause of depression (Mnich *et al,* 2014). Depressed patients were however more likely to blame psychosocial stressors rather than biological or genetic factors but to a lesser extent, compared to the general population, as the cause of their depression (Pilkington *et al,* 2013). This means that depressed patients have a greater recognition for the role of biological factors than that of the general public.

3.2 Diagnosis and Treatment of depression

A diagnosis of depression is made using as set of criteria known as the Diagnostic and Statistical Manual of Mental Disorders (APA, 2013). This manual helps to classify the different types of depression for a targeted approach to therapy.

3.2.1 Major depressive disorder

DSM-V Criteria for Major Depressive Disorder (MDD) includes a depressed mood or a loss of interest or pleasure in daily activities for more than two weeks, impaired social, occupational, educational function. At least 5 out of 9 of the symptoms below should persist almost daily. These symptoms include:

1. Daily depressed mood or irritability for a majority of the day

2. Decreased pleasure or interest in numerous daily activities

3. Change in appetite that has led to significant weight change (5%)

4. Insomnia or hypersomnia

5. Psychomotor retardation or agitation

6. Fatigue and loss of energy

7. Inappropriate guilt or feelings of worthlessness

8. Decreased cognitive ability showing lower ability to think or concentrate as well as more indecisiveness

9. Suicidality, constant thoughts of death or suicide (APA, 2013)

3.2.2 Dysthymic disorder

Dysthymic disorder is a persistent depressive disorder with the same physical and cognitive symptoms of depression that is less severe but longer lasting. The DSM-V manual represents a diagnosis for dysthymic disorder in the following way:

The diagnosis is made if a patient has experienced a depressed mood for a majority of the day, on a mostly daily basis that continues for a minimum of 2 years. This includes experiencing of 2 or more of the following symptoms that has caused a significant impairment in social or work functioning:

1. Change in appetite.
2. Insomnia or hypersomnia.
3. Decreased energy or fatigue.
4. Lowered self-esteem.
5. Poor concentration or difficulty making decisions.
6. Feelings of hopelessness (APA, 2013).

3.2.3 Substance-Induced Mood Disorder

Substance-induced mood disorder is defined as a constant and noticeable disturbance of mood caused by the direct physiological effect of exposure to a substance. This type of mood disorder is commonly found in patients that are undergoing substance abuse rehabilitation or treatment. The mood disorder can include depressed mood, mania or a mixture (APA, 2013). This disorder has a shorter course than the other depressive illnesses because it only represents itself on withdrawal of a substance or during intoxication of the substance (APA, 2013).

3.2.4 Adjustment Disorder with Depressed Mood

The resultant depressive symptoms in this type of disorder occur due the presence intense emotional or psychological stress. The stressor, that can be a recurring situation or an isolated event, could manifest itself as family disturbances, divorce, career failure or bereavement. Acute adjustment disorder lasts for a number of months but a chronic adjustment disorder can still be present long after the stress has occurred (APA, 2013). The symptoms of this disorder are not

as severe as those of Major depressive disorder and have the same long duration that Dysthymic disorder has (APA, 2013).

3.2.5 Mood Disorder caused by a current Medical Condition

This disorder is characterized by the presence of depressive symptoms that appear to be the direct physiological consequence of a general medical condition. This is a type of depression that is brought about by the presence of a medical condition such as Parkinson's disease or hypothyroidism. The symptoms of this type of depressive disorder include the following:

1. Late onset of depressive symptoms
2. Known underlying medical condition
3. Atypical presentation of a specific psychiatric diagnosis
4. Absence of personal and family history of psychiatric illnesses
5. Illicit substance use
6. Medication use
7. Treatment resistance or unusual response to treatment
8. Sudden onset of mental symptoms
9. Abnormal vital signs (APA, 2013)

Depression can also be present as a primary symptom in other psychiatric conditions such as posttraumatic stress disorder (PTSD), schizoaffective disorder as well as anxiety disorders that include panic disorder, agoraphobia, social phobias and generalized anxiety disorder.

3.3 Treatment

The management of patients is a step-wise process. The following describes the initial recommendations for patient management as stated by the American Psychiatric Association (2010).

1. Establish and maintain a therapeutic alliance- the physician collaborates with the patient in making decisions and considers the patients factors and preferences when deciding upon treatment type.
2. Completion of the psychiatric assessment – a complete patient history is taken which includes a general medical history as well as a psychiatric history that includes mental status examination, family history of mental disorders as well as response to major life events.
3. Evaluation of the safety of the patient – a careful suicide risk evaluation is done of each patient. The risk of the patients harm to themselves or others is evaluated. Suicidal thoughts, attempts, plans are identified as well as any general medical conditions that can increase the tendency to act on suicidal ideas. The patients' level of hydration, self-care and nutrition is also evaluated.
4. Establish the appropriate setting for treatment – a setting that will protect the safety of the patient as well as improve the condition of the patient without being too restrictive.
5. Evaluate quality of life and any functional impairment – the activity of the patient with regard to work, school and family is evaluated as well as the presence of any dysfunction.
6. Collaborate with other health professionals for the care of the patient
7. Monitor the psychiatric status of the patient – the response to treatment is evaluated.
8. Enhance the adherence to treatment.
9. Educate the patient and their family.

3.4 Pharmacotherapy

Antidepressants are recommended as the first choice of treatment for patients with mild to moderate major depressive disorder (APA, 2010). The choice of type on antidepressant is based the individuals patients safety or tolerability to the anticipated side effects. The pharmacological profile (half-life, drug interactions, action on cytochrome P450 enzymes etc) of each of the drugs is also evaluated to suit the patient. Factors such as patient preference and cost are also considered. Selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), bupropion and mirtazapine are usually preferred to the older tricyclic antidepressants (TCAs) (APA, 2010). The response to treatment as well as the emergence of side effects (e.g gastrointestinal symptoms, sedation, insomnia, activation, changes in weight, and cardiovascular, neurological, anticholinergic, or sexual side effects) is regularly monitored to ensure the safety of the patient (APA, 2010). It is recommended that treatment with antidepressants should be commenced and continues to proceed during the acute period which is around the phase of four to eight weeks, this is done in order to achieve remission at a much faster rate in the acute depressive episode. Treatment is then continued for four to five months, this phase is known as the continuation phase and is aimed at keeping the patient in remission. After this continuation phase has been completed, which will equate to at least six months after the treatment had been started, the physician will then decide based on the patients history whether or not the antidepressant treatment should be continued in order to prevent the further occurrences of depressive episodes (Serna *et al,* 2010).

Factors to consider when choosing type of antidepressant treatment:

1. Preference of the patient
2. Half-life which is the time taken for half of the drug to be metabolized in the body
3. Cost of the types of antidepressant considered
4. Response to previous exposure to antidepressant if there had been a previous antidepressant used
5. Relative efficacy and effectiveness of each antidepressant considered
6. Safety, tolerability, and potential side effects

7. Presence of any co-existing psychiatric conditions and general medical conditions
8. Potential drug interactions with any concomitant drugs a patient may be using before commencing treatment with an antidepressant

Factors to monitor during antidepressant treatment:

1. Persistence of symptoms and response to treatment
2. Degree of danger to self and others as well as the potential for suicide
3. Signs of mania
4. Presence of other disorders such as alcoholism and substance abuse
5. General medical conditions
6. Quality of life
7. Presence of any side effects to treatment
8. Patient adherence

3.5 Electroconvulsive therapy

Electroconvulsive therapy (ECT) is used to treat patients that are non-responsive to pharmacologic and psychotherapeutic interventions, also in patients with severe major depressive disorder and those with impaired functioning who have not responded to various types of medication (APA, 2010). This type of therapy is also used in patients who have shown catatonic or psychotic symptoms as well as those who have a compromised state of health or are severely suicidal (APA, 2013)

3.6 Psychotherapy

This type of treatment is initially recommended for patients with mild to moderate major depressive disorder. Patients with a presence of interpersonal difficulties or significant psychosocial stressors are more likely to have psychotherapy (APA, 2010). In order to assess patients response to treatment and safety, psychotherapy treated patients is monitored regularly (APA, 2010). In Denmark, 55% of patients with major depression had been treated with antidepressants only or in combination with psychotherapy (15%) whilst some patients (30%) were receiving psychotherapy alone (OECD, 2012). Individual patient factors such as symptom severity, goals and type of therapy, presence of social supports as well as co-operation with treatment are considered when deciding upon the frequency of patient visits (APA, 2010)

3.7 Antidepressant treatment

The first antidepressants to be discovered were the inhibitor of serotonin and noradrenaline reuptake, imipramine and the monoamine oxidase inhibitor iproniazid. The use of these antidepressants together with electroconvulsive therapy has contributed to a therapeutic process which led to the sharp decline of the number of depressed patients being kept in psychiatric facilities (Vetulani and Nalepa, 2000). Since the discovery of these initial drugs, new compounds with a similar mechanism of action have been synthesised leading to great progress in the attempts of improving antidepressant therapy.

Irreversible monoamine oxidase inhibitors that blocked the action of both the monoamine oxidase A and B isoforms were used initially but were later replaced by selectively irreversible drugs such as the monoamine oxidase A inhibitor clorgyline or the monoamine oxidase B inhibitor selegeline however these drugs have been replaced by a reversible monoamine oxidase inhibitor moclobemide (Kennedy, 2006).

In addition to these improvements in drug therapy, there has been a considerable amount of progress with the monoamine reuptake inhibitors. The tricyclic antidepressants such as imipramine and amitriptyline which inhibited the reuptake of noradrenaline and serotonin as well as acting as antagonists at the Alpha-1, Histamine-1 and muscarinic receptors and were the initial choice of treatment had been largely replaced by more selective drugs with less side effects. These drugs are the selective serotonin re-uptake inhibitors (SSRIs) such as fluoxetine

as well as the serotonin (5HT) and noradrenaline (NA) reuptake inhibitors (SNRIs) such as venlafaxine.

3.7.1 Early theories on antidepressant action

The monoamine hypothesis of depression states that there is a single mechanism for the physiology of depression as well as antidepressant therapy, this mechanism shows that depression occurs as a result of decreased functioning in 5HT and/or NA which is normalised by antidepressants (Willner *et al,* 2012). To further prove this theory, studies in which monoamine had been depleted in patients consistently showed vital need for functional monoaminergic pathways to combat depression; with all currently available treatments aimed at restoring compromised monoamine functioning (Delgado, 2000; Millan *et al*, 2000; Pacher et al, 2001). The monoamines have been implicated in the aetiology of depression based upon the antidepressant effects shown by hydrazine derivatives such as iproniazid.

3.7.2 Antidepressant drugs mechanism of action

Irreversible monoamine oxidase inhibitors (MAOIs) exert their effect through blockage of the enzymes responsible for degradation of monoamines. Though these enzymes have proven to be effective, they are poorly tolerated because of their side effects instead; reversible monoamine oxidase inhibitors are preferred because of their better safety margins and tolerability (Millan, 2004). There has been considerable debate as to the actual mechanism of action of antidepressants on monoamines however, studies in which neurotransmitter depletion had been done showed compelling evidence that indeed the mechanism of action of antidepressant is as conceived, enhancement of 5HT and NA neurotransmission (Willner *et al,* 2012). Though various classes of antidepressants exert their effects through different ways, there are some common characteristics that these drugs share. The first mechanism being that all antidepressants make use of monoamine systems through their interaction with either the catabolic enzymes, receptors or transporters for monoamine reuptake (Millan, 2004). Also, all antidepressants act as multi-target agents by acting on numerous receptors in order to increase monoamine concentrations.

Tricyclic antidepressants (TCAs) such as imipramine and amitriptyline exert their effects by blocking the re-uptake of NA and 5-HT however, due to their indiscriminate target profiles; these drugs also antagonise α1-adrenoceptors, muscarinic receptors, and histaminergic receptors, as well as cardiac ion channels (Schatzberg, 2002). It is this multi target action that gives the TCA group of antidepressants their poor tolerability profile. The safest class of antidepressant drugs (ADs) is currently the SSRIs, although this class also has a spectrum of side effects, they have proven to be better tolerated than TCAs and MAOIs (Millan, 2004).

Despite their superior safety, SSRIs are not as effective as TCAs; they still are the preferred choice of AD treatment in long term depressive states (Millan, 2004). The selectivity of SSRIs had been considered the reason for the lower efficacy, this theory led to the development of venlafaxine, a serotonin and noradrenaline re-uptake inhibitor (SNRI) (Schatzberg, 2002). SNRIs are considered to be more effective than SSRI with a rapid activity even though they share the same side effects of SSRIs (Millan, 2004).

With the use of antidepressants, there is a delay of 3-4 weeks to reach therapeutic efficacy which has proven to be unavoidable and there is still much debate as to whether or not these drugs can provide rapid but sustained relief from depression (Wong and Licinio, 2004).

Although rapid elevations in extracellular levels of monoamines are induced by antidepressants, the lag in efficacy is shown to be due to the initiation of neuro plastic events which can include neurogenesis, alteration of neuronal architecture, modifications in receptor density and intracellular signalling and changes in synaptic transmission as well as architecture (Manji *et al,* 2003).

Transcription factors such as cAMP-responsive element binding protein, effector immediate early genes such as Arc, neurotrophins like brain derived neurotrophic factor (BDNF) and anti-apoptopic proteins such as bcl-2 are the mediators that have been linked to the ability which antidepressants have to increase neuronal proliferation and resilience as well as the ability to combat changes caused chronic stress and excessive cortisol secretion (Wong and Licinio, 2004). Neuronal plasticity as well as cellular models of G-protein/receptor coupling has proven to be important factors that contribute to the characterisation of novel antidepressants (Milllan, 2004). The current limitations of SSRI/SNRI treatments most likely derive from the poor knowledge of the pathophysiology of major depression, in common with other psychiatric disorders (Artigas, 2015).

All antidepressants take at least two weeks before any sort of improvement can be seen. With some cases it may take up to eight weeks. Even though the clinical therapeutic effects take time before their benefits can be seen, the side effects can be experience immediately. This often leads to a decrease in compliancy among patients starting their treatment for the first time.

3.7.2.1 Fluoxetine and Citalopram

Fluoxetine is an SSRI that is primarily prescribed for conditions such as depression, obsessive-compulsive disorders, and Bulimia nervosa. It is also prescribed for anxiety disorders, particularly generalized anxiety disorders, anxiety and impulse control disorders (Rossiter *et al*, 2010). Fluoxetine is the first choice of SSRI when prescribed to children or adolescents. It has to be used with caution in the elderly, patients with hepatic or renal impairment and diabetic patients. Elderly patients have been shown to be more susceptible to experience the CNS side effects such as agitation, nervousness and excessive sedation. In paediatric patients, fluoxetine is shown to be effective in the treatment of depression from the age of seven years old. They should however be used with caution in paediatrics due to the fact that all antidepressants have an increased risk of suicide in children. Fluoxetine should also be used with caution in pregnant patients because of the risk of premature birth. When used in conjunction with other serotonergic agents, its been shown to increase the risk of serotonin syndrome which shows itself as pyrexia, restlessness, agitation, rigidity and gastrointestinal symptoms. The most common side effects are nausea, weight gain, increased appetite, confusion, chest pains, palpitations and hypertension (Rossiter *et al*, 2010). One of the main differences between fluoxetine and citalopram is that fluoxetine has a longer half-life (3 days) than all other SSRIs whereas citalopram has a lower potential for interaction with other drugs. Fluoxetine is an inhibitor of the enzyme CYP2D6 which makes it prone to a number of drug interactions when compared to citalopram. Some of the drugs that need to be monitored when used in conjunction with fluoxetine include diazepam, warfarin, lithium and carbamazepine.

Citalopram has been favored for use over amitriptyline due to its better safety profile. It has little anticholinergic effects as well as less cardiotoxicity (Rossiter *et al*, 2010). It has a considerably lesser half life than that of fluoxetine (36 hours). Citalopram is a weak inhibitor of cytochrome P450 therefore has less drug interactions. The S-enantiomer of citalopram is known as escitalopram which is also a frequently prescribed antidepressant.

3.7.2.2.Venlafaxine

Venlafaxine is a serotonin and noradrenaline re-uptake inhibitor (SNRI) which also acts as a weak dopamine re-uptake inhibitor. It is mainly used for the treatment of major depression and generalised anxiety disorders. It is contra-indicated for use in paediatrics mostly because the risk to benefit ratio in patients under the age of 18 had not been established. The most common side effects are that of a CNS origin, these include headache, insomnia, dizziness, nervousness, visual disturbance and somnolence. Venlafaxine is also shown to cause gastrointestinal effects such as dry mouth, anorexia, constipation, nausea and vomiting. It is also shown to cause sexual dysfunction, a side effect which has been shown to decrease patient compliance. The cardiovascular side effects are hypertension, palpitations, postural hypotension and tachycardia (SAMF, 2010). The sexual dysfunction caused by venlafaxine is often associated with a lack in adherence (Segrave and Ballon, 2014).

3.7.3 Genetic factors that predict response to treatment

Genetic factors play a very important role in determining the type of clinical response to antidepressant drugs, which is then manifested as the behavioural changes noted by physicians as progress. Overall, these genetic factors add a further element of complexity to the already complex neurobiological elements involved in the clinical response to SSRI and SNRI. Polymorphisms of the promoter region of the Serotonin transport system (SERT) have shown to be responsible for susceptibility to major depression as well as response to antidepressant therapy (Collier *et al*, 1996). A better response to treatment with SSRIs has been associated with heterozygotes and homozygotes of the long variant compared to homozygotes of the short variant (Zanardi *et al,* 2000).

Single nucleotide polymorphisms in 5-HT related genes such as the previously mention SERT and tryptophan hydroxylase 1 also show a relationship with antidepressant treatment response (Peters *et al,* 2004). Increased functioning and expression of 5-HT1a receptors resulting from the G (-1019) polymorphism in the promoter region leads also to increased risk for depression, poor antidepressant response and suicide (Lemonde *et al,* 2003). Likewise, catecholamine-related genes have also been associated to antidepressant response. Phosphodiesterase

genes involved in amine signalling pathways and polymorphisms of the KCNK2 gene are often associated with a greater susceptibility to major depression and antidepressant response, these also have been associated with treatment resistance (Wong et al, 2006). Numerous amounts of SNPs in the BDNF gene have been identified, with one of them that have been associated with major depression and antidepressant response.

Polymorphisms of a glucocorticoid receptor related gene known as FKPB5 have also been involved in antidepressant response and recurrence of depressive episodes (Binder *et al,* 2004). Also, polymorphisms associated with inflammatory- related genes have also been found to be associated with susceptibility to depression and response to treatment (Wong *et al,* 2008). As expected due to their mechanism of action, clinical response to SNRIs and SSRIs is also influenced by genes that are not linked to monoaminergic neurotransmission (Uhr *et al,* 2008). Thus, polymorphisms of ABCB1, which is involved in drug transport across the blood-brain barrier, have an influence on the brain concentrations of antidepressant drugs thus determine the response to treatment (Uhr *et al,* 2008).

3.8 Controversies in antidepressant therapy

Over the past few years, there has been considerable debate as to the efficacy of antidepressants compared to placebo. In 2008, Irving Kirsch and colleagues published a meta-analysis which stated that for a majority of patients, the difference in clinical improvement between the SSRI antidepressant drug and placebo was not significant. However, despite increased compliance, new drugs did not surpass the efficacy of some tricyclic drugs such as clomipramine (Danish University Antidepressant Group, 1986, 1990). He stated that their data does indicate a small advantage for drug over placebo that is statistically significant only for major depressive disorder but had no effect on Moderate depression (Kirsch, 2008).The results of the meta-analysis showed that patients with moderate depression receiving placebo recovered just as well as the patients receiving medication did. This brought into question the efficacy of antidepressants, which have been used for over fifty years prior to the publishing of this meta-analysis. From the results of the meta-analysis, Kirsch concluded that SSRIs offer no advantage over placebo, antidepressants do not affect the long term outcome of depression and suicide, and that current recommendations on antidepressant prescribing should be reconsidered due to their benefits compared to risks.

There have been clinical trials with a chosen sample patients population that have shown remission and response rates of 40% and 60% respectively when treated with the standard antidepressant drugs which includes SSRIs and TCAs (Tollefson and Holman, 1994; Thase *et al*, 2001). In contrast to this finding however, naturalistic studies such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) show a bleaker result that is less promising with remission and response rates of 30% and 50% respectively after treatment with citalopram (Artigas, 2015). The results of this finding from real patients have indicated that a large amount of patients that have been diagnosed with depression that are receiving standard antidepressant therapy have just showed partial responses therefore, these patients require further treatment with lithium, atypical antipsychotics or additional treatment such as electroconvulsive therapy (Carvalho *et al*, 2009; Mayberg *et al*, 2005). One of the most well known limitations antidepressant therapy is that their clinical action is slow to show an effect on the patient. This often raises doubt as to their efficacy among patients thus causing a decrease in patient compliance. The efficacy figures shown above is that which is typically shown in 6 to 8 week periods, this is when antidepressant drugs begin to show a difference from placebo treatment.

In contrast, it has been shown that 39% of patients do reach remission (defined as a score of ≤7 on the Hamilton Rating Scale for Depression or ≤10 on the Montgomery–˚Asberg Depression Rating Scale) after eight weeks of antidepressant therapy (Kennedy, 2006). Another study showed that all antidepressants were superior to placebo regardless of the outcome measures applied (Delini-Stula *et al,* 1995). Compared to placebo, TCAs have been found to have a greater efficacy in the short term treatment of major depression (Storosum *et al*, 2001).

Antidepressants were also shown to have a greater effect on moderate and severe depression than placebo did (Vöhringer and Ghaemi, 2011). However, though the effect that antidepressants have on depression is evident, a lot of consideration has to be given to the risk to benefit ratio of using them. Antidepressants commonly carry the risk of developing side effects such as sedation, apathy, fatigue, weight gain, nausea and sexual dysfunction along with the beneficial therapeutic effects.

Chapter Summary

The etiology of depression is a topic that has been investigated for decades. The causes have often been linked chemical imbalances within the brain. Diagnosis of depression is made based on certain criteria from a manual known as the DSM-V. Treatment of depression is not only dependant on drugs in the form of antidepressants but also on therapeutic sessions with a psychiatrist. Drugs used in the treatment of depression have been developed following years of research into finding novel ways to treat the condition. The different classes have different modes of action. The three main classes used are SSRIs, SNRIs and TCAs.

Chapter Four: Method

4.1 Study Site

The Charlotte Maxeke Johannesburg Academic hospital (CMJAH) has a specialized out-patient psychiatric clinic which operates on a Wednesday and Friday. The psychiatric out-patient clinic at the hospital was purposively selected from all public sector academic sites in Gauteng since at this clinic there is an adequate patient load to provide sufficient prescriptions for the study. This clinic offers treatment to patient with numerous psychiatric disorders such as MDD, Bipolar disorder, psychosis, anxiety disorders and schizophrenia. Approximately 100 patients attend this clinic per week of which 40 are patients that are being treated for anxiety or depressive disorders. The orderly functioning of the clinic by appointment as well as the records of patients being treated by the psychiatric out-patient clinic been kept on site had allowed for convenient collection of the data from the records. Patient records from January 2011 to September 2014 were included in the study. All the patient records that were used were of patients who were currently attending the clinic for treatment. The inclusion criteria was:

- Patients were over the age of 18 years
- Attended the clinic for treatment
- Received prescriptions for antidepressants

No patients receiving antidepressant therapy were excluded from the study.

4.2 Sample Size

Prior to obtaining the permission from the CEO, a sample size had to be calculated. For the purposes of this study, the required sample size of 1535 prescriptions was calculated (Epi-Info version 7), using a confidence level of 99% and a confidence interval of 0.025. A sample size was calculated to determine the number of prescriptions it was necessary to survey in order to produce results sufficiently powered to derive conclusions. Patients who had been visiting the clinic for treatment of MDD and GAD were included to measure the use of antidepressants. All other records had been excluded.

$$ss = \frac{Z^2 \times (p) \times (1-p)}{c^2}$$

$$ss = \frac{2.58 \times 0.5 \times (1-0.5)}{0.025}$$

Where:

Z = Z value eg 1.96 for 95% confidence interval

P = percentage picking a choice, expressed as a decimal (0.5 used for sample size needed)

C = confidence interval, expressed as a decimal

4.3 Ethics

Permission to use patient records was also obtained from the head of the unit as well as the CEO of the hospital (Appendix B)

Permission to conduct the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M130654) (Appendix A).

The Ethics committee approved the study in the condition that the identity of the patients used will be protected as a part of respecting their privacy. The patients' anonymity was protected by using unique study specific patient numbers instead of patient names. No patient names were recorded on the case report forms, only study patient numbers. The links between study generated (coded) data and identifiable (patient) data was kept in a password protected file on a computer located in the department of pharmacology, with access only to the researcher and supervisor.

4.4 Data collection

The clinic makes use of an appointment book which is used to maintain order of appointments with between the doctors on duty and the patients. The patient numbers of patients attending the clinic for depression and anxiety were obtained using this book. Patient numbers were

chosen according to the ICD code. Patients with a diagnosis of anxiety, MDD and a mixed diagnosis were purposively chosen. The following ICD codes that were included are in Appendix D.

Each ICD code had been included in the file, either alone or in combination. All patients using antidepressants had been included in the study. Concomitant drugs captured to provide a more complete picture of drug usage of patients.

Once the files were obtained, the information of each prescription in the patient file was then recorded on the data collection sheet. In order to reach the calculated sample size of 1536 prescriptions, it was necessary to record prescription data from January 2011. Information that was extracted from records:

- Date of prescription
- Race
- Gender
- Age
- Marital status
- Employment status
- ICD-10 Code (diagnostic notes)
- Drug name
- Drug dose
- Dosage instructions
- Concomitant drug information

4.5 Data Analysis

Data abstracted on to case report forms was then captured on a purpose-designed spread sheet using Microsoft Excel 2010. The DDD of each indication for which each antidepressant is prescribed was tabulated according to the literature and the actual PDD of each prescription was calculated and compared with the DDD. Each dose of every antidepressant used was recorded. In order to get the PDD of each antidepressant had been calculated as the average of

each antidepressant prescribed. This was then compared with the international guidelines of the DDD.

For the purposes of this study, the statistical analysis program STATA version 13 was used. The data had then been analyzed according to the objectives which had been set. The patient demographics were the first variables to be analyzed. Data was coded (as per appendix 3) and loaded into the programme. Chi-squared tests were run to see if there were any statistically significant associations between patient variables and type of antidepressant chosen.

In order to describe the characteristics of the patient population, descriptive statistics such as means, frequency of use, frequency tables, proportions and ratios were used. When operating on the data statistically, confidence level of 99%, a confidence interval of 0.025 were used and the p-value was considered significant if less than 0.05.

Logistic regression was used to determine variance between antidepressant prescribed, demographic factors as well as the duration of treatment. This was also done to determine if there is an association between diagnoses. All of these tests were recommended by a statistician according to previous drug utilization reviews which had used the same tests to measure the use of antidepressants.

4.6 Costing

The Pharmacy tariff is applied when medicines are dispensed based on a prescription. The charge for a medicine is comprised of the itemized cost as well as the facility fee that is levied per prescription. All of these items on the national tender are included in the list of charges that is circulated by the department of health. The facility fee is fixed according to the level of the facility. In the case of the Charlotte Maxeke Johannesburg Academic Hospital, every consultation is charged at R40.00, this fee is inclusive of the pharmacy tariff.

All medicine costing in South Africa are controlled through the single exit price (SEP) mechanism which lists the only price that a medicine can be charged at. The cost of treating a patient with antidepressants can be measured using the prescription data obtained then calculating the cost using the single exit pricing and the pharmacy tariff as listed by the

department of health and released on specific dates (SA, 2009). In the public sector, the medicine is priced according to the contract price which is awarded by a tender.

The number of tablets used, taking dose into consideration, was multiplied by the date-appropriate single exit price to derive a unit cost. In South Africa, the single exit price (SEP) is the maximum price which a medicine is allowed to be charged at. In the public sector, medication is priced according to the contact price by which a company supplies the medicine based on a tender contract. Prices of each antidepressant were used according to prices from invoices in the pharmacy. The prices used was from the year 2014 and had been used as a guideline for the pricing of the study period.

Chapter Summary

The study site and methods used to conduct the retrospective drug utilization review had been stated. The costing of each antidepressant was calculated according to the tender price list.

Chapter Five: Results

5.1 Patient Demographics

5.1.1 Gender

At the Charlotte Maxeke Johannesburg Academic hospital, patient prescriptions were recorded from January 2011 till September 2014. The total number of patients being treated with antidepressants at the psychiatric out-patient department, during that time, was 135. The total number of prescriptions that were recorded and analyzed was 1606. The patient population consisted of 41 male (30.3%) and 94 female patients (69.7%).

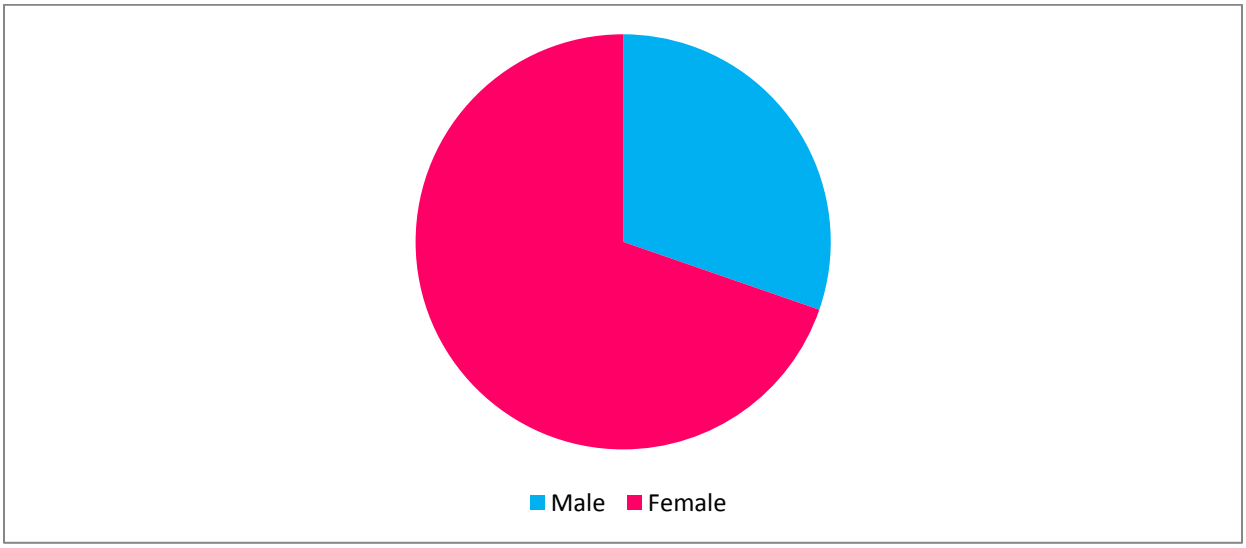


Figure 5.1.1: Gender composition of the patient population The patient population which consists of 69.70% female and 30.30% male patients.

The proportion of males to females was 1: 2.3 (standard error= 0.40), with a 99% confidence interval [0.57, 0.77] for females and [0.22, 0.43] for males. This means that for each patient that visited the facility, there had been more than twice that number who were females.

5.1.2 Patient Ethnicity

The population consisted of various ethnicities of which 35.70% (N=48) were Black, 10.30% (N=14) were Colored, 13.30% (N=18) were Indian and 40.70% (N=55) of which were White.

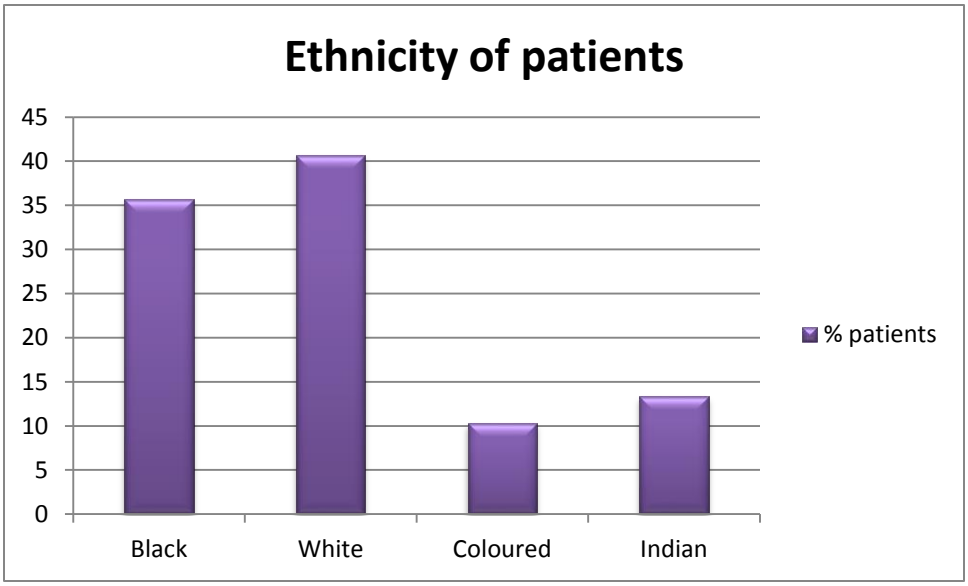


Figure 5.1.2: Ethnicity composition of this group of patients. The patient population consisted of mostly of White patients (40.70% followed by Black patients (35.70%) the Indian (13.30%) and Colored (10.30%).

5.1.3 Ethnicity and gender

The number of black male and female patients had been nearly equal with white patients having been composed of more females than males. For coloured and Indian patients, there had been more males than female patients.

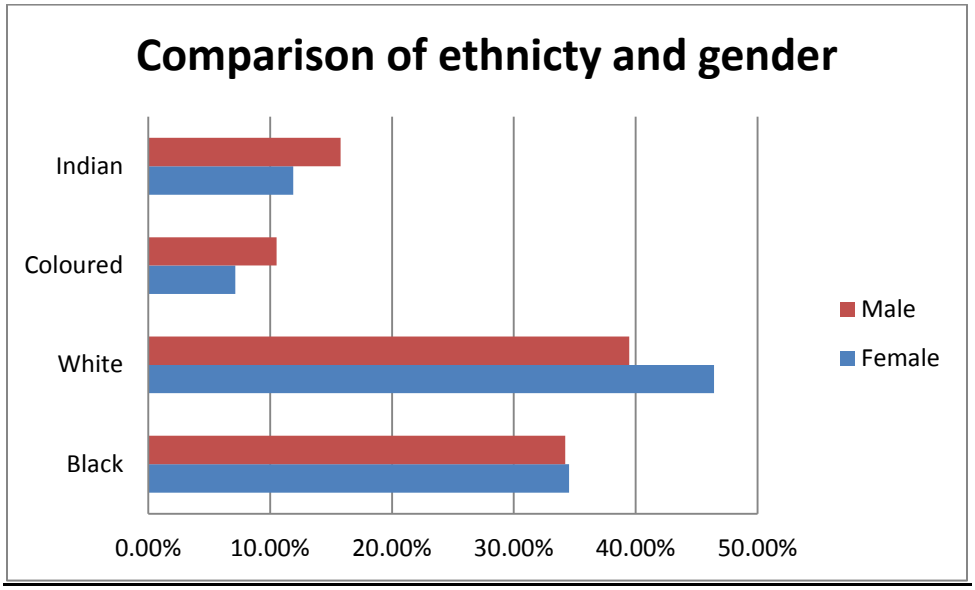


Figure 5.1.3: The comparison of ethnicity and gender. A comparison of the various ethnic groups with gender shows there were higher amounts of female patients for white and black groups whilst there were more males in the coloured and Indian groups.

5.1.4 Age

The average age of all the patients was 50.16 years (SD= 16.32). The sample patient population had consisted of 1.48% of patients who were under the age of 20 years. More than two thirds of this population was adults whose ages had ranged from 20 to 59, with a contribution of 71.30% of the total patient sample group. Patients aged 60 and over formed the remainder of the patient population with 27.22%. The patients were grouped into the three major

age groups in order to compare the use of antidepressants across various patients. By dividing the ages into three main groups, it allows for a clear comparison to be made between young adults and adolescents that are grouped as under 20s, adults and the elderly, since these age stratifications may have translated to clinical consequences with prescribing preferences.

Table 5.1.1:Percentage of patients according to age groups. . The age groups are divided into the three main categories namely under 20, 20-59 and 60 and over to compare the use between each major phase of life

Age Groups	Percentage (%)
under 20	1.48
20-59	71.30
60 and over	27.22

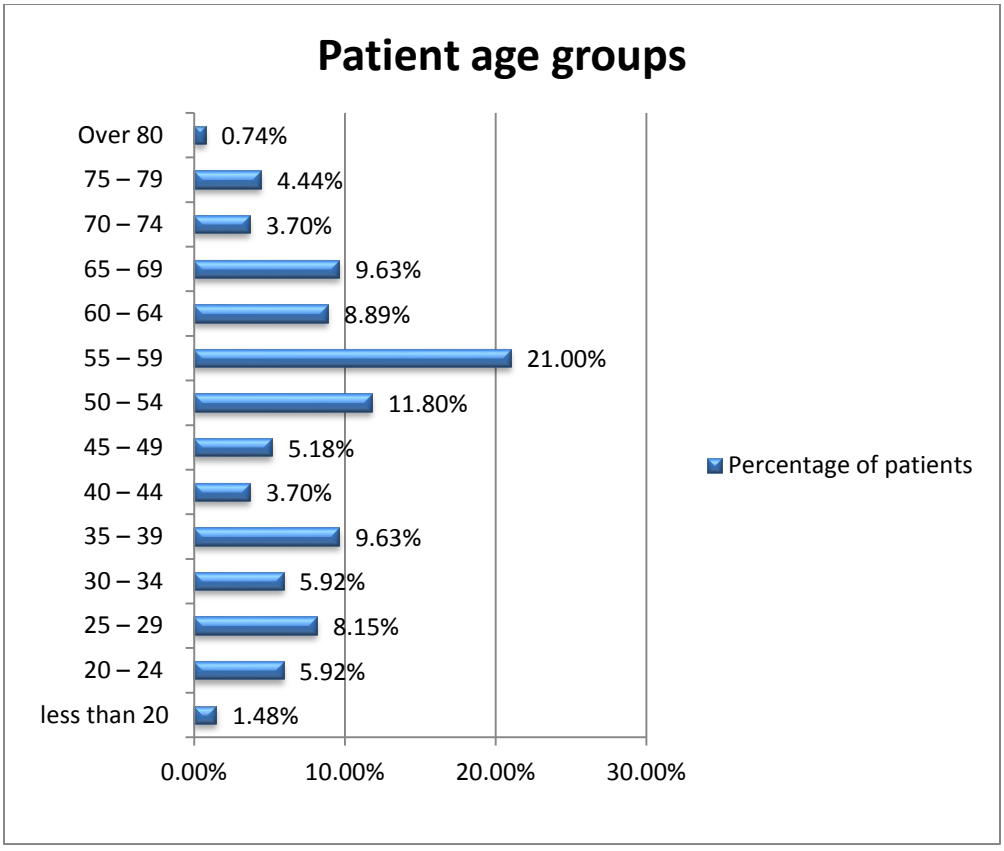


Figure 5.1.4: grouping of patients according to age intervals. The amount of patients in each age group is represented showing the 55-59 age group as the one with the most amount of patients.

The big category of ages 20-59 was divided into smaller categorical age groups in order to refine the usage statistics and potentially identify any prescribing patterns.

The majority of patients were aged between 55-59 followed by patients aged between 50 and 54 (21,00% and 11.80% respectively).

5.1.4.1 Age and gender comparison

For patients aged 20-30, there had been a higher percentage of males compared to females. The same trend had followed in the 31-40 age group. However, there had been a higher percentage of females in the 51-60 age groups as well as the over 60 age group.

Table 5.1.2: a gender comparison is shown across the various age groups.

Age groups	Female	Male
Under 20	2.38%	0.00%
20-30	11.90%	26.31%
31-40	14.28%	18.42%
41-50	9.52%	10.52%
51-60	34.52%	23.68%
Over 60	27.38%	21.05%

5.1.5 Employment status

As a part of the patient demographic, the employment status of patients was also recorded. Unemployed patients consisted of 50.40% of the patient population whilst only 23.70% of patients were employed and the remainder was pensioners (25.90%).

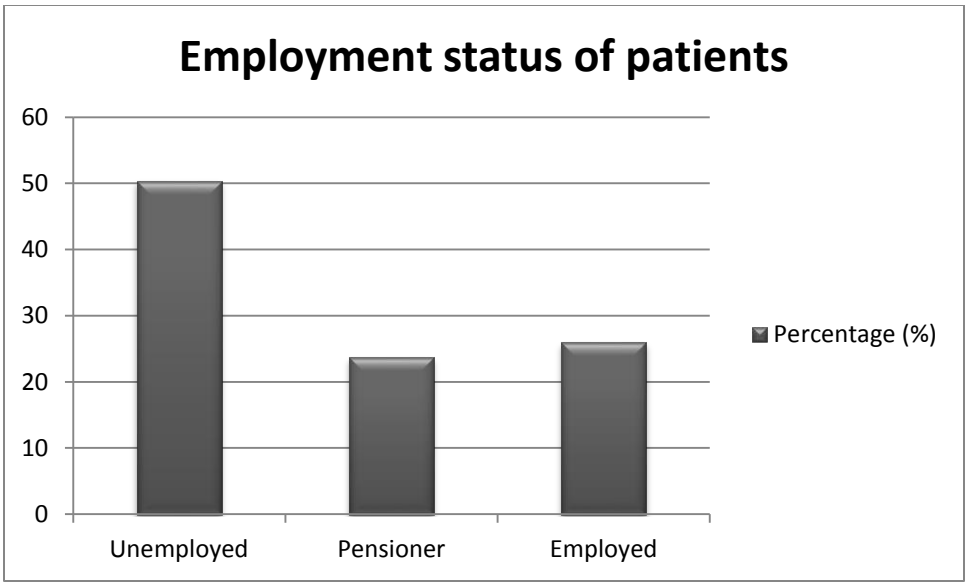


Figure 5.1.5: The patient population as divided with regard to employment status. The employment status of the patient population is shown with most as the patients listed as unemployed.

The employment status was recorded according to the information recorded on the patients file. It had not taken into account part time workers or those with informal employment, it was simply recorded on the basis of whether the patient considered themselves employed or not at the time of the study.

5.1.6 Marital Status

The marital status of patients was also recorded as a part of the patient demographics. Married patients consisted of 54.81% of the sample whilst single, widowed or divorced patients were 45.19%.

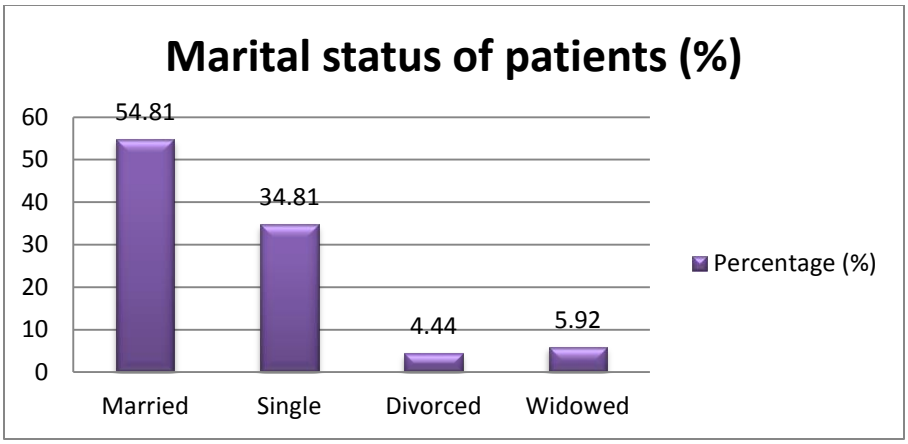


Figure 5.1.6: Marital status of the patient population. Patients, who are single, divorced or widowed shown as being less than the married patients.

5.1.6.1 Marital status and gender comparison

The percentages of female and male patients who are married and single were relatively similar for both groups.

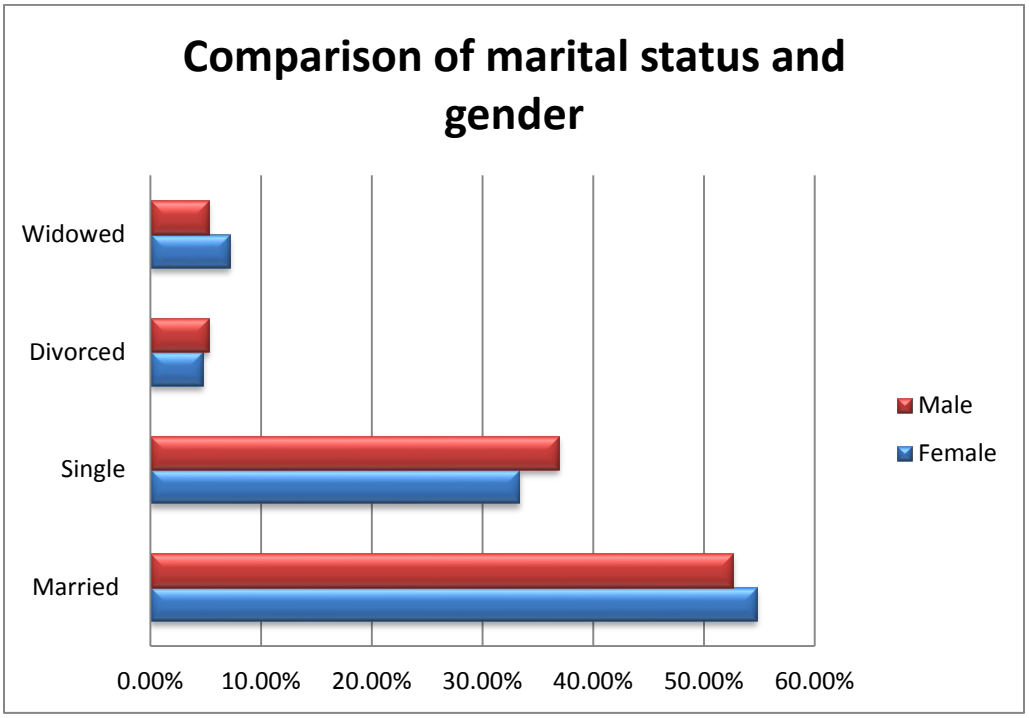


Figure 5.1.7: Marital status and gender comparison. Married female patients were the largest group to have received a prescription for antidepressants.

5.2 Diagnosis

Of the 135 patients attending the psychiatric out- patient clinic, the ICD 10 codes which are used when identifying the patients' diagnosis had been recorded. More than half of the patients had been diagnosed with major depressive disorder or MDD (62.29%). Second to this had been patients with generalized anxiety disorder (GAD). Patients who had also been receiving treatment for a bipolar mood disorder had also been receiving antidepressant therapy (11.48%). Mild depression and MDD with psychotic features were the least present diagnosis (0.82% and 4.92% respectively).

Table 5.2.1: Percentage of patients with each represented diagnosis. Most patients had been diagnosed with major depressive disorder (MDD) followed by MDD with features of a generalized anxiety disorder (GAD), the least common diagnosed disorder had been that of mild depression.

Diagnosis	Percentage of patients (%)	99% confidence interval
MDD	62.29	0.45-0.67
GAD	14.75	0.07-0.23
MDD and psychosis	4.92	0.01-0.12
Mild depression	0.82	0.005-0.94
MDD and epilepsy	5.74	0.02-0.13
MDD and Bipolar disorder	11.48	0.05-0.19

5.2.1 Diagnosis and antidepressant use

The type of antidepressant prescribed had been shown to have been influenced significantly by the ICD 10 code or diagnosis ($p<0.0001$) as shown in a Pearson Chi-squared test.

Table 5.2.2: Diagnosis and antidepressant prescribed. The diagnosis of a patient had an association with the type of antidepressants prescribed. The use of the three groups of antidepressants is shown in relation to the diagnosis made.

Diagnosis	Fluoxetine (N)	Citalopram (N)	Venlafaxine (N)
MDD	11	40	25
GAD	3	10	5
MDD and psychosis	3	1	2
Mild depression	0	0	1
MDD and epilepsy	2	4	1
MDD and Bipolar disorder	3	8	3
Total	22	63	37

5.2.2 Diagnosis and patient factors

The types of patient factors that may influence the diagnosis had been analysed using the chi squared test to determine if there had been any statistically significant relationship. The patient demographic which correlated with the diagnosis was race (p=0.008). This was determined using the Pearson chi-squared test.

Table 5.2.3: Comparison of diagnosis and ethnicity. When comparing the diagnosis among the ethnic groups represented in the study, it is shown that white patients were more frequently diagnosed with MDD and Bipolar disorder than any other group whilst black and Indian patients mostly received antidepressants for MDD.

Diagnosis	Black	White	Coloured	Indian
MDD	31	27	4	14
GAD	6	9	2	1
MDD and psychosis	1	4	1	0
Mild depression	0	0	1	0
MDD and epilepsy	3	3	0	1
MDD and Bipolar disorder	1	11	2	0

Pearson chi^2 (18)= 35.48; p= 0.008

Of the total of 1606 prescriptions which had been the repeats for the 135 patients, 672 had been for citalopram, 560 had been made for venlafaxine, 259 for fluoxetine. The mean dose for each antidepressant is shown in section 5.3.

Chi-squared tests

```
. tabulate ICD AD, chi2
```

ICD	AD 1	2	3	4	Total
1	11	40	25	0	76
1.2	3	10	5	0	18
1.3	3	1	2	0	6
1.5	0	0	1	0	1
1.6	2	4	1	0	7
4	3	8	3	0	14
7	0	0	0	13	13
Total	22	63	37	13	135

```
          Pearson chi2(18) = 145.5831   Pr = 0.000
```

```
. tabulate MSTATUS AD, chi2
```

MSTATUS	AD 1	2	3	4	Total
1	11	31	24	8	74
2	8	29	5	5	47
3	1	1	4	0	6
4	2	2	4	0	8
Total	22	63	37	13	135

```
          Pearson chi2(9) =  16.9539   Pr = 0.049
. tabulate RACE AD, chi2
```

RACE	AD 1	2	3	4	Total
1	10	29	3	8	50
2	8	24	22	1	55
3	1	7	2	2	12
4	3	3	10	2	18
Total	22	63	37	13	135

```
          Pearson chi2(9) =  29.8003   Pr = 0.000
```

```
. tabulate OCCUPATION AD, chi2
```

OCCUPATION	AD 1	2	3	4	Total
1	9	38	17	4	68
2	5	8	14	5	32
3	8	17	6	4	35
Total	22	63	37	13	135

Pearson chi2(6) = 12.7194 Pr = 0.048

5.3 Use of antidepressants

Throughout the duration of the study, there had been three antidepressants that were prescribed. These antidepressants were the SSRIs fluoxetine and citalopram as well as the SNRI venlafaxine.

Table 5.3.1: Dosing of each antidepressant. The frequency (number of prescriptions) of which each antidepressant is prescribed is shown along with the mean dose of each.

Antidepressant	Mean Dose(mg)	Range (mg)	Standard dev.	Frequency
Fluoxetine	35.45	20-60	16.27	259
Citalopram	29.51	20-60	12.37	672
Venlafaxine	239.18	75-300	63.33	560
Total prescriptions				1491

Table 5.3.1.1: The PDD and DDD of each antidepressant.

Antidepressant	PDD(mg)	DDD(mg)
Fluoxetine	35.45	20
Citalopram	29.51	20
Venlafaxine	239.18	150

Of the total patient population, almost half had been prescribed citalopram as their antidepressant (51.61%), followed by venlafaxine (30.33%) then fluoxetine (18.03%).

Table 5.3.2: Amount of each antidepressant prescribed. The most commonly prescribed antidepressant was citalopram.

Antidepressant type	Percentage (%)	CI - 99%
Fluoxetine	18.03	0.09-0.26
Citalopram	51.64	0.35-0.58
Venlafaxine	30.33	0.18-0.38

5.3.1 Dosing of antidepressants

The most commonly prescribed antidepressant, as mentioned previously, had been citalopram. The 20mg form of this drug had been the most frequently prescribed dose. Eventhough venlafaxine had been prescribed to a lesser extent, the 225mg form of the drug had been as widely prescribed as the 40mg dose of citalopram.

Table 5.3.3: Antidepressants with their respective doses and the percentage of patients on each antidepressant. The dose of each antidepressant prescribed is shown along with the percentage of patients to which these antidepressants were prescribed, the most common of which being the 20mg citalopram.

Antidepressant	Dose	Patients using AD (%)
Fluoxetine	20mg	8.19%
	40mg	5.74%
	60mg	4.09%
Citalopram	10mg	1.64%
	20mg	25.41%
	30mg	7.38%
	40mg	13.11%
	60mg	4.10%
Venlafaxine	75mg	1.64%
	150mg	3.28%
	225mg	13.11%
	300mg	12.29%

5.3.2 Antidepressants and gender

The type of antidepressant used was recorded for the patient population.

Table 5.3.4: Antidepressant and gender comparison. Use of antidepressants across gender groups is shown to compare the most commonly prescribed type with a gender perspective

	Fluoxetine (%)	Citalopram (%)	Venlafaxine (%)
Male	23.86	44.74	31.57
Female	15.11	53.49	31.40

As shown previously with the total patient population, most males and females had been prescribed citalopram, although it had been prescribed to 12.33% more of the female patients (Males: 44.74%; Females: 53.49%). Fluoxetine was however prescribed to a slightly greater extent to males than females (males: 23.86%; females: 15.11%). With regards to venlafaxine, the prescribing frequency among both males and females had been relatively similar (males: 31.57%; females: 31.40%).

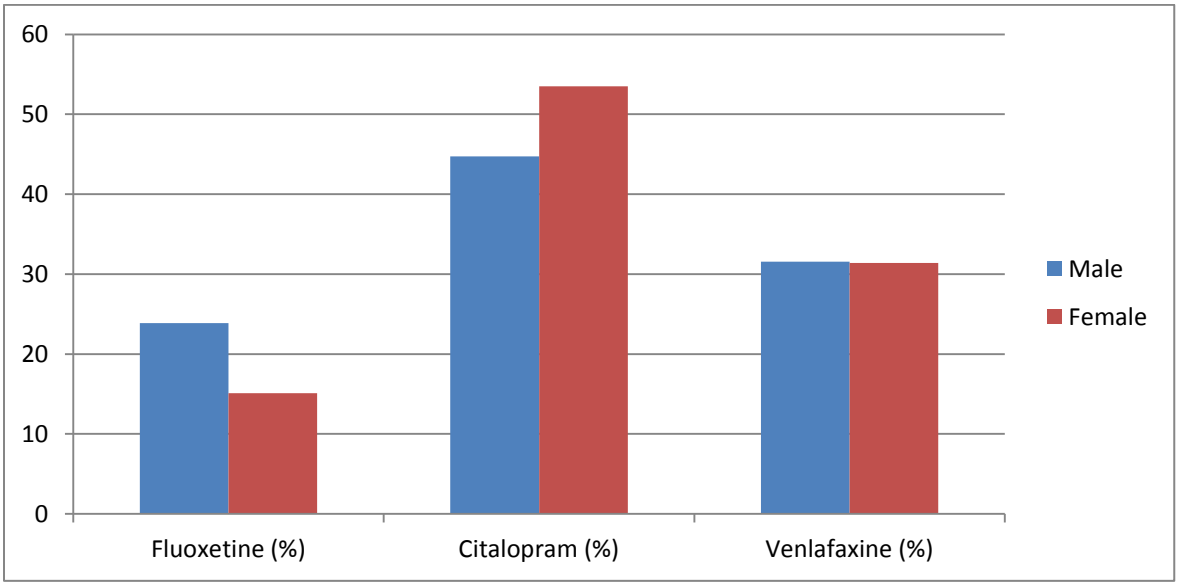


Figure: 5.3.1: Antidepressant use divided by the gender. The graph shows the greater extent to which citalopram and venlafaxine had been prescribed to female patients whilst fluoxetine had been the preferred antidepressant among male patients.

5.3.3 Antidepressant use in various age groups

As previously shown, the preferred choice of antidepressant was the SSRI citalopram. When the various age groups have been considered however, there were some exceptions to the general prescribing practice. Fluoxetine had been used equally to citalopram in the younger than 20 age group. . Within the 20-24 group, a majority had been prescribed citalopram (77.78%) with the remainder of the group having received prescriptions for fluoxetine (22.22%), none of the patients in this group had received venlafaxine. A similar type of pattern is shown in the proceeding 25-29 age group except for an increase in the number of patients on fluoxetine and the addition of venlafaxine which is used for the first time compared to the previous age groups. The same type of pattern of prescribing had followed to the 30-34 and 35-39 age group with citalopram being the drug of choice. In the 40-44 age group, no patients had been prescribed fluoxetine, and interestingly the use of citalopram (40%) had been less than that of venlafaxine (60%). In the 45-49 age group citalopram and venlafaxine had been used in equal amounts (33.33% for all three). The use of citalopram and fluoxetine had been equal in the 65-69 age group with venlafaxine emerging as the drug of choice in these patients. Venlafaxine had been preferred over fluoxetine and citalopram in patients aged above 75.

From the age group 40-44 years and older, the use of venlafaxine had been more frequent than that of fluoxetine, in contrast to the previous age groups where they had either been preferred in nearly equal amounts or fluoxetine had been prescribed more frequently.

Table 5.3.5: Antidepressant use in smaller age groups. The use of each type of antidepressant is shown in the various age groups with intervals of around five years. Citalopram dominates as the most frequently prescribed antidepressant among most age groups with the exception of the 65-69 group where venlafaxine is the common antidepressant.

Age groups	Fluoxetine (%)	Citalopram (%)	Venlafaxine (%)
less than 20	50.00	50.00	-
20 – 24	22.22	77.78	-
25 – 29	27.30	63.80	9.90
30 – 34	14.30	41.40	14.30
35 – 39	25.65	48.70	25.65
40 – 44	-	40.00	60.00
45 – 49	33.33	33.33	33.33
50 – 54	19.05	54.76	26.16
55 – 59	13.09	48.82	38.10
60 – 64	-	63.63	36.36
65 – 69	28.56	28.56	42.88
70 – 74	-	50.00	50.00
0ver 75	25.00	25.00	50.00

Although the Pearson chi squared test had shown that the type of antidepressant chosen is not influenced by patient age ($p=0.810$), the linear regression test had shown that an increase in age is associated with an increase in the use of antidepressants ($b=0.015$; $p<0.001$). The result of the t-test ($t=3.58$) had shown that our co-efficient (0.015) is statistically significant (standard

error=0.04; CI 95%= 0.07-0.24) the older the patient, the more likely they are to be prescribed an antidepressant.

The results of an ordinal logistic regression test of antidepressant and age showed a statistically significant likelihood ratio (LR) of 12.80 and probability (p=0.0003). As shown with the linear regression test, an increase in age is associated with an increase in the use of antidepressants (b=0.36), but to a greater extent than the previous test (SE=0.010; CI 95%= 0.15-0.56).

These tests were done after consultation with a statistician. They were done in order to determine which patient variables are related to the antidepressant prescribed and if there is an association between the two.

5.3.4 Ethnic groups and antidepressant use

The use of antidepressants among the ethnic groups of the patient population were tabulated to show the frequencies to which these antidepressants were prescribed in each group. Citalopram had been the preferred antidepressant in Black, Coloured and White patients (57.14%; 58.30% and 44.00% respectively). Venlafaxine had been prescribed to a much greater extent in the Indian population (55.60%). Fluoxetine had been prescribed more to Black patients than other race group with the same group having Venlafaxine prescribed to the least amount of patients. With Indian patients, an equal amount of patients had been prescribed fluoxetine and citalopram, as mentioned previously, this group had the most patients receiving venlafaxine therapy. In White patients however, an almost equal amount of patients had received citalopram or venlafaxine (44.00% and 40.00% respectively).

The patient race has been shown to vary with the type of antidepressant chosen ($p< 0.0001$)

Pearson chi2 (9)= 29. 80; pr<0.0001

Table 5.3.6: Ethnicity and the type of antidepressant chosen. This has shown to vary with each race group with Indians receiving the most venlafaxine prescriptions blacks being more likely than white or coloured to be prescribed fluoxetine.

Ethnicity	Fluoxetine (%)	Citalopram (%)	Venlafaxine (%)
Black	25.87 (N=10)	62.57 (N=29)	11.55 (N=3)
Coloured	13.86 (N=1)	63.86 (N=7)	22.26 (N=2)
Indian	20.40 (N=3)	20.40 (N=3)	59.30 (N=10)
White	14.77 (N=8)	44.62 (N=24)	40.61 (N=22)

In addition to having an influence on the antidepressant prescribed as well as the diagnosis as mentioned previously, the patient race also has been found to correlate with the dose prescribed (p= 0.004).

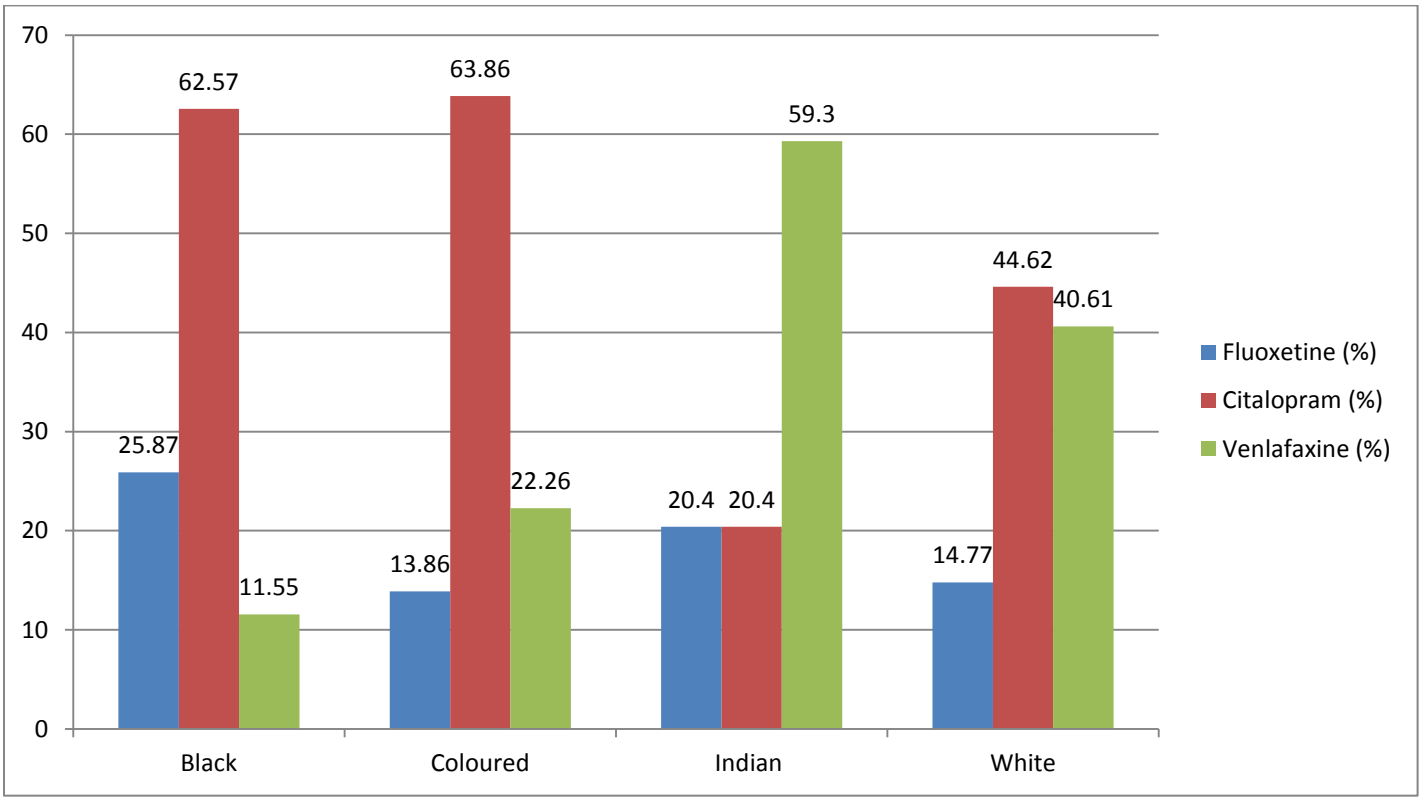


Figure 5.3.3: The use of antidepressants with the ethnic groups. The use of antidepressants among the four ethnic groups is shown to have varied greatly. Citalopram had

been the preferred choice of antidepressant for all races except Indians to whom venlafaxine had been prescribed to more patients.

An ordinal logistic regression test showed that race had a statistically significant relationship with a likelihood ratio of 5.45 and a p value of 0.01. The coefficient was 0.38 (SE=.0165; CI 95% 0.06-0.70).

5.3.5 Employment factors in antidepressant use

As part of the patient demographics factors such as their employment status had been recorded to help try and understand the various types of patient factors that may have an influence on the type of antidepressant chosen. The three groups which the patient population had been divided into were employed, unemployed (which included housewives and students) and pensioners.

With employed patients, citalopram had been the most frequently prescribed (52.40%) followed by fluoxetine (26.66%) then venlafaxine (20.94%). With regard to unemployed patients, who had formed a majority of the patient population, as with the employed counterparts, citalopram had been the most frequently prescribed drug but to a greater extent of 57.86% compared to the 52.40% of employed patients. In the unemployed group of patients, the second most frequently prescribed drug was venlafaxine (26.96%) followed by fluoxetine (15.19%). The trend of prescribing had deviated slightly with pensioners. In this group, the majority of patients had been prescribed venlafaxine (43.95%), in contrast to the previous two groups for which citalopram had been the most frequently prescribed. For pensioners however, the second most frequently prescribed drug in this population had been citalopram (25.00%).

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Pearson chi2 (6)=12.71; Pr = 0.049

When the chi squared test had been performed on this data set, it had shown that there was a correlation between employment status and antidepressant type that is prescribed.

Table 5.3.7: Employment status and antidepressant prescribed. The employment status of each patient is considered along with the type of antidepressant prescribed

Employment	Fluoxetine (%)	Citalopram (%)	Venlafaxine (%)
Employed	26.66 (N=8)	52.40 (N=17)	20.94 (N=6)
Unemployed	15.19 (N=9)	57.86 (N=38)	26.96 (N=17)
Pensioners	20.84 (N=5)	30.21 (N=8)	48.95 (N=14)

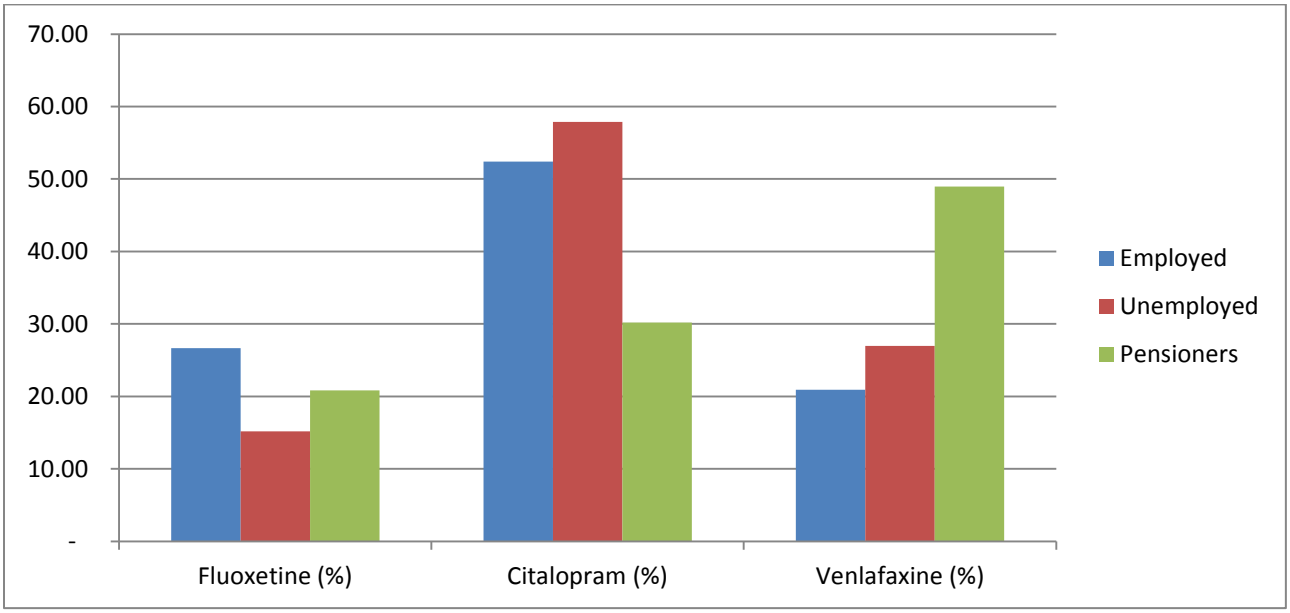


Figure: 5.3.4: Graph comparison of antidepressant prescribed and employment status. The prescribing pattern when the patient employment status had been considered showed venlafaxine had been the preferred drug when prescribing to pensioners (43.74%) whilst fluoxetine had been preferred after citalopram in employed patients.

5.3.6 Antidepressant use related to marital status

Marital status had also been used to identify is this type of patient demographic has an influence on the type of antidepressant prescribed. As previously mentioned, a majority of patients were married at the time of data collection followed by patients who considered themselves as single. In married patients, the most frequently prescribed antidepressant was citalopram (45.49%) followed by venlafaxine (36.42%) and then fluoxetine (18.49%). Single patients had a slightly different pattern of prescribing with citalopram being prescribed to a greater extent (65.24%) in this group, followed by fluoxetine (20.56%). Patients who had identified themselves as divorcees had been prescribed venlafaxine (66.66%) more frequently than any other drug. Within this group of patients, fluoxetine and citalopram had been prescribed in equal amounts. Patients who had experienced the death of their spouse had also been prescribed venlafaxine more frequently (50.00%) with fluoxetine and citalopram used equally in these patients.

The type of antidepressant chosen was shown to be influenced by the marital status of the patient (p= 0.048)

Pearson chi2 (9)= 16.95; pr= 0.048

Table 5.3.8: Marital status and antidepressant prescribed. A comparison of the use of antidepressants with the marital status of a patient showed varied prescribing patterns, single patients had included patients who considered themselves as single as well as divorced or widowed patients. It shows the high preference of citalopram to a greater extent in single patients.

Marital status	Fluoxetine (%)	Citalopram (%)	Venlafaxine (%)
Married	18.49 (N=11)	45.49 (N=31)	36.42 (N=24)
Single	20.56 (N=8)	65.24 (N=29)	14.18 (N=5)
Divorced	16.67 (N=1)	16.67 (N=1)	66.66 (N=4)
Widowed	25.00 (N=2)	25.00 (N=2)	50.00 (N=4)

5.4 Concomitant drug use

The use of concomitant drugs has also been measured. The most commonly prescribed agents are anti-epileptic agents but can be used as anxiolytic and mood stabilizers. Among the other drugs that had been prescribed simultaneously with antidepressants were anti-psychotic drugs, systemic anti-histamines and drugs used in pain management.

Table 5.4.1: the most frequently prescribed concomitant drug

	Active Ingredient	% of patients	no. of patients
Anti-epileptics			
	Valproic acid	10.65%	13
	Lamotrigine	15.57%	19
	Gabapentin	24.60%	30
	Clonazepam	39.34%	48
	Carbamazepine	4.92%	6
Anti-psychotic			
	Quetiapine	8.20%	10
	Risperidone	18.03%	22
Systemic anti-histamine			
	Promethazine	19.67%	24

Table 5.4.2: Patient demographic summary.. Female patients received more than two thirds of the prescriptions for antidepressants. Of all ethnic groups, white patients accounted for the most antidepressant prescriptions along with patients in the 20-59 age group. The unemployed and married were also majority groups in this patient population.

Variable	**% or Mean (SD)**
Gender	
Male	30.30%
Female	69.70%
Patient Ethnicity	
Black	35.70%
White	40.70%
Coloured	10.30%
Indian	13.30%
Age Groups	
Under 20	1.48%
20-59	71.30%
60 and over	27.22%
Employment Status	
Unemployed	50.40%
Pensioner	23.70%
Employed	25.90%
Marital Status	
Married	54.81%
Single	34.81%
Divorced	4.44%
Widowed	5.92%
Diagnosis	
MDD	62.29%
GAD	14.75%
MDD and psychosis	4.92%
Mild depression	0.82%
MDD and epilepsy	5.74%

MDD and Bipolar disorder	11.48%
Antidepressant type	
Fluoxetine	18.03%
Citalopram	51.64%
Venlafaxine	30.33%

5.5 Cost of Antidepressants

. The cost of each antidepressant is shown according to prices supplied by the National Department of Health (NDoH) which shows the most expensive antidepressant to be venlafaxine

Antidepressant	Dose	Quantity used (amount x pack size)	Cost per unit	% of Patients using AD (*N*)	Total cost
Fluoxetine	20mg	30 x 20mg	R6.32	8.19% (10)	R63.20
	40mg	60 x 20mg	R12.64	5.74% (7)	R88.48
	60mg	90 x 20mg	R18.96	4.09% (5)	R94.80
Citalopram	10mg	15 x 20mg	R3.20	1.64% (2)	R6.40
	20mg	30 x 20mg	R6.40	25.41% (31)	R198.40
	30mg	45 x 20mg	R9.60	7.38% (9)	R86.40
	40mg	60 x 20mg	R12.80	13.11% (16)	R204.80
	60mg	90 x 20mg	R19.20	4.1% (5)	R96.00
Venlafaxine	75mg	30 x 75mg	R39.65	1.64% (2)	R79.30
	150mg	30 x 150mg	R73.54	3.28% (4)	R294.16
	225mg	30 x 150mg + 30 x 75mg	R110.05	13.11% (16)	R1760.80
	300mg	60 x 150mg	R143.90	12.29% (15)	R2158.50
Total per month				**100.00% (122)**	**R 5131.24**

The most expensive antidepressant used had been venlafaxine with a total cost of R4291.46 per month to treat the 37 patients who had been prescribed that type of antidepressant. Patients who had received venlafaxine had a greater return rate than the other antidepressants for repeats. The extent of which had been calculated to be up to 5 months more than the other antidepressants. The average cost of treating each of the 37 patients with venlafaxine R115.97 per month.

The most commonly prescribed dose for both fluoxetine and citalopram had been the 20mg which costs R6.32 and R6.40 respectively. The total cost of using fluoxetine to treat the 22 patients had been R246.48 per month, with an average cost of R11.20 per patient per month.

As mentioned previously, citalopram had been prescribed to a greater number of patients than any other antidepressant. The total cost of using citalopram was R592.63 per month. The average cost of treating each patient using citalopram was R8.11 per month.

The following is the average number of repeats per patient from January 2011 to September 2014:

Average number of repeats for patients on fluoxetine:

259 prescriptions for fluoxetine/ 22 patients = 11.77 repeats

Average number of repeats for patients on citalopram:

672 prescriptions for citalopram/ 63 patients = 10.67 repeats

Average number of repeats for patients on venlafaxine:

560 prescriptions for venlafaxine/ 37 patients = 15.13 repeats

The medicine possession ratio measures the percentage of time a patient has access to medication. This is used as a means of measuring the patient compliance to medication

$$\text{Medicine possession ratio (MPR)} = \frac{\text{Total Days supply in period}}{\text{Last fill date} - \text{First fill date} + \text{Last fill days supply}}$$

The MPR ranged from 90% to 87.5% in this study.

5.6 Cost of concomitant drugs

Table 5.6.1: Cost of concomitant drugs. The cost of each concomitant drug is shown with the cost per unit (one month of treatment)

	Active Ingredient	Average Cost per unit	% of patients	Total Cost
Anti-epileptics				
Valproic acid		R107.64	7.51% (13)	R1399.32
Lamotrigine		R61.47	11.04% (19)	R1167.93
Gabapentin		R128.88	17.44% (30)	R3866.40
Clonazepam		R153.69	27.91% (48)	R7377.12
Anti-psychotic				
Quetiapine			5.81% (10)	
Risperidone		R13.27	12.79% (22)	R291.94
Systemic anti-histamine				
Promethazine		R68.97	13.95% (24)	R1655.28
Pain Management				
Carbamazepine		R31.47	3.48%(6)	R188.82

The cost involved in the use of concomitant drugs had been calculated as a means to demonstrate the total cost of treating a single patient at the clinic. The most expensive drug that had been prescribed was the antiepileptic clonazepam with a cost of R153.69 per unit. This had been the most frequently prescribed drug with 48 patients, resulting in a total cost of R7377.12.

The cheapest drug used was the anti-psychotic risperidone, which resulted in a total cost of R291.94 for the 22 patients who had received treatment with the drug.

5.7 Change of antidepressant

Over the duration of the study, there had been just two patients who have had their antidepressants changed. One patient had been changed from citalopram to venlafaxine, whilst the other patient had been changed from fluoxetine to venlafaxine. Both patients were female and middle-aged.

Chapter summary

This study confirmed the findings of other drug utilization reviews with antidepressants being prescribed more to females than males. SSRIs have been the drug of choice for most patients. Patient factors as well as the choice of antidepressant were compared and the cost of per patient per prescription of each antidepressant was calculated.

Chapter Six: Discussion

This study found a number of factors associated with antidepressant use, many of which are similar to the findings of other antidepressant DURs. Through the analysis of the prescriptions from the sample population, valuable information had been obtained on the types of patients seeking treatment for depression and anxiety disorder as well as the types of antidepressants used by each patient group. The way in which the antidepressants were prescribed as well as the patient factors that are associated with prescribing had also been determined using various statistical tests. This has been the first study to be conducted on antidepressant usage in the public sector. Other studies that were done in South Africa used a similar methodology with the exception that those records were from medical aid data from the private sector. This meant that whilst the previous studies had used computerized records, this study made use only of the paper records, as is available in the public sector, which does not use computer based records. A similar methodology was used for this study because it was the same type usage that was to be analysed.

The DURs in South Africa measured varied types usage patterns with regards to antidepressants. While the basic descriptive statistics remained the same, the other DURs measured usage based entirely on the information that was available. One South African study measured patient demographics such as age, gender, race, marital status, urban/rural location, employment status, as well as educational qualification (Tomlinson *et al,* 2009). This has been one of the only studies in South Africa that measured the patient demographics of depressed patients to such an extent. Most other studies have simply measured the age and gender of patients using antidepressants and then focused more on the classes of antidepressant prescribed. It was because of this lack of specific information on the patient population of patients using antidepressant that this study gathered the type of characteristics as listed previously.

Truter and Kotze in 1997 compared the PDD with the DDD of SSRIs from a medical aid database with another study done in a similar manner with the exception of the study population which had focused on a sample of 98 adolescents and young adults (Kairuz *et al,* 2003). In this study the PDD and DDD was compared across the patient sample for per drug per patient. This study had a varied age group as opposed to the other studies which focused just on a particular age group. All the South African studies showed that SSRIs were considered to be the drug of

choice for MDD and anxiety disorders (Truter, 2010; Kairuz *et al,* 2003; Truter and Kotze, 1997). The patient population characteristics of those using medical aid funded facilities and those using the public sector do vary considerably, the usage patterns in the latter mentioned groups has not been determined. This study was done as a means to add to the current information about the use of antidepressants.

6.1 Gender

6.1.1 There are more prescriptions for antidepressants for women

The fact that there are a greater proportion of women to men who are depressed is one of the most widely documented finding in the epidemiology of depression. Within most studies, the proportion of women had been nearly double or one and a half times greater than that of men. In this study, the proportion of males to females was 1: 2.3 (standard error= 0.40), with a 99% confidence interval [0.57, 0.77] for females and [0.22, 0.43] for males. This means that for each patient that visited the facility, there had been more than twice that number who were females. As shown in a number of other studies, there are more female patients receiving antidepressant therapy than males. Other antidepressant drug utilization reviews that have used patient information from countries in Europe have reported the same findings where there had been more than 65% of the entire patient population consisting of females (Bauer *et al,* 2008; Aarts *et al,* 2014; Serna *et al,* 2010). The results of the Danish study aimed at investigating sick leave in patients with depression found similar results with 59.69% of the patient sample being female (Gasse *et al,* 2013). The same has been shown in the United States, only more so, with a 70% of the patient population on antidepressant therapy being females (Lin *et al,* 2011). The higher prevalence of depression in females than males can be directly linked to this as it is known that depression has been shown to be twice as likely to occur in women as in men (Rihmer and Angst, 2008).

The results from the South African mental health and stress study shows that there were more females than males who had received treatment or sought medical attentions because the group consisted mostly of females (53.7%) (Tomlinson *et al,* 2009). In 2009, results from a private medical aid scheme in South Africa showed that of these patients 53.74% were female

(Truter, 2010). Another South African study on mental health patterns had shown that women were more likely to seek treatment overall however, among 12-month cases there had been no significant gender differences for mood disorders (Seedat *et al,* 2009). This is largely so when the patient population has a variation of age ranges. It has also been shown those women of low-income and those that are living in low and middle income countries have been documented to be at a particularly high risk of developing depression (Bennet *et al,* 2004).
There have been deviations in the proportion of male to female when younger age groups of children and adolescents had been studied for the off-label use of antidepressants, where the proportions are almost equal (Dorks *et al,* 2013) leading to research into the gender bias of depression occurrence into post-pubertal females (Jang *et al,* 2009).

6.1.2 Females seek treatment more frequently

One of the reasons why there are consistently more females found in depressed patient groups than males is because of the help seeking behavior of males which is considerably lower than that of females (Angermeyer *et al,* 2013). The common belief among the public regarding mental health problems has often being a subject of interest. This is largely because of the relationship to stigma about recovery. Mental disorders such as psychosis, schizophrenia and depression have often been related to increased stigma in the community as well as the decreased expectation of recovery (Read *et al,* 2014). The common view of the public, which has proven to be quite resilient, is that the treatment of depression should rather consist of a psycho-social treatment over a bio-genetic or pharmacological treatment approach (Hughes *et al,* 2011). This bias may have contributed to the larger number of prescriptions for females in this study.

6.1.3 Gender roles in relation to depression

One study has been conducted to compare the depressive symptoms in women in Asia and western countries, this study has shown that most older Korean women had reported been responsible for their domestic chores which is rarely or never shared with their husbands in addition, these women have shown households that are mainly patriarchal dominated which has led to a strictly defined role of the women in households, this increased stress has been shown to be a cause of marital distress and depressive symptoms (Jang *et al,* 2009). In this

study, although no social information was recorded, the employment status of patients had been collected to show whether they are employed, pensioners or unemployed.

6.1.4 Marital status and gender comparison

The percentages of female and male patients who were married and single were relatively similar for both groups. One study had shown that there had been an almost equal percentage of women and men who had been considered single or married and that there had been a higher proportion of women than men who had been widowed or divorced (Strohschein *et al,* 2005). There had been gender differences in depressive symptoms by age which were significant ($p=0.016$) when married men were compared to married women (Jang *et al,* 2009). In contrast, patients in Beijing and Shanghai had displayed higher depressive symptoms in men aged 50-70 years old who had been living without a spouse than those who had been married, whilst the marital status of women had not showed any significant relationship with depression (Pan *et al,* 2008). This difference between patients in Western environments and these shown in Asian societies showing the gender differences in the health benefit of being married could be caused by the social and cultural environment of Asian societies which have strictly demarcated gender roles which places more emphasis and importance of the patriarchal roles (as mentioned above). One study had shown that the relationship between gender and marital status was statistically significant ($p<0.001$) which shows that there is a gender difference in the correlation of marital status with depressive symptoms (Jang *et al,* 2009). In the same study, men who had been divorced or separated had reported higher amounts of depressive symptoms than married men did across all age groups. The difference observed in men had not been shown in members of the opposite sex. The difference in the symptoms of depression observed across varied marital statuses had not been shown in women aged 75 years and older including women who had been separated, divorced or widowed (Jang *et al,* 2009).

6.1.5 Age and gender comparison

For patients aged 20-30 and 31-40 years, there had been a higher percentage of males compared to females.. This showed that males in this sample may be more likely to suffer from a depressive episode at an earlier age than females. However, there had been a higher percentage of females in the 51-60 age groups as well as the over 60 age group. This trend shows that the onset of major depression occurs for females at a later age than males. As previously mentioned, epidemiological studies done on patients suffering from depression have consistently shown that there are more women than men patients receiving treatment. Most studies have described the ratio of women to men as 2:1. The differences in gender patterns had been shown only from patients from 11 to 14 years onwards (Kessler, 2003). This has raised interest into the role of sex hormones in the etiology of depression among women especially since women report changes in depressed mood associated with experiences that cause changes in sex hormones for example as with patients going through menopause who have to use hormone replacement therapy and those patients on oral contraceptives (Hunter *et al,* 1986). However, regarding pregnancy, there has been limited research which has been done to study the effects of pregnancy on the onset and occurrence of major depression which has instead found higher rates of depression among non-pregnant patients (Hunter *et al,* 1986). Researchers has shown that for women who are married, depressive symptoms has increased as age increased (B=0.02; p=0.043) (Jang *et al,* 2009).

6.1.6 Antidepressants and gender

The type of antidepressant used was recorded for the patient population. As shown previously with the total patient population, most males and females had been prescribed Citalopram, although it had been prescribed to 12.33% more of the female patients (Males: 36.60%; Females: 48.93%).

Fluoxetine was however prescribed to a slightly greater extent to males than females (males: 22%; females: 13.83%). In 1995, in a study on a SA medical aid database, of a total of 2117 patients on fluoxetine, 72.8% were female and 27.2% were male (Truter and Kotze, 1997). Female patients (62.33%) were more frequently prescribed SSRIs and SNRIs than males (Van Schalwyk and Truter, 2010).

With regards to venlafaxine, the prescribing frequency among both males and females had been relatively similar (males: 26.30%; females: 28.72%). Males had been prescribed amitriptyline slightly more than females (males: 12.10%; females: 8.51%). The most commonly prescribed antidepressant active ingredients were fluoxetine (13.92%), citalopram (14.09%), escitalopram (14.60%) and imipramine (19.77%) in this patient population where 814540 antidepressants were prescribed of which 12549 had been prescribed to patients 18 and younger, of these patients 53.74% were female (Truter, 2010). In the current study, venlafaxine had been prescribed in nearly equal amounts among males and females. Citalopram was prescribed more to females than males whilst fluoxetine was prescribed more to males than females.

The prescribing patterns of TCAs were studied using patients who are on a private medical aid scheme, data from 1996 (1982 patients) and 2002/2003 (2345 patients) were used (Truter and Kotze, 2006). Almost two-thirds of these patients were female (67.41% in 1996 and 57.53% in 2002/2003) (Truter and Kotze, 2006). Interestingly, TCAs were more frequently prescribed to males than females in the younger age groups in 1996 but in the older age groups in 2002/2003 (Truter and Kotze, 2006) this could be mainly due to the use of TCAs in pain management in recent times.

6.2 Patient Ethnicity

Differences in depressive symptoms as well as the prevalence of depression are found to vary among various ethnic groups. This patient demographic had been recorded in order to measure whether this type of variance is also evident in the patient population. Some studies have shown that the prevalence of depression is similar among ethnic groups eventhough there are differences in the treatment rates and diagnosis of patients (USDHHS, 2001). The results of these studies had shown that ethnic minorities are the least likely to seek or receive treatment for depression as well as the least likely to use specialized mental health facilities, in addition they also have longer delays before initiating treatment for depression compared to white patients in the US (Wang *et al,* 2005). The treatment preferences also varies between ethnic groups as well with Whites and Natives in the US preferring medication to counseling whilst Asians, Hispanics and African Americans preferring counseling to medication (Givens *et al,* 2007).

One study has shown that there are differences in the type of depressive symptoms reported between Latino African-American and white patients with Latinos reporting more symptoms than either African-American or white groups (Kemp *et al,* 1999). Another study has also shown that Whites and African-Americans experienced the same amounts of depressive symptoms with Mexican Americans showing to have a higher level of depression compared to the previous two groups (Neff and Hope, 1993). Another study had shown that both the past year and lifetime prevalence of major depression varied between ethnic groups with the largest prevalence being found with Puerto Rican patients and the lowest found among Chinese and Filipino groups (Gondalez *et al* 2010). A similar type of study had reported the type of factors that may contribute towards a patients vulnerability to depression with regard to ethnicity, this study had shown that Hispanic patients were largely concerned with factors such as change in environment, control of events and affiliation to groups whilst whites were more concerned about issues that had been related to achievement and African-Americans were the least concerned with factors that related to intimacy (Bernstein*l,* 1992). One study had shown that race or ethnicity differences in depression are mixed with results of some studies showing that the African Americans and Hispanics have reported lower rate of depression and symptoms of depression (Williams and Sternthal, 2010). Another study showing the differences of depression among individuals who had been incarcerated has shown that the greatest difference between depressed inmates had been due to their race (Roxburgh and MacArthur, 2014).

The population in the current study consisted of various ethnicities of which 35.7% (N=48) were Black, 10.3% (N=14) were colored, 13.3% (N=18) were Indian and 40.7% (N=55) of which were White. In the United States, patients who were part of their patient population in that study, 86% were of Caucasian origin (Lin *et al,* 2011). Another US study showed that the duration of major depression diagnosis had been higher in Puerto Ricans, Mexican Americans and African Americans compared to Whites (Gondalez *et al,* 2010).

Given the demographic of our country where South Africa consists of 76.4% Black, 9.1% White, 8.9% Coloureds and 2.5% Indian or Asian (STATS SA, 2013), it is quite interesting to note that there were more White patients than Black patients who had sought treatment at the facility and more Indian than Coloured patients even though the demographics of South Africa as a whole shows that Coloureds are in a greater proportion to Indians. Also, in the public sector there is a

larger percentage of black patients as compared to the private sector. This contrasts the results of this study where there had been a greater percentage of white patients at this psychiatric facility. Results from the South African stress and health study analysed 4351 adult South Africans of all ages and all racial groups. The sample of patients had been diagnosed with major depression (Tomlinson *et al,* 2009). The group consisted mostly black patients (76.2%) followed by coloureds (10.4%), white (3.4%) and Indian/Asian (3.4%). This shows a great variation from the results found at the Charlotte Maxeke Johannesburg Academic hospital with regard to the proportions of each racial group, this could be because of this study's smaller sample size or due to the fact that the hospital is situated in a densely urban area to which mostly residents from Johannesburg or nearby surrounding areas attend the facility for treatment which reduces the chance of having patients from rural areas.

We could attribute the lower level of Black patients to White patients in this sample group due to the type of help seeking behavior of Black patients. A study conducted on 4351 adults across South Africa to show the help seeking behavior of patients with a mood or anxiety disorder had shown that black patients (OR=25, $\chi 2=12.81$, $p=0.005$) were more likely to have accessed the complementary and alternate medicine sector rather than seek help from a health professional (Seedat *et al,* 2009). With this is mind, it is easy to assume that the reason for not having a large amount of Black patients is due to the fact that Black patients would rather consult traditional healers or other forms of complementary medicine choices than visit a medical professional to seek advice and treatment. Diseases of a mental origin are often considered a spiritual matter among some cultures, including African traditions (Seedat *et al,* 2009). This helps to explain why Western and modern medicine is avoided to a certain extent in conditions such as depression because of the belief that these conditions have to be dealt with using traditional medicine or advice and remedies. Whites (OR=10.9) and coloreds (OR= 4.1) were more likely than blacks to have seen a psychiatrist and whites were found to be more likely than blacks to have used mental health services (Seedat *et al,* 2009). Studies have shown the varied beliefs of depression and its treatment between different ethnic groups with ethnic minority groups being less likely to believe that the cause of depression is a biological change (Givens *et al,* 2007). These same minority groups had also less faith in using antidepressants in the treatment of depression, they had been more likely to believe in non pharmacological treatment such as counseling and prayer as these patients felt that antidepressants were addictive (Givens *et al,* 2007).

One study that had been conducted using Medicaid patient information in the US had shown that the patient's race had an influence on the type of antidepressant prescribed (Melfi *et al,* 2000). The study had shown that of all those patients receiving antidepressant therapy, whites were found to be more likely than patients of an African descent to have been given SSRIs (Melfi *et al,* 2000).

6.2.1. Ethnicity in relation to other patient factors

In this study the amount of black male and female patients had been nearly equal with white patients having been composed of more females than males. For coloured and Indian patients, there had been more males than female patients. There have not been many studies which have been done to compare the rate of depression among race groups whilst comparing the gender factors of these patients as well. Most studies that compared gender differences had been primarily done in White patients.

One study had shown a comparison of various patient factors such as age and gender with relation to a patient's ethnicity. The ethnicities used in this study were Chinese, Filipinos, Vietnamese, Cubans, Mexican Americans, Puerto Ricans, black Caribbean Americans, African Americans and Whites, all of whom live in the United States. It had shown the variances between ethnic groups with regard to prevalence rates, age of onset, disability, treatment use and severity of depression. In this study, patients aged 18-24 were found to be more abundant in Mexican Americans than any of the other race groups. Mexican Americans had also shown the largest amount of patients aged 25-34 compared to every other ethnicity which had the majority of patients in the 35-44 age group. With regard to the relationship between gender and ethnicity, every race group had a larger percentage of female patients than males with the exception of Cubans, Mexican Americans Puerto Ricans and Caribbean Black Americans. The same study has shown that the age of onset of depression varied among foreign born and US born ethnic groups with Cuban and Puerto Rican groups showing a significantly earlier age for the onset of major depression. The odds of a major depressive episode occurring had also shown to vary between ethnic groups with Puerto Ricans, Mexicans and African Americans showing a significantly higher odds of having a recurrence compared to Whites (Gondalez *et al,* 2010).

6.2.2 Ethnic groups and antidepressant use

The use of antidepressants among the ethnic groups of the patient population had been tabulated to show the frequencies to which these antidepressants were prescribed in each group. Citalopram had been the preferred antidepressant in Black, Coloured and White patients (57.14%; 58.30% and 44.00% respectively). The patient race has been shown to be associated with the type of antidepressant chosen ($p< 0.0001$).

In correspondence with the finding that race has been associated with the diagnosis and antidepressant chosen; race has also been found to have an influence on the dose prescribed to patients ($p= 0.004$). Black patients were more likely than any other group to receive a dose of 20mg of citalopram and fluoxetine. White and black patients were prescribed 30mg of citalopram, 40mg of citalopram and fluoxetine and 75mg of venlafaxine with the same frequency however many more white patients had been prescribed the 60mg citalopram or the 225mg and 300mg dose of venlafaxine .. Coloured patients were more likely to receive a dose of 40 mg.

6.3 Age groups in relation to depression

The average age of all the patients was 50.16 years (SD= 16.32). The majority of patients were aged between 55-59 years followed by patients aged between 50 and 54 years (21% and 11.8% respectively). This is higher than the results of the SASH study where the mean age had been 37.0 years (Tomlinson, *et al,* 2009). In certain European countries the average age of patients receiving antidepressant therapy had been slightly lower than shown here at 46.8 years (SD=14.7) (Bauer *et al,* 2008). In the Netherlands, researchers had used a patient population consisted of 14,926 patients who were receiving antidepressant therapy, which had shown that this group presented with the average age of 65.5 years (SD=10.5) (Aarts *et al,* 2014). One South African study done on a medical aid population showed that the average age of patients

on antidepressants were 53.4 years (SD= 14.5 years), the average age of the male participants was 54.0 years (SD=15.4 years) and the average of the female patients were 53.2 years (SD=14.2 years) (Truter and Kotze, 1997).

Interestingly, the use of antidepressants, which is measured by the composition of this patient sample, had been shown to increase with an increase in age with the exception of the 30-34 years which showed close to a 3% decrease from the 25-29 ages whilst the 40-44 year age groups had shown a 6% decrease from the 35-39 range. A Danish study had reported similar finding with 10.53% in the 18-24 years age range, 21.01% in the 25-34 year range 27.10% in the 35-44 group with a slight decline in the 45-54 age range to 25.35%, however there had been a deviation in the 55- 64 group where the prevalence had decreased sharply to 16.0% (Gasse *et al,* 2013). The use of antidepressants was shown to be much lower for the 60-64 age group with a decrease of nearly 12% compared to the 55-59 years age patients. The increase in antidepressant use in the elderly age groups could also be related to increasing loneliness, physical health problems and other disabilities as well as the worsening of chronic diseases (Aarts *et al,* 2014; Parabiaghi *et al,* 2011). In order to compare the use of certain antidepressants over a time span, a local study using information from a medical aid database from the year 1996 and 2002/2003 showed the changing patient demographics of those who had been prescribed amitriptyline largely due to the fact that it is prescribed more frequently for pain management than depression (Truter and Kotze, 2006). A large number of patients were in the age group of 40-69 years (67.51% in 1996 and 49.68% in 2002/2003) whilst there was a few patients younger than 20 years (3.79% in 1996 and 8.66% in 2002/2003) (Truter and Kotze, 2006). In comparison the average age of patients in 1996 was 52.99 (SD=16.02) and 42.66 (SD=16.48) in 2002/2003 (Truter and Kotze, 2006). Other studies have also shown similar patterns with regard to antidepressant use and age. In one study, the majority of patients (21.40%) were aged between 35 and 44, patients aged 18-24 had accounted for 15.00% of patients, with a slight increase to 16.20% in the 25-34 age group. The least amount of patients, 6.60% belonged to the over 75 age group (Gondalez *et al,* 2010).

Patients under the age of 20 had only accounted for 1.48% of the total patient population in this study. This sample had been from the psychiatric ward out-patients so that only patients treated for depression and anxiety or some form of bi-polar disease had been represented here. The

use of antidepressants is generally not recommended in children and adolescents due to the fact that they are more likely to develop a suicidal tendency on these drugs. There is a black box warning on the package inserts explaining this. The result of this warning has caused the diagnosis of depression and subsequent use of antidepressants in patients under the age of 18 years; this conversely had been linked with an increase in suicide rates among children and adolescents (Courtet *et al*, 2014). A study in Germany measuring the use of antidepressants in children and adolescents for both depression and off-label uses showed that the prevalence of antidepressant use was 1.84 per 1000 children in 2004, 1.57 in 2005 and 1.66 in 2006 from the children treated with antidepressants, 56.30% had been diagnosed with a depressive disorder. (Dorks *et al,* 2013).

6.3.1 Antidepressant use in various age groups

As previously shown, the preferred choice of antidepressant is the SSRI citalopram. When the various age groups have been considered however, there were some exceptions to the general prescribing practice. Fluoxetine had been used equally to citalopram in the less than 20 years age group. The off-label use of antidepressants in this age group of patients has often being a topic of investigation. In Germany, this type of antidepressant use had been investigated further using a patient sample that consisted of children and adolescents which showed that amitriptyline had accounted for a total of 7.39% of antidepressants prescribed within the group while fluoxetine consisted of 12.03% of prescriptions (Dorks *et al,* 2013). Interestingly, prescriptions for citalopram only contributed to 6.76% of the total antidepressants prescribed (Dorks *et al,* 2013). The SNRI venlafaxine had been prescribed to 1.54% of all the patients under the age of 17 (Dorks *et al,* 2013). A study to show the prescribing patterns in patients younger than 18 showed that SSRIs accounted for 55.91% of antidepressant prescriptions which was ahead only of TCAs which contributed to 32.32% of prescriptions. These two antidepressants accounted for 79.49% of the antidepressant cost (Truter, 2010). Another study which had aimed at investigating the prescribing patterns of SSRIs and SNRIs in patients 19 and younger showed that 440 patients younger than 19 years receiving antidepressant therapy which had accounted for 6.20% of patients of any age receiving antidepressants (Van Schalwyk and Truter, 2010). The average age of these patients was 14.21 (SD=3.05) years with the majority of patients being older than 12 years old (77.13%) (Van Schalwyk and Truter, 2010). Antidepressants prescribed to patients 18 and younger, from a private medical scheme

database, 12549 antidepressants were prescribed to this patient population out of the total of 814540 antidepressants prescribed in the year 2009 (Truter, 2010).

With regard to the current study, within the 20-24 years range, an overwhelming majority had been prescribed citalopram (77.78%) with the remainder of the group having received prescriptions for fluoxetine (22.22%), none of the patients in this group had received venlafaxine. A similar type of pattern is shown in the proceeding 25-29 age range except for an increase in the number of patients on fluoxetine and the addition of venlafaxine which is used for the first time compared to the previous age groups. The same type of pattern of prescribing had followed to the 30-34 and 35-39 age range with citalopram being the drug of choice.

In this study, the 40-44 age range, no patients had been prescribed fluoxetine, and interestingly the use of citalopram (40%) had been less than that of venlafaxine (60%). Fluoxetine had been used for the first time in the 45-49 age range which had shown an equal amount of use for citalopram and venlafaxine (33.33% for all three). From the 40-44 age range onwards, the use of venlafaxine had been more frequent than that of fluoxetine, in contrast to the previous age groups where they had either been preferred in nearly equal amounts or fluoxetine had been prescribed more frequently.

The use of citalopram and fluoxetine had been equal in the 65-69 age range with venlafaxine emerging as the drug of choice in these patients. Venlafaxine had been preferred over fluoxetine and citalopram in patients aged above 75. When the use of antidepressants is investigated in the elderly, higher age categories showed a higher prevalence of antidepressant use such as the age group of 72–77 years of age group use being 6.5% (SD = 0.8) and in elderly > 78 years of age group being 7.4% (SD = 1.7) when compared with the two lower age categories 45–64 year age group being 6.3% (SD = 2.3) and 65– 71 years age group being 6.0% (SD = 1.3) (Aarts *et al,* 2014). The increase in antidepressant use in the elderly age groups could also be related to increasing loneliness, physical health problems and other disabilities as well as the worsening of chronic diseases (Aarts *et al,* 2014;Parabiaghi *et al,* 2011).

Although the Pearson chi squared test had shown that the type of antidepressant chosen is not influenced by patient age because of the high p-value (0.810), the linear regression test had shown that an increase in age is associated with an increase in the use of antidepressants

(b=0.015; p=0.001). The result of the t-test (t=3.58) had shown that our co-efficient (0.015) is statistically significant (standard error=0.04; CI 95%= 0.07-0.24). This shows that the use of antidepressants is likely to increase with an increase in age.

The results of an ordinal logistic regression test of antidepressant and age showed a statistically significant likelihood ratio (LR) of 12.80 and probability (p=0.0003). As shown with the linear regression test, an increase in age is associated with an increase in the use of antidepressants (b=0.36), but to a greater extent than the previous test (SE=0.010; CI 95%= 0.15-0.56).

6.4 Employment status in relation to depression

Unemployed patients consisted of 50.4% of the patient population. Depression has often been associated with reduced productivity, work absenteeism (Gasse *et al,* 2013). This could be because of financial burdens and stress which have caused the depression or it could be as a result of lack of interest in work or absenteeism which could have caused a previously employed patient to become unemployed. This trend in depressed patients where they have taken long periods of sick leave is shown where among those with sick leave, nearly 67.8% had taken sick leave for longer than 8 weeks and 34.3% longer than a period of 26 weeks, this high rate of sick leave can be related to job losses because of the depression (Bratberg *et al,* 2009; Lund *et al,* 2008). Other studies in South Africa had shown similar finding where 69.2% of the patients had been unemployed at the time of the study (Tomlinson *et al,* 2009).

The high rate of unemployment could also be representative of the high rate on unemployment in South Africa however, in Europe a study showed that over various countries, only 13.7% of the patients were unemployed and 50.1% of the sample had been in paid work at the time of the study (Bauer *et al,* 2008). Only 23.7% of patients were employed in this study. The remainder of the patient sample was pensioners (25.9%), this can be related to the age groups where there had been over 26% of the patients that were over the age of 59 years. It is clear that employment can be a major source of stress which does contribute to the aetiology of depression. Earlier findings have shown that there is no specific event which can contribute to major job stress instead it is an accumulation of a number of minor events in the workplace to which many individuals blame as the source of their discomfort at work (Iavovides *et al,* 2003). Jobs stress has been associated with changes in both physical and mental health.

The way in which patients have increased tendency to stay away from work is a well documented occurrence however; there have been few studies to document the sick leave patterns of patients during the course of taking antidepressants. In the US, researchers have found that before use of antidepressants, sick leave had been relatively high but then decreases after the treatment is initiated (Birnbaum *et al,* 2000). There have been a number of studies which have shown that the presence of mental illness had been linked with negative employment outcomes with a diminished ability to obtain and keep their employment (Adler *et al,* 2004; Cowell *et al,* 2009). Conversely, longitudinal studies have revealed that there is a clear relationship between unemployment and mental health which showed that there is a mental health benefit when patients move from unemployment to employment whilst there is a decline in the state of mental health when moving from employment to unemployment with these participants showing an increased likelihood to develop depressive symptoms (Murphy and Athanasou *,* 1999).

6.4.1 Employment factors in antidepressant use

When the chi squared test had been performed on this data set, it had shown the employment status influence antidepressant type that is prescribed.

As part of the patient demographics factors such as their employment status had been recorded to help try and understand the various types of patient factors that may have an influence on the type of antidepressant chosen. The three groups which the patient population had been divided into were employed, unemployed (which included housewives and students) and pensioners.

6.5 Marital Status and depression

Married individuals have been shown to enjoy longer lives due to their better mental and physical health compared to individuals who were non-married (Earle *et al,* 1998; Ross 1995). The positive mental health benefits of being married could be attributed to a number of reasons such as financial security due to the earning of the spouse, access to economic resources because some labor markets command higher wages for individuals who are married as well as the social support which is tendered for by spouses (House *et al,* 1988). However, recent studies have shown a clear association between depression and marital dissatisfaction (Whisman *et al,* 2004; Coyne *et al,* 2002).

The marital status of patients was also recorded as a part of the patient demographics because in previous studies, the marital status had shown to be a predictor or have an influence on the depressive state as well as to a certain extent had an association with the types of antidepressant chosen (Bauer *et al,* 2008; Serna *et al,* 2010). In Denmark, 29.66% of patients receiving antidepressant therapy had been single whilst 58.75% had been married or living with a domestic partner. There is evidence of an association between marital status, divorce rate and depression (Merikangas *et al,* 1985). Studies have reported that rates of depression are higher among married women than non-married women (Gove, 1972), the rates of divorce are found to be greater in patients with a history of a mental disorder, and divorced patients were more likely to develop a psychiatric condition (Merikangas *et al,* 1985). Though early studies that had shown that women who are married more of a mental health vulnerability than non-married women because of their restricted roles and social isolation due to home and economic dependence on a male partner (Gove, 1972), these findings have been largely discredited or not supported with a number of other studies showing that the mental health benefits of being married has been equally found in both males and females (Ross, 1995; Kim and McKenry, 2002; Simon, 2002). This confirms the finding in another study which showed that amicable marriage continues to be beneficial for the mental health of an individual (Strohschein *et al,* 2005).

Married patients consisted of 54.81% of the sample whilst single, widowed or divorced patients were 45.19% in this study. The finding that more than half of the patient sample in a population that had been receiving antidepressant therapy is consistent with other studies in Europe where

56.8% of the patients studied were married or living with a domestic partner (Bauer *et al,* 2008) and the same pattern is shown in local studies for which more than half of the patients had been married at the time (Tomlinson *et al,* 2009). This finding can, bring into question the numerous studies which have shown that the benefits of marriage are positive for both mental and physical healths with married individuals showing lower rates of depression than those who are single, divorced or have been widowed (Williams 2004; Afifi *et al,* 2006; Inaba *et al,* 2005). However, no research was undertaken in this study on the state of the marriage (just of its existence) and so it may be that the marriage contributed to loss of resilience on our participants.

Patients who were divorced accounted for the least amount of patients with 4.44%, followed by widowed (5.92%). This finding could be attributed to the fact that some studies have shown patients who have been widowed for a long time do not show more signs of distress than those who are continuously married (Umberson *et al*, 1992). This supports the theories which show that the initial stress caused by bereavement tends to have less of an effect on the psychological well being of an individual the more time passes from the time of bereavement (Strohschein *et al,* 2005). More than one third of the patients had considered themselves as single (34.81%).

There was a correlation between type of antidepressant chosen and type of the marital status of the patient ($p= 0.048$) in this study however, there are little current studies that have been done which compares the use of antidepressants with regard to the type of antidepressant chosen.

6.6 Patient Diagnosis

As a means of standardizing diagnosis of patients across various health facilities throughout the world, a set of codes which cover types of diseases, abnormal findings, symptoms and signs, social circumstances as well as complaints for causes of injury or disease was developed. This code is known as the ICD 10 codes which are the 10^{th} revision of the International statistical classification of diseases and related health problems (WHO, 2007). The ICD code classification is considered one of the oldest as well as the most supported classifications in illness. It is of great use for record keeping purposes because it is a standardized system that uses numeric nomenclature as a means for identification of patient's illnesses. The system had been criticized for not being suitable in cases where little or no information is available about the patient and where they have to be classified based on the symptoms.

F00-F99 is used to identify mental and behavioral disorders. The ICD codes for mental and behavioral disorders covers extensive conditions as well as their subdivisions so that a precise diagnosis can be made as well as to guide the kind of treatment to which a patient is prescribed. The code covers a range of conditions that include dementia, schizophrenia, bipolar disorder, depressive disorder and a range of anxiety disorders and phobias. Patient records with following diagnosis were included in the sample: MDD, GAD, MDD with psychotic features, Mild depression, MDD with epilepsy and MDD with Bipolar disorder (BPD).

The ICD 10 codes which are used when identifying the patients' diagnosis had been recorded. More than half of the patients had been diagnosed with major depressive disorder or MDD (56.30%). Second to this had been patients with MDD showing features of a generalized anxiety disorder (GAD) which had accounted for 13.3% of the sample patient population diagnosis. Antidepressant and anxiolytic medications are often used to treat anxiety or depression in the general population. This is much lesser than that shown in a drug utilization review which showed that 51.1% of all patients, in a sample that represented various countries, had received antidepressant treatment for an anxiety disorder (Bauer *et al,* 2008).

Patients who had also been receiving treatment for a bipolar mood disorder had also been receiving antidepressant therapy (10.37%). Mild depression and MDD with psychotic features were the least present diagnosis (0.74% and 4.44% respectively).

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6.7 Prescribing

In South Africa, the primary health care facilities ensure that treatment is standardized by using treatment protocols for mental disorders in order to encourage a better mental health for patients with these disorders as well as a useful practical guide for health care providers to be able to effectively manage these psychiatric disorders across both the district and the community levels (Burn *et al*, 2007). These protocols are in accordance with the Standard Treatment Guidelines and the Essential Drug List (EDL). The medicines that are listed in these guidelines and the drug list include anxiolytics, antidepressants, antipsychotics, mood stabilizers and antiepileptic drugs which are prescribed according to the diagnostic ICD-10 code that each patient is assigned. These lists, guidelines as well as the drugs are made readily available at

hospitals where patient with these mental disorders are being treated. These protocols and guidelines are to assist non-psychiatric health care providers such as medical officers and psychiatric nurses who are involved in the daily care and management of patients who use their facilities not only per province but throughout the public health care system in South Africa (Burns *et al*, 2007). The use of the essential drug list and these treatment guidelines are in accordance with the WHO recommendation that where there is a policy of community mental health care and its integration into general health services, essential drugs must be made available at these levels of care and the mental health workers who are authorized to administer these drugs (WHO, 2009).

In spite of the incorporation of mental health services into the public health care system as well as standardized treatment procedures, South Africa still has a great challenge in the form of limited mental health human resources, low ranking of mental health as a public health priority, lack of infrastructure , the biomedical orientation of health care and poor information systems to monitor mental health service delivery which poses difficulties in the prescribing of these medicines as well (Lund *et al*, 2007). According to the South African Nursing Council and prescribing guidelines, primary health care nurses are not allowed to initiate prescriptions but they are allowed to continue prescriptions or they may also prescribe in emergency situations (WHO-AIMS, 2007). These nurses are not allowed to make any changes to prescriptions such as dose changes or change of the type of drugs, they are allowed to hand-out medicines and provide instructions on use if necessary. All types of doctors in the primary health care system are allowed to prescribe any of the medicines on the essential drug list (Department of health, 2012).

Table 6.7.1: Distribution of health professionals. The estimated number of health professionals per 100 000 population shows the lack of available health professionals especially those in a specialized field

Mental health professional	**Estimate of mental health professionals per 100 000 population**
Psychiatric nurses	10.08
Psychiatrists	0.28
Other medical doctors (not specialized in psychiatry)	0.45
Psychologists	0.32
Social workers	0.4
Occupational therapists	0.13
Other health or mental health workers	0.28

Within the private health sector, the number of health professionals available is slightly better than that of the public health sector however, in a study investigating the use of SNRIs and SSRIs in patients younger than 19, general practitioners prescribed 67.76% of prescriptions while psychiatrists only prescribed 14.96% (Van Schalwyk and Truter, 2010) this shows that psychiatrists are consulted with less often than a general practitioner. This raises the question whether or not these patients have been adequately evaluated before commencing antidepressant therapy. This could possibly mean that the type of antidepressant chosen may not be suitable. Within this patient population, Venlafaxine had been prescribed to 6.32% of patients eventhough they are contraindicated in this patient population whilst Paroxetine had accounted for 5.96% of prescriptions though it is not recommended due to the possibility of suicidality side effects (Van Schalwyk and Truter, 2010).

A study using prescription data from a South African organization which evaluates the use of chronic medication for various medical aid companies had been done to show the prescribed daily dose of fluoxetine in 2117 patients in 1995 (Truter and Kotze, 1997). It showed that 86.5%

of females received a PDD of 20mg with 87.9% of males receiving the same PDD (Truter and Kotze, 1997). There had been a sudden increase in the use of fluoxetine in the age interval of 30-40 years for females and in the age interval of 40-50 years for males; this shows that males generally used fluoxetine at a later stage in life compared to females (Truter and Kotze, 1997).

In the U.S, a study using data from a Medical Expenditure Panel Survey database during the period of 2004-2007 had shown that a majority of patients were prescribed SSRI/SNRI antidepressants (71%) whereas only a small amount of patients had been prescribed the older generation TCAs (3%) (Lin *et al,* 2011).

At the Charolotte Maxeke Johannesburg Academic Hospital (CMJAH) hospital however, prescribing is better due to the fact that it is a third degree referral centre which means that the staff is very well trained and available. Antidepressants were prescribed

In the public sector, as mentioned previously, prescribing is done according to the Essential drug list (EDL) and the standard treatment guidelines (STGs). The WHO describes Essential medicines as those that satisfy the priority health care needs of the population. The list was designed for essential medicines to be available within the context of a functional health system at all times in adequate quantities, dosages and forms with adequate quality and at a price the community can afford (NDoH, 2012). In the South African public health sector, the prescribing of any drug is limited to the essential drug list. The purpose of designing the EDL was:

- To ensure the availability and accessibility of essential medicines to all citizens.
- To ensure the safety, efficacy and quality of drugs.
- To ensure good prescribing and dispensing practices.
- To promote the rational use of drugs by prescribers, dispensers and patients through provision of the necessary training, education and information.
- To promote the concept of individual responsibility for health, preventive care and informed decision-making.

For MDD, the EDL recommends TCAs in the form of amitriptyline or imipramine as the first line of therapy with a starting dose of 25mg per day with a maximum dose of 150mg or either of the SSRIs in the form of citalopram and fluoxetine. If a sedating antidepressant is required and a

TCA cannot be used, mianserin is to be prescribed (NDoH, 2012). In the current study, the only antidepressants prescribed were SSRIs and the SNRI venlafaxine. In contrast to the EDL and STG recommendations there had been no TCAs prescribed neither was mianserin used for any of the patients in the clinic. Venlafaxine was not mentioned in the EDL guidelines eventhough it was widely prescribed in this study. This shows that the actual prescribing patterns does differ from the STGs.

6.7.1 Prescribing patterns with regard to diagnosis

As expected, the diagnosis of a patient, which had been noted using the ICD 10 codes, had a great influence on the type of antidepressant chosen ($p<0.0001$). For patients with MDD, who represented more than half of the patient population, citalopram had been the most frequently prescribed antidepressant, accounting for 52.63% of prescriptions for patients with MDD followed by venlafaxine (32.90%) and then fluoxetine (14.47%). Amitriptyline had not been prescribed to any of the patients diagnosed with MDD. Patients who had been diagnosed as having MDD with feature of a generalized anxiety disorder had shown a similar pattern of prescribing with citalopram (55.56%) being the first choice followed by venlafaxine (27.78%), which is lower than the MDD group. In these patients, the percentage of those on fluoxetine (16.70%) had been slightly higher than patients who had been diagnosed as having solely MDD.

In patients who had been diagnosed with MDD and psychosis, the pattern of diagnosing had deviated from the first 2 groups. Fluoxetine had been preferred among these patients to a greater extent than venlafaxine and citalopram. The second drug of choice for prescribers when treating these patients had shown to be venlafaxine with citalopram being the least preferred, in contrast to the patients with MDD alone and MDD with GAD who had received more citalopram than any other antidepressant. MDD with epilepsy had shown more patients receiving Citalopram, followed by fluoxetine and then venlafaxine. In bipolar mood disorder with MDD, once again citalopram had been prescribed more than any other antidepressant, with fluoxetine and venlafaxine being prescribed in equal amounts.
In total, citalopram had been the most widely prescribed drug, accounting for 51.46% of all antidepressants. The second most widely prescribed was venlafaxine (30.33%) then fluoxetine (18.03%). This shows the way in which amitriptyline has been phased out from being used as

treatment for depression and is only used for pain management purposes. The study clearly demonstrates the way in which SSRIs such as citalopram and fluoxetine and the SNRI Venlafaxine have replaced the need for the use of older TCAs such as amitriptyline. The use of SSRIs had seen a 5.8-fold increase in use between 1991 and 2011 (Aarts *et al,* 2014).

Although the potency of SSRIs are often debated upon when they are compared to TCAs and other older antidepressants, most psychiatrists and other health professionals agree that they should be used as the first choice of drugs because of their lower side effect profile. An older drug utilization review conducted in Denmark that approximately 75% of had TCAs prescribed to them, whilst SSRIs were only used by 10% of the population (Rosholm *et al,* 1993). This shows the way in which the use of antidepressants has changed over the years.

This finding has been mirrored in other studies, one that had been conducted over various countries in Europe. It showed that the most commonly prescribed antidepressant had been an SSRI (63.30%) which is then followed by SNRIs (13.60%) (Bauer *et al,* 2008). The study confirms the increased use of SSRIs in the elderly and middle-aged population; this is most likely due to the low toxicity, mild adverse drug reaction profile and no need for plasma monitoring (Parabiaghi *et al,* 2011). SSRIs prescribed ranged from 31.7% in Germany to 81.5% in France (Bauer *et al,* 2008). In Spain, the most frequently prescribed group of antidepressants were SSRIs at 68.80% followed by TCAs at 18.20% (Serna *et al,* 2010). In the US, the trend of TCA prescribing had been even less than that of the European counterparts. SSRI/SNRI type antidepressants were prescribed to 71% of the patients in contrast to the 3% of patients that were prescribed older antidepressants such as TCAs (Lin *et al,* 2011).

In children and adolescents of all the antidepressants prescribed, only 41.72% were for SSRIs with a large number being for 33.99% of prescriptions in the German sample (Dorks *et al,* 2013). Studies done in South Africa had shown a similar finding. In another study where a private medical scheme database had been used to investigate the SNRIs and SSRIs in the children and adolescent patient population, it had been shown that SSRIs and SNRIs were prescribed to 50.68% of these patients (Van Schalwyk and Truter, 2010). Comparing the use of specific SSRIs, in 1995 fluoxetine had been the most frequently prescribed SSRI accounting for 63.3% of all the SSRIS followed by paroxetine accounting for 28.5% (Truter and Kotze, 1997). Surprisingly, citalopram accounted for only 9.2% of all the SSRIs prescribed and venlafaxine

only 0.5% (Truter and Kotze, 1997) perhaps because generic versions of these medicines were not available at that time.

TCAs were prescribed for only 1.5% of patients in the Netherlands and 8.6% in Austria but accounted for 26.5% of antidepressants prescribed in Germany (Bauer *et al,* 2008). When a study with a greater time span is conducted to show the way in which antidepressants are prescribed, amitriptyline and paroxetine had been the most commonly prescribed antidepressant with mirtazapine and venlafaxine being the other antidepressants prescribed but to a lesser extent (Aarts *et al,* 2014). It is often found that amitriptyline is preferred for its other indications. If a study is done on a larger patient sample with a larger patient population and takes into account other types of diagnosis with the antidepressant being the predictor for a patient being chosen to be part of the sample, it can be shown that the prevalence of use on TCAs is relatively high. The high prevalence in the use of TCAs might be explained by the numerous indications for which these drugs are also prescribed; this includes neuropathic pain (Raymond *et al,* 2007).

Of the total of 1606 prescriptions which had been the repeats for the 135 patients, 672 had been for citalopram, 560 had been made for venlafaxine, 259 for fluoxetine and 115 for amitriptyline. A study in Denmark showed that of all the antidepressants prescribed, to the patient population which consisted of over 25 000 patients, 71.53% had been an SSRI drug, 10.89% a TCA antidepressant and 5.32% an SNRI (Gasse *et al,* 2013).

The SSRIs citalopram and fluoxetine had been prescribed more frequently than any other class of drug to these patients in this study. SNRIs in the form of venlafaxine followed secondly with the older generation TCAs no longer used in the treatment of depression; instead it is used for its other indications in pain management.

6.7.2 Diagnosis and patient factors

One of the objectives of the study had been to determine if there are any patient factors such as gender, age, race, marital status or even employment status that may have an influence on the diagnosis of the patient. In order to determine if there is an association between these factors and the diagnosis, chi squared tests had been performed to create a probability value. Of all the patient factors, the race of a patient had been shown to have an influence on the diagnosis made by the health professional (p=0.008).

There have been numerous studies that have been done in order to investigate the kinds of factors that affect the health professional's decision in making a diagnosis and prescribing. Theoretical models have shown, through the examination of sociological influences, that the decision made by a health professional is influenced by four characteristics namely: the health professionals relationship with the patient, the health professionals relationship with the health care system (the setting of the practice), the characteristics of the health care professional such as age, specialty, race, gender, as well as the characteristics of the patient namely race, gender and age (Clark *et al,* 1991). There have been other studies which have re-iterated the findings of these papers (Bradley, 1991 and Gabe, 1990).

6.8 Use of antidepressants

Of the total of 1606 prescriptions which had been the repeats for the 135 patients, 672 had been for citalopram, 560 had been made for venlafaxine, 259 for fluoxetine and 115 for amitriptyline.

A drug utilization research method that is used for the analysis of data is the Defined Daily Dose (DDD) method. DDD is known as the dose which corresponds to the average dose per day for a drug, when used for the main indication in adults (WHO, 2003). There are limitations to the use of the DDD because a large percentage of drugs are used for off –label indications, therefore are used at different dosages. The DDD is a technical unit of measurement, and is not necessarily equivalent to the average doses actually prescribed. Therefore, the prescribed daily dose (PDD) is used to overcome the limitations of the DDD. The PDD is the average of the

actual prescribed dose of the drug and is obtained the dosing instructions in prescriptions (Truter and Kotze, 1997). The PDD was calculated by multiplying the number of tablets dispensed during the period and the strength per tablet divided by the number of days supplied. In this study the PDD for fluoxetine was 35mg which is above the WHO DDD of 20mg. The PDD of citalopram was 29mg. Venlafaxine in this study had been prescribed at a PDD of 239mg which higher than the WHO DDD of 100mg. Changes in antidepressant type as well as stopped therapy as a result of review in therapy can sometimes cause a reduction in the PDD as shown. A New Zealand based study showed that the PDD calculated in that patient population for citalopram was between 24-28 mg between 1999 and 2005. The same study showed the PDD for fluoxetine ranged between 18mg and 25mg from 1997 to 2005 with the PDD peaking mid-point then finally decreasing to the lowest PDD of 18mg. With regards to venlafaxine the PDD ranged from 113-205mg from between 1999 – 2004 (Ministry of Health, 2007). In one study the result of change of antidepressant which caused a 9.5% reduction in the mean PDD (Johnson *et al,* 2012). Using a sample of 98 adolescents and young adults in South Africa, investigated the prescribing patterns of TCAs and SSRIs, investigators found that the SSRIs were more likely to be prescribed within a close range of the DDD than the TCAs (Kairuz *et al,* 2003).

In this study, of the total patient population, almost half had been prescribed citalopram as their antidepressant (51.64%), followed by venlafaxine (30.33%) then fluoxetine (18.03%). The finding of the dominance of SSRIs has been mirrored in another study which showed that it been prescribed to 69.6% of participants with SNRIs contributing to 13.7% (Bukh *et al,* 2013). In South Africa, fluoxetine had been most commonly prescribed (36.5%), then citalopram (22.14%) followed by escitalopram (17.15%) (Van Schalwyk and Truter, 2010). In the US, SSRI/SNRI type antidepressants were prescribed to 71% of the patients in contrast to the 3% of patients that were prescribed older antidepressants such as TCAs (Lin *et al,* 2011). The results of a study in Europe showed that the most commonly prescribed antidepressants were SSRIs (63.3% of all patients) which is then followed by SNRIs (13.6% of all patients) (Bauer *et al,* 2008). The prescribing of different antidepressant groups varied between countries, this was shown as SSRIs prescribed ranged from 31.7% in Germany to 81.5% in France (Bauer *et al,* 2008).

These two antidepressants classes of SSRIs and TCAs accounted for 79.49% of the antidepressant cost (Truter, 2010). This type of practice is evident even though other studies

had shown that there had been a shift from the prescribing of TCAs to the better tolerated SSRIs (Guaiana *et al,* 2005; Lawrenson *et al,* 2000; Van Marwijk *et al,* 2001).

The way in which the prescribing of SSRIs had come to dominate was shown in the study by the increase in the number of prescription from 1.0 million in 1991 to 20.8 million in 2005 (Chen *et al,* 2008). Of all the 16,886 antidepressants prescribed, 7,044 (41.72%) were SSRIs, 5,739 (33.99%) were TCAs (Bauer *et el,* 2008). The number of prescriptions for TCAs increased steadily from 1991 in which it was 4.7 million to 6.4 million in 2001, it then showed a slight decrease in 2002 to 6.0 million but then proceeded to drastically decline to 3.7 million in 2005 (Chen *et al,* 2008). In contrast, a study done from 2007-2011, amitriptyline and paroxetine were the most commonly prescribed antidepressants with mirtazapine and venlafaxine being the other antidepressants that were also commonly prescribed, but to a lesser extent (Aarts *et al,* 2014).

A study to show the prescribing patterns in patients younger than 18 years showed that SSRIs accounted for 55.91% of antidepressant prescriptions which was ahead only of TCAs which contributed to 32.32% of prescriptions. TCAs were prescribed for only 1.5% of patients in the Netherlands and 8.6% in Austria but accounted for 26.5% of antidepressants prescribed in Germany (Bauer *et al,* 2008). An older study that had been done using information from a medicines certification centre in 1995 showed that the most frequently prescribed antidepressant at that time had been TCAs accounting for 40.9% of all the antidepressants followed by SSRs which together accounted for a total of 75% of all antidepressants prescribed (Truter and Kotze, 1997). In patients over 55 years, the preferred antidepressants were amitriptyline and paroxetine (Aarts *et al,* 2014).

One of the main aims of this study was to show what kind of patient factors had an influence on the type of antidepressant prescribed. In studies conducted internationally, the following patient factors have been found to have an influence on the type of antidepressant prescribed, female gender (Aparasu *et al,* 1998; Ganguli *et al,* 1997), white patients compared to non-white patients (Aparasu *et al* 1998; Wells *et al,* 1994), older age, higher education level and repeated visits to a psychiatrist (Well *et al,* 1994).

6.8.1 Repeated use of antidepressant types

Based on the number of prescriptions for each antidepressant used and by the number of patients using each antidepressant, an average number of repeats had been calculated. The antidepressant with the most number of repeats was venlafaxine with an average of 15.13 repeats followed by fluoxetine with 11.77 repeats and citalopram with 10.67 repeats. This shows that patients on venlafaxine had shown the greatest persistence in returning for their medicine, which could indicate better compliance. This could be attributed to the better side effect profile of the drug so perhaps that it was better tolerated in the patients who have used it. The medicine possession ratio (MPR) is one way of measuring compliance. One south African study showed that after the first 4 months, only 34% of the patients were compliant with statistical significance shown between compliance and the active ingredient ($p<0.001$) (Slabbert *et al*, 2015). However, the MPR is not a clear indication that the patient is actually using the medication.

One study had found the types of drugs that are associated with better compliance, which were maprotiline (48.1%) followed by venlafaxine (35%), mirtazapine (29%), citalopram (29.6%), clomipramine (29.6%) and fluoxetine (26%) (Serna *et al,* 2010). One South African study showed that patients receiving venlafaxine had the greatest compliance (Slabbert *et al.,* 2015).

The high number of average repeats could be an indication of good adherence to the treatment regimen with the number of repeats being higher than the expected averages of antidepressants. A study in Spain had showed that half of the patients had abandoned or finished off their treatment during the second and fourth month while only 25% of the patients continued treatment for longer than 11 months (Serna *et al,* 2010). One study has shown that 28% to 40% of patients being treated for depression discontinued their medication causing significant increases in their health care expenditures owing to more complaints or hospitalization (Olfson *et al,* 2006).

Interestingly, half of the men had stopped their treatment after 2 months and half the women after 3 months. Compliance was found to be acceptable in only 22% of patients; there were differences in the duration of treatment between both males and females only in the first four months however, after the four months, these differences disappeared (Serna *et al,* 2010). Men are shown to be more likely to stop antidepressant therapy due to the sexual dysfunction

caused by the use of antidepressants (Segraves and Ballon, 2014). With regards to adherence it was shown that only 23% of patients in the study had highly adhered to their medications (Lin *et al,* 2011). One of the most important findings of this study was that only one out of five patients complied with treatment (duration of more than four months) with treatment periods being much shorter in males, 50% of which had abandoned treatment after two months (Serna *et al,* 2010). The therapy-related factors that can contribute to patient adherence include the number of medications, complexity of the treatment regimen, side effects, dosing frequency and the cost of treatment (Balkrishnan, 1998). In the current study it is unknown why the compliance was so good but, it is possible to speculate that the minimal cost of treatment coupled with professional patient management and short waiting times contribute to the persistence of patient with their treatment.

6.9 Concomitant drug use

Of all the drugs that had been prescribed with the antidepressants simultaneously, the most commonly prescribed of which had been Gabapentin and Clonazepam. Both of these are anti-epileptic agents that can be used as mood stabilizers and anxiolytics respectively.

The most commonly prescribed anti-psychotic drug had been risperidone. The use of antidepressants together with anti-psychotics has been widely documented; especially to note the efficacy of these drugs used together (Adams *et al,* 2013; Rief *et al,* 2016). One study showed that among all of the psychotropic drugs prescribed together with antidepressants, anxiolytics was prescribed to a greater extent than antipsychotics or hypnotics and sedatives (Cheung *et al,* 2015).

Systemic antihistamines in the form of promethazine had also been prescribed to a number of patients. This antihistamine is sometimes used to treat insomnia or sleeplessness over a short period due to the highly sedative property of the drug (Rossiter *et al,* 2010).

6.10 Costing

Depression is a disease of a chronic nature, there is an economic burden caused by depression not only in the direct cost involved in treating the condition in a continuous manner but also due to the indirect costs involved from a societal perspective. Depression adds to the economic burden as a result of its high prevalence, under-diagnosis and under-treatment (Ho *et al,* 2016). As a result of which the economic burden is increased due to possible hospitalization and days lost at work. The reasons why studies which measure the cost effectiveness of treatment have become vital within recent times is because of factors such as the increasing age of the population as well as limited economic growth and scarcity of resources which contributes to the importance of making more efficient use of resources that are available. By making use of such studies that measure the realistic cost of treating a depressed patients, health care providers are able to make better decisions that can benefit the patients as well as have economic advantages.

Studies done in the US have estimated that the cost of dealing with depression had amounted to USD 43.7 billion in the year 1990, of these costs, 76% had been indirect costs which include items such as days of lost work production as well as negative impact on other medical conditions (Greenberg *et al,* 1999). A similar kind of study had been done in the UK at the same time period to assess the total cost of treating depression. This study had shown that the total cost of treating depression had been GBP 4.4 billion in England and Wales, with 86.70% of the cost being accounted for as indirect costs (Kind and Sorenson, 1993). When the same study had been conducted 10 years later in the year 2000, it had shown that the total cost had increased drastically to GBP 9 billion, 96% of which had been from indirect costs (Thomas and Morris*,* 2003). A US based study showed that economically, of the $8747 annually spent on all health care, $447 of which were spent on MDD-specific medication (Lin *et al,* 2011).

In this study, the cost of treating each patient with antidepressants had been calculated by considering the patients dose and the cost per unit as shown on the public sector database price list, according to the tender prices at which these drugs are acquired.

The most expensive antidepressant used had been venlafaxine with a total cost of R5332.66 per month to treat the 37 patients who had been prescribed that type of antidepressant. This has also been shown in other studies where the cost effectiveness of using the different types of antidepressants had been compared. Patients who had received venlafaxine had a greater

return rate than the other antidepressants for repeats. The extent of which had been calculated to be up to 5 months more than the other antidepressants. The average cost of treating each of the 37 patients with venlafaxine R144.12 per month. This same type of pattern had been shown in international studies as well (Sado *et al*, 2009).

Fluoxetine had been the cheapest antidepressant with only a small difference, of between R1.02 and R3.00, as compared to the slightly more expensive citalopram. The most commonly prescribed dose for both fluoxetine and citalopram had been the 20mg which costs R8.44 and R9.46 respectively. The total cost of using fluoxetine to treat the 22 patients had been R329.16, with an average cost of R14.96.

As mentioned previously, citalopram had been prescribed to a greater number of patients than any other antidepressant. The total cost of using citalopram had been R865.59. The average cost of treating each patient using citalopram had been R13.74.

Since the development and use of SSRIs, there has been many studies that have been done to compare the cost effectiveness of using SSRIs and TCAs, with the results often showing that SSRIs are more cost effective for the treatment of depression compared to the older generation TCAs (NICE, 2004). A private medical scheme database showing prescribing in patients 18 years and younger, the total cost of antidepressant prescribing was R1 581 480 for the year 2009 with an average cost of R126, 02 per item (Truter, 2010). SSRIs and TCAs were most frequently prescribed and together accounted for 79.49% of the total cost (Truter, 2010). The highest cost was for SNRIs (R322.94 per product), selective mono-amine oxidase inhibitors (R177.20) and SSRIs (R155.52) (Truter, 2010).

A study done in Japan to compare the cost of antidepressant therapy alone with a combination of cognitive behavioral therapy and antidepressants had shown that the cost of combination therapy was JPY 449 655 per patient per year whilst antidepressant therapy alone had been JPY 422 244 per patient for the year (Sado *et al,* 2009).

It is clearly shown in this study that the use of SSRIs dominates above the use of other antidepressants. The main disadvantage of using SSRIs was that these drugs cost more compared to TCAs however, a study by Frank *et al* in 2001 show that although the cost of the drug itself is higher, the total cost of health care for a patient receiving SSRI therapy are the same or lower than the total health care cost of patients on other antidepressants.

The cost involved in the use of concomitant drugs had been calculated as a means to demonstrate the total cost of treating a single patient at the clinic. The cost of each of the concomitant drugs was shown in section 5.6. The cheapest drug used was the anti-psychotic risperidone, which resulted in a total cost of R291.94 for the 22 patients who had received treatment with the drug.

An adequate amount of funds is made available to purchase the basic essential psychotropic drugs which are then distributed at different levels of health care which ensure that these drugs are available in all provinces by their respective governing bodies, according to the National Department of Health. This however, is not the case in reality in the public health sector with health professionals which shows that prescribing is limited according to what drugs the hospital is able to acquire; this is regulated by the availability of funds. Depression thus represents an important health problem, which is associated not only with a reduction in patients 'quality of life, but also with a high social cost, directly, in terms of healthcare resource utilization, and indirectly, in terms of lost productivity.

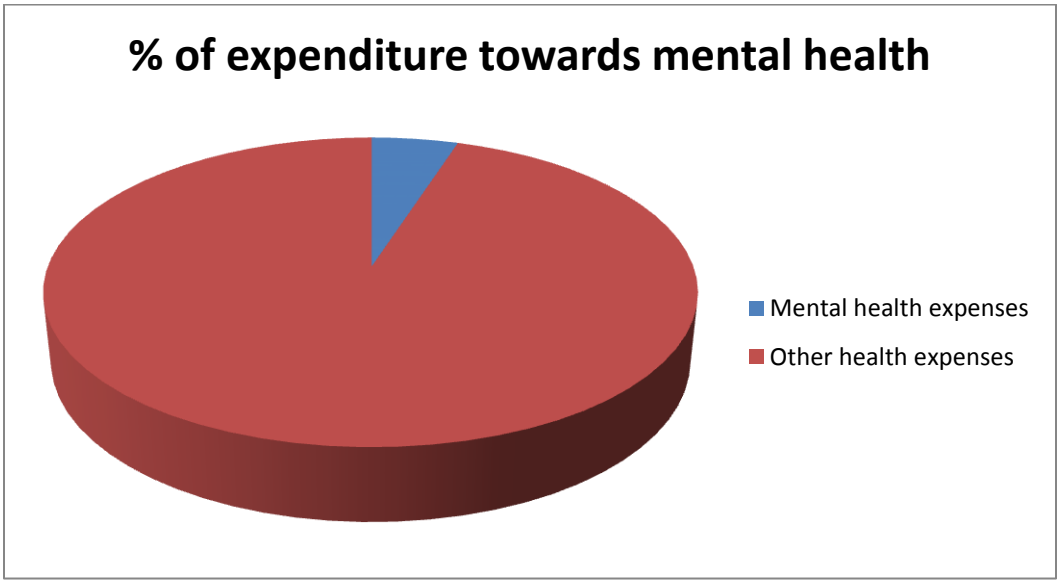


Figure 6.10.1: the percentage of the health care budget shows that a large proportion is spent on other health care expenses (95%) and only a small portion (5%) is dedicated to mental health expenses (WHO-AIMS, 2007).

The total cost of mood disorders that includes depression in the European union have been estimated to stand at around €113.4 billion, half of which has been related to the direct cost of sick leave which accounts for a large percentage of this (Gustavsson *et al,* 2011).

6.11 Change of antidepressant.

Throughout the study, there had been only 2 patients who had their types of antidepressant changed. The first of which was a 62 year old Black female which had her antidepressant changed from 20mg of citalopram to an end dose of 225mg of venlafaxine. She had first been tapered down off the citalopram dosing by reducing the dose slowly in intervals of a week at a time from 20mg to 10mg. She had then been moved onto venlafaxine in which a similar procedure was used to slowly increase the dose from 37.5mg a day for one week to 75mg per day for one week gradually doubling the dose until the total dose of 225mg had been reached. In order to achieve this dose she had to take 1 of the 75mg capsules as well as 1 of the 150mg capsules. She had been on the Citalopram for two months before the antidepressant was changed to venlafaxine.

The other patient was a 46 year old white female who had also been changed from fluoxetine to venlafaxine. She had also started on a low dose of fluoxetine of 20mg for a period of five months before she had been changed over to venlafaxine which was slowly increased weekly to reach an end dose of 150mg.

6.12 Limitations of the study

This study could have been conducted on a larger patient population to achieve a result that would be of greater statistical significance. The sample size was calculated for number of prescriptions and not by number of patients. A greater number of patients could have been used from a number of psychiatric out-patient clinics in order to achieve a result which represents a greater variety of patients.

This study had only considered antidepressants that are prescribed to treat psychiatric conditions. The off-label uses of these drugs therefore have not been included in this study which does not show the extent to which antidepressants are prescribed for other conditions. In addition, the use of antidepressants for other registered indications for example pain relief for diabetic neuropathy, was not considered in this study, since the study is restricted to the psychiatric out-patient clinic.

Since this study was a retrospective review of records, only direct medication costs were calculated and indirect costs were not considered.

Chapter Summary

The results of this study were compared with the results of both international and local drug utilization reviews. As expected, there had been a number of similarities in the results but, there had been a number of differences as well.

Chapter Seven: Conclusions and future studies

This study has shown the way in which the treatment of depression has shifted from TCAs, as shown in older drug utilization reviews, to the newer SSRIs and SNRIs. This could be attributed to the better safety profile which decreases the need for therapeutic monitoring and the introduction of generics for the SSRIs and SNRIs which contain costs.

In this South African population, a majority of the prescriptions had been made to female patients. Depression is more prevalent in women however; this could also show that women seek treatment more frequently than men. The finding concurs with international studies which show that depression is more prevalent in women than men.

Previous international studies have shown that the prevalence of depression varies among different race groups. Patient ethnicity was one of the factors which was considered an important epidemiological factor worth considering, the results of which has shown that the majority of which were patients of a Caucasian origin followed by Black, Indian and Coloured patients respectively. This patient factor has showed to have an association with the types of antidepressant prescribed.

The average age of the patients had been within close range of those of other antidepressant drug utilization reviews. The employment statuses as well as the marital statuses had also been considered as a means to gather more information about the type of population to which antidepressants were prescribed. Unemployed patients had formed the majority of the population whilst a majority of the population is married. That finding brings into question some of the studies which have concluded that married individuals are shown to enjoy a longer and healthier life both mentally and physically.

Citalopram had been the most frequently prescribed antidepressant among the entire patient population. SSRIs and SNRIs were prescribed in accordance with EDL guidelines according to the diagnosis. The EDL guidelines were not followed with TCAs not being used at all with venlafaxine, a drug which had not being mentioned in the EDL and STGs list, being prescribed often at the treatment facility.

Future studies can be done over a larger patient population in the public sector should be considered in order to provide more information on the prescribing patterns of antidepressants as well as the demographics of patients using these drugs.

This study had not taken into account the off-label use of antidepressants due to the fact that it had only collected data from a specialized psychiatric clinic. In order to have clearer insight into the manner in which these drugs are prescribed in the public sector, more studies should be done on patients receiving antidepressants for other conditions such as neuropathic pain in diabetes.

Chapter summary

The findings of this study provides useful information on the use of antidepressants in this particular patient population. The small sample size could be a limitation of the study however, this leaves room for future studies in the public sector with a greater sample size.

References:

Aarts N, Noordam R, Hofman A, Tiemier H, Stricker BH, Visser LH. 2014. Utilization patterns of antidepressants between 1991 and 2011 in a population-based cohort of middle-aged and elderly. *European Psychiatry* 29: 365–370.

Adams CE, Bergman H, Irving CB, Lawrie S. 2013. Haloperidol versus placebo for schizophrenia. Cochrane Database System. http://dx.doi.org/10.1002/14651858.CD003082.pub3 (John Wiley & Sons Ltd.).

Adler DA, Irish J, McLaughlin TJ, Perissinotto C, Chang H, Hood M. 2004. The work impact of dysthymia in a primary care population. *General Hospital Psychiatry* 26(4): 269–76.

Afifi TO, Cox BJ, Enns MW. 2006. Mental health profiles among married, never-married, and separated/divorced mothers in a nationally representative sample. *Social Psychiatry and Psychiatric Epidemiology* 41(2): 122–129.

American Psychiatric Association (APA). 2000. Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM-IV). Washington, DC: APA.

American Psychiatric Association (APA). 2013. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V). Washington, DC: APA.

American Psychiatric Association (APA). 2010. Practice guideline for the Treatment of Patients with Major Depressive Disorder (3rd edition). Washington, DC: APA.

Angermeyer M, Matschinger H, Carta M, Schomerus G. 2013. Changes in the perception of mental illness stigma in Germany over the last two decades. *European Journal of Psychiatry* , http://dx.doi.org/10.1016/j.eurpsy.2013.10.004

Aparasu RR, Mort J R, Sitzman S. 1998. Psychotropic prescribing for the elderly in office-based practice. *Clinical Therapeutic Journal* 20: 603–616.

Artigas F. 2015. Development in the field of antidepressants, where do we go to now. *European Journal of Neuropsychopharmacology* 25: 657–670.

Bartels SJ, Horn S, Sharkey P, Levine K. 1997. Treatment of depression in older primary care patients in health maintenance organizations. International Journal of Psychiatric Medicine 27, 215–231.

Bauer M, Monz BU, Montejo AL, Quail D, Dantchev N, Demyttenaere K, Cebrian A, Grassi L, Perahia DGS, Reed C, Tylee A. 2008. Prescribing patterns of antidepressants in Europe: Results from the Factors Influencing Depression Endpoints Research (FINDER) study. *European Psychiatry* 23: 66-73.

Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR. 2004. Prevalence of depression during pregnancy: systematic review. *Obstetrics and Gynecology* 103: 698–709.

Bernstein BL. Central issue importance as a function of gender and ethnicity. 1992. *Current Psychological Research Reviews* 10(4):241-252.

Bhagwagar Z, Rabiner EA, Sargent PA, Grasby PM, Cowen PJ. 2004. Persistent reduction in brain serotonin1A receptor binding in recovered depressed men measured by positron emission tomography. *Molecular Psychiatry* 9:386–392.

Birmaher B, Waterman GS, Ryan ND, Perel J, McNabb J,Balach L.1996. Randomized, controlled trial of amitriptyline versus placebo for adolescents with “treatment-resistant” major depression. *Journal of the American Academy of Child* 24: 483-492.

Birnbaum HG, Cremieux PY, Greenberg PE, Kessler RC. 2000. Management of major depression in the workplace. Disease Management & HealthOutcomes7 (3): 163–171.

Bradley CP. 1991. Decision-making and prescribing patterns—a literature review. *Family Practice* 8(3):276–287.

Bratberg E, Gjesdal S, Maeland JG. 2009. Sickness absence with psychiatric diagnoses: individual and contextual predictors of permanent disability. *Health Place* 15(1): 308–314.

Bukh JC, Bock C, Vinberg M, Kessing LV. 2013. The effect of prolonged duration of untreated depression on antidepressant treatment outcome *Journal of Affective disorders* 145: 42-48.

Burns J, King H, Saloojee S. 2007. KZN Treatment Protocol for Mental Disorders. KwaZulu Natal Provincial Directorate for Health.

Carvalho AF, Machado JR, Cavalcante JL. 2009. Augmentation strategies for treatment-resistant depression. *Current Opinions in Psychiatry* 22: 7–12.

Chen Y, Kelton CM, Jing Y, Guo JJ, Li X, Patel NC. 2008. Utilization, price, and spending trends for antidepressants in the US Medicaid program. *Research in Social and Administrative Pharmacy* 4: 244–257.

Cheung K, Aarts N, Noordam R, van Blijderveen JC, Sturkenboom MC, Ruite R, Visser LE, Stricker BH. 2015. Antidepressant use and the risk of suicide: A population-based cohort study. *Journal of Affective disorders* 174: 479-484

Clark J A, Potter DA, McKinlary JB. 1991. Bringing social structure back into clinical decision making. *Social Science & Medicine* 32(8): 853–866.

Collier DA, Stober G, Li T, Heils A, Catalano M, Di Bella D, Arranz MJ., Murray RM, Vallada HP, Bengel D, Muller CR, Roberts GW, Smeraldi E, Kirov G, Sham P, Lesch KP.1996. A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. *Molecular Psychiatry* 1: 453–460.

Compass BE, Connor-Smith J, Jaser SS. 2004. Temperament, stress reactivity, and coping: implications for depression in childhood and adolescence. *Journal of Clinical Child and Adolescent Psychology* 33: 21–31.

Courtney M, Dworsky A, Brown A, Cary C, Love K, Vorhies, V. 2011. Midwest evaluation of the adult functioning of former foster youth: Outcomes stage 26. Chicago: Chapin Hill at the University of Chicago.

Cowell AJ, Luo Z, Masuda YJ. 2009. Psychiatric disorders and the labor market: an analysis by disorder profiles. *Journal of Mental Health Policy* 12(1): 3–17.

Courtet P, Jaussent I, Lopez-Castromann J, Gorwood P. 2014. Poor response to antidepressants predicts new suicidal ideas and behavior in depressed outpatients. *European Neuropsychopharmacology* 14: 1650- 1658.

Coyne JC, Thompson R, Palmer SC. 2002. Marital quality, coping with conflict, marital complaints, and affection in couples with a depressed wife. *Journal of Family Psychology* 16: 26–37.

Danish University Antidepressant Group. 1986. Citalopram: Clinical Effect Profile in Comparison with Clomipramine: A Controlled Multicenter Study. *Psychopharmacology* 90: 131-138.

Danish University Antidepressant Group.1990. Paroxetine: A Selective Serotonin Reuptake Inhibitor Showing Better Tolerance, but Weaker Antidepressant Effect than Clomipramine in a Controlled Multicenter Study. *Journal of Affective Disorders* 18: 289–299.

Delgado P.L. 2000. Depression: the case for monoamine deficiency. *Journal of Clinical Psychiatry* 6: 7 –11.

Delini-Stula A, Mikkelsen H, Angst V.1995. Therapeutic efficacy of antidepressants in agitated anxious depression - a meta-analysis of moclobemide studies. *Journal of Affective Disorders* 35: 21-30.

Department of Health. 2006. Standard Treatment Guidelines and Essential Drugs List. 3rd ed. Pretoria: National Department of Health

Diagnostic and Statistical Manual of Mental Disorders. 2000. 4th Edition. APA.

Dorks M, Langner I, Dittmann U, Timmer A, Garbe E. 2013. Antidepressant drug use and off-label prescribing in children and adolescents in Germany: results from a large population-based cohort study. *European Journal of Child and Adolescent psychology* 22: 511–518.

Dube SR, Cook ML, Edwards VJ. 2010. Health-related outcomes of adverse childhood experiences in Texas. *Preventive Chronic Disease* 7: 52-64.

Earle JR, Smith MH, Harris CT, Longino CF. 1998. Women, marital status and symptoms of depression in a midlife national sample. *Journal of Women and Aging* 10(1): 41–57.

Farmer AE, McGuffin P. 2003. Humiliation, loss and other types of life events and difficulties: a comparison of depressed subjects, healthy controls and their siblings. *Psychological Medicine* 33: 1169–1175.

Frank L, Revicki D, Sorensen SV, Shih Y. 2001. The economics of selective serotonin reuptake inhibitors in depression: A critical review. *CNS Drugs* 15(1): 59–83.

Friis R and Nandunjappa G. 1986. Diabetes, depression and employment status. *Social Science and Medicine* 23: 471-475.

Gabe, J. 1990. Towards a sociology of tranquilizer prescribing. *British Journal of Addiction* 85: 41–48.

Ganguli M, Mulsant B, Richards S, Stoehr G, Mendelsohn A. 1997. Antidepressant use over time in a rural older adult population: The MOVIES project. *Journal of the American Geriatric Society* 45: 1501–1503.

Garcia-Cebrian A, Bauer M, Montejo A, Dantchev N, Demyttenaere K, Gandhi P, Grassi L, Monz B, Perahia DGS, Quail D, Tylee A. 2008. Factors influencing depression endpoints research (FINDER): Study design and population characteristics. *European Psychiatry* 23: 57-65

Gasse C, Peterson L, Chollet J, Saragoussi D. 2013. Pattern and predictors of sick leave among users of antidepressants: A Danish retrospective register-based cohort study. *Journal of Affective Disorders* 151: 959–966.

Givens JL, Houston HK, van Voorhees BW, Ford DE, Cooper LA. 2007. Ethnicity and preferences for depression treatment. *General Hospital Psychiatry* 29: 182-191.

Gondalez HM, Tarraf W, Whitfield KE, Vega WA. 2010. The epidemiology of major depression and ethnicity in the United States. *Journal of Psychiatric research* 44: 1043-1051

Gove, W. 1972. The relationship between sex roles, marital status and mental illness. *Social Forces* 51: 34–44.

Greenberg PE, Stiglin LE, Finkelstein SN, Berndt ER. 1993. The economic burden of depression in 1990. *Journal of Clinical Psychiatry* 54:405-418.

Greenberg PE, Kessler RC, Birnbaum HC, Leong SA, Lowe SW, Berglund PA, Corey-Lisle PK. 2003. The economic burden of depression in the United States: how did it change between 1990 and 2000? Journal of. Clinical Psychiatry 64: 1465–1475.

Groenewegen HJ, Uylings HB. 2000. The prefrontal cortexand the integration of sensory, limbic and autonomic information. *Progress in Brain Research* 126: 3–28.

Guaiana G, Andretta M, Corbari L, Mirandola M, Sorio A, D'Avanzo B. 2005. Antidepressant drug consumption and public health indicators in Italy, 1955 to 2000. *Journal of Clinical Psychiatry* 66: 75-85.

Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, Dodel R, Ekman M, Faravelli C, Fratiglioni L, Gannon B, Jones DH, Jennum P, Jordanova A, Jonsson L, Karampampa K, Knapp M, Kobelt G, Kurth T, Lieb R, Linde M, Ljungcrantz C, Maercker A, Melin B, Moscarelli M, Musayev A, Norwood F, Preisig M, Pugliatti M, Rehm J, Salvador-Carulla L, Schlehofer B, Simon R, Steinhausen HC, Stovner L J Vallat JM,Van den Berg P, Vos P, Xu W, Wittchen HU, Jonsson B, Olesen J. 2011. Cost of disorders of the brain in Europe 2010. European Neuropsychopharmacology 21(10): 718–779.

Gustavsson A,Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, Dodel R, Ekman M, Faravelli C, Fratiglioni L, Gannon B, Jones DH, Jennum P, Jordanova A, Jonsson L, Karampampa K, Knapp M, Kobelt G, Kurth T, Lieb R, Linde M, Ljungcrantz C, Maercker A, Melin B, Moscarelli M, Musayev A, Norwood F, Preisig M, Pugliatti M, Rehm J, Salvador

Hansson M, Chotai J, Bodlund O. 2010. Patients' beliefs about the cause of their depression. *Journal of Affective Disorders* 124: 45-59.

Herrenkohl EC, Herrenkohl RC, Egolf BP. 2003. The psychosocial consequences of living environment instability on maltreated children. *American Journal of Orthopsychiatry* 73(4): 367 380.

Ho SC, Chong HY, Chaiyakunapruk N, Tangiisuran B, Jacob SA. 2016. Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A systematic review. *Journal of Affective Disorders* 193: 1-10

Hess D. 2004. Retrospective Studies and Chart Reviews. *Respiratory Care* 49:1171–1174.

Holsboer F, Ising M. 2010. Stress hormone regulation: biological role and translation into therapy. *Annual Review of Psychology* 61: 81–109.

House JS, Landis KR, Umberson D. 1988. Social relationships and health. *Science* 241(4865): 540–545.

Hughes J, Gabbay M, Funnell E, Dowrick C. 2011.Exploratory review of placebo characteristics reported in randomized placebo controlled antidepressant drug trials. *Pharmacopsychiatry* 44: 1–8.

Hunter M, Battersby R, Whitehead M. 1986. Relationships between psychological symptoms, somatic complaints and menopausal status. *Maturitas* 8: 217-228.

Iacovides A, Fountoulakis KN, Kaprinis S, Kaprinis G. 2003. T he relationship between job stress, burnout and clinical depression. Journal of Affective Disorders 75 : 209–221

Ilyas S, Moncrieff J. 2012. Trends in prescriptions and costs of drugs for mental disorders in England,1998–2010. *British Journal of Psychiatry* 200: 393–398.

Inaba A, Thoits PA, Ueno K, Gove WR, Evenson RJ, Sloan M. 2005. Depression in the United States and Japan: gender, marital status, and SES patterns. *Social Science & Medicine* 61(11): 2280–2292.

Jang S, Kawachi I, Chang J, Boo K, Shin H, Lee H, Cho S. 2009. Marital status, gender, and depression: Analysis of the baseline survey of the Korean Longitudinal. *Study of Ageing* 69: 1608-1615.

Jodo E, Chiang C, Aston-JonesG. 1998. Potent excitatory influence of prefrontal cortex activity on noradrenergic locus coeruleus neurons. *Neuroscience* 83: 63–79.

Johnson CF, MacDonald HJ, Atkinson P, Buchanan AI, Downes N, Dougall N. 2012. Reducing long term antidepressants can reduce drug burden: a prospective observational cohort study. *British Journal of general practice* e773-e779

Jordan S, Koprivica V, Chen R, Tottori K, Kikuchi T, Altar A. 2002. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT1A receptor. *European Journal Of Pharmacology* 441: 137–140.

Kairuz TE, Truter I, Hugo J, Foxcroft CD. 2003 Prescribing patterns of tricyclic and selective serotonin reuptake inhibitor antidepressants among a sample of adolescents and young adults. Pharmacoepidemiol Drug Safety 12:379–82.

Karege F, Vaudan G, Schwald M, Perroud N, La Harpe R. 2005. Neurotrophin levels in postmortem brains of suicide victims and the effects of antemortem diagnosis and psychotropic drugs. *Molecular Brain Research* 136: 29–37.

Kemp BJ, Krause JS, Adkins RA. 1999. Depressive symptomatology among African-American, Latino, and Caucasian participants with SCI. *Rehabilitation Psychology* 44: 235-47.

Kendler KS, Gardner CO. 2011. A longitudinal etiologic model for symptoms of anxiety and depression in women. *Psychological Medicine* 41: 2035–2045.

Kennedy S. 2006. A review of antidepressant treatments today. *European Neuropsychopharmacology* 16: 619–624.

Kessler RC. 2003. Epidemiology of Women and depression. *Journal of Affective disorders* 74: 5-13.

Kim HK, McKenry M. 2002. The relationship between marriage and psychological well-being. *Journal of Family Issues* 23(8): 885–911.

Kind P, Sorensen J. 1993. The costs of depression. *International Clinical Psychopharmacology* 7:191-195.

Kirsch I. 2008 Challenging Received Wisdom: Antidepressants and the Placebo Effect. *McGill journal of medicine* 11(2): 219-222.

Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ. 2008. Initial Severity and Antidepressant Benefits: A Meta- Analysis of Data Submitted to the Food and Drug Administration. *Public Library of Science Medicine* 5(2): 45-62.

Krohnmuller K, Backenstrass M, Victor D , Postelnicu I, Schenkenbach C, Joest K, Fiedler P, Mundt C. 2011. Quality of marital relationship and depression: Results of a 10-year prospective follow-up study 128: 64-71

Lawrenson RA, Tyrer F, Newson RB, Farmer RD. 2000.The treatment of depression in UK general practice: selective serotonin reuptake inhibitors and tricyclic antidepressants compared. *Journal of Affective Disorders* 59:149-157.

Lemonde S, Turecki G, Bakish D, Du L, Hrdina PD, Bown CD, Sequeira A, Kushwaha N, Morris SJ, Basak A, Ou XM, Albert PR. 2003. Impaired repression at a 5-hydroxytryptamine1A receptor gene polymorphism associated with major depression and suicide. *Journal of Neuroscience* 23: 8788–8799.

Lemos JC, Wanat MJ, Smith JS, Reyes BA, Hollon NG, Van Bockstaele EJ, Chavkin C, Phillips PE. 2012. Severe stress switches CRF action in the nucleus accumbens from appetitive to aversive. *Nature* 7420: 402–406.

Lin H, Erickson SR, Balkrishnan R. 2011. Antidepressant Utilization, Adherence, and Health Care Spending in the United States: The Case of MDD Patients 2000-2007. *Health Outcomes Research in Medicine* 2: 79-89.

Lucas G, Compan V, Charnay Y, Neve RL, Nestler EJ, Bockaert J, Barrot M, Debonnel G. 2005. Frontocortical 5-HT4 receptors exert positive feedback on serotonergic activity: viral transfections, subacute and chronic treatments with 5- HT4 agonists. *Biological Psychiatry* 57: 918–925.

Lund C, Kleintjies S, Kakuma R, Flisher AJ. 2010. Public sector mental health systems in South Africa: inter-provincial comparisons and policy implications. *Social Psychiatric Epidemiology* 45: 393-404

Lund C, Stein DJ, Flisher AJ, Mehtar S. 2007. Challenges faced by South African health services in implementing the Mental Health Care Act. *South African Medical Journal* 97(5): 352-353.

Lund T, Kivimaki M, Labriola M, Villadsen E, Christensen KB. 2008. Using administrative sickness absence data as a marker of future disability pension: the prospective DREAM study of Danish private sector employees.Occupational and Environmental Medicine 65(1): 28–31.

Luppa M, Heinrich S, Angermeyer MC, Konig HH, Riedel-Heller SG. 2007. Cost-of-illness studies of depression: a systematic review Journal of Affective Disorders. 98: 29–43.

Mathers C, Loncar D. 2006. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine 3(*11): e442.

Mathews A, MacLeod C. 2005. Cognitive vulnerability to emotional disorders. Annual Review of *Clinical Psychology* 1: 167–195.

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH. 2005. Deep brain stimulation for treatment-resistant depression. *Neurons* 45: 651–660.

Manji HK, Quiroz JA, Sporn J, Payne JL, Denicoff K, Gray NA, Zarate CA, Charney DS. 2003. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult to treat depression. *Biological Psychiatry* 53: 707– 742.

Melfi C, Croghan T, Hanna MP, Robinson RL. 2000. Racial variation in antidepressant treatment in a medic aid population. *Journal of Clinical Psychiatry* 61(1): 16–21.

Merikangas KR, Prusoff BA, Kupfer D, Frank E. 1985. Marital adjustment in major depression. *Journal of Affective disorders* 9: 5-11

Mersky JP, Topitzes J, Reynolds AJ. 2013. Impacts of adverse childhood experiences on health, mental health, and substance use in early adulthood: A cohort study of an urban minority sample in the US. *Child Abuse & Neglect* 37(11): 917–925.

Meyer JH, 2012. Neuro-imaging markers of cellular function in major depressive disorder: implications for therapeutics, personalized medicine and prevention. *Clinical Pharmacology and Therapeutics* 91: 201–214.

Millan MJ, Lejeune F, Gobert A. 2000. Reciprocal autoreceptor and heteroceptor control of serotonergic, dopaminergic and adrenergic transmission in frontal cortex: a review, and relevance to the actions of antidepressant agents. *Journal of Psychopharmacology* 14: 114–138.

Ministry of Health. 2007. Patterns of Antidepressant Drug Prescribing and Intentional Self-harm Outcomes in New Zealand: An ecological study. Wellington: Ministry of Health.

Mnich E, Makowski A, Lambert M, Angermeyer M, von dem Knesebeck O. 2014. Beliefs about depression - do affliction and treatment experience matter? Results of a population survey from Germany. *Journal of Affective Disorders* 149- 383-396.

Monroe SM, Simons AD/ 1991. Diathesis-stress theories in the context of life-stress research: implications for the depressive disorders. *Psychological Bulletin* 110: 406–425.

Mork A, Pehrson A, Brennum LT, Nielsen SM, Zhong H, Lassen AB, Miller S, Westrich L, Boyle NJ, Sanchez C, Fischer CW, Liebenberg N, Wegener G, Bundgaard C, Hogg S, Bang Andersen B, Stensbol TB. 2012. Pharmacological effects of LuAA21004: a novel multimodal compound for the treatment of major depressive disorder. *Journal of Pharmacology* Experiments 340: 666–675.

Murphy GC, Athanasou JA. 1999. The effect of unemployment on mental health. Journal of *Occupational Psychology* 72: 83–99.

Murray CJ, Lopez AD. 1997. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 349: 1498-1504

Naismith SL, Norrie LM, Mowszowski L, Hickie IB, 2012. The neurobiology of depression in later-life: Clinical, neuropsychological, neuroimaging and pathophysiological features. *Progress in Neurobiology* 98: 99–143.

Nash J, Nutt D. 2007. Antidepressants. *Psychiatry: Specific treatments and disorders* 6:7 289-295.

National Collaborating Centre for Mental Health Commissioned by NICE. Management of depression in primaryand secondary care, National Clinical Practice Guideline Number 23. London: National Collaborating Centre for Mental Health, 2004.

National Department of Health (NDoH).User guide – UPFS version 1.Guide Reviewed and Edited by UPFS Tariff Committee 2009.

Neff JA, Hope SK. 1993. Race/ethnicity, acculturation, and psychological distress: fatalism and religiosity as cultural resources. *Journal of Community Psychology* 21: 3-20.

Nuijten M, Brignone M, Marteau F, den Boer JA, Hoencamp E. 2012. Cost-Effectiveness of Escitalopram in Major Depressive Disorder in the Dutch Health Care Setting. *Clinical Therapeutics* 34: 1364-1378.

Nutt DJ, 2002. The neuropharmacology of serotonin and noradrenaline in depression. *International clinical pharmacology* 17**:** S1–12.

OECD. 2012. Sick on the Job? Myths and Realities about Mental Health and Work. Mental Health and Work, OECD Publishing

Olfson M, Marcus SC, Tedeschi M. 2006. Continuity of antidepressant treatment for adults with depression in the United States. *American Journal of Psychiatry* 163:101-108.

Pacher P, Kohegyi E, Kecskemeti V, Furst S. 2001. Current trends in the development of new antidepressants. *Current Medicinal Chemistry* 8: 89–100.

Pan A, Franco OH, Wang Yf, Yu Z, Ye X, Lin X. 2008. Prevalence and geographic disparity of depressive symptoms among middle-aged and elderly in China. *Journal of Affective Disorders*, 105(1–3): 167–175.

Pan Y, Kuo K, Chan H, McCrone P. 2014. Cost-effectiveness and cost-utility of selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants in depression with comorbid cardiovascular disease. *Journal of Psychiatric* Research 74: 29-43.

Parabiaghi A, Franchi C, Tettamanti M, Barbato A, D'Avanzo B, Fortino I. 2011. Antidepressants utilization among elderly in Lombardy from 2000 to 2007: dispensing trends and appropriateness. *European Journal of pharmacology* 67(10):1077–83.

Pearlin LI, Schooler C. 1978. The structure of coping. *Journal of Health and Social Behaviour* 19: 2–21.

Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. 2006. The Danish Civil Registration System. A cohort of eight million persons. DanishMedicalBulletin 53 (4): 441–449.

Peters EJ, Slager SL, McGrath PJ, Knowles JA, Hamilton SP. 2004. Investigation of serotonin related genes in antidepressant response. *Molecular Psychiatry* 9: 879–889.

Pilkington P, Reavley N, Jorm A. 2013. The Australian public's beliefs about the causes of depression: associated factors and changes over 16years. *Journal of Affective Disorders* 150: 356–362.

Prince M, Patel V, Saxena S. 2007. No health without mental health. *Lancet* 370: 859-877.

Raymond CB, Morgan SG, Caetano PA. 2007. Antidepressant utilization in British Columbia from 1996 to 2004: increasing prevalence but not incidence. Psychiatry Service 58:79–84.

Read J, Cartwright C, Gibson K, Shiels C, Magliano L. 2015. Beliefs of people taking antidepressants about causes of their own depression. *Journal of Affective Disorders* 174: 150-156

Read J, Cartwright C, Gibson K, Shiels C, Haslam N. 2014. Beliefs of people taking antidepressants about causes of depression and reasons for increased prescribing rates. *Journal of Affective Disorders* 168: 236–242

Rief W, Barskyb AJ, Bingelc U, Doeringa BK, Schwartingd R, Wöhrd M, Schweigere U. 2016. Rethinking psychopharmacotherapy: The role of treatment context and brain plasticity in antidepressant and antipsychotic interventions. Neuroscience and Biobehavioral Reviews 60: 51–64

Rihmer Z, Angst J. 2008. Mood Disorders: Epidemiology (Chapter 13.2) in. Sadock BJ and Sadock VA (Eds). Kaplan & Sadock's Comprehensive Textbook of Psychiatry. (8th Edition). Lippincott Williams and Wilkins. New York, p1578.

Riolo S, Nguyen T, Greden J, King C. 2005. Prevalence of depression by race/ethnicity: Findings from the national health and nutrition examination survey III. *American Journal of Public Health* 95(6): 998–1000.

Rogoz Z. 2013. Combined treatment with atypical antipsychotics and antidepressants in treatment-resistant depression: preclinical and clinical efficacy. *Pharmacology repor*ts 65: 1535 - 1545

Rosholm J, Hallas J, Gram LF. 1993. Outpatient Utilization of antidepressants: A prescription database analysis. *Journal of Affective disorders* 27: 21-28

Ross CE. 1995. Reconceptualizing marital status as a continuum of social attachment. *Journal of Marriage and the Family* 57: 129–140.

Rossiter D, editor. 2010. South African Medicines Formulary. 9th edition. Cape Town: Health and Medical Publishing Group of the South African Medical Association.

Roxburgh S, MacArthur KR. 2014. Childhood adversity and adult depression among the incarcerated: Differential exposure and Vulnerability by race/ethnicity and gender. *Child Abuse and Neglect* 38: 1409-1420.

Sado M, Knapp M, Yamauchi K, Fujisawa D, So M, Nakagawa A, Kikuchi T, Ono Y. 2009. Cost-effectiveness of combination therapy versus antidepressant therapy for management of depression in Japan. *Australian and New Zealand Journal of Psychiatry* 43: 539-547

Schatzberg AF. 2002. Pharmacological principles of antidepressant efficacy. *Human Psychopharmacology* 17: S17– S22.

Schoenfelder EN, Sandler IN, Wolchik S, MacKinnon D. 2011. Quality of social relationships and the development of depression in parentally-bereaved youth. *Journal of Youth Adolescent* 40: 85–96.

Seedat S, Williams DR, Herman AA, Moomal H, Williams SL, Jackson PB, Myer L, Stein DJ. 2009. Mental health service use among South Africans for mood, anxiety and substance use disorders. *South African Medical Journal* 99(5 Pt 2): 346–352.

Segraves RT, Balon R. 2014. Antidepressant induced sexual dysfunction in men. *Pharmacology, Biochemistry and Behavior* 121: 132-137

Serna M, Cruz I, Real J, Gasco E, Galvan L. 2010. Duration and adherence of antidepressant treatment (2003 to 2007) based on prescription database. *European Psychiatry* 25: 206–213.

Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, Rafi-Tari S. 2004. Limbic-frontal circuitry in major depression: a path modelling metanalysis. *Journal of Neurological Imaging* 22: 409–418.

Simon, R. 2002. Revisiting the relationships among gender, marital status and mental health. *American Journal of Sociology* 107(4): 1065–1096.

Slavich GM, Monroe SM, Gotlib IH. 2011. Early parental loss and depression history: associations with recent life stress in major depressive disorder. *Journal of Psychiatric Research* 45: 1146–1152.

Stewart A. 1998. Choosing an antidepressant: effectiveness based pharmacoeconomics. *Journal of Affective disorders* 48: 125-133.

Storosum JG, Elferink A, van Zwieten B, van den Brink W, Gersons B, van Strik R, Broekmans BW. 2001. Short-term efficacy of tricyclic antidepressants revisited: a meta-analytic Study. *European Neuropsychopharmacology* 11: 173–180.

Strohschein L, McDonough P, Monette G, Shao Q. 2005. Marital transitions and mental health: Are there gender differences in the short-term effects of marital status change*? Social Sciences and Medicine* 21: 2293- 2303.

Thase ME, Trivedi MH, Rush AJ. 1995. MAOIs in the con temporary treatment of depression. *Neuropsychopharmacology* 12: 185–219.

Thomas CM, Morris S. 2003. Cost of depression among adults in England in 2000. British *Journal of Psychiatry* 183:514-519.

Tollefson GD, Holman SL. 1994. How long to onset of anti- depressant action: a meta-analysis of patients treated with fluoxetine or placebo. *International Clinical Psychopharmacology* 9: 245–250.

Tomlinson M, Grimsrud AT, Stein DJ, Williams DR, Myer L. 2009. The epidemiology of major depression in South Africa: results from the South African stress and health study. *South African Medical Journal* 99:367-373.

Treadway MT, Zald DH. 2011. Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neuroscience and Biobehavioral Reviews* 35: 537–555.

Truter I. 2010. Antidepressant prescribing to patients aged 18 years and younger: a pharmacoepidemiological study. 13th Euro Abstracts (Conference presentation)

Truter I, Kotze T. 1997. An investigation into the prescribed daily dose of fluoxetine. *South African Medical Journal* 87 (12) 1738-1743

Truter I, Kotze T. 2007. Prescribing of tricyclic antidepressant drugs in a South African primary care patient population. *International Journal of Pharmacy Practice* 14: 301-310

Turner RJ, Avison WR. 2003. Status variations in stress exposure: Implications for the interpretation of research on race, socioeconomic status, and gender. *Journal of Health and Social Behavior* 44(4): 488–505.

Tylee A, Gastpar M, Lepine JP, Mendlewicz J. 1999. DEPRES II (Depression Research in European Society II): a patient survey of the symptoms, disability and current management of depression in the community. *International Journal of Clinical Psychopharmacology* 14:139-151.

Uhr M, Tontsch A, Namendorf C, Ripke S, Lucae S, Ising M, Dose T, Ebinger M, Rosenhagen M, Kohli M, Kloiber S, Salyakina D, Bettecken T, Specht M, Putz B, Binder EB, Muller Myhsok B, Holsboer F. 2008. Polymorphisms in the drug transporter gene ABCB1 predictant in depressant treatment response indepression. Neurons 57:203–209.

Umberson D, Wortman CB, Kessler RC. 1992. Widowhood and depression: Explaining long-term gender differences in vulnerability. *Journal of Health and Social Behavior* 33: 10–24.

United States Department of Health and Human Services (USDHHS). Mental health: culture, race and ethnicity — a supplement to mental health: a report of the Surgeon General. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services, Rockville, MD; 2001.

Unverir P, Atilla R, Karcioglu O, Topacoglu H, Demiral Y, Tuncok Y. 2006. A retrospective analysis of antidepressant poisonings in the emergency department: 11 years' experience. *Human Toxicology* 25:605-612.

Van Marwijk HW, Bijl D, Ader HJ, de Haan M. 2001. Antidepressant prescription for depression in general practice in The Netherlands*. Pharmacological World Science* 23: 46 -59.

Van Scalkwyk K, Truter I. 2010 Prescribing patterns of selective serotonin reuptake inhibitors and selective serotonin and noradrenaline reuptake inhibitors in children and adolescents in a South African private practice setting. *Values in health* 13 (7) A384 (Conference Presentation).

Vetulani J and Nalepa I. 2000. Antidepressants: past, present and future. *European Journal of Pharmacology* 405: 351–363

Vitiello B and Swedo S. 2004. Antidepressant medications and children. *New England Journal of Medicine* 350: 1489–1491.

Vöhringer PA, Ghaemi SN. 2011. Solving the Antidepressant Efficacy Question: Effect Sizes in Major Depressive Disorder. *Clinical Therapeutics* 33(12): B49-B61.

Wang PS, Berglund P, Olfson M, Pincus HA, Wells KB, Kessler RC. 2005. Failure and delay in initial treatment contact after first onset of mental disorders in the National Co-morbidity Survey Replication. *Archives of General Psychiatry* 62(6):603–13.

Wells KB, Katon W, Rogers B, Camp P. 1994. Use of minor tranquilizers and antidepressant medications by depressed outpatients: Results from the medical outcomes study*. American Journal of Psychiatry* 151(5): 694–700.

Whisman MA, Uebelacker LA, Weinstock LM. 2004. Psychopathology and marital satisfaction: the importance of evaluating both partners. *Journal of Clinical Psychology* 72: 830–838.

WHO, 2008. The Global Burden of Disease: 2004 Update.

Williams DR, Sternthal M. 2010. Understanding racial-ethnic disparities in health: Sociological contributions. *Journal of Health and Social Behavior* 51: S15–S27 (Extra Issue).

Williams K. 2004. The transition to widowhood and the social regulation of health: consequences for health and health risk behavior. *The Journals of Gerontology Series B, Psychological Sciences and Social Sciences* 59(6): S343–349

Widom C, DuMont K, Czaja SJ. 2007. A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. *Archives of General Psychiatry* 64(1): 49-58.

Willner P, Scheel-Krüger J, Belzung C. 2012. The neurobiology of depression and antidepressant action. *Neuroscience and behavioural reviews* 38: 73-85.

Wing JK, Cooper JE, Sartorius N. 1974. Measurement and classification of psychiatric symptoms: An instructional manual for the PSE and CATEGO program. London. England: Cambridge University Press.

Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L , Jennum P, Lieb R, Maercker A, ,Preisig M, Salvador Carulla L, Simon R, Steinhausen HC. 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology* 21(9):655–679.

Wittchen HU. 2002. Generalized anxiety disorder: prevalence, burden, and cost tosociety. *Depression and Anxiety* 16(4):162-171

Wong ML, Dong C, Maestre-Mesa J, Licinio J.2008. Polymorphisms in inflammation-related genes are associated with susceptibility to major depression and antidepressant response. *Molecular Psychiatry* 13: 800–812.

World Health Organization 2013. Improving Health Systems and Services for Mental Health (Mental Health Policy and Service Guidance Package). Geneva

World Health Organization-Assessment Instrument for Mental Health Service .2007. WHO AIMS Report on Mental Health System in South Africa. WHO and Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa.

Worster A. 2004. Advanced Statistics: Understanding Medical Record Review (MRR) Studies. *Academic Emergency Medicine* 11: 187- 192

Wright BM, Eiland III EH, Lorenz R. 2013. Augmentation with atypical antipsychotics for depression: A review of evidence-based support from the medical literature. *Pharmacotherapy* 33: 344–359.

Zanardi R, Benedetti F, DiBella D, Catalano M, Smeraldi E. 2000. Efficacy of paroxetine in depression is influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *Journal of Clinical Psychopharmacology* 20:105–107.

Zito JM, Tobi H, de Jong-van den Berg LT, Fegert JM, Safer DJ, Janhsen K. 2006. Antidepressant prevalence for youths: A multi-national comparison. *Pharmacoepidemiology and Drug Safety* 15(11) 793–798.

Appendices

Appendix A: Permission from the Human Research ethics Committee

R14/49 Ms Nirvana Bagwathpersad

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130654

NAME: (Principal Investigator)	Ms Nirvana Bagwathpersad
DEPARTMENT:	Pharmacology Helen Joseph Hospital Psychiatric Out-Patient Facility
PROJECT TITLE:	Antidepressant Prescribing in Gauteng: A Public Sector Drug utilization Review
DATE CONSIDERED:	28/06/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Mrs Shirra Moch
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	10/07/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

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

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Letter for permission to conduct research at the CMJAH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. L. Mngomezulu
Office of the Clinical Director
Tell: (011): 488-3365
Fax: (011): 488-3753
11th June 2014

Ms. Nirvana Bagwathpersad
Department of Pharmacy and Pharmacology
School of Therapeutic Sciences

Dear Ms. Bagwathpersad

RE: "antidepressant prescribing in Gauteng: a public sector drug utilization review"

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic hospital will not in anyway incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the Head of Department and Unit Manager or Sister in Charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / not supported

pp _____
Dr. M.J. Mofokeng 13/06/2014
Clinical Director
DATE:

Approved / ~~not approved~~

_____ CEO
Ms. G. Bogoshi
Chief Executive Officer
DATE: 13/06/2014

Appendix C: Data variables coding

Variable	Type	Number
Sex	Female	1
	Male	2
Race	Black	1
	White	2
	Coloured	3
	Indian	4
Employment status	Unemployed	1
	Pensioner	2
	Employed	3
Marital status	Married	1
	Single	2
	Divorced	3
	Widowed	4
ICD Code	MDD	1
	MDD.GAD	2
	MDD.Psychosis	3
	Mild Depression	4
	MDD.Epilepsy	5
	MDD.BPD	6
Antidepressant	Fluoxetine	1
	Citalopram	2
	Venlafaxine	3
	Amitriptyline	4

Appendix D: ICD-10 codes with their definitions

ICD-10 code	Definition
F32	Depressive disorder
F32.0	Mild depressive episode
F32.1	Moderate depressive episode
F32.2	Severe depressive episode without Psychotic symptoms
F32.3	Severe depressive episode with psychotic symptoms
F32.8	Other depressive episodes
F32.9	Depressive Episode, unspecified
F33	Recurrent depressive disorder, current episode mild
F33.1	Recurrent depressive disorder, current episode moderate
F33.2	Recurrent depressive disorder, current episode severe with no psychotic symptoms
F33.3	Recurrent depressive disorder, current episode sever with psychotic symptoms
F33.4	Recurrent depressive disorder, currently in remission
F33.8	Other recurrent depressive disorders
F34	Persistent mood disorders
F34.0	Cyclothymia
F34.1	Dysthymia
F40	Phobic disorders
F40.0	Agoraphobia
F40.1	Social Phobia
F41.1	Generalized anxiety disorder
F41.2	Mixed Anxiety and depressive disorder
F42	Obsessive compulsive disorder