TREATMENT OF PARKINSON’S DISEASE IN SOUTH AFRICA AND INVESTIGATION OF RISK FACTORS CAUSING DYSKINESIAS

R. GAIDA

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TREATMENT OF PARKINSON’S DISEASE IN SOUTH AFRICA AND INVESTIGATION OF RISK FACTORS CAUSING DYSKINESIAS

By

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Submitted in fulfilment of the requirements for the degree of Magister Pharmaciae to be awarded at the Nelson Mandela Metropolitan University

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Co-Supervisor: Prof J. Carr
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- Last, but definitely not least, my parents, brother, friends and family
I, Razia Gaida, 207060291, hereby declare that the dissertation for my qualification of Magister Pharmaciae is my own and has not been previously submitted for assessment to another university or for another qualification.
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<th>Description</th>
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<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;</td>
<td>Serotonin receptor gene</td>
</tr>
<tr>
<td>AIM</td>
<td>Abnormal involuntary movement</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical-Therapeutic-Chemical</td>
</tr>
<tr>
<td>BBB</td>
<td>Blood brain barrier</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>COMT</td>
<td>Catechol-o-methyl-transferase</td>
</tr>
<tr>
<td>DATATOP</td>
<td>Deprenyl (selegiline) and tocopherol antioxidative treatment</td>
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<td>D&lt;sub&gt;1&lt;/sub&gt;, D&lt;sub&gt;2&lt;/sub&gt;, D&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Dopamine receptor genes</td>
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<td>DC90%</td>
<td>Drug cost 90%</td>
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<td>DDD</td>
<td>Defined daily dose</td>
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<tr>
<td>DU90%</td>
<td>Drug utilisation 90%</td>
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<td>DUR</td>
<td>Drug utilisation review</td>
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<td>ELLDOPA</td>
<td>Early versus Later Levodopa in Parkinson’s Disease</td>
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<td>FRTI</td>
<td>Faculty of Health Sciences Research, Technology and Innovation</td>
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<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
</tr>
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<td>HREC</td>
<td>Human Research Ethics Committee</td>
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<td>LID</td>
<td>Levodopa-induced-dyskinesia</td>
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<td>LRRK2</td>
<td>Leucine-rich repeat kinase 2</td>
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<tr>
<td>MAO-B</td>
<td>Monoamine oxidase B</td>
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<td>MIMS</td>
<td>Monthly Index of Medical Specialties</td>
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<td>MPTP</td>
<td>1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine</td>
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<td>mRNA</td>
<td>Messenger ribonucleic acid</td>
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<td>Nicotinamide adenine dinucleotide phosphate</td>
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<tr>
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<tr>
<td>NAPPI</td>
<td>National Pharmaceutical Product Interface</td>
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<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
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<td>NMS</td>
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<td>NOS</td>
<td>Nitric oxide synthase</td>
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<td>PDD</td>
<td>Prescribed daily dose</td>
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<td>PINK-1</td>
<td>PTEN-induced putative kinase 1</td>
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<td>Mitochondrial polymerase gamma 1</td>
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<td>QoL</td>
<td>Quality of life</td>
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<td>Rapid eye movement</td>
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<td>UPDRS</td>
<td>Unified Parkinson’s disease rating scale</td>
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ABSTRACT

Background: Levodopa is still thought of as the 'gold standard' symptomatic treatment for Parkinson’s disease. However, after four to five years of treatment, levodopa efficacy tends to decline even if there was a good initial therapeutic response. The ideal treatment of Parkinson’s disease is a much debated issue with a range of guidelines available.

Objectives: This study was undertaken to analyse medication use and prescribing patterns as well as to determine the risk factors involved in causing dyskinesias in Parkinson’s sufferers.

Methods: The study consisted of two parts, namely a drug utilisation review (DUR) and a questionnaire survey. There were 25 523 antiparkinsonian records consisting of 5 168 patients for the year 2010. The questionnaires were verbally administered to patients diagnosed with Parkinson’s disease. A total of 43 patients were interviewed.

Results: The average age of the population was 70.74±10.37 years, with the oldest patient being 100 years. Females constituted 59.17% (5 168: n = 3 058) of the total number of patients. The most common antiparkinsonian products dispensed were combination drugs containing levodopa with a decarboxylase inhibitor and some with a COMT-inhibitor as well (46.5%; n = 11 875). Males represented 53.49% (43: n = 23) of the patients included in the questionnaire survey. A review of the medical records showed that patients with dyskinesias were diagnosed with Parkinson’s disease at a younger age and had experienced longer disease duration.

Conclusion: Parkinson’s disease is an under-recognised condition in South Africa. Treatment needs to be individualised and based on evidence-based guidelines. Further studies in South Africa, as well as SSA (sub-Saharan Africa), need to be conducted on both the prevalence as well as the treatment of Parkinson’s disease.
CHAPTER 1

Introduction
1.1 Introduction

‘This formidable opponent has left my movements slow and clumsy. But I am determined to fight back. I watch my family and friends watching me as I tread cautiously down stairs holding tightly onto the banister. They walk in front of me in case I should fall, concern evident in their furtive backward glances.’ (Ronald Rodrigues, Parkinson’s sufferer, 2011).

Patients suffering from Parkinson’s disease end up living a life of frustration and lost independence. They suffer embarrassment due to a widespread lack of knowledge and understanding of Parkinson’s disease which has a negative effect on the social aspects of patients’ lives. Caregivers need to adjust their expectations of the patient and be supported by doctors and the community to cope with their mood swings, the debilitating adverse effects of medication and disease progression such as dyskinesias, as well as the immense emotional distress faced by Parkinson’s sufferers on a daily basis.

This study was undertaken to determine the risk factors involved in causing dyskinesias in Parkinson’s sufferers as well as to analyse medication use and prescribing patterns. It consists of two parts, a drug utilisation review (DUR) and a questionnaire survey. The DUR portion involves the analysis of a prescription database requested from a national community pharmacy group, providing objective data. The questionnaire surveys provide objective data such as patient demographics and drug use; and subjective data such as the perceived benefit of the medication and severity of dyskinesias.

1.2 Background to the study

Parkinson’s disease is a progressive neurodegenerative disorder which affects one in every 100 people over the age of 65 years (Singh, Pillay and Choonara, 2007: 29). It is characterised by three hallmark symptoms: bradykinesia (slowed movement), tremor and muscle rigidity (Singh, et al., 2007: 29; Obeso, Olanow, and Nutt 2000: 2). The underlying pathology of Parkinson’s disease is a loss of the dopamine
producing neurons in the substantia nigra of the brain (Foster and Hoffer, 2003: 177). Therefore, it is logical that the aim of treatment would be to increase the levels of dopamine in the brain.

The aetiology of idiopathic Parkinson’s disease remains largely unknown, but studies have shown there are genetic and even environmental links, often with an interplay between the two (Schapira and Jenner, 2011: 1 050). Some studies have indicated that the earlier in life that Parkinson’s disease presents, the more likely it is that there is a genetic link (Nelson, Berchou and LeWitt, 2005: 1 075; Warner and Schapira, 2003: 16). This has been determined by twin and family studies in the hope of identifying the susceptible genes. The most important risk factor however is, simply, aging (Schapira and Jenner, 2011: 1 049).

Patients are diagnosed with Parkinson’s disease after a series of neurological examinations and diagnostic tests. There is a risk of misdiagnosis, especially during the early stages of Parkinson’s disease). For example, the misdiagnosis rate in Italy ranged from approximately 10% by movement disorder specialists to 50% when the patient is seen in a primary health care facility (Alberio and Fasano, 2011: 326).

There is little reported on the incidence and prevalence of Parkinson’s disease in Africa due to the lack of studies and the short life expectancy of the population (Okubadejo, Bower, Rocca and Maraganore, 2006: 2 050). It has been shown, however, that the population aged 60 years and older is expected to double in SSA by 2030 and double again by the year 2050 (Velkoff and Kowal, 2007: 4). In fact, the number of older people in SSA is growing faster than the rest of the world and will continue to do so in the future (Velkoff and Kowal, 2007: 5). As ageing is a risk factor in the development of Parkinson’s disease, it would be important to determine the incidence and prevalence of Parkinson’s disease in SSA in order to determine the future economic burden society may face. An article looking at Parkinson’s disease in Africa, with particular focus on Tanzania, reported that there was an overwhelming shortage of health workers and resources (Pearce and Wilson, 2007: 116). Infectious diseases like HIV and malaria tended to overshadow neurological disorders like Parkinson’s disease in these regions (Pearce and Wilson, 2007: 116). One study
(Dotchin, Msuya and Walker, 2007: 122) indicated that there is a low incidence of Parkinson’s disease in SSA, but noted that studies had only been conducted on small populations previously. Some reasons put forth for this low reported incidence include under diagnosis of Parkinson’s disease, differences in diagnostic criteria and early mortality in these populations due to other causes (Dotchin, et al., 2007:122).

A South African study conducted in Durban aimed to determine the prevalence of Parkinson’s disease amongst black South Africans (Cosnett and Bill, 1988: 281). The records of all patients seen in a neurological consultation at three provincial hospitals in Durban for a period of seven years between 1978 and 1985 were summarised and amounted to a total of 2 638 records. The three hospitals included were King Edward VIII hospital which dealt mostly with black South Africans, R.K. Khan hospital, which dealt mostly with Indian patients and Addington hospital which dealt mostly with white patients (Cosnett and Bill, 1988: 282). The researchers also obtained data regarding the annual consumption of levodopa at the three hospitals under investigation. Of the total number of consultations, 1 984 were black South Africans, 395 were Indian and 259 were white South Africans. Of the black South Africans, the total number of Parkinson’s disease cases were three and the calculated rate per 1 000 patients amounted to 1.5, whereas, for white South Africans, the total number of Parkinson’s disease cases seen was six and the calculated rate per 1 000 patients was 23.1 (Cosnett and Bill, 1988: 282). The total amount of levodopa consumed at each of these hospitals was determined in relation to the total number of outpatients seen. It was shown that Addington hospital dealing mostly with white South Africans consumed on average six times more levodopa (24 530g) per year than King Edward VIII which dealt mostly with black South African patients (4 470g) (Cosnett and Bill, 1988: 282). The age group with the highest prevalence of Parkinson’s disease was found to be 50 years and younger (22.8%) in the case of black South Africans and decreasing with increasing age to just 1.8% of patients in the 70 year age group. These percentages were calculated according to the total number of consultations for each race group. White South Africans showed 47.8% of patients with Parkinson’s disease in the age group 50 years and younger, decreasing to 14.3% in the 70 year age group which was still higher than that of the black South Africans. Indian South Africans held an intermediate position (Cosnett
and Bill, 1988: 283). The study concluded that the lower rate of Parkinson’s disease amongst black South Africans could be due to the lower life expectancy or failure of elderly patients to attend hospitals (Cosnett and Bill, 1988: 283). This study was conducted more than 20 years ago and the need for updated information in South Africa is important to determine the number of patients currently suffering from Parkinson’s disease and to project the number of patients expected to suffer from this condition in the future.

In the more developed northern hemisphere, the prevalence is higher, since the life expectancy of the population is longer possibly due to various genetic and environmental factors. Approximately 100 000 people are living with Parkinson’s disease in America (Obeso, et al., 2000: 2) and in Europe there is an incidence of 1.8% in people between the ages of 65 to 69 years with the incidence increasing to 2.6% in people aged 85 to 89 years (De Rijk, Launer, Berger, Breteler, Dartigues, Baldereschi, Fratiglioni, Lobo, Martinez-Lage, Trenkwalder and Hofman, 2000: 21). In 2005, the number of individuals suffering from Parkinson’s disease in the 10 most populated countries in the world, was between 4.1 and 4.6 million and is expected to double by 2030 (Keus, Oude Nijhuis, Nijkrake, Bloem and Munneke, 2012: 1).

1.3 Problem definition

Levodopa is still thought of as the ‘gold standard’ symptomatic treatment for Parkinson’s disease. However, after four to five years of treatment, levodopa efficacy tends to decline even if there was a good initial therapeutic response (Singh, et al., 2007: 30; Stern, 2001: 27; Garret, Rosas, Simões, Vieira and Costa, 1998: 99).

Long-term treatment with levodopa results in the emergence of pharmacodynamic changes to the response of the drug. Patients tend to experience motor fluctuations and dyskinesias. Dyskinesias will occur in up to 80% of patients who have been on levodopa therapy for long periods of time and they tend to occur first on the side more severely affected by the Parkinson’s disease (Ha and Jankovic, 2011: 8). A major controversy in Parkinson’s disease therapy is whether to withhold levodopa as
the initial therapy in order to delay the onset of dyskinesias or to provide the patient with this ‘gold standard’ therapy in order to obtain maximum symptomatic control. Dyskinesias are loosely classified as either choreic or dystonic (Nadjar, Gerfen and Bezard, 2009: 2; Thanvi, Lo and Robinson, 2007: 385-386). The underlying molecular mechanism for the development of these dyskinesias is poorly understood. Several studies agree that young age of disease onset, disease severity and high doses of levodopa increase the risk for dyskinesias (Calabresi, Di Filippo, Ghiglieri, Tambasco and Picconi, 2010: 1 106; Voon, Fernagut, Wickens, Baunez, Rodriguez, Pavon, Juncos, Obeso and Bezard, 2009: 1 140; Encarnacion and Hauser, 2008: 58; Thanvi, et al., 2007: 384; Sossi, de la Fuente-Fernandez, Schulzer, Adams and Stoessl, 2006: 1 051). Recently, studies into the levodopa dose per kilogram have revealed this to be another important factor to consider when determining a patients’ risk for the development of dyskinesias (Sharma, Bachmann and Linazasoro, 2010: 492; Sharma, Ross, Rascol and Brooks, 2008: 495).

This study will consider the patterns of prescribing for Parkinson’s disease in South Africa in order to identify the most commonly prescribed drugs and the economic burden these costs place on the patients. Patients will also be interviewed and their medical records retrospectively reviewed in order to determine whether the above risk factors do indeed play a role in the development of dyskinesias in patients with Parkinson’s disease.

1.4 Research objectives

The primary aim of the study is:
To analyse the treatment of Parkinson’s disease in South Africa and investigate the risk factors involved in the onset of dyskinesias.

The specific objectives of the DUR are to:

• determine the gender and age distribution of patients diagnosed with Parkinson’s disease;
• analyse the prescribing patterns for Parkinson’s disease in the private sector on a national level; and
• determine the average cost of medication per annum.

The specific objectives of the questionnaire survey are to:

• determine the age of onset of Parkinson’s disease;
• establish when levodopa therapy was initiated, relative to the date of diagnosis;
• determine if and when the emergence of dyskinesias occurred;
• determine the severity of the dyskinesias;
• assess the risk factors involved in the emergence of these dyskinesias.

1.5 Division of chapters

The final dissertation is divided as follows:

• Chapter 1 - Introduction
• Chapter 2 - An Overview of Parkinson’s Disease
• Chapter 3 - Treatment of Parkinson’s Disease
• Chapter 4 - Methodology
• Chapter 5 - Results and Discussion of the Drug Utilisation Review
• Chapter 6 - Results and Discussion of the Questionnaire Survey
• Chapter 7 - Conclusion
CHAPTER 2
An overview of Parkinson’s disease
2.1 Introduction

In Parkinson’s disease, the disease process affects the darkly pigmented substantia nigra, an area which produces a large amount of dopamine. Damage to the substantia nigra will give rise to the hallmark symptoms of bradykinesia, tremor and rigidity. In Parkinson’s disease there is a decrease in the normally high levels of dopamine found in the basal ganglia, due to the death of the dopamine producing cells of the substantia nigra. Parkinson’s disease is a slowly progressive disease associated with increasing disability. The basis of treatment would therefore be to increase the levels of dopamine in the basal ganglia (Weicker, Kinscherf, Diserens, Deigner and Struder, 2001: 17).

2.2 Etiology of Parkinson’s disease

The aetiology of Parkinson’s disease is seen to be a combination of environmental and genetic factors, but genetic predisposition is increasingly seen as the main cause (Schapira and Jenner, 2011: 1 050). The earlier the onset of Parkinson’s disease, the more likely there is a genetic link (Nelson, et al., 2005: 1 075; Warner and Schapira, 2003: 16). 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a toxin that is relatively specific to the neurons causing Parkinson’s disease in animal models (Sian, Youdim, Riederer and Gerlach, 1999). MPTP is able to induce most of the biochemical, pathological and clinical features of Parkinson’s disease in nonhuman primates (Sian, et al., 1999).

The mutated genes found in familial Parkinson’s disease include genes encoding for mitochondrial proteins such as Parkin, PTEN-induced putative kinase 1 (PINK-1), DJ-1, mitochondrial polymerase gamma 1 (POLG1) and genes coding for non-mitochondrial proteins such as α-synuclein and leucine-rich repeat kinase 2 (LRRK2) (Aquilano, Baldelli, Rotilio and Ciriolo, 2008: 2 418; Zhang, Dawson and Dawson, 2006: 37). The strongest risk factor for the development of Parkinson’s disease, however, is aging (Schapira and Jenner, 2011: 1 050). Unfortunately, little is known with respect to understanding what processes are involved in aging that make it such a prominent risk factor. A review in the United Kingdom reported that environmental
factors involved a range from general factors including industrialisation, well water, rural environments and plant-derived toxins, to more specific causes such as carbon monoxide, carbon disulfide and organic solvent exposure (Schapira and Jenner, 2011: 1050).

With respect to environmental influences, a study was conducted which aimed to determine the effect of caffeine intake on the risk of Parkinson’s disease in males and females (Ascherio, Zhang, Hernán, Kawachi, Colditz, Speizer and Willett, 2001: 56). Among men, there was a significant inverse relationship between coffee intake and Parkinson’s disease risk. With women there was a U-shaped relationship, with the lowest risk being amongst women consuming one to three cups of coffee on a daily basis (Ascherio, *et al.*, 2001: 59). However, the association could be due to components of coffee other than caffeine. To address this, the study looked at the risk of Parkinson’s disease and the intake of caffeine from non-coffee sources. Among the men, there was a strong inverse relationship between the intake of caffeine from non-coffee sources and the risk of Parkinson’s disease and amongst women there were no significant associations found. The findings of this study were consistent with the results of similar studies conducted in Germany and Sweden (Ascherio, *et al.*, 2001: 60).

A six week randomised placebo controlled trial was done to determine the effect of caffeine in Parkinson’s disease (Postuma, Lang, Munhoz, Charland, Pelletier, Moscovich, Filla, Zanatta, Romenets, Altman, Chuang and Shah, 2012: 652). A total of 76 patients were screened and 61 were randomised to 100 to 200mg of caffeine twice daily compared to placebo. Patients were included in the study if they were conclusively diagnosed with idiopathic Parkinson’s disease and also suffered from excessive daytime sleepiness (Postuma, *et al.*, 2012: 652). The results showed that there were decreases in Unified Parkinson’s Disease Rating Scale (UPDRS) scores, but not significantly. Also, there were no significant differences found in fluctuations and dyskinesias with caffeine compared to placebo nor was there any decrease in somnolence (Postuma, *et al.*, 2012: 654, 655). However, there were decreases in bradykinesia and rigidity and the caffeine was not found to increase action tremors (Postuma, *et al.*, 2012: 654). However, the study had many limitations and further
2.2.1 Lewy bodies in Parkinson’s disease

The Lewy body is a neuronal inclusion containing α-synuclein found in the substantia nigra and other regions which are associated with significant loss of neurons (Gibb and Lees, 1988: 745; Wakabayashi, Tanji, Odagiri, Miki, Mori and Takahashi, 2012: 1). They are also present in many surviving cells of the substantia nigra in Parkinson’s disease patients and can therefore serve as a diagnostic marker (Gibb and Lees, 1988: 745). The actual mechanism of Lewy body neuroprotection or neurotoxicity is not well understood. The idea of neurodegeneration caused by Lewy bodies was based on the fact that there was neuronal loss in the areas of predilection for the Lewy bodies including the substantia nigra. The number of Lewy bodies in patients with mild to moderate neuronal loss in the substantia nigra is higher than in patients with severe neuronal depletion which suggests that Lewy bodies are found in dying neurons. Also, Lewy bodies may affect axonal transport and the cortical density of Lewy bodies could be a correlate of cognitive impairment in Parkinson’s disease (Wakayabashi, et al., 2012: 7).

Lewy neurites are found to be present before Lewy bodies at most sites (Del Tredici and Braak, 2012: 597). They are likely derived from cytoskeletal elements and are associated with the disruption of axonal and cellular functioning. The resulting impaired neuronal transport leads to the formation of α-synuclein in the neuronal soma and contributes to the formation of Lewy bodies (Del Tredici and Braak, 2012: 597). Incidental Lewy body disease in which incidental Lewy neurites and Lewy bodies are seen in neurologically asymptomatic patients is described in unaffected elderly patients, and may represent a preclinical phase of the disease (Del Tredici and Braak, 2012: 599).
2.3 Incidence and Prevalence of Parkinson’s disease

There is an approximately 1.5 times higher risk of Parkinson’s disease for men than women (Burn, 2007: 78; Fargel, Grobe, Oesterle, Hastedt and Rupp, 2007: 208; Miller and Cronin-Golomb, 2010: 2 695). The incidence of a disease is the number of new cases identified over a period of time in a defined area, whereas the prevalence of a disease is the number of existing cases of a particular disease in a defined area.

Overall there are not many incidence or prevalence studies available on Parkinson’s disease (Dorsey, Constantinescu, Thompson, Biglan, Holloway, Kieburtz, Marshall, Ravina, Schifitto, Siderowf and Tanner, 2007: 384-386). However, of those that have been conducted, there is a trend to the effect that there is a higher incidence of Parkinson’s disease in more developed countries where people have a longer life expectancy as opposed to developing countries where the life expectancy is shorter. However, the life span may not be the only confounding factor. Other influences such as environmental conditions and genetic differences also play a role.

Studies in the United States show a prevalence of approximately 100 000 people with Parkinson’s disease with the average age of onset being 60 years (Obeso, et al., 2000: 2). European studies report an incidence of 1.8% in patients between the ages of 65 and 69 years, with an increase to 2.6% of patients between the ages of 85 and 89 years (De Rijk, et al., 2000: 21).

A Spanish study determined the prevalence of Parkinson’s disease and other parkinsonian disorders in three Spanish communities (Benito-León, Bermejo-Pareja, Rodríguez, Molina, Gabriel and Morales, 2003: 269). The study showed that 68% of the total 118 subjects were affected with Parkinson’s disease. The prevalence of Parkinson’s disease was also shown to increase with age, but decrease beyond the ages of 80 years for men and 85 years for women (Benito-León, et al., 2003: 269). The survey confirmed a higher prevalence in males than females. However, it did show a higher prevalence for women between the ages of 80 years to 84 years. Prevalence figures are influenced by disease duration and incidence and the higher
prevalence in this age group could be due to a difference in survival after the disease onset (Benito-León, et al., 2003: 273).

African studies, however, have demonstrated a much lower incidence of Parkinson’s disease, but there is limited information regarding the prevalence of this disease in Africa (Okubadejo, et al., 2006: 2 050). The incidence of Parkinson’s disease increases with age from 1.7/10 000 person-years between the ages of 50 years and 59 years to 9.3/ 10 000 person-years between the ages of 70 years to 79 years.

2.4 Diagnosis of Parkinson’s disease

Patients are diagnosed with Parkinson’s disease after a series of neurological examinations and diagnostic tests. Two of the three cardinal symptoms of Parkinson’s disease, bradykinesia, tremor and rigidity, need to be present before a diagnosis can be made, however, this is just a guideline (Berg and Poewe, 2012: 1; Marjama-Lyons and Koller, 2001: 24).

Parkinson’s disease is characterised by the progressive loss of dopaminergic neurons in the substantia nigra of the brain, resulting in dopamine depletion (de la Fuente-Fernández, 2012: 696). Radiotracer neuroimaging such as dopamine transporter (DAT) SPECT (DaTSCAN) is being used as a diagnostic tool (de la Fuente-Fernández, 2012: 696). However, the clinical diagnosis of Parkinson’s disease has an accuracy of 84% in early disease. This means that use of the DaTSCAN may not be necessary on a large scale and may be reserved for challenging patients (de la Fuente-Fernández, 2012: 699). According to the NICE (National Institute for Health and Clinical Excellence) guideline, patients suspected of having Parkinson’s disease should be referred quickly, untreated, to a specialist for diagnosis and ongoing follow-up (Stewart, 2007: 240).

A study of 253 patients who were not being treated with levodopa or dopamine agonists, with disease duration of 10 years or less, aimed to determine gender differences in disease onset and clinical presentation (Haaxma, Bloem, Borm, Oyen, Leenders, Eshuis, Booij, Dluzen and Horstink, 2007: 819). The study showed that
women were on average two years older (53.4 years) when diagnosed compared to men (51.3 years). A total of 67% of the women presented with tremor at symptom onset compared to men where only 48% presented with tremors regardless of age at onset (Haaxma, et al., 2007: 821). When bradykinesia or rigidity was the initial symptom, the age of onset tended to be three years younger in both genders (Haaxma, et al., 2007: 821, 823). The results of the study suggest that the later age at onset for women may demonstrate a slower development of clinical Parkinson’s disease, (Haaxma, et al., 2007: 821). There have also been gender differences identified with regards to dyskinesias. Women tend to experience dyskinesias more frequently and with more severity than men (Lyons, Hubble, Tröster, Pahwa and Koller, 1998: 118; Miller and Cronin-Golomb, 2010: 2696).

Determining the age of onset of the initial symptoms of Parkinson’s disease helps classify the patients as juvenile indicating onset before the age of 20 years, young onset, indicating onset between 21 years and 40 years, and late onset, which indicates onset over the age of 40 years (Reider, Halter, Castelluccio, Oakes, Nichols, Foroud, and the Parkinson Study Group, 2003: 275). A study was conducted to determine the reliability of the reported age of clinical onset of Parkinson’s disease (Reider, et al., 2003: 275). Medical records were consulted, self-administered questionnaires were distributed to be completed at home by either the patient or a family member as well as a survey instrument completed during face-to-face interviews conducted by the medical practitioner based on the responses given by the patient or family member (Reider, et al., 2003: 275). Upon analysing the data, it showed that there was little difference in the reliability when compared by gender, the initial symptom of Parkinson’s disease and the years of education. However, factors that did affect the reliability were age at the exam and the duration of the disease. Younger respondents were less reliable and those reporting the duration of clinical disease between five years to nine years had lower reliability (Reider, et al., 2003: 277). The overall result showed that there was only a minor difference between the ages obtained from medical records and the reported age of onset obtained from the patients and family. This indicates that asking patients about their age of onset of the first symptom of Parkinson’s disease is likely to be accurate and
the researcher does not necessarily have to examine medical records (Reider, et al., 2003: 278).

2.5 Classification of Parkinson’s disease

Parkinson’s disease is classified into stages according to the presentation of symptoms. One way of describing these stages is by using the Hoehn and Yahr scale (Hoehn and Yahr, 1967: 433).

The Hoehn and Yahr scale breaks down the progression of Parkinson’s disease into different stages characterised by the symptoms exhibited by the patient and is summarised in Table 2.1. Progression from one stage to the next is thought to occur due to natural disease progression and in the absence of treatment. There are also different subtypes of Parkinson’s disease. These include those who are tremor-dominant, akinetic-rigid and those with postural instability (Insight Medicine Information, 2011: 5).

Table 2.1 Hoehn and Yahr classification of Parkinson’s disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Unilateral symptoms, minimal or no functional impairment</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Bilateral symptoms, but no balance impairment</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Bilateral symptoms, mild to moderate disability, but patient still physically independent</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Severe disability, but able to walk or stand unassisted</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Bed-ridden or confined to a wheelchair unless assisted</td>
</tr>
</tbody>
</table>

(Source: Hoehn and Yahr, 1967: 433)

The UPDRS is the major rating scale used to assess the severity of Parkinson’s disease (McNamara, 2009). The scale is divided into four sections and is summarised in Table 2.2. A neurologist would observe the patient’s performance when moving arms, legs or body. The performance is then scored on a scale of
zero to four, where zero is normal and four is severe. Therefore, the higher the overall score, the greater the severity of the condition (McNamara, 2009).

Table 2.2 Unified Parkinson’s Disease Rating Scale divisions

<table>
<thead>
<tr>
<th>Division</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part I</td>
<td>Mentation, behaviour and mood</td>
</tr>
<tr>
<td>Part II</td>
<td>Activities of daily living</td>
</tr>
<tr>
<td>Part III</td>
<td>Motor</td>
</tr>
<tr>
<td>Part IV</td>
<td>Complications</td>
</tr>
</tbody>
</table>

(Source: Goetz, Poewe, Rascol, Sampaio and Stebbins, 2003: 738)

2.6 Dyskinesias

Dyskinesias are defined as impaired voluntary movements which result in fragmented movement which only cease during sleep (Prashanth, Fox and Meissner, 2011: 32). The incidence of dyskinesias varies widely, from 9% to 80%. This is due to the fact that there are many risk factors to take into account (Thanvi, et al., 2007: 384). Such risk factors include age of disease onset, dose and duration of levodopa and even unknown genetic factors (Calabresi, et al., 2010: 1106; Voon, et al., 2009: 1140; Thanvi, et al., 2007: 384). Up to 90% of patients tend to develop dyskinesias within 10 years of Parkinson’s disease onset. However, it is important to remember that not all patients on levodopa therapy will develop dyskinesias (Ha and Jankovic, 2011: 8; Prashanth, et al., 2011: 31). Dyskinesias were recognised with the advent of levodopa and are therefore termed LiDs (levodopa-induced dyskinesias) and are a major limitation in the therapy of Parkinson’s disease (Prashanth, et al., 2011: 32). These involuntary movements can have a negative impact on the patients’ quality of life.

2.6.1 Classification of dyskinesias

Dyskinesias are classified as either choreic which involves a series of hyperkinetic, purposeless dance like movements or dystonic which involves abnormal, sustained
muscle contractions (Nadjar, et al., 2009: 2; Thanvi, et al., 2007: 385-386). Mild levodopa induced choreic movements tend to be non-disabling and are often not noticed by the patients themselves, but rather by family members (Ha and Jankovic, 2011: 8). Dyskinesias are commonly seen affecting the muscles of the jaw, tongue, neck and face (Calabresi, et al., 2010: 1 106). Peak dose dyskinesias often involve the muscles of the neck, axial and upper limb (Ha and Jankovic, 2011: 8). The different types of LIDs are summarised in Table 2.3 below.

Table 2.3 Different types of levodopa-induced dyskinesias

<table>
<thead>
<tr>
<th>Types of levodopa-induced dyskinesias</th>
<th>Explanation</th>
</tr>
</thead>
</table>
| Peak dose dyskinesia | Most common form of LID  
Associated with peak plasma levels of levodopa  
Dose reduction may help attenuate them |
| Diphasic dyskinesia | Occur when the levels of levodopa are increasing or decreasing  
Do not occur at peak plasma levels  
Usually dystonic in nature  
Decreasing the dose of levodopa does not improve the condition  
Increased doses may be of more benefit |
| Off state dystonia | Occur when levodopa levels in the plasma are low  
Generally present as painful muscle contractions occurring in one foot  
Responds to levodopa therapy |
| On state dystonia | Occur when the plasma levels of levodopa are high |
| ‘Yo-yo’ dyskinesia | Occur at any time |

2.6.2 Theories into the development of dyskinesias

The pathophysiology and underlying molecular mechanism for the development of these dyskinesias is poorly understood. Several studies agree that young age of disease onset, disease severity and high doses of levodopa increase the risk for dyskinesias (Calabresi, et al., 2010: 1 106; Voon, et al., 2009: 1 140; Encarnacion and Hauser, 2008: 58; Thanvi, et al., 2007: 384; Sossi, et al., 2006: 1 051). Pulsatile stimulation of the dopamine receptors is also thought to play a role in the development of dyskinesia since it has been noted that the storage and clearance of striatal dopamine is dramatically reduced in the presence of severe nigrostriatal lesions. This has led to an effort to provide a more constant infusion of levodopa through the use of intraduodenal infusions (Calabresi, et al., 2010: 1 106-1 107; Thanvi, et al., 2007: 384).

Studies into the levodopa dose per kilogram have revealed this to be another important factor to consider when determining a patients’ risk for the development of dyskinesias (Sharma, et al., 2008: 495; Sharma, et al., 2010: 492). Interest in these types of studies was sparked when it was observed that not all patients on similar levodopa doses develop dyskinesias as 60% of patients remain free of any dyskinesia after four to six years of therapy (Sharma, et al., 2010: 492). A possible explanation for this is the body weight of the patient (Sharma, et al., 2010: 492). This was also seen as the reason for women experiencing dyskinesias more frequently than men. Women weighed less and were receiving higher levodopa doses per kilogram (Miller and Cronin-Golomb, 2010: 2 696).

A cohort study carried out by Sharma and colleagues (Sharma, McNamara, Hasoon, Vassallo and Ross, 2006: 499) in 2006 involved 220 patients suffering from Parkinson’s disease. The aim of the study was to identify new risk factors for the development of dyskinesia. At the second assessment, 29 new patients started exhibiting dyskinesia. It was noted that these patients had lost weight during the course of the study (72kg ± 15kg to 66kg ± 17kg). The patients exhibiting dyskinesia were receiving a significantly higher dose of levodopa per kilogram body weight (8.4mg/kg ± 3.5mg/kg as opposed to 6.0mg/kg ±3.9mg/kg).
Another study carried out (Sharma, *et al.*, 2008: 493-496) manipulated data from two ropinirole versus levodopa studies (056 and REAL-PET) to calculate the levodopa dose per kilogram body weight. The study revealed that only the levodopa dose per kilogram body weight was a significant risk factor in the development of LID (Sharma, *et al.*, 2008: 495). Other factors such as gender, the absolute levodopa dose, weight and the overall disease severity were not as significant (Sharma, *et al.*, 2008: 495).

2.7 Non-motor symptoms

In Parkinson’s disease there are also many non-motor symptoms (NMS), some of which have a greater negative impact on the patients’ quality of life than the motor symptoms. These NMS may appear before the motor symptoms are even recognised, (Park and Stacy, 2009: 293) and may also be present at more advanced stages of the disease (Chaudhuri and Schapira, 2009: 464). These NMS contribute to the immense complexity that is Parkinson’s disease and makes therapy challenging.

It is well understood that there has been neuronal degeneration when patients present with early motor symptoms, but exactly when that degeneration began is a subject of much debate, and may vary between patients (Braak, *et al.*, 2003: 197; Lang, 2011: 776). The early NMS of Parkinson’s disease may play an important role in the early diagnosis of the condition (Lang, 2011: 775).

However, some of the early NMS, such as olfactory deficit and gastrointestinal disturbances, are not specific to Parkinson’s disease and are common amongst the general population. This creates difficulty in attributing them to preceding symptoms in the development of Parkinson’s disease.

Other NMS experienced by Parkinson’s patients include disorders of mood and affect causing apathy, anhedonia, depression, cognitive dysfunction, hallucinations as well as complex behavioural disorders including impulse-control disorders.
Sensory dysfunction with pain is experienced by almost all patients. Sleep-wake cycle disturbances are also commonly experienced. Autonomic dysfunction resulting in orthostatic hypotension, urogenital dysfunction as well as constipation is also present in a large number of patients (Ceravolo, Rossi, Kiferle, and Bonuccelli, 2010; Poewe, 2008:14).

### 2.7.1 Olfactory deficit

The first lesions occur in the olfactory structures (Braak, Del Trecidi, Rüb, de Vos, Jansen Steur and Braak, 2003: 208). However, there are other causes of olfactory dysfunction such as head injuries or smoking and since olfactory dysfunction appears in other neurological conditions such as Alzheimer’s disease and multiple system atrophy, it is not specific for Parkinson’s disease (Lang, 2011: 779).

### 2.7.2 Neuropsychiatric symptoms

Neuropsychiatric symptoms are seen in patients with Parkinson’s disease despite the common idea that the disease has no impact on sense and intellect (Poewe, 2008: 16). Depression, anxiety, psychosis, cognitive dysfunction and dementia are the neuropsychiatric symptoms focused on in this section.

#### 2.7.2.1 Depression

Depression has been found to affect up to 75% of patients with Parkinson's disease (Poewe, 2008: 16; Chaudhuri, Healy and Schapira, 2006: 238; Cummings, 1992: 444). The underlying biological mechanism involves a decreased level of 5-hydroxyindolacetic acid, a metabolite of serotonin, in the cerebrospinal fluid as well as decreased 5-HT₁A receptor binding (Chaudhuri, et al., 2006: 238). Even though it is common of Parkinson’s disease, depression is often not diagnosed and therefore may go untreated (Shulman, Taback, Rabinstein and Weiner, 2002: 193; Ceravolo, et al., 2010; Lyons and Pahwa, 2011: 310).
2.7.2.2 Anxiety

Anxiety is closely related to the motor fluctuations associated with Parkinson’s disease. Patients experience more anxiety in the ‘off’ period which is a period of akinesia unrelated to the timing of the levodopa dose, and the anxiety may be improved by medication (Ceravolo, et al., 2010; Chaudhuri, et al., 2006: 238). In addition, patients may experience panic attacks, phobias and generalised anxiety disorder (Ceravolo, et al., 2010; Chaudhuri, et al., 2006: 238).

2.7.2.3 Psychosis

Psychosis and hallucinations are one of the most challenging NMS of Parkinson’s disease and sometimes require the patient to be placed in a nursing home. Hallucinations have a prevalence of up to 40% in patients suffering from Parkinson’s disease (Poewe, 2008: 17; Chaudhuri, et al., 2006: 238). They generally begin as a benign condition, but more problematic symptoms such as delirium, delusions and paranoid behaviour become increasingly common as the condition progresses (Chaudhuri, et al., 2006: 238). Psychotic symptoms may be triggered by all of the major classes of antiparkinsonian therapy, but it is more likely to occur with the dopamine agonists than with levodopa (Poewe, 2008: 17). Generally, interventions are aimed at decreasing the dose of the offending dopaminergic agent and adding an atypical antipsychotic if necessary. However, with this comes the risk of potentially worsening the motor symptoms (Ceravolo, et al., 2010). Clozapine is the only drug with proven antipsychotic effects which does not cause worsening of the motor symptoms (Ceravolo, et al., 2010; Poewe, 2008: 18).

2.7.2.4 Cognitive dysfunction and dementia

The risk of dementia is approximately six times higher in Parkinson’s disease than in a normal, healthy individual (Ceravolo, et al., 2010; Park and Stacy, 2009: 294; Chaudhuri, et al., 2006: 239). The underlying pathophysiology of dementia is likely related to the development of cortical Lewy bodies (Poewe, 2008: 17; Chaudhuri, et al., 2006: 239) and could even be due to genetic influences (Svenningsson,
Westman, Ballard and Aarsland, 2012: 698). A 15 year long study, originally directed at determining optimal early treatment for Parkinson's disease, and which subsequently reported on the problems experienced by these patients over the duration of the study period (Hely, Morris, Reid and Trafficante, 2005: 190). Only one third of the original 149 patients survived the full duration of the study. Cognitive impairment was present in 84% of patients and 48% of this group displayed the signs of dementia (Hely, et al., 2005: 194).

2.7.3 Sleep abnormalities

Sleep disorders are a very common feature of Parkinson's disease with a prevalence ranging from 75% to 98% (Ceravolo, et al., 2010; Poewe, 2008: 18). The problem includes difficulty falling asleep, frequent awakening during the night, muscle cramps, dystonia or nocturnal motor symptoms which involve difficulty turning in bed, motor restlessness or restless legs syndrome. Additional problems include bladder dysfunction, nocturnal confusion and excessive daytime sleepiness (Ceravolo, et al., 2010; Poewe, 2008: 18). Features of the sleep disorders of Parkinson's disease include a fragmented sleep pattern, reduced sleep efficiency, reduced slow-wave sleep, reduced rapid-eye movement sleep and rapid eye movement behaviour disorder (Poewe, 2008: 18).

2.7.3.1 Rapid eye movement behaviour disorder

Rapid eye movement behaviour disorder is characterised by a loss of rapid eye movement sleep muscle atonia. It is associated with a disruption of normal REM (rapid eye movement) sleep, as a result of which patients experience jerking and sometimes even violent movements of the limbs which may cause themselves or their partners injury (Ceravolo, et al., 2010; Poewe, 2008: 18).

2.7.3.2 Excessive daytime sleepiness

Excessive daytime sleepiness is also a common sleep disorder of Parkinson’s disease and affects up to 50% of the population (Ceravolo, et al., 2010). The severity
of the excessive daytime sleepiness has no relation to the patients' nocturnal sleep disorders. Factors that contribute to excessive daytime sleepiness include motor disability, the impact of antiparkinsonian medication on alertness, the presence of depression or dementia and any concurrent mental illness (Ceravolo, et al., 2010).

2.7.4 Autonomic dysfunction

Dysautonomia is a common NMS of Parkinson’s disease. The cause of dysautonomia is degeneration of CNS neurons involved in the control of the autonomic nervous system as well as the peripheral postganglionic neurons (Ceravolo, et al., 2010). Dysautonomia generally presents with the symptoms of orthostatic hypotension, constipation and urinary and sexual dysfunction, all of which can have a negative impact on the patient’s quality of life (Ceravolo, et al., 2010; Poewe, 2008: 15).

2.7.4.1 Orthostatic hypotension

The prevalence of orthostatic hypotension varies widely in Parkinson’s disease with values ranging from 30% to 58% (Ceravolo, et al., 2010). Orthostatic hypotension usually develops late in the disease and may also be as a result of dopaminergic therapy (Ceravolo, et al., 2010; Chaudhuri, et al., 2006: 239).

2.7.4.2 Constipation

Lewy body pathology in the peripheral autonomic nervous system also affects the myenteric plexus which contributes to the development of constipation (Poewe, 2008: 16). Constipation is a commonly reported problem of Parkinson’s disease and it frequently precedes development of the disease (Ceravolo, et al., 2010; Poewe, 2008: 16; Chaudhuri, et al., 2006: 240).
2.7.4.3 Urogential dysfunction

Urogenital dysfunction includes erectile and ejaculatory failure and is reported by about 60% of male patients (Ceravolo, et al., 2010; Poewe, 2008: 17). Sildenafil has proved to be safe and effective in the treatment of erectile dysfuntction in Parkinson’s disease (Ceravolo, et al., 2010). Patients also tend to develop detrusor muscle hyperactivity which leads to urinary urgency and frequency, nocturia, incomplete bladder emptying and urge incontinence (Ceravolo, et al., 2010; Poewe, 2008: 17).
CHAPTER 3
Treatment of Parkinson’s Disease
3.1 Introduction

There are certain objectives to be achieved in order to provide Parkinson’s disease patients with effective treatment. These objectives are listed in Table 3.1. Guidelines published by the South African Medical Journal and the NICE for the treatment of Parkinson’s disease are referred to in this chapter.

Table 3.1 Objectives of Parkinson’s disease therapy

<table>
<thead>
<tr>
<th>Objectives of Parkinson’s disease therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy - decrease Parkinsonian symptoms while trying to reduce disease progression</td>
</tr>
<tr>
<td>Safety - at least decrease the risk of adverse effects</td>
</tr>
<tr>
<td>Costs – to as far as possible reduce costs associated with therapy</td>
</tr>
</tbody>
</table>


3.2 Treatment options

There are many treatment options for the management of Parkinson’s disease, of which levodopa is only one. The different treatments available according to the SAMF (South African Medicines Formulary) 2012 are summarised in Table 3.2.
Table 3.2 Treatments available for Parkinson’s disease in South Africa

<table>
<thead>
<tr>
<th>Chemical Subgroup</th>
<th>Chemical substance</th>
<th>Tradename/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopa and dopa derivatives</td>
<td>• Levodopa in combination with a dopamine decarboxylase inhibitor such as carbidopa or benserazide</td>
<td>• Sinemet®/Carbilev® (levodopa/carbidopa)</td>
</tr>
<tr>
<td></td>
<td>• Levodopa in combination with a dopamine decarboxylase inhibitor and catechol-o-methyl-transferase (COMT) inhibitor</td>
<td>• Madopar® (levodopa/benserazide)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stalevo®</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>Ergot derivatives</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bromocriptine</td>
<td>• Parlodel®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Aspen Bromocriptine®</td>
</tr>
<tr>
<td>Non-ergot derivatives</td>
<td>• Ropinirole</td>
<td>• Requip®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Requip XL®</td>
</tr>
<tr>
<td></td>
<td>• Pramipexole</td>
<td>• Pexola®</td>
</tr>
<tr>
<td>Monoamine oxidase type B (MAO-B) inhibitors</td>
<td>• Rasagiline</td>
<td>• Azilect®</td>
</tr>
<tr>
<td></td>
<td>• Selegiline</td>
<td>• Parkilyne®</td>
</tr>
<tr>
<td>COMT-inhibitors</td>
<td>• Entacapone</td>
<td>• Comtan®</td>
</tr>
<tr>
<td>Anticholinergic agents</td>
<td>• Biperiden</td>
<td>• Akineton®</td>
</tr>
<tr>
<td></td>
<td>• Trihexyphenidyl</td>
<td>• Benzhexol®</td>
</tr>
<tr>
<td></td>
<td>• Orphenadrine</td>
<td>• Disipal®</td>
</tr>
<tr>
<td>Amantadine derivatives</td>
<td>• Amantadine</td>
<td>• Symmetrel®</td>
</tr>
</tbody>
</table>


Levodopa is able to alleviate all of the cardinal motor symptoms of Parkinson’s disease. Certain of the other agents may not be as effective as levodopa in treating
the bradykinesia, gait disturbances and other symptoms of advanced Parkinson’s disease, but they are useful when managing the mild disabilities that are associated with early Parkinson’s disease (Nelson, et al., 2005: 1079). These agents are generally used as monotherapy to delay the initiation of levodopa therapy, or they are used in combination with levodopa in order to decrease the total levodopa requirement. These drugs complement levodopa therapy as they either increase dopamine activity in the brain or decrease the peripheral metabolism of levodopa to prolong its activity. Due to these factors, lower doses of levodopa can be used to achieve the same clinical effect as if it was used alone.

3.2.1 Levodopa

Dopamine cannot cross the blood brain barrier (BBB), thus levodopa is used instead. Levodopa is the immediate metabolic precursor of dopamine. It is decarboxylated in the brain by the enzyme dopamine decarboxylase to produce dopamine. When administered alone, only about one to three percent of the total levodopa dose crosses the BBB to enter the brain. This is since the rest of it is metabolised peripherally, by dopamine decarboxylase, to produce dopamine, which cannot cross the BBB. This means that when used alone, levodopa must be given in very large doses (Singh, et al., 2007: 32).

In order to overcome this problem, levodopa is given in combination with a peripheral dopamine decarboxylase inhibitor, such as carbidopa or benserazide, which does not cross the BBB. As a result, the peripheral metabolism of levodopa is reduced and larger amounts are available to cross the BBB, where it is decarboxylated to produce dopamine (Aminoff, 2007: 443-444). The pharmacokinetics of levodopa differs when paired with carbidopa and benserazide (Goldstein, Gopinathan, Neophytides, Hiesiger, Walker and Nelson, 1984: 227). When combined with benserazide the peak dose of levodopa is higher and is achieved sooner, but also declines more rapidly. Generally, levodopa has a half-life of approximately 45 to 90 minutes with the peak therapeutic response expected after two to three weeks of therapy (Halkias, et al., 2007: 262).
3.2.1.1 Benefits of levodopa

Levodopa is able to alleviate all of the cardinal motor symptoms of Parkinson’s disease. It is especially effective in relieving bradykinesia (Aminoff, 2007: 444). It does not stop the progression of Parkinson’s disease, but it does lower the mortality rate. Many patients have reported an improvement in their quality of life with levodopa treatment (Aminoff, 2007: 444).

3.2.1.2 Adverse effects of levodopa

The onset, type and severity of side effects are some of the major disadvantages of levodopa treatment. The adverse effects of levodopa may be divided into the general adverse effects and the motor effects. Both these topics are discussed in this section.

3.2.1.2.1 General adverse effects

Levodopa can cause gastrointestinal disturbances such as nausea and vomiting. This occurs in 80% of patients when levodopa is administered alone, but in only 20% of patients when carbidopa is administered in combination with levodopa. There are cardiovascular effects such as arrhythmias, (Singh, et al., 2007: 32) although the incidence is low. The incidence of arrhythmia is further reduced when levodopa is taken in combination with carbidopa. The patient may experience behavioural effects such as depression, anxiety, insomnia, confusion, delusions, hallucinations, nightmares and euphoria (Aminoff, 2007: 444-446). These effects occur more often in patients receiving combination treatment because higher levels of levodopa enter the brain. Other effects include mydriasis (pupil dilation), acute glaucoma, blood dyscrasias, hot flushes and precipitation or aggravation of gout (Aminoff, 2007: 444-446; Rezak, 2007: 216).
3.2.1.2.2 Motor effects

Fluctuations in response to levodopa therapy will occur. Such fluctuations include dyskinesias and motor fluctuations. If the motor fluctuations are associated with the timing of the levodopa dose, it is referred to as the ‘wearing off’ phenomenon. These fluctuations are thought to occur because the patient is no longer able to store dopamine in the brain (Murata, 2009: 18). Dyskinesias are abnormal, involuntary movements ceased only by sleep (Prashanth, et al., 2011: 32). The incidence of dyskinesias varies widely, from 9% to 80% (Thanvi, et al., 2007: 384). Approximately 50% of patients develop motor complications five years after the initiation of levodopa treatment, which increases to 70% after 15 years (Benbir, Özekmekçi, Apaydin, Delil and Erginöz, 2006: 732).

3.2.1.3 Contraindications to levodopa

Patients who suffer from closed-angle glaucoma may not receive levodopa as it may further increase intraocular pressure. Levodopa may exacerbate active peptic ulcer disease because levodopa has been known to cause gastric bleeding. Patients with a history of malignant melanoma or patients with suspicious undiagnosed skin lesions may not receive levodopa as it is a precursor of melanin and may activate malignant melanoma. Levodopa is also contraindicated in patients under the age of 25 years (Aminoff, 2007: 446; Halkias, et al., 2007: 264, ed. Rossiter, 2012: 462). It is advised to avoid levodopa in pregnancy and lactation. Its use in porphyria is deemed safe (ed. Turner, 2010: 444).

3.2.2 Dopamine agonists

Dopamine agonists are divided into two groups, the ergot derivatives such as bromocriptine, and the newer generation non-ergot derivatives such as pramipexole and ropinirole. These agents can be used as initial treatment of Parkinson’s disease in the early stages to delay the onset of levodopa therapy. Dopamine agonists can also be used in combination with levodopa in order to decrease the overall dose of levodopa that is to be used by enhancing the antiparkinsonian effects of the drug.
(Singh, et al., 2007: 33). Unlike levodopa, the dopamine agonists are not dependent on dopa-decarboxylase which is needed to convert levodopa into dopamine. Some common adverse effects associated with the use of pramipexole and ropinirole are confusion, insomnia, hallucinations, dizziness, dyskinesias, somnolence, nausea constipation, peripheral oedema and postural hypotension (ed. Rossiter, 2012: 459). These dopamine agonists are also associated with sudden sleep episodes. Patients may fall asleep without any prior warning which compromises their ability to operate machinery (ed. Rossiter, 2012: 458-459). Dopamine agonists do not compete with dietary amino acids for absorption, nor do they require further activation in the brain as is the case with levodopa (Stern, 2001: 29). These drugs have a longer half-life than levodopa and may provide longer periods of symptomatic relief (Stern, 2001: 29).

3.2.3 MAO-B inhibitors

MAO-B inhibitors, such as rasagiline and selegiline, are useful agents in Parkinson’s disease management. These drugs act by irreversibly inhibiting the breakdown of dopamine by monoamine oxidase B, thus increasing its levels. Therefore, when used in combination with levodopa, they may allow the total dose of levodopa to be reduced (Singh, et al., 2007: 33). A few hours after these agents are orally administered, there is very little parent compound left, however, this is of little consequence due to the irreversible nature of the inhibition (LeWitt, 2009: 1352).

3.2.4 COMT-inhibitors

COMT-inhibitors, such as entacapone, act to inhibit the peripheral metabolism of levodopa by the enzyme catechol-o-methyltransferase thus increasing the plasma levels of levodopa. COMT-inhibitors are used to extend the effects of levodopa and are generally used in combination with other antiparkinsonian drugs (Nelson, et al., 2005: 1079-1085).
3.3 Guidelines for the treatment of Parkinson’s disease

According to a guideline published in the South African Medical Journal, in the early, milder stages of the disease when the patient is not showing many symptoms, therapy with an anticholinergic, a dopamine agonist, amantadine or an MAO-B inhibitor may be useful as first line therapy (Carr, Kies and Fine, 2009: 756). As the patient progresses and the symptoms become more obvious, levodopa has a role to play. Neurologists may consider administering domperidone, a dopamine antagonist, concurrently with levodopa in order to reduce the incidence of peripheral side effects caused by the dopaminergic drug (Carr, et al., 2009: 756). The NICE guideline states that the treatment for Parkinson’s disease is open to interpretation as there are no definitive results for studies comparing the effectiveness of one drug class against the other (Stewart, 2007: 241). The guideline does, however, state that levodopa, dopamine agonists and MAO-B inhibitors have a role to play in the early stages of the disease. This is largely in agreement with the South African guideline, however, the NICE guideline does not promote the use of anticholinergic agents, especially in older patients due to the risk of neuropsychiatric effects (Stewart, 2007: 241).

Once the patient has passed into the moderate to severe stage of Parkinson’s disease, they will be afflicted with motor fluctuations and an increasing burden of NMS (Carr, et al., 2009: 756). At this point, the problem may be the short half-life of levodopa as well as its narrow therapeutic window. Other agents such as the dopamine agonists, COMT-inhibitors or MAO-B inhibitors may be of benefit as adjunctive therapy to levodopa with dosage adjustments to obtain maximum symptom relief (Carr, et al., 2009: 756). The NICE guideline also recommends the use of these agents in the later stages of the disease and corresponds with the recommendations of the South African guideline (Stewart, 2007: 241).

There are many available options for the management of Parkinson’s disease. However, the appropriate timing of implementation of particular agents has not been determined. This resulted in a lack of concrete guidelines for the management of this disease and means that neurologists need to rely on clinical experience.
3.4 Previous studies concerning dyskinesias

There have been numerous studies into the therapies and development of dyskinesias in patients with Parkinson’s disease. There has not yet been an effective solution developed which has been able to eradicate the presence of dyskinesias.

3.4.1 Risk factors concerning levodopa therapy

Certain risk factors have been identified which are thought to cause dyskinesias. These include age of onset, gender, initial symptoms, evolution of the Hoehn and Yahr stage, severity of the nigrostriatal lesions, the year that levodopa was introduced relative to the date of diagnosis and the initial dose of levodopa (Thanvi, et al., 2007: 386-387; Benbir, et al., 2006: 726-732; Kumar, Van Gerpen, Bower and Ahlskog, 2005: 342; Kostić, Marinković, Svetel, Stefanova and Przedborski, 2002: 9; Garret, et al., 1998: 99-102).

3.4.1.1 The ELLDOPA trial

One of the most well-known studies in Parkinson’s disease history is the ELLDOPA study (Early versus Later Levodopa in Parkinson’s Disease) study. This placebo-controlled, randomised, double-blind control trial aimed to determine whether or not levodopa slows down or hastens the progression of Parkinson’s disease (Fahn, 1999: 532).

A washout design was used to examine the effect of levodopa on disease progression. No other antiparkinsonian medication was allowed in the study to avoid any confounding influence of other drugs. Treatment naive patients with early Parkinson’s disease were randomised to receive either placebo or levodopa 150mg, 300mg or 600mg daily for a 40 week period. This was to be followed by a two week washout period at which point any symptomatic benefit ought to have disappeared. The first evaluation was performed at baseline and the second after the two week washout period, which was 42 weeks after initiation of treatment. This means that both evaluations were performed in a drug-free state (Fahn, 1999: 532).
predicted, levodopa had a clear superior symptomatic benefit compared with placebo in the first 40 weeks.

Of the 361 patients enrolled in the study, 317 took the medication for the defined period of 40 weeks and 311 completed the additional two week washout period (The Parkinson Study Group, 2004: 2502). At the end of the two week washout period, the UPDRS scores showed worsening in all groups except the arm of the levodopa group receiving 600mg daily (Henchcliffe and Severt, 2011: 609; The Parkinson Study Group, 2004: 2502). During the two week washout period the UPDRS scores of the three levodopa groups worsened, but not as much as the placebo group and the patients in the 600mg arm performed the best. However, the adverse effects associated with levodopa such as nausea, dyskinesias, infection, hypertonia and headache were more pronounced in the group receiving 600mg daily (The Parkinson Study Group, 2004: 2502).

The overall conclusion of the study group was that there was no evidence found to suggest that levodopa accelerated the worsening of Parkinson’s disease over the full 42 week period of observation (The Parkinson Study Group, 2004: 2503). The continued benefit of levodopa after the washout period is consistent with disease modification but subsequent measurements have suggested that the washout period may have been insufficient to eliminate fully the effect of the medication on symptoms and that levodopa may have a longer term effect on parkinsonism than previously anticipated (Henchcliffe and Severt, 2011: 609; The Parkinson Study Group, 2004: 2503).

### 3.4.1.2 Continuous levodopa administration

The idea of the continuous administration of levodopa to reduce dyskinesias associated with fluctuating levels of dopamine (Marin, Aguilar and Obeso, 2006: 647; Block, Liss, Reines, Irr, and Nibbelink, 1997: 23) has received much interest. Instead of levodopa, use has been made of a subcutaneous implant of apomorphine which is another potent dopaminergic agonist to reduce the incidence of dyskinesia in MPTP treated primates (Bibbiani, Costantini, Patel and Chase, 2005: 73-74). The implanted
animals remained stable for up to six months without demonstrating any dyskinesias (Bibbiani, *et al.*, 2005: 75). However, the continuous delivery of a dopaminergic stimulant into the human striatum remains a problem as previous routes of administration were considered inconvenient. These methods of administration also caused side effects or possessed limited efficacy (Bibbiani, *et al.*, 2005: 77).

In humans, a study comparing a controlled-release preparation of levodopa to an immediate release formulation demonstrated that there was no difference in terms of dyskinesia but there was an improvement in the UPDRS scores with respect to the activities of daily living subscore. The controlled release group performed better than the immediate release group (Block, *et al.*, 1997: 26). The controlled-release preparation showed a significant yearly improvement on the UPDRS activities of daily living scale (Bibbiani, *et al.*, 1997: 25).

### 3.4.1.3 Levodopa dose

According to the World Health Organisation (WHO) the Defined Daily Dose (DDD) is the assumed average maintenance dose per day for a drug used for its primary indication in adults (WHO Collaborating Centre for Drug Statistics and Methodology, 2009). When given in combination with a dopa-decarboxylase inhibitor like carbidopa, the DDD for levodopa is decreased to 600mg (WHO International Working Group for Drug Statistics Methodology).

It has been seen that LIDs are more commonly associated with high daily doses of levodopa. These doses range from 400mg to 600mg daily (Benbir, *et al.*, 2006: 732; Jankovic, 2005: 12; The Parkinson Study Group, 2004: 2 502; Schrag and Quinn, 2000: 2 301).

### 3.4.1.3 Age and disease severity

With regards to age, it was found that younger patients tend to experience dyskinesias more frequently than older patients. One study (Garret, *et al.*, 1998: 101) showed that of 50 patients with disease duration of 10 years and longer 56%
developed drug-induced dyskinesias within the first 10 years of the disease. The mean age of patients who developed these dyskinesias was 53.9±6.2 years. This is in accordance with a population-based study in Olmstead County, Minnesota in the United States of America (Kumar, et al., 2005: 343) which looked at patients with Parkinson’s disease incidence between the years 1976 to 1990. The study demonstrated that patients between the ages of 40 and 49 years and those between the ages of 50 and 59 years presented with 40% and 53% incidence respectively whereas patients between 60 and 69 years, 70 and 79 years and 80 and 89 years presented with 26%, 16% and 14% incidence, respectively.

The earlier study (Garret, et al., 1998: 102) concluded that the onset of dyskinesias was also related to disease severity. This conclusion was supported by another prospective cohort study which followed a total of 40 patients who were at least 50 years of age and did not present with LID at the start of the study (Kostić, et al., 2002: 9-10; 13). Of the patients who had begun levodopa therapy at Hoehn and Yahr stage three, 90% developed dyskinesia. In the group of patients who had been started on levodopa at stage two of the disease, 54% developed dyskinesias and of the patients initiated on levodopa in stage one, a total of 70% developed dyskinesias. The study noted that patients beginning therapy in stage three developed LIDs significantly earlier than the other two groups (Kostić, et al., 2002: 10). The studies agree that the disease severity at the point of levodopa initiation plays a role in the development of dyskinesias.

3.4.2 Ropinirole versus levodopa

In order to delay the initiation of levodopa therapy and the incidence of LID, some neurologists prefer to begin therapy with a dopamine agonist such as ropinirole whose efficacy in Parkinson’s disease has been demonstrated (Rascol, Brooks, Korczyn, De Deyn, Clarke and Lang, 2000: 1 484).

Two randomised double-blind studies (Hauser, Rascol, Korczyn, Jon Stoessl, Watts, Poewe, De Deyn and Lang, 2007: 2 409; Rascol, et al., 2000: 1 487) were conducted comparing ropinirole with levodopa as initial therapy in the onset of
dyskinesias. The earlier study (Rascol, et al., 2000: 1 484-1 491) compared the safety and efficacy of ropinirole with that of levodopa over a five year period in 268 patients with early Parkinson’s disease. After the five year period it was found that the cumulative incidence of dyskinesia in the ropinirole group was 20% as opposed to the 45% incidence in the levodopa group (Rascol, et al., 2000: 1 487). The second study (Hauser, et al., 2007: 2 409) supported the previous findings. The results showed that patients randomised to the ropinirole exhibited lower incidence of dyskinesia and the average time to onset of dyskinesia was also significantly longer. However, in the later study, the UPDRS scores of patients randomised to the levodopa group showed greater improvement than the corresponding ropinirole scores (Hauser, et al., 2007: 2 410).

### 3.4.3 Entacapone and levodopa

Entacapone, a selective, potent and reversible peripherally acting COMT-inhibitor, will extend the half-life of levodopa by approximately 50% to 75% and decreases the fluctuation in levodopa blood levels, thus reducing the incidence of LID (Marin, et al., 2006: 647; Smith, Jackson, Al-Barghouthy, Rose, Kuoppamaki, Olanow and Jenner, 2005: 307). According to the WHO, the DDD for levodopa in combination with both a decarboxylase inhibitor and entacapone is further decreased to just 450mg. Initiating therapy with a combination of entacapone and levodopa as opposed to levodopa alone, has shown to reduce the induction and severity of dyskinesias in MPTP-lesioned primates as opposed to those being treated with levodopa/carbidopa (Marin, et al., 2006: 647).

A study was conducted which demonstrated that combination therapy with entacapone and levodopa could reduce the incidence and severity of LIDs (Marin, et al., 2006: 646). The study was conducted on male rats treated with either levodopa alone or levodopa in combination with entacapone. The end result showed that the rats receiving levodopa alone showed a gradual increase of AIMs (abnormal involuntary movements). The rats receiving the combination therapy also demonstrated such AIMs in the beginning but did not experience an increase over the period of therapy (Marin, et al., 2006: 648).
The findings of this study were prompted another study which considered the differences in dyskinesia incidence between MPTP-treated primates and patients with Parkinson’s disease when treated with entacapone as opposed to pulsatile levodopa therapy (Smith, et al., 2005: 307). The aim of this was to determine whether the concurrent administration of entacapone with levodopa would decrease the incidence of dyskinesias in MPTP-lesioned primates. The four times daily administration of entacapone with levodopa showed significantly enhanced motor responses together with the reduced frequency and severity of dyskinesia (Smith, et al., 2005: 307). However, as the study was conducted on primates, the optimal dosage and therapy for humans would have to be determined (Smith, et al., 2005: 313).

3.4.4 Selegiline and levodopa

The most important study involving selegiline is the DATATOP (deprenyl (selegiline) and tocopherol antioxidative treatment) study which showed that selegiline, with or without tocopherol, is ‘neuroprotective’ which means that it reduces the rate of progression of Parkinson’s disease (Olanow, et al., 2003: 1; Ward, 1994: 217). The study also found that the antiparkinsonian effects of selegiline continued for at least six weeks after its discontinuation (LeWitt, 2009: 1352). This is due to the irreversible nature of the inhibition. It was shown that a full recovery of the inhibition required longer than four weeks (LeWitt, 2009: 1352). A review of the effects of selegiline and rasagiline stated that one study showed there was no difference in effect between selegiline and placebo whilst others showed only a mild symptomatic benefit (LeWitt, 2009: 1352). The same results were shown for rasagiline (LeWitt, 2009: 1353). Clinical experience has also shown that selegiline in combination with dopamine replacement therapy only offers limited benefits (LeWitt, 2009: 1353).

3.4.5 Rasagiline and levodopa

A double blind, parallel group, randomised, delayed start clinical trial was conducted in order to determine the effect of early and later initiation of rasagiline on the progression of disability in Parkinson’s disease (Parkinson study group, 2004: 561).
Rasagiline is a selective irreversible inhibitor of monoamine oxidase type B. The group had, six months previously, conducted another study randomising patients to once daily rasagiline or placebo. In this second phase of that initial study, patients who were receiving 1mg or 2mg of rasagiline continued to receive that dosage and those who were previously receiving placebo were now given rasagiline 2mg (Parkinson Study Group, 2004: 561). This study aimed to determine if the patients with earlier initiation demonstrated better functional status at one year. The results showed that patients receiving rasagiline for one year demonstrated less symptom progression than those patients receiving rasagiline for just six months (Parkinson Study Group, 2004: 564).

### 3.4.6 Levetiracetam for the management of LIDs

Lately, the effect of the antiepileptic agent levetiracetam in reducing LID has been investigated. Levetiracetam is generally used as add-on therapy for the treatment of partial-onset seizures (Zesiewicz, Sullivan, Maldonado, Tatum and Hauser, 2005: 1206). The two studies discussed below agree that levetiracetam could be used to reduce the severity of LID experienced by Parkinson’s patients.

One study (Zesiewicz, et al., 2005: 1206) utilised nine patients suffering from Parkinson’s disease who were experiencing peak dose dyskinesia which was moderately disabling for at least 25% of the awake day. These patients were treated with levetiracetam of which the dose was titrated upward to reach a maximum of 3000mg, given for up to 60 days (Zesiewicz, et al., 2005: 1205). The primary outcome measure of the study was the proportion of the awake day the patient spent in the ‘on’ phase without dyskinesia or without troublesome dyskinesia. The study group aimed to determine the tolerability and preliminary efficacy of levetiracetam in reducing LID in Parkinson’s disease patients (Zesiewicz, et al., 2005: 1206). Patients had to achieve at least a 70% concordance with the primary investigator for diary rating of ‘on’ and ‘off’ time. Of the three women and six men who were enrolled in the study, 56% dropped out before the end point. Two patients withdrew before completing their diaries and were not included in the final analysis. Two patients withdrew due to somnolence, one due to dizziness and confusion as well as another
patient due to obtundation which is defined as a greatly reduced state of consciousness without being comatose.

At the end of the study, the mean dose of levetiracetam was 625mg daily with none of the four patients reaching the endpoint having received the maximum allowable dose of 3000mg per day (Zesiewicz, et al., 2005: 1207). Two of the patients achieved satisfactory dyskinesia control at 750mg and 1000mg respectively. Mean percent ‘on’ time without dyskinesia or troublesome dyskinesia increased from 43% at baseline to 61% at endpoint. There was no increase in ‘off’ time (Zesiewicz, et al., 2005: 1207). Overall, the symptoms of Parkinson’s disease were much improved in two patients, unchanged in three, minimally worse in one patient and much worse in one patient.

A further study was conducted to determine the safety and efficacy of levetiracetam for the management of LID (Stathis, Konitsiotis, Tagaris and Peterson, 2011: 267). The study involved a multicenter, double-blind, placebo-controlled, parallel group, crossover trial. The levodopa treated Parkinson’s patients received levetiracetam 500mg per day and was titrated upward to 1000mg daily. The primary efficacy was determined by the percentage change in ‘on with LID’ time from patient diaries. The results of the studies showed a percentage change of ‘on with LID’ waking time decreased by 3.8% at 500mg per day and 7.8% at 1000mg daily (Stathis, et al., 2011: 267). However, there was no decrease in ‘off’ time as shown by the abovementioned study as well. One patient withdrew due to adverse effects. The adverse effects, of which the most common included dizziness and somnolence, were more prominent in the 500mg per day group than the 1000mg per day. This indicates that it is possible for tolerance to be developed to the adverse effects associated with levetiracetam (Stathis, et al., 2011: 269). The study showed that a dose of 1000mg per day with slow titration can be useful in treating LID (Stathis, et al., 2011: 270).
3.5 Previous drug utilisation analyses

Any previous drug utilisation studies found using the respective databases were included. These were then analysed and compared to the findings of the DUR. This section focuses on studies concerning the prescribing patterns of Parkinson’s disease as well as the cost of treatment.

3.5.1 Prescribing patterns of antiparkinsonian medication

A Singaporean study (Tan, Yeo, Tan, Pavanni and Wong, 2012: 511) aimed to determine the prescribing patterns of antiparkinsonian medication in Singapore. They also included a survey to determine which factors were considered by neurologists when prescribing these medications (Tan, et al., 2012: 511).

The study population included 182 men and 124 women of the average age of 64.4±9.9 years. The majority of patients were in Hoehn and Yahr stage three of the disease (Tan, et al., 2012: 512). Analysis showed that levodopa in combination with a decarboxylase inhibitor, such as carbidopa or benzerazide, was the most commonly prescribed drug with 92.3% of the study population receiving one of these combinations. Interestingly, it was the levodopa/beneserazide combination which was more popular (Tan, et al., 2012: 513). Patients in later stages, such as Hoehn and Yahr stage three to five, of the disease were also using higher doses of levodopa compared to those in earlier stages (Tan, et al., 2012: 513). Dopamine agonists made up 26.8% of the total medications used, with the next being benzhexol and then selegilene. The COMT-inhibitors and amantadine use was less than 10%. The majority of the population was on monotherapy or a two drug combination therapy. Almost 40% of these patients were on monotherapy with levodopa. It also showed that patients on levodopa were in more advanced stages of the disease than those who were not, but no relationship was found between the use of dopamine agonists and disease severity (Tan, et al., 2012: 513). When asked, the neurologists claimed that factors that most influenced their decisions included stage of disease, cost of the drug, patient compliance and drug company sponsorship.
The group also found that 64.5% of the patients were also receiving medication unrelated to Parkinson’s disease which had the potential to interact with their antiparkinsonian medication (Tan, et al., 2012: 513). Other medication being used by 12 of the patients included benzodiazepines such as alprazolam, clonazepam, diazepam and lorazepam (Tan, et al., 2012: 513).

Another study in Italy demonstrated a similar result (Leoni, Martignoni, Cosentino, Michielotto, Calandrella, Zangaglia, Riboldazzi, Oria, Lecchini, Napp and Frigo, 2002: 151). Levodopa was the most commonly prescribed drug (54%) followed by dopamine agonists and anticholinergic agents (Leoni, et al., 2002: 151). Some of the other medications prescribed unrelated to Parkinson’s disease included anxiolytics and sedative hypnotics (Leoni, et al., 2002: 153).

### 3.5.2 Cost of treatment

With the number of Parkinson’s sufferers increasing, the cost of care rises too. Due to the complicated nature of the symptoms and complications of Parkinson’s disease and its therapy, medical treatment alone is not enough. This means that caring for the patient can become quite expensive (Keus, et al., 2012: 1). As many as 18 different disciplines can become involved in the care of a patient suffering from Parkinson’s disease (Keus, et al., 2012: 1).

A study conducted in Germany aimed to determine the cost and trend of resource utilisation in patients with Parkinson’s disease over a period of four years (Winter, Balzer-Geldsetzer, von Campenhausen, Spottke, Eggert, Oertel and Dodel, 2010: 18). The resource utilisation was recorded over a 12 month period. The study group made use of instruments such as patient diaries and questionnaire surveys (Winter, et al., 2010: 19). Two cohorts of patients were used, one from 2000 and the other from 2004. Disease severity was classified according to the Hoehn and Yahr stages. The total costs calculated were from the societal perspective and included both direct and indirect costs. The direct costs were made up of payments made by health insurance companies and patient co-payments. Health insurance spending included inpatient care, outpatient care, costs of additional services such as physiotherapy,
occupational therapy and speech therapy, costs for any special equipment required by the patient, home care including both formal and informal care. Formal care was that provided by health care professionals and informal care was that provided from family and friends. Drug costs were also included (Winter, et al., 2010: 19). The indirect costs involved included productivity losses due to premature retirement related to Parkinson’s disease or temporary sickness.

In 2000 a total of 145 patients were included of which 97 were men and 48 women. The cohort of 2004 included 133 patients, but after a drop out of 13 patients, 120 remained to participate in the study. Of these 120 patients, 82 were male and 38 were female. The number of patients in stages four and five were higher in the cohort from 2000 than 2004 (Winter, et al., 2010: 20), therefore costs were calculated for each Hoehn and Yahr stage separately. Depending on the stage, the total costs for 2004 were 25% to 31% higher than in 2000. The direct and indirect costs both increased with the Hoehn and Yahr stages.

The overall resource utilisation increased by 25% to 31% over the total four year study period. This is due to the increasing prevalence of Parkinson’s disease. Changing trends in the utilisation of health care resources can lead to short term effects that can cause a dramatic increase or decrease costs (Winter, et al., 2010: 21). The study also mentioned that there is an increase toward prescribing of dopamine agonists as opposed to levodopa (Winter, et al., 2010: 21). Due to the fact that these newer drugs are so expensive, it has elevated costs of Parkinson’s disease. The drug treatment constituted 12% to 32% of the total costs and consists 61% to 73% of dopaminergic drugs.

The study concluded that Parkinson’s disease places a significant burden on society and this burden is expected to increase in the coming years. The introduction of new healthcare programmes and technologies can produce rapid changes in the utilisation of health care resources (Winter, et al., 2010: 22).

A study conducted in Ontario, Canada aimed to determine the burden of Parkinson’s disease (Guttman, Slaughter, Theriault, DeBoer and Naylor, 2003: 313). Databases
were used and the subjects were matched with controls. The study assessed the prevalence of Parkinsonism, physician and drug related costs, hospital admissions and utilisation for Parkinson’s patients compared with the controls. The study made use of a prevalence group which used databases from 1992/1993 to 1998/1999 and a cohort group utilising information from the fiscal year 1993/1994 (Guttman, et al., 2003: 314).

Results from the prevalence group showed a 25.8% increase in the number of patients from 1992 to 1998 (Guttman, et al., 2003: 315). There was also a 5.4% age-adjusted prevalence for men over this time period and 9.8% for women. The proportion of patients under the age of 60 years was between 8.5% and 9.5% for men and 6.2% and 7.3% for women. The majority of patients were over the age of 60 years (Guttman, et al., 2003: 315).

Results from the cohort group showed that physician costs were 1.4 times higher for patients than for the controls (Guttman, et al., 2003: 315). Over the six years of the study, 68.4% of Parkinson’s patients were admitted to hospital compared to 56.9% of the control group. The total number of hospitalised cases of Parkinson’s disease decreased over the six years. Another finding of the study showed that the number of hospitalisations did not increase with age and severity of disease (Guttman, et al., 2003: 315). The average cost of drugs for the study period was six times higher than the controls. This is mostly due to the high cost of antiparkinsonian drugs (Guttman, et al., 2003: 316). The study concludes that the demonstrated increase in prevalence of Parkinson’s disease and the definitive economic burden that it places on society is reason enough to stimulate further investigation into the cause of Parkinson’s disease and development of preventative strategies (Guttman, et al., 2003:318).

A study conducted in Europe investigated the effect of dyskinesias in the Quality of Life (QoL) and economic cost of drug therapy (Péchevis, Clarke, Vieregge, Khoshnood, Deschaseaux-Voinet, Berdeaux and Ziegler, 2005: 956). Six patients were enrolled all of whom fell at different points on the disability scale to provide potentially varying QoL scores and health-economic outcomes. The QoL scores
were determined using a series of tests. These included the UPDRS, the Montgomery-Asberg Depression Rating Scale and their medical histories. Also used was the generic QoL questionnaire, the Short Form-36 and a Parkinson’s disease specific instrument, the Parkinson’s disease Quality of Life scale (Péchevis, *et al.*, 2005: 957). The Parkinson’s disease Quality of Life scale includes questions pertaining to daily activities and whether the patient is able to perform them without difficulty, as well as the emotional wellbeing of the patient such as the presence of depression, embarrassment to go out in public because of the disease or problems with personal relationships. The patients were required to keep a diary over a six month period and costs were calculated based on the items and activities recorded in the diary (Péchevis, *et al.*, 2005: 957).

The results showed that increasing dyskinesia scores were associated with a significant reduction in QoL scores (Péchevis, *et al.*, 2005: 958). However, dyskinesias measured using the UPDRS did not have effects on activities of daily living scores after adjusting for fluctuation, disease and country. The study showed that there was a significant association between increasing dyskinesia severity and depression (Péchevis, *et al.*, 2005: 959) which means that the decreased QoL could be due to the adverse effects on mood (Péchevis, *et al.*, 2005: 961). Dyskinesias were also associated with a significant increase in health-related costs (Péchevis, *et al.*, 2005: 960). It was shown that each unit increase in dyskinesia severity, when measured using the UPDRS, resulted in a total additional cost of €562 per patient over the six month period (Péchevis, *et al.*, 2005: 960).

In the Netherlands, a group of researchers examined how they could improve community healthcare for patients with Parkinson’s disease (Keus, *et al.*, 2012: 1). The aim was to make the plan adaptable to other countries. An examination of the current therapy was evaluated then a regional expert centre for Parkinson’s patients was set up. This centre served as a tertiary referral centre for a large region. The centre was also responsible for initiating and conducting clinical trials and then distributing the newly acquired knowledge to the public at large (Keus, *et al.*, 2012: 1-2).
Evidence based guidelines were developed for allied health care professionals. These included physiotherapists particularly, as well as occupational therapists, speech and language therapists, dieticians, specialist nurses, psychologists, social workers, sex therapists and neurologists (Keus, et al., 2012: 2, 4). The NICE guidelines for Parkinson’s disease agree with this, stating that all Parkinson’s patients should have access to specialised nursing care, physiotherapy, occupational therapy as well as speech and language therapy (Stewart, 2007: 239). The researchers then developed a multifaceted implementation strategy called ParkinsonNet and a number of expert health care professionals interested in the project were selected and trained to work at each of them in the different regions. The training included measures to ensure that the professionals always communicated regularly and effectively with each other. Transparency and continuous education and exchange of knowledge were also encouraged (Keus, et al., 2012: 3). Figure 3.1 is a summary of the nine steps involved in the process of setting up this system.
When ParkinsonNet was evaluated it showed that the quality of care provided to Parkinson’s patients was improved and the volume of patients per therapist more than doubled while saving costs. It also showed that therapists treating more than nine Parkinson’s patients per year were more connected than those treating 10 or less and this connectedness was shown to influence clinical decisions concerning patients (Keus, et al., 2012: 4).
CHAPTER 4

Methodology
4.1 Introduction

This study consisted of two parts, namely a drug utilisation review and a questionnaire survey. The drug utilisation portion of the study involved the analysis of prescription records obtained from a national retail pharmacy group. The questionnaire survey portion was a semi-structured questionnaire which was verbally administered to patients by the researcher and a review of patient medical files was conducted at the hospitals of Groote Schuur (associated with the University of Cape Town) and Tygerberg (associated with Stellenbosch University) in the Western Cape Province and sourced from the Parkinson’s disease support group in the Eastern Cape Province.

4.2 Ethical approval

Before the study was initiated, approval had to be obtained from the Department of Pharmacy, the Faculty of Health Sciences Research, Technology and Innovation (FRTI) Committee and the Human Research Ethics Committee (REC-H) of the Nelson Mandela Metropolitan University (NMMU). Approval also had to be obtained from the Faculty of Health Sciences HREC at the University of Cape Town (UCT) as well as the Faculty of Health Sciences HREC at the University of Stellenbosch. See appendices A, B and C for the proof of ethical approval of these committees in order of mention.

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data (The World Medical Association, 2008: 1). This study utilises identifiable human data and thus the principles of the Declaration of Helsinki were consulted and adhered to in the formulation of the methodology.
4.3 Study Design

Research design can be broadly categorised into two groups, namely exploratory and conclusive studies. Exploratory design provides insights and understanding to a particular phenomenon and the information that is required is only very loosely defined. The research process is flexible and unstructured and therefore subject to change during the study. The sample is usually quite small and not representative of the population as a whole. The analysis of the primary data is qualitative and the results obtained from these studies are only tentative. The results of exploratory studies are generally followed by further exploratory or conclusive studies (Malhotra, 1999: 84). Conclusive studies are done to test for specific hypotheses. The information needed is clearly defined and the research process is formal and structured. The sample is large and representative of the population under study. The analysis of the primary data is quantitative and the results can be seen as conclusive. The results of such conclusive studies are generally used in decision making processes. (Malhotra, 1999: 84).

This study consists of conclusive elements. The DUR is identified as conclusive since the information needed is clearly defined, the sample is large and the data analysis is quantitative. The questionnaire survey portion of the study is also conclusive as the method of analysis of the primary data is quantitative and the information required is clearly defined.

The drug utilisation study was a cross-sectional study. A cross-sectional study is defined as one which focuses on a single sample from which data is obtained at a single point in time. Although the records included in the database span a period of one year, the information was obtained on only a single occasion (Malhotra, 1999: 89). The data is retrospective in nature as the patients had already been entered into the database at the time of analysis and no new patients were added during the course of the study.

The questionnaire survey is defined as an empirical, descriptive study. Empirical studies are those that provide evidence on the basis of actual observation or
experimentation (Merriam-Webster). A descriptive study involves the description of phenomena using statistical analysis (Mouton and Marais, 1988: 43).

4.4 Literature Review

An extensive literature review was conducted during the period February 2011 until July 2012. The literature review was performed to obtain knowledge about Parkinson’s disease, drug utilisation and the chosen methods of data collection. Appropriate books, internet websites and journal articles were consulted. Electronic information, including local and international journal articles was obtained through the use of PubMed®, ScienceDirect®, EBSCOHost® and library search engines of the universities included in the study.

4.5 Drug utilisation study

Drug utilisation was defined by the WHO in 1977 as ‘the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences’ (WHO, 2003: 8). The main aim of drug utilisation research is to facilitate the rational use of drugs in a population. Drug utilisation research is conducted to determine the pattern of drug use, the quality of use, the determinants of use and the outcomes of drug use. Such studies also provide insight into the efficiency of drug use that is, determining whether a certain drug provides value for money (WHO, 2003: 8-9). The DUR was a structured process wherein a primary sample group was identified and analysed in terms of medicine usage, drug prescribing and drug dosage.

4.5.1 Health Care System in South Africa

South Africa has two health care sectors. The public health care sector provides health care facilities and services through government funding to members of the population who cannot afford the medical costs. The private health care sector provides health care facilities and services to those individuals able to pay for medical costs either from personal funds or private medical aid schemes. In 2004
only 18.5% of persons over the age of 20 years had access to medical benefits (Lehohla, 2004: 27). In 1999 over two thirds of the white population of South Africa had access to medical benefits whereas with the black population, only 8.9% had access. Between 1995 and 1998, public health care was the sector most commonly used and there has been an increase in its usage since (Lehohla, 2004: 31). It is shown that white South Africans are the group most likely to utilise private health care facilities while the black and coloured populations are most likely to utilise the public health services (Lehohla, 2004: 31). This study focuses on patients in the private health care sector with or without a medical aid.

A national community pharmacy group provided a database containing all records for the time period of 1st January to 31st December of years 2008, 2009 and 2010. The database consists of all CNS prescription records for the above-mentioned time period. The data requested is from the whole of South Africa.

4.5.2 Data Collection

The information provided was anonymous and patient confidentiality was maintained at all times. Patients were identified only by a patient code. Geographical location was indicated by predetermined divisions of the provinces in the database. Data analysis makes use of the divisions provided by the database where some of the provinces were combined into one region. An extract of the database as well as a list of data fields provided is included as Appendix D.

The data contained all records for CNS drug prescriptions in the year 2010. The only criteria for inclusion in the primary study sample were:

- Use of medication which has been licensed by the Medicines Control Council of South Africa for the treatment of Parkinson’s disease; and
- being aged 50 years or older.
Data were obtained as text delineated files for each month. The data were then exported in Microsoft Access®. The data received was compatible with Microsoft Excel®.

4.5.3 Data analysis

There were 25 523 antiparkinsonian records for the year 2010. The extracted data contained information about patients receiving antiparkinsonian medication on a chronic basis.

Demographic information, such as age and gender were missing from a number of records. A total of 3 954 records were excluded due to the exclusion criteria being patients under the age of 50 years. A further nine records were excluded due to the patients being over the age of 100 years and another 149 records due to there being no age recorded. A total of 218 records were excluded for unspecified gender. The letter ‘U’ and a blank area are indications of invalid entries identified. Records which indicated a zero ‘sales value’ or zero ‘units sold’ were excluded as this implies that the records were incorrectly captured or the items were not dispensed. So-called ‘nonsensical’ sales values (those between R0.01 and R0.76) were also excluded. This brings it to a total 4 320 records excluded due these discrepancies. Certain patient profiles consisting of a total of 34 records were excluded as only half of the information pertinent to analysis was available. This brought the total analysed records to 25 523.

There was no way to identify single patients within the database as more than one patient on the same medical aid was listed under the same profile number and differed only by the dependant number. To allow for identification of individual patients, a formula was derived to provide each patient with a unique numerical identifier. This was done by multiplying the profile number by 100 and adding the dependant number.
4.6 Questionnaire-based survey

The purpose of this portion of the study was to determine the age of onset of Parkinson’s disease, establish when levodopa therapy was initiated relative to the date of diagnosis, determine the use of other medications even if not antiparkinsonian medication, determine if and when the emergence of dyskinesias occurred, determine the severity of the dyskinesia and assess the risk factors involved in the emergence of dyskinesia.

At the public hospitals of Groote Schuur and Tygerberg, the specialised Parkinson’s disease clinic hours were used to source patients. The patient files were scanned in numerical order and patients were selected based on the inclusion criteria of the study. The medical records were available at the time of interview for review. A total of nine patients were obtained at Groote Schuur Hospital and 22 patients were obtained from Tygerberg Hospital.

In Port Elizabeth, patients from the Parkinson’s disease support group were contacted and asked to participate in the study. Those who consented were visited at a time and place of his/her choice. Thereafter, the respective neurologists were contacted to request access to the patients’ medical records. A total of 12 patients were obtained from the support group. The questionnaire used is included as Appendix E and the request form sent to the neurologists as Appendix F. The patient consent forms, both English and Afrikaans are included as Appendix H and Appendix I, respectively.

4.6.1 Advantages and disadvantages of questionnaires

According to Mouton and Marias (1988: 50), the best research strategy for conducting a descriptive, general interest study is by making use of sample surveys. Closed-ended and open-ended questions may be asked; allowing for the provision of both facts and opinions and beliefs (Behr, 1983: 150-151). Questionnaires may be introspective or extrospective. They are considered introspective when the respondent is answering questions about him- or herself and extrospective when the
respondent is answering questions about someone else (Behr, 1983: 151). The questionnaire used in this study is introspective.

The advantages of a questionnaire survey is that it is relatively simple to administer and distribute, there is reliable data collection as response options are generally limited and the coding, analysis and interpretation of the data is generally quite simple (Malhotra, 1999: 178). The advantage of verbal administration is that it allows the patient to ask questions if they do not understand what is required of them and also allows the researcher to question the patient further in order to obtain the necessary information. The advantage of the researcher administered questionnaire is a high response rate as the researcher personally conducted the interviews using English and Afrikaans as the acceptable languages.

The disadvantage of verbally administering questionnaires is time restriction. It may result in the study population being decreased or inadequate information being obtained from patients due to time constraints. Another disadvantage would be bias in the answers resulting from prompting from the researcher if the patient misunderstands the questions. Also as humans, the patients will be aware that they are participating in research and react to the situation and this may result in possible bias as well. Inability to accurately recall information from the past may also reduce the reliability of the data (Malhotra, 1999: 178). However, despite these disadvantages, surveys are still a very commonly used form of data collection (Malhotra, 1999: 178).

A review of patient medical records was also conducted. The researcher made use of a data collection sheet (Appendix G) which extracted information from the patient medical records concerning: the date of diagnosis; current disease severity; initial therapy prescribed; date of levodopa initiation; initial dose of levodopa; current levodopa regimen; other Parkinsonian medications the patient is receiving; incidence of dyskinesia and latency to onset of dyskinesia. Patient confidentiality was maintained at all times. The researcher ensured that no names or details that could be traced back to particular patients were present on documents.
4.6.2 Development of the questionnaire

A questionnaire was developed pertaining to information found in the literature review. Ethics approval by the FRTI and the Human Ethics Committees of all three universities involved was obtained.

After approval was obtained, a pilot study was conducted to determine how long it would take to administer the questionnaire and if the language used was clearly understood by the patients. The pilot study conducted at Groote Schuur Hospital showed that it would take approximately 15 minutes to verbally administer the questionnaire to the patient and minor changes were made to the questionnaire following the pilot study.

4.6.3 Study site

The study population was to consist of 50 patients from Groote Schuur Hospital in Cape Town who have been under the medical supervision of a well-known neurologist from January until June 2011. These patients had been conclusively diagnosed with Parkinson’s disease by this neurologist and were currently on levodopa therapy.

Groote Schuur Hospital is a large academic training institution of the University of Cape Town with an extensive patient population. Many of the patients comprising the population of the researcher’s previous study (Gaida, Kubashe and Truter, 2010) visited the chosen neurologist for examinations and confirmation of diagnosis and disease severity. The attending neurologist was a respected professional and academic in his field. The patients’ medical records would be obtained from the hospital record department. Data were to be collected over a six month period (January to June 2011). Systematic random sampling was to be employed and the first 50 files, arranged in alphabetical order, of patients with Parkinson’s disease was selected, that is the first 25 male and the first 25 female patients who were willing to participate in the study.
The following patients were excluded from the study:

- patients younger than 50 years as Parkinson’s disease is more common in patients this age and older (Goetz, et al., 2003: 743); and
- patients who have been on levodopa therapy less than one year. The patient is unlikely to experience any side effects from levodopa therapy or any dyskinesias due to disease progression before this stage (Madden, Morris, Graham, Katekar and Wade, 1995: 48).

The data collection began in May 2011. The neurology outpatient clinic at Groote Schuur hospital operated on Tuesday afternoons and Thursday mornings. The researcher would attend these clinic sessions and select the patient folders of those diagnosed with Parkinson’s disease in numerical order and proceed to interview the patients. This was the form of random sampling undertaken by the researcher as selecting patients in alphabetical order as previously desired was not possible. In August 2011 the researcher went on a six month international exchange programme, thus there was a break in the data collection until March 2012. During this period of time it was decided that the patient population at Groote Schuur may be too small to obtain the desired number of 50 patients. Tygerberg hospital was therefore approached for ethics approval which was granted to the researcher. Tygerberg hospital was chosen as it is another public sector hospital in Cape Town with a neurologist and runs a specialised Parkinson’s disease clinic every two weeks. The Parkinson’s disease support group in Port Elizabeth was also used as the specialised clinic at Tygerberg Hospital was not yielding as many patients as originally anticipated. The eventual number of patients interviewed was 43.

### 4.6.4 Data analysis

The questionnaires were coded and captured onto a purpose-designed spreadsheet using Microsoft Excel®. The results were analysed using descriptive and inferential statistics and compared with literature findings.
4.7 Confidentiality

Confidentiality was maintained in both the DUR and questionnaire survey. The database analysed did not provide any identifiable reference to patients. The questionnaire survey maintained separation between the consent forms and the questionnaires to ensure confidentiality. The questionnaires of interviews conducted at the different hospitals were combined to ensure that patients could be identified at a particular site. The informed consent forms were reviewed separately as a means of record keeping. All of these documents were safely stored at the researcher’s home. The consent forms are attached as Appendices H and I.

4.8 Limitations

Limitations of both the DUR and questionnaire survey were identified and are described separately below.

The most important limitations of the DUR were:

- The database profiles may not be an accurate representation of the South African population.
  - The patient information was not linked for the different stores of the retail pharmacy group within the database. It is therefore possible that certain patients collected prescriptions from different stores in other regions where different profiles were used, thus the total number of individual patients may not be an accurate reflection of the actual number of patients due to the duplication of profiles.

- Demographic information for the entire database population could not be accurately determined.
  - The age and/or gender fields were either empty, contained different entries for the same patient, or were stated as unknown for a large number of patients.

- The exact dispensing date was not given.
  - It was not possible to determine an accurate time frame for drug utilisation as only the months were provided and not the individual dates for each dispensed prescription.
The most important limitations of the questionnaire based survey were:

- Design of forms
  - The information sought in the forms was very specific and patients may not have been able to provide accurate records. This is particularly so since the majority of the patient population were elderly and impairment of memory may have played a role in the accuracy of information.

- Study population
  - The questionnaires were limited to certain age groups which reduced the potential number of participants.
  - The interviews were conducted only in English and Afrikaans. For example, Xhosa is a language widely spoken in the Eastern Cape. Therefore patients speaking a language other than English or Afrikaans could not be interviewed, thus further reducing the number of participants.
  - As mentioned above, due to the age of the study population, memory impairment may have been a problem.
CHAPTER 5
Results and Discussion of the Drug Utilisation Review
5.1 Introduction

The following chapter focuses on describing and analysing the main findings of the DUR. The population analysed was provided by a national private community (retail) pharmacy group and consisted of all the records of antiparkinsonian drug prescriptions captured during the year 2010. The database was analysed at different levels with overall demographic statistics being provided for the complete dataset, as well as an overview of the drug classes and substances identified and distribution of prescriptions per month. The patient population was analysed to provide statistics on gender ratio, mean age of the population as well as the distribution of prescriptions and patients per region. The drug use and sales value was also investigated. In this chapter, patient statistics and regional statistics will be analysed and discussed.

5.2 Overview of patient information

Demographic information of the patients including age, gender and regional distribution was available. Of the 25,523 antiparkinsonian products dispensed, there were 5,168 patients identified with 3,058 (59.17%) being females and 2,110 (40.83%) being males. This gives a female to male ratio of 1:0.68. The average number of prescriptions dispensed to male patients was 5.55 ± 6.88 over the year whereas 4.51 ± 5.44 was the average for females. The chi-squared test shows a statistical significant result (p <0.05) but this is due to the large sample. The practical significance, as indicated by Cramér's V (0.07), is small.

Many studies have shown that Parkinson’s disease is more common in men than women (Fall, Axelsson, Fredriksson, Hansson, Lindvall, Olsson and Granéurus, 1996: 638; Fargel, et al., 2007: 208; Miller and Cronin-Golomb, 2010: 2695; Shulman, 2007: 12), but in this patient population it was shown that there were in fact more females than males. However, Japanese studies have shown a female prevalence in Parkinson’s disease (Kimura, Kurimura, Wada, Kawanami, Kurita, Suzuki, Katagiri, Daimon, Kayama and Kato, 2002: 296; Kusumi, Nakashima, Harada, Nakayama and Takahashi, 1996: 201). Another study conducted in France showed a prevalence ratio of Parkinson’s disease of 1.40% in patients over the age of 65 years with no
significant difference between males and females (Tison, Dartigues, Dubes, Zuber, Alperovitch and Henry, 1994: 113). According to the midyear population estimate of 2010, 51% of the South African population was female (Statistics South Africa, 2010: 3). This could partly explain why females were the dominant gender in the population. The result of this study was in keeping with another which analysed databases between the years 2005 to 2008. It was found that for each year female patients constituted 56% to 60% of the total population (van der Merwe, 2010: 96).

The total population aged 50 years and older in South Africa according to the midyear population estimate of 2010 was 14.94% with 8.30% being female and 6.64% being male (Statistics South Africa, 2010: 9).

The average age of the population was 70.74±10.37 years, with the oldest patient being 100 years. It is important to keep in mind that only patients aged 50 years and older were included in the study. The Italian study (Leoni, et al., 2002: 151) included a cohort of 130 idiopathic Parkinson’s patients with a mean age of 68.6±9.9 years. The males were, on average, slightly older than the female patients. The age range was 38 years to 87 years (Leoni, et al., 2002: 151). A French study (Tison, et al., 1994: 112) included only patients aged 65 years and older with an average age of 74.9 years.

For all tables and figures, denotation with a single ‘n’ will refer to either the number of patients or prescriptions within the sample or the total value in Rands. The age distribution according to gender is summarised in Table 5.1 and depicted in Figure 5.1 according to 10 year intervals.

Table 5.11 Age and gender of patients who were prescribed antiparkinsonian agents

<table>
<thead>
<tr>
<th>Gender</th>
<th>Average Age ± SD</th>
<th>Oldest patient(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>70.37±10.66 years</td>
<td>100 years</td>
</tr>
<tr>
<td>Male</td>
<td>71.17±9.88 years</td>
<td>95 years</td>
</tr>
<tr>
<td>Both genders</td>
<td>70.74±10.37 years</td>
<td>100 years</td>
</tr>
</tbody>
</table>
Figure 5.1 demonstrates that the highest prevalence of Parkinson’s disease was in the age category of 70 years to 79 years for both males and females. The reason for the decrease beyond this age could be due to mortality, or the general low life expectancy in South Africa, which is shown to be 53.3 years for males and 55.2 years for females (Statistics South Africa, 2010: 3). Also, in South Africa, only 0.71% of the population is over the age of 80 years (Statistics South Africa, 2010: 9). A Spanish study showed that the prevalence of Parkinson’s disease increased with age, but decreased beyond the ages of 80 years for men and 85 years for women (Benito-León, et al., 2003: 269) which was in keeping with the results of the current study.

5.3 Overview of antiparkinsonian drug prescriptions

All antiparkinsonian drug prescriptions for the patient population selected across South Africa are represented in this section. Details such as the regional distribution of prescriptions across predefined areas of the country, the number of times the
prescription may be repeated, the drug classes identified and the sub-classes thereof are discussed.

5.3.1 Antiparkinsonian products dispensed

A total of 5,168 patients were dispensed 25,523 antiparkinsonian products throughout the year. This amounts to an average of 4.94±10.42 products per patient, indicating that patients were on combination therapies. The majority of these products were dispensed to females (54.05%). The age and gender distribution of patients is summarised in Figure 5.2.

Figure 5.2 Percentage of antiparkinsonian products dispensed by age and gender

Looking at the products dispensed according to age groups, it was seen that the majority of the products were dispensed to patients between the ages of 70 years to 79 years for both genders. This age group constituted a total of 32.28% of the total study population and they were prescribed 35% of all antiparkinsonian products. Table 5.2 shows the average number of prescriptions received by gender and age.
### Table 5.12 Average number of prescriptions received by gender and age

<table>
<thead>
<tr>
<th>Age categories</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59 years</td>
<td>3.44±2.70</td>
<td>4.10±4.34</td>
</tr>
<tr>
<td>60-69 years</td>
<td>4.46±2.56</td>
<td>5.92±6.94</td>
</tr>
<tr>
<td>70-79 years</td>
<td>4.99±3.92</td>
<td>5.78±3.63</td>
</tr>
<tr>
<td>80-89 years</td>
<td>5.24±7.41</td>
<td>5.81±8.82</td>
</tr>
<tr>
<td>≥90 years</td>
<td>4.27±5.82</td>
<td>5.58±5.70</td>
</tr>
</tbody>
</table>

As can be seen, the average number of prescriptions for males was higher than females in each age category by at least one. The highest average number of prescriptions for females was in the age category 80 years to 89 years and for males this was 60 years to 69 years. This could mean that males could have experienced more severe disease than females. It was also seen that a total of 81.67% of prescriptions were repeats.

According to the ATC (Anatomical-Therapeutic-Chemical) nomenclature, antiparkinsonian agents are N04 as a group and then further divided according to the various chemical groups. Figure 5.3 indicates the frequency of antiparkinsonian product prescribing, Figure 5.4 indicates the frequency of antiparkinsonian product prescribing according to gender and Table 5.3 summarises all the antiparkinsonian products dispensed in terms of chemical subgroups, tradenames and active ingredients.
Figure 5.3 Frequency of antiparkinsonian products dispensed according to active ingredients

![Graph showing frequency of antiparkinsonian active ingredients.]

- Amantadine: 3.67%
- Biperidine: 0.97%
- Entacapone: 10.90%
- Levodopa/carbidopa: 83.93%
- Levodopa/benserazide/entacapone: 5.77%
- Orphenadrine: 4.40%
- Pramipexole: 7.27%
- Ropinirole: 64.56%
- Selegiline: 14.86%
- Tolcapone: 4.30%
- Amantadine: 0.10%

\( n_{rx} = 25\,523 \)

Figure 5.4 Frequency of antiparkinsonian active ingredients according to gender

![Graph showing frequency of antiparkinsonian active ingredients by gender.]

- Tolcapone
- Selegiline
- Ropinirole
- Pramipexole
- Orphenadrine
- Levodopa/carbidopa/entacapone
- Levodopa/benserazide
- Levodopa/carbidopa
- Entacapone
- Biperidine
- Amantadine

[Bar charts for male and female frequencies are shown, with different colors representing each gender.]
<table>
<thead>
<tr>
<th>Chemical subgroup</th>
<th>Chemical substance</th>
<th>Tradename/s*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td><strong>Dopa and dopa derivatives (N04BA)</strong></td>
<td>Levodopa in combination with a dopamine decarboxylase inhibitor such as carbidopa or benserazide</td>
<td>Sinemet®</td>
<td>4 201</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbilev®</td>
<td>6 385</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tevo® carbidopa/levodopa levodopa/carbidopa</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Madopar® levodopa/benserazide</td>
<td>728</td>
</tr>
<tr>
<td></td>
<td>Levodopa in combination with a dopamine decarboxylase inhibitor and COMT-inhibitor</td>
<td>Stalevo®</td>
<td>547</td>
</tr>
<tr>
<td><strong>Dopamine agonists (N04BC)</strong></td>
<td>Ropinirole</td>
<td>Reqip®</td>
<td>941</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requip® XL</td>
<td>941</td>
</tr>
<tr>
<td></td>
<td>Pramipexole</td>
<td>Pexola®</td>
<td>8 282</td>
</tr>
<tr>
<td><strong>MAO-B inhibitors (N04BD)</strong></td>
<td>Selegiline</td>
<td>Parkilyne®</td>
<td>522</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eldepryl®</td>
<td>20</td>
</tr>
<tr>
<td><strong>COMT-inhibitors (N04BX)</strong></td>
<td>Entacapone</td>
<td>Comtan®</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tasmar®</td>
<td>12</td>
</tr>
<tr>
<td><strong>Anticholinergic agents (N04A)</strong></td>
<td>Biperidin</td>
<td>Akineton®</td>
<td>1 409</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disipal®</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Orphenadrine</td>
<td>Akineton®</td>
<td>1 409</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disipal®</td>
<td>0</td>
</tr>
<tr>
<td><strong>Anticholinergic agents (N04A)</strong></td>
<td>Biperidin</td>
<td>Akineton®</td>
<td>1 409</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disipal®</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Orphenadrine</td>
<td>Akineton®</td>
<td>1 409</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disipal®</td>
<td>0</td>
</tr>
</tbody>
</table>
It was seen that the majority of antiparkinsonian products dispensed (46.5%) were combination drugs containing levodopa with a decarboxylase inhibitor and some with a COMT-inhibitor as well. Adding the values of these agents showed that a total of 11,875 products dispensed contained levodopa. This was expected as levodopa is considered the gold standard treatment of Parkinson’s disease (Garret, et al., 1998: 99; Stern, 2001: 27; Singh, et al., 2007: 30). The second most dispensed group of drugs were the dopamine agonists which include pramipexole and ropinirole. These made up a total of 10,164 of the products dispensed (39.80%). The levodopa-containing products and dopamine agonists are both classified as dopaminergics. These were followed by the anticholinergic agents benzhexol and orphenadrine making up 2,352 of the total number of products dispensed (9.20%). The MAO-B inhibitor selegiline and the anti-viral agent amantadine only made up 2.12% and 1.80% of the total products dispensed, respectively. These results are in keeping with other studies conducted (Leoni, et al., 2002: 149-157; Tan, et al., 2012: 511-514). When examining the frequency of antiparkinsonian product prescribing by gender, it was seen that males were prescribed the levodopa-containing products whereas females were preferably prescribed the dopamine agonist pramipexole.

The drug utilisation 90% (DU90%) represents the prescribed drugs which account for 90% of the volume (Bergman, Popa, Tomson, Wettermark, Einarson, Åberg and Sjöqvist, 1998: 115). When calculating the DU90% it was seen that 22,970.70 prescriptions would account for 90% of the total (n = 25,523). Figure 5.5 indicates the active ingredients identified by in order of prescribing frequency.

The levodopa-containing products, dopamine agonists, pramipexole and ropinirole, as well as the anticholinergic agent biperidine, constitute 90% of the overall drug prescribing for Parkinson’s disease. As there are no definitive guidelines for the management and treatment of Parkinson’s disease, there can be no comparison. However, as levodopa is considered the gold standard of Parkinson’s disease treatment and is therefore expected to constitute a large proportion of the overall prescriptions.
The products bromocriptine, a dopamine agonist, trihexyphenidyl, an anticholinergic agent, and rasagiline, a monoamine oxidase B inhibitor are products recognised for the treatment of Parkinson’s disease in South Africa according to the SAMF (ed. Rossiter, 2012: 458, 462, 464) but were not prescribed throughout the year 2010. Bromocriptine is not the choice of dopamine agonist in the private sector as the neurologists and patients have access to both pramipexole and ropinirole. Bromocriptine is instead used for cessation of lactation. A guideline for the treatment of Parkinson’s disease published by the Scottish Intercollegiate Guidelines Network (2010: 19) does not recommend the use of ergot derived dopamine agonists such as bromocriptine for the first line treatment of Parkinson’s disease due to the risk of developing moderate to severe cardiac valvulopathy. According to the SAMF (ed. Rossiter, 2012: 458) trihexyphenidyl is a drug more commonly found in the public sector. The population analysed was private sector and would therefore not utilise this product. Rasagiline was launched recently in 2009 in South Africa with a retail price of R1 024.38 which would deter many patients from opting to use it. The following Table 5.4 represents the average age and standard deviation for patients grouped according to the prescribed drug. Age calculations were then further investigated through the isolation of male and female patients for each drug.
## Table 5.4 Average ages of patients prescribed antiparkinsonian products

<table>
<thead>
<tr>
<th>Average age ±SD in years</th>
<th>Active ingredients</th>
<th>Amantadine</th>
<th>Biperidine</th>
<th>Entacapone</th>
<th>Levodopa-containing products</th>
<th>Orphenadrine</th>
<th>Pramipexole</th>
<th>Ropinirole</th>
<th>Selegiline</th>
<th>Tolcapone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average patient age ±SD (both genders)</strong></td>
<td></td>
<td>68.07±0.00</td>
<td>67.94±1.27</td>
<td>67.05±0.00</td>
<td>73.69±2.04</td>
<td>66.68±0.00</td>
<td>68.47±1.06</td>
<td>69.18±3.15</td>
<td>71.21±0.27</td>
<td>69.00±0.00</td>
</tr>
<tr>
<td><strong>Age range (in years)</strong></td>
<td>51-86</td>
<td>50-96</td>
<td>55-82</td>
<td>50-100</td>
<td>50-90</td>
<td>50-99</td>
<td>50-100</td>
<td>50-98</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td><strong>Female patient average age ±SD (in years)</strong></td>
<td>68.87±0.00</td>
<td>67.53±3.16</td>
<td>66.68±0.00</td>
<td>73.69±2.42</td>
<td>67.07±0.00</td>
<td>67.27±0.24</td>
<td>69.15±3.89</td>
<td>70.93±1.08</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Male patient average age ±SD (in years)</strong></td>
<td>67.50±0.00</td>
<td>70.15±5.32</td>
<td>67.26±0.00</td>
<td>73.04±3.04</td>
<td>66.00±0.00</td>
<td>69.54±1.81</td>
<td>69.08±3.33</td>
<td>71.19±1.05</td>
<td>69.00±0.00</td>
<td></td>
</tr>
</tbody>
</table>
The levodopa-containing products were used by patients across the entire age range investigated. This was the case for almost all products with the exception of amantadine, entacapone and tolcapone. The average age of both males and females did not differ greatly amongst the products which showed that there were no preferred products for particular age groups.

5.3.2 Area distribution of prescriptions

The areas provided represented South Africa in seven predefined regions of the country. These regions include ‘Central Division’, ‘Eastern Cape’, ‘Free State Division’, ‘Kwa-Zulu Natal’, ‘Mpumalanga’, ‘Northern Division’, ‘North West Province Division’ and ‘Western Cape’. The ‘Central Division’ was made up of Gauteng and the ‘Northern Division’ represented the Northern Cape and Limpopo Province. The prescription distribution through the areas is demonstrated in Table 5.5.

The average number of prescriptions per region was 3190.38±1 106.44 over the period of one year. The large standard deviation is due to patients travelling throughout the year and obtaining medication in different regions. The Western Cape held the highest proportion of prescriptions, 5 799±6.99 (22.72%) even though it did not possess the largest population in the country. The rest of the regions were similar in number of prescriptions. Gauteng houses the largest proportion of the country’s population, but had the third lowest proportion of prescriptions. Possible reasons for this distribution may be that the Western Cape has the largest number of the particular community pharmacy group in the country, other regions possessed larger rural areas without access to community pharmacies, or that the Western Cape holds a higher percentage of retired persons with access to medical aid. The Western Cape had the highest average number of prescriptions at 377.82±0.90 over the year. The regional distribution of patients is shown in Figure 5.6 below.
Table 5.5 Distribution of antiparkinsonian prescriptions per region

<table>
<thead>
<tr>
<th>Area</th>
<th>Prescriptions</th>
<th>Estimated South African population ≥50 years percentage*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Gauteng</td>
<td>2 716</td>
<td>10.64%</td>
</tr>
<tr>
<td>Eastern Cape</td>
<td>3 064</td>
<td>12.00%</td>
</tr>
<tr>
<td>Free State</td>
<td>3 331</td>
<td>13.05%</td>
</tr>
<tr>
<td>Kwa-Zulu Natal</td>
<td>2 900</td>
<td>11.36%</td>
</tr>
<tr>
<td>Mpumalanga</td>
<td>2 292</td>
<td>8.98%</td>
</tr>
<tr>
<td>North West Province</td>
<td>2 986</td>
<td>11.70%</td>
</tr>
<tr>
<td>Northern Cape and Limpopo</td>
<td>2 435</td>
<td>9.54%</td>
</tr>
<tr>
<td>Western Cape</td>
<td>5 799</td>
<td>22.72%</td>
</tr>
<tr>
<td>Total</td>
<td>25 523</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

(*Source = Statistics South Africa, 2010: 14)

Figure 5.6 Regional distribution of patients
There were patients who had travelled throughout the year and obtained prescriptions in other regions. Figure 5.7 therefore, provides an approximation of the number of patients in each region.

Figure 5.7 Frequency of dopaminergic prescriptions per region

The average number of prescriptions for levodopa-containing products per region was 1484.38±687.96 and the average number of dopamine agonist prescriptions was 1270.50±313.21. The Western Cape held the highest volume of both levodopa-containing products and dopamine agonists in terms of the total number of prescriptions as well as the overall volume of antiparkinsonian products dispensed. The total was 3558 higher than the average and constituted 86.95% of the total antiparkinsonian prescriptions for the region. The Western Cape was followed by the Free State (n = 2865) and the Eastern Cape (n = 2824). This follows the pattern of the overall prescription distribution across South Africa which demonstrates the dominance of these two drug groups in prescribing.
5.3.3 Annual distribution of antiparkinsonian prescriptions

The annual distribution of antiparkinsonian prescriptions provided information regarding the initial diagnosis and treatment and alteration of drug therapy. Figure 5.8 illustrates the number of antiparkinsonian prescriptions dispensed per month and Figure 5.9 illustrates the patient distribution throughout the year.

Figure 5.8 Number of antiparkinsonian products dispensed per calendar month

![Number of prescriptions per month graph](image)

The monthly dispensing of products remained largely unchanged throughout the year. This could indicate that patients were compliant in taking their medication. There was an increase from February to April and another gradual increase from September to December. The average number of prescriptions dispensed for the year was 72.86±58.07 which amounts to 6.07 products per month. Figure 5.9 below shows the number of patients per calendar month.

Figure 5.9 clearly demonstrates that there were more female than male patients for each month. The month of December held the highest number of patients (n = 1 876). The slight increase in patients throughout the year did not necessarily indicate an increased incidence of Parkinson’s disease but could mean that patients
transferred their prescriptions from other pharmacies or pharmacy groups to the one under consideration in this study. The average number of prescriptions dispensed each month by gender are summarised below in Table 5.6.

Figure 5.9 Number of patients receiving antiparkinsonian products per calendar month

Table 5.6 Average number of prescriptions dispensed per month for the year 2010

<table>
<thead>
<tr>
<th>Months</th>
<th>Average number of prescriptions ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>January</td>
<td>1.23±0.56</td>
</tr>
<tr>
<td>February</td>
<td>1.21±0.55</td>
</tr>
<tr>
<td>March</td>
<td>1.21±0.55</td>
</tr>
<tr>
<td>April</td>
<td>1.21±0.53</td>
</tr>
<tr>
<td>May</td>
<td>1.23±0.57</td>
</tr>
<tr>
<td>June</td>
<td>1.21±0.55</td>
</tr>
<tr>
<td>July</td>
<td>1.21±0.57</td>
</tr>
<tr>
<td>August</td>
<td>1.22±0.56</td>
</tr>
<tr>
<td>September</td>
<td>1.22±0.57</td>
</tr>
<tr>
<td>October</td>
<td>1.23±0.61</td>
</tr>
<tr>
<td>November</td>
<td>1.22±0.57</td>
</tr>
<tr>
<td>December</td>
<td>1.22±0.57</td>
</tr>
</tbody>
</table>
The above table indicates that males had a higher average number of prescriptions than females for each month. For females, the average number seemed to remain stable throughout the year ranging from 1.21 to 1.23 prescriptions per patient per month. For males, the range was 1.33 to 1.39 prescriptions per patient per month.

### 5.3.4 Dopaminergic prescribing

Figures 5.10 and 5.11 below indicate the number of prescriptions of levodopa-containing products and dopamine agonists prescribed per month over the year.

Figure 5.10 Individual number of prescriptions of levodopa-containing products dispensed per month

The total number of prescriptions for levodopa-containing products throughout the year indicated an increase from March to April and then remained fairly constant for the rest of the year. The trendline showed that there was an overall increase in the number of prescriptions throughout the year.
If these curves are compared to the total annual distribution for all antiparkinsonian drugs to those for individual drug groups, the pattern shows to be similar as these two groups were dominant. The number of dopamine agonist prescriptions did not vary greatly over the year; there was a slight increase from February to March and again from October to November, but with a constant range of 700 to 900 prescriptions per month throughout the year. Figures 5.12 to 5.15 show the distribution of levodopa-containing products and dopamine agonists as a function of age.

Figure 5.12 Annual distribution of levodopa-containing product prescriptions per month for patients between 50 and 69 years of age
The age group 60 to 69 years held the higher proportion of prescriptions \((n = 2,988)\). This group also constituted a higher proportion of the overall study population as compared to the age group 50 to 59 years. Also, patients aged 60 years or older may have had more severe symptoms than those in the 50 year age group and required higher doses to provide symptom relief. There was an overall increase in the number of prescriptions in the 60 year age group \((n = 89)\). Patients in the 50 to 59 years age group may have been recently diagnosed and were presenting with mild symptoms therefore not requiring high doses of levodopa. The age group 60 to 69 years demonstrated an increase in the month of April then remained fairly constant for the rest of the year with the exception of a slight increase in October. The 50 year age group demonstrated a much more gradual increase throughout the year with an overall increase of only 31 prescriptions.

Figure 5.13 Annual distribution of levodopa-containing product prescriptions per month for patients aged 70 years and older

The age group 70 to 79 years held the highest number of prescriptions \((n = 4,748)\). This group also constituted the largest proportion of the overall patient population. There is a sharp increase in the number of prescriptions from March to April and continues to increase throughout the year. The age group 60 to 69 years held the second highest proportion of prescriptions \((n = 2,988)\) closely followed by the age...
group 80 to 89 years (n = 2 938). This group also demonstrated an increase in the month of April and then remained fairly constant for the rest of the year. The age group 90 years and older demonstrated the lowest number of prescriptions as they constituted the lowest proportion of the overall population. There was an overall decrease in the number of prescriptions throughout the year which could be due to mortality in this group.

When calculating the prescribed daily dose (PDD) of levodopa-containing products it was found that the majority of patients (n = 2 056) were receiving 300mg daily which is half the DDD for levodopa. There were 1 659 patients receiving 200mg of levodopa daily and 1 207 patients receiving 400mg as a total daily dose. Only 994 patients were receiving the 600mg DDD. The overall average PDD of levodopa was calculated to be 1 183.01mg±3 809.31mg daily. This indicates the vast range of PDDs seen in the study population. The lowest PDD was found to be 3.33mg (n = 4) of levodopa while the largest PDD was seen to be 45 000mg (n = 2) of levodopa in the population. There were 84 patients receiving 2 000mg of levodopa and more on a daily basis and 8 155 patients receiving daily doses of levodopa lower than 600mg. This shows that patients were receiving lower doses of levodopa than the stipulated DDD. This could mean that doctors in South Africa prefer prescribing lower doses of levodopa or that majority of patients in the population were not experiencing severe symptoms or were in the earlier stages of the disease.

Figure 5.14 shows that the dopamine agonists pramipexole and ropinirole were prescribed more frequently in the younger patient categories. The age group 60 to 69 years held the highest number of prescriptions (n = 3 277) and demonstrated an increase in the number of prescriptions throughout the year. This is in keeping with another study which stated that patients with early disease may be given dopamine agonists to delay the onset of levodopa therapy (Singh, et al., 2007: 33). Patients between the ages of 50 and 69 years may have been recently diagnosed or are still in the early stages of the disease. Dopamine agonists may be used as initial therapy to provide relief of milder symptoms. When comparing this to the levodopa-containing products, it was seen that the 50 year age group received more dopamine
agonists \( (n = 2\,169) \) than levodopa-containing products \( (n = 870) \) throughout the year.

Figure 5.14 Annual distribution of dopamine agonist prescriptions per month for patients between 50 and 69 years of age

Upon comparison, all three of the age groups shown in Figure 5.15 received more levodopa-containing products than dopamine agonists. This could be due to the
greater symptom relief provided by levodopa as compared to pramipexole or ropinirole. Patients between the ages of 70 to 79 years received the highest number of dopamine agonists (n = 3 211). These patients received the largest proportion of antiparkinsonian prescriptions overall (n = 35%). This group may be experiencing more severe symptoms compared to the younger groups and require combination therapy for symptomatic relief. Mortality may be the reason for the decrease in patient numbers in the older age groups.

When calculating the PDD of pramipexole, the average was seen to be 1.21mg±1.82mg. The highest PDD was 12mg (n = 3) and the lowest was 0.0042mg (n = 2). The low PDDs were not repeat prescriptions. The high ODDS, however, were repeat prescriptions. The most commonly prescribed PDD for pramipexole was 0.125mg (n = 2 861), the second most common 0.25mg (n = 2 088) and the third most common PDD was 0.5mg (n = 639). Only 22 patients were receiving 2.5mg which is the DDD for pramipexole. Looking at the average, it can be seen that most patients (n = 7 859) were receiving lower doses than the DDD.

For ropinirole, the average PDD was seen to be 5.98mg±8.77mg. The majority of patients (n = 239) were receiving 3.73mg of ropinirole daily which is almost half that of the recommended WHO DDD. The second most commonly prescribed PDD was 7.47mg (n = 216) and the third, 1.87mg (n = 138). The lowest PDD was 0.05mg (n = 1) and the highest PDD was found to be 59.73mg (n = 1). The low PDD was not a repeat prescription and was the only prescription recorded for the patient throughout the year. The high PDDS were repeated prescriptions and patients were receiving them on a chronic basis. A total of 1 358 patients were receiving doses lower than the DDD of 6mg.

5.3.5 Combined dopaminergic prescribing

Dopaminergic products include levodopa-containing products and dopamine agonists. It was shown that 3 295 patients received a levodopa-containing product throughout the year while 3 166 patients received a dopamine agonist. This indicates that patients were prescribed combination therapies. Figure 5.16 shows the regional
distribution of prescriptions of patients receiving a combination of these dopaminergic products.

Figure 5.16 Regional distribution of patients receiving dopaminergic prescriptions

5.4 Cost of antiparkinsonian medication

The total sales value of antiparkinsonian products for the year 2010 was R8 500 496.49. The total sales value includes patient as well as medical aid payments. Figure 5.17 indicates the total sales value by gender and Figure 5.18 indicates the percentage of spending by age category.

Figure 5.17 shows that although there were more females than males in the total population, more spending was attributed to male patients (55.46%), but females were dispensed more products throughout the year (54.04%). A reason for this could be that males experience more severe disease or side effects and therefore require more symptomatic treatment, or are more open about verbalising problems and concerns to medical practitioners.
Figure 5.17 Distribution of patient spending according to gender

Figure 5.18 Percentage sales value of antiparkinsonian products according to age and gender

Figure 5.18 shows that a large majority (38.85%) of the cost was attributed to the age group 70 to 79 years. This group also constituted the largest proportion of
patients (32.27%) and received the highest number of products (35.00%). Patients in this age group are most likely to be in the more severe stages of the disease and therefore require higher doses and more supplementation in an attempt to effectively control symptoms of the disease and the side effects of the medications.

The two individual products with the highest sales values were levodopa/carbidopa (45.67%) and pramipexole respectively (25.63%). Levodopa/carbidopa 100mg showed to be the product with the highest sales volume (number of prescriptions identified) (38.59%). The class of products with the highest percentage sales value were the dopamine replacement therapies containing levodopa, followed by the dopamine agonists pramipexole and ropinirole. The drug cost 90% (DC90%) indicates which products constituted 90% of the total cost of antiparkinsonian medication. Figure 5.20 shows the active ingredients identified ranked according to decreasing sales value.

Figure 5.19 Percentage spending on antiparkinsonian active ingredients according to gender
The DC90% of the total cost of antiparkinsonian products for the year was calculated to be R7 650 446.84. The products which constituted the DC90% include the levodopa-containing products and the dopamine agonists pramipexole and ropinirole. When comparing this to the DU90%, it can be seen that fewer products constitute the DC90%. This could be due to the cost of the individual products.

5.4.1 Levodopa-containing products

Given that levodopa-containing agents are available in different strengths and combination formulas, the following section outlines the sales volume, the total sales value per item and the average cost per unit, where the unit is a tablet or capsule. The cost per unit may have varied throughout the year due to the increasing cost of medicines, the different prices set by medical aid schemes, the number of units dispensed and the pack size of the product selected.

5.4.1.1 Levodopa/carbidopa

This section focuses on the sales volume and value of levodopa/carbidopa containing products according to tradenames. The SEP (single exit price) was
implemented in 2004 which regulated the maximum annual price increase without any allowance for discounts on medication. (Pretorius, 2011: 2; National Drug Policy for South Africa, 1996: 9). The aim of the SEP was to make medication more accessible to patients due to reduced prices. (Pretorius, 2011: 2). Figures 5.21 to 5.24 provide information for all levodopa-containing antiparkinsonian products and Tables 5.7 and 5.8 indicate the average cost of the levodopa-containing products.

Figure 5.21 Percentage sales volumes for individual levodopa/carbidopa antiparkinsonian tradename product strengths

The highest sales volume for a formulation of levodopa/carbidopa was Carbilev® 25/100mg tablets (44.94%), followed by Sinemet® 25/100mg tablets (20.91%) and Carbilev® 25/250mg tablets (15.28%). It follows that the highest sales value was Carbilev® 25/100mg (43.89%), with the second being Carbilev® 25/250mg (19.20%) and the third Sinemet® 25/100mg (18.79%). This could be due to the fact that the average price per unit of Carbilev® 25/250mg was R494.20 as opposed to Sinemet® 25/100mg which was R348.66. Sinemet® CR 50/200mg has the fourth highest sales value. The total sales for Carbilev® as a tradename amounted to R2 448 829.10, whereas the Sinemet® total was R1 428 085.13, a difference of R1 020 743.97 which is 41.68% less than Carbilev®. Carbilev® 25/100mg had the highest cumulative sales value for the Carbilev® brand and Sinemet® 25/100mg for the Sinemet® brand. This
showed that doctors preferred prescribing the lower dose of the levodopa/carbidopa combination. Sinemet® CR 50/200mg is the only controlled release preparation of levodopa/carbidopa and had the third highest sales volume with the fourth highest cumulative sales value. The Madopar® brand is the only levodopa/benserazide combination. Madopar® 250mg tablets and Madopar® HBS (hydrodynamically balanced system) capsules which is a slow release preparation, are the only two products in the Madopar® brand. Together these two products made up a sales value of R344 024.46 with Madopar® 250mg tablets having the higher sales volume (n = 619; 85.03%) and value (n = R275 679.68; 80.13%). Madopar® is not the first choice of levodopa preparations. If the patient is not experiencing sufficient symptomatic relief, Madopar® is the alternative choice.

Table 5.7 Average cost per pack for all levodopa/carbidopa preparations according to tradenames

<table>
<thead>
<tr>
<th>Tradename</th>
<th>Average cost per pack</th>
<th>Single exit price*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbilev® 25/100mg tablets</td>
<td>R354.32</td>
<td>R356.14</td>
</tr>
<tr>
<td>Carbilev® 25/250mg tablets</td>
<td>R494.20</td>
<td>R505.81</td>
</tr>
<tr>
<td>Sinemet® 25/100mg tablets</td>
<td>R348.66</td>
<td>R364.36</td>
</tr>
<tr>
<td>Sinemet® 25/250mg tablets</td>
<td>R463.84</td>
<td>R498.33</td>
</tr>
<tr>
<td>Sinemet® CR 50/200mg tablets</td>
<td>R505.91</td>
<td>R523.78</td>
</tr>
<tr>
<td>Teva® Carbi-Levo 25/100mg tablets</td>
<td>R334.73</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Teva® Carbi-Levo 25/250mg tablets</td>
<td>R445.44</td>
<td>Unavailable</td>
</tr>
</tbody>
</table>

(*Source: ed. Snyman, 2010: 1.7.1 – 42)
Figure 5.22 Percentage sales value of levodopa/carbidopa containing antiparkinsonian tradename products

5.4.1.2 Levodopa/carbidopa/entacapone

Levodopa in combination with the COMT-inhibitor entacapone allows for lower doses of levodopa due to the decreased metabolism by entacapone. Figures 5.23 and 5.24 indicate the sales volume and percentage sales value of the levodopa/carbidopa/entacapone combination product while Table 5.8 indicates the cost per unit and single exit prices of this product.
Figure 5.23 Sales volume of levodopa/carbidopa/entacapone containing antiparkinsonian tradename products

Table 5.8 Average cost per unit for all levodopa/carbidopa/entacapone strengths according to tradenames

<table>
<thead>
<tr>
<th>Strength</th>
<th>Average cost per unit</th>
<th>Single exit price*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stalevo® 50/12.5mg FC tablets</strong></td>
<td>R896.09</td>
<td>R1 039.48</td>
</tr>
<tr>
<td><strong>Stalevo® 100/25mg FC tablets</strong></td>
<td>R914.31</td>
<td>R1 039.48</td>
</tr>
<tr>
<td><strong>Stalevo® 150/37.5mg FC tablets</strong></td>
<td>R914.17</td>
<td>R1 039.48</td>
</tr>
</tbody>
</table>

(*Source: ed. Snyman, 2010: 1.7.1 – 43)
For the Stalevo® brand, the highest sales volume (n = 273) and cumulative sales value (n = R308 028.66) is Stalevo® 150/37.5/200mg FC (film coated) tablet.

5.4.2 Dopamine agonists

The following section focuses on the sales volume and value of the dopamine agonists pramipexole and ropinirole. This group showed the second highest prescribing frequency.

5.4.2.1 Pramipexole

The following Figures 5.25 and 5.26 show the sales volume and percentage sales value of these products. Table 5.9 shows the cost per unit and corresponding single exit prices of these products.
Figure 5.25 Sales volume of pramipexole containing antiparkinsonian tradename products

Table 5.9 Average cost per unit for all pramipexole tradename strengths

<table>
<thead>
<tr>
<th>Strength</th>
<th>Average cost per unit</th>
<th>Single exit price*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pexola® 0.125mg tablets 100</strong></td>
<td>R313.29</td>
<td>R298.36</td>
</tr>
<tr>
<td><strong>Pexola® 0.25mg tablets 100</strong></td>
<td>R554.36</td>
<td>R591.99</td>
</tr>
<tr>
<td><strong>Pexola® 1mg tablets 100</strong></td>
<td>R1 028.06</td>
<td>R1 117.37</td>
</tr>
</tbody>
</table>

(*Source: ed. Snyman, 2010: 1.7.1 – 43)
Although Pexola® 0.125mg had the highest sales volume, Pexola® 0.25mg had the highest cumulative sales value. This is due to the cost per unit. The price increases dramatically with increasing strength of the formulation.

### 5.4.2.2 Ropinirole

The following Figures 5.27 and 5.28 show the sales volume and percentage sales value of these products. Table 5.10 shows the cost per unit and corresponding single exit prices of these products.
Figure 5.27 Percentage sales volume of ropinirole containing antiparkinsonian tradename products

![Percentage sales volume of ropinirole containing antiparkinsonian tradename products](image)

Table 5.140 Average cost per unit for all ropinirole tradename strengths

<table>
<thead>
<tr>
<th>Strength</th>
<th>Average cost per unit</th>
<th>Single exit price*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requip® 0.25mg tablets 210</td>
<td>R272.07</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Requip® 0.25mg tablets 84</td>
<td>R115.38</td>
<td>R110.64</td>
</tr>
<tr>
<td>Requip® 0.5mg tablets 84</td>
<td>R204.23</td>
<td>R205.26</td>
</tr>
<tr>
<td>Requip® 1mg tablets 84</td>
<td>R255.62</td>
<td>R271.15</td>
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<tr>
<td>Requip® 2mg tablets 84</td>
<td>R471.98</td>
<td>R522.15</td>
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<tr>
<td>Requip® 5mg tablets 84</td>
<td>R759.09</td>
<td>R834.77</td>
</tr>
<tr>
<td>Requip® XL 2mg starter pack tablets 42</td>
<td>R298.13</td>
<td>R326.54</td>
</tr>
<tr>
<td>Requip® XL 2mg tablets 28</td>
<td>R208.50</td>
<td>R217.57</td>
</tr>
<tr>
<td>Requip® XL 4mg tablets 28</td>
<td>R263.34</td>
<td>R278.02</td>
</tr>
<tr>
<td>Requip® XL 8mg tablets 28</td>
<td>R444.07</td>
<td>R495.72</td>
</tr>
</tbody>
</table>

(*Source: ed. Snyman, 2010: 1.7.1 – 43)
Figure 5.28 Percentage sales value of ropinirole containing antiparkinsonian tradename products

Of the immediate release formulations, Requip® 1mg tablets had the highest sales volume, but Requip® 2mg tablets had the highest cumulative sales value. This is due to the higher average cost price per unit of Requip® 2mg which was R603.20 compared to that of Requip® 1mg which was R283.98. Looking at the extended release formulations, Requip® XL 8mg tablets had the highest cumulative sales value, but was only marginally higher in sales volume than Requip® XL 4mg tablets.

5.5 Summary of major findings

The major findings of the DUR were as follows:

- There were more females (59.17%) than males;
- The average number of prescriptions for the year was higher for males (5.55±6.88) than females (4.51±5.44);
- The highest prevalence of Parkinson’s disease was in the age group 70 years to 79 years for both genders (32.28%); this group also received the highest number of products (35%) throughout the year;
• An average of 4.94 products were dispensed to each patient throughout the year;
• The majority of products were dispensed to females (54.05%);
• The majority of antiparkinsonian products dispensed (46.5%) were combination drugs containing levodopa;
• The second most dispensed group of drugs were the dopamine agonists (39.80%);
• Levodopa-containing products, dopamine agonists, pramipexole and ropinirole, as well as the anticholinergic agent biperidine constituted the DU90%;
• Males were prescribed the levodopa-containing products whereas females were preferably prescribed the dopamine agonist pramipexole;
• The Western Cape held the highest volume of both levodopa-containing products and dopamine agonists in terms of the total number of prescriptions as well as the overall volume of antiparkinsonian products dispensed (3 558 ; 86.95%);
• There was an overall increase in the number of levodopa-containing product prescriptions throughout the year;
• The age group 70 to 79 years held the highest number of levodopa-containing product prescriptions (n = 4 748);
• The number of dopamine agonist prescriptions did not vary greatly over the year;
• The dopamine agonists pramipexole and ropinirole were prescribed more frequently in the younger patient categories;
• The most commonly PDD of levodopa was found to be 300mg with the average being 1 183.01mg±3 809.31mg daily;
• The most commonly PDD of pramipexole was found to be 0.125mg with the average being 1.21mg±1.82mg;
• The most commonly PDD of ropinirole was 3.73mg with the average being 6.00mg±8.77mg;
• Patients aged 70 years and older received more levodopa-containing products than dopamine agonists;
• There were 3 295 patients who received a levodopa-containing product throughout the year while 3 166 patients received a dopamine agonist; this indicates that patients were prescribed combination therapies;
• The total sales value of antiparkinsonian products for the year was R 8 500 496.49;
• More spending was attributed to male patients (55.46%);
• The majority (38.85%) of the cost was attributed to the age group 70 to 79 years;
• The products which constituted the DC90% include the levodopa-containing products and the dopamine agonists pramipexole and ropinirole;
• The two individual products with the highest sales values were levodopa/carbidopa (45.67%) and pramipexole (25.63%);
• The highest sales volume for a formulation of levodopa/carbidopa was Carbilev® 25/100mg tablets (44.94%);
• The individual tradename product with the highest sales value was Carbilev® 25/100mg (43.89%); and
• The total sales for Carbilev® as a tradename amounted to R24 488 29.10, whereas Sinemet® totalled at 41.68% less than Carbilev®.
CHAPTER 6

Results and Discussion of Questionnaire Survey
6.1 Introduction

The results of both the patient questionnaires and the review of medical records will be discussed in this chapter. The patient questionnaires will be discussed in Section 6.2. The results of the medical record reviews will be discussed in Section 6.3 and divided into eight subsections for each section of the questionnaire.

6.2 Patient questionnaires

A total of 43 completed questionnaires were analysed. Although the weight of the patient was requested in the questionnaire, not enough patients were able to provide this information to allow for meaningful analysis. The levodopa dose per kilogram weight was therefore not taken into account when considering the risk factors involved in causing dyskinesias.

6.2.1 Demographics

A total of 23 males (53.49%) were interviewed. It has been seen that there is an approximately 1.5 times higher risk of Parkinson’s disease for men than women (Burn, 2007: 78; Fargel, et al., 2007: 208; Miller and Cronin-Golomb, 2010: 2695). This study reported that Parkinson’s disease is more common in males than females with an approximate ratio of 1.15. Figure 6.1 demonstrates the ethnic distribution of patients.

The majority of participants were coloured (n = 22; 51.16%) with the second highest ethnic group being white (n = 16; 37.21%). The coloured patients were identified in the public sector while the white group was made up mostly of private sector patients (68.75%). One patient was listed as ‘Other’ as the patient was both Indian and coloured. Further investigation is warranted in terms of the demographical distribution as these results may not be accurate representation of the ethnic division of Parkinson’s disease in the South African population.
14 patients were aged between 71 to 75 years (32.56%) and constituted the largest age group overall. The age group 66 to 70 years constituted the second largest group with seven patients identified (16.28%). The male patients were also found to be older than the females. Of the 23 male patients, 73.91% were aged 66 years or older as compared to females where only 11 (55%) of patients were found to be 66 years or older. Figure 6.2 shows the distribution of patients as a function of gender and age.
Figure 6.2 demonstrates that males were most prevalent in the age groups 71 to 75 years and 66 to 70 years. Females were most prevalent in the age group 71 to 75 years and 50 to 55 years. This shows that females were younger than male patients on average. An Italian study included 130 Parkinson’s patients with a mean age of 68.6±9.9 years (Leoni, et al., 2002: 151). The study also showed that the male patients were slightly older than the female patients; which was in keeping with the results of this study.

The majority of patients were diagnosed between five and 10 years before the onset of the study (n = 15; 34.88%) and 14 were diagnosed more than 10 years before the onset of the study (32.56%). Figure 6.3 shows the duration of disease of patients between the ages of 50 to 70 years.

Figure 6.3 Disease duration in years of patients between the ages of 50 to 70 years

There were eight patients up to the age of 70 years diagnosed less than five years before the onset of the study. A total of six patients were diagnosed more than 10 years before the onset of the study. This means that there were some patients who experienced early onset Parkinson’s disease, particularly the patients in the 50 to 55 years age group. Figure 6.4 shows the disease duration of patients over the age of 70 years.
Figure 6.4 Disease duration in years of patients aged 70 years and older

Figure 6.4 shows that the older patients were mostly diagnosed more than 10 years ago (n = 6). There were very few patients in the older age groups and this was most likely due to a higher mortality rate in these age groups.

There were three sites included in the study. Groote Schuur Hospital, Tygerberg Hospital in Cape Town and the Parkinson’s disease support group in Port Elizabeth. The majority of the patients were from Tygerberg Hospital (n = 22; 51.16%), with the support group in Port Elizabeth being the second largest pool of patients (n = 12; 27.91%).

6.2.2 Therapy

All patients were diagnosed with Parkinson’s disease and on levodopa therapy with 90.70% (n = 39) of patients reporting levodopa to be the first drug they were prescribed for Parkinson’s disease. Most patients (n = 15) were diagnosed between five and 10 years ago with 14 patients being diagnosed more than 10 years ago and 10 patients having been diagnosed fewer than five years ago. There were also four patients who could not remember when they were diagnosed. When asked about the
duration of levodopa therapy, it was found that 14 patients were using levodopa for two to four years and 12 were using levodopa for longer than 10 years. A total of 15 patients were using levodopa for the entire duration of their diagnosis. Figure 6.5 indicates the strengths of levodopa products used at the time of the study.

Figure 6.5 Strengths of levodopa-containing products used

The majority of patients were using levodopa/carbidopa 100/25mg. There were five patients found to be using a combination of two levodopa-containing products. These were a combination of a controlled release and standard release products or a higher strength levodopa/carbidopa 250/25mg in combination with a lower strength 100/25mg. A total of 36 (83.72%) patients were also using other medications such as antihypertensives, hypoglycaemic agents, lipid lowering agents and antidepressants, which were unrelated to the motor symptoms of Parkinson’s disease. Figure 6.6 indicates the PDDs of levodopa.
It can be seen from Figure 6.6 that the majority of patients were prescribed a daily dose of 300mg of levodopa (n = 7; 16.28%). The second largest group of patients received 600mg (n = 6; 13.95%) which is the DDD for levodopa. The average PDD was 750mg±452mg. There were two patients receiving a PDD of 2000mg. There were 22 patients (51.16%) receiving doses higher than 600mg.
Of the 10 patients diagnosed less than five years ago, nine (90%) were receiving doses of levodopa of 600mg or lower. There were 12 patients diagnosed more than...
10 years ago. Of these patients, eight were receiving daily doses of 700mg and higher of levodopa. Both patients receiving 2000mg of levodopa were diagnosed more than 10 years ago. Of the patients diagnosed between five and 10 years ago (n = 15), nine patients (60%) were receiving daily doses of 700mg or higher of levodopa. This shows that patients with longer disease duration were receiving higher daily doses of levodopa.

### 6.2.3 Dyskinesias

A positive incidence of dyskinesias was reported by 13 patients (30.23%). There were four patients unsure about the incidence while the rest of the 25 patients reported no experience of dyskinesias. Of those reporting a positive incidence, seven were males and six were females. Table 6.1 below indicates the observed frequencies of gender distribution of the patients reporting a positive incidence of dyskinesias. Figure 6.9 represents the age groups of patients with dyskinesias.

Table 6.1 Gender distribution of patients reporting a positive incidence of dyskinesias

<table>
<thead>
<tr>
<th>Gender</th>
<th>Dyskinesias</th>
<th>No/Unsure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>30</td>
</tr>
</tbody>
</table>

The table shows that there was no statistically significant difference in gender distribution of patients reporting a positive incidence of dyskinesias. The chi-square test also yielded a non-significant test result with a p-value of 0.9753.
Figure 6.9 Age groups of patients with reported incidence of dyskinesias

![Bar chart showing number of patients in different age groups]

Figure 6.9 shows that the majority of patients presenting with dyskinesias were in the age groups 56 to 60 years (n = 4) and 71 to 75 years (n = 4). When looking at this proportion in relation to the overall population it was seen that 66.67% of patients between the ages of 56 and 60 years developed dyskinesias while 28.57% of patients between the ages of 71 to 75 years reported a positive incidence. Previous studies found that younger patients tend to experience dyskinesia more frequently than older patients. One study (Garret, et al., 1998: 101) reported that the mean age of patients who developed dyskinesia was 53.9±6.2 years. This is in accordance with a study (Kumar, et al., 2005: 343) which demonstrated that patients between the ages of 40 and 49 years and those between the ages of 50 and 59 years presented with an incidence of 40% and 53%, respectively whereas patients between 60 and 69 years, 70 and 79 years and 80 and 89 years had incidences of 26%, 16% and 14% respectively. When dividing the patients in this study into the age groups used by another (Kumar, et al., 2005), it was seen that patients in the age groups 50 to 60 years, 61 to 70 years and 71 to 80 years demonstrated an incidence of dyskinesias of 45.45%, 16.67% and 31.58% respectively. Figure 6.10 indicates the duration of illness of the patients indicating a positive incidence of dyskinesias.
Five patients were diagnosed more than 10 years ago (38.46%). Of the total number of patients in the study population diagnosed more than 10 years ago (n = 15), the proportion reporting a positive incidence of dyskinesias was 35.71%. Five were diagnosed between five and 10 years ago (38.46%). Of the 15 patients diagnosed between five and 10 years ago, 33.33% (n = 5) reported a positive incidence of dyskinesias. A total of three patients were diagnosed less than five years ago (23.08%). There was one patient who reported to be unsure about the date of diagnosis. Figure 6.11 indicates the subjective severity of the dyskinesias reported by patients. Table 6.2 indicates the observed frequencies of dyskinesias according to disease duration.
Table 6.2 Observed frequencies of dyskinesias in patients according to disease duration

<table>
<thead>
<tr>
<th>Disease duration as from date of diagnosis</th>
<th>Dyskinesias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No/Unsure</td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>5-10 years</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>11+ years</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Not sure</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>13</strong></td>
<td><strong>30</strong></td>
</tr>
</tbody>
</table>

Only a very small difference was seen in dyskinesia frequency. The chi-square test yielded a non-significant result with a $p$-value of 0.9519.

Figure 6.11 Severity of dyskinesias as reported by patients

The dyskinesias were not considered disabling by four patients. They were still able to perform daily activities without much difficulty. Another four reported that the dyskinesias were severely disabling. They required assistance with the majority of activities attempted during the day. There were three patients who considered dyskinesias completely disabling. These patients were unable to perform any activities of daily life without assistance.
Figure 6.10 indicates the duration of levodopa therapy of patients with positive incidence of dyskinesias and Figure 6.12 indicates the relative strengths of levodopa therapies currently being used by patients with positive incidence of dyskinesias. Table 6.3 indicates the observed frequencies of dyskinesias according to the duration of levodopa therapy.

Table 6.3 Observed frequency of dyskinesias in patients according to duration of levodopa therapy

<table>
<thead>
<tr>
<th>Levodopa duration</th>
<th>Dyskinesias</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No/Unsure</td>
<td></td>
</tr>
<tr>
<td>2-4 years</td>
<td>5</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>5-7 years</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>8-10 years</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>11+ years</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Not sure</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Statistical analysis showed that there were some differences. However, due to the small sample size, the chi-square test yielded a non-significant result with a $p$-value of 0.4138.

Figure 6.12 Duration of levodopa therapy for patients with positive incidence of dyskinesia
Figure 6.12 shows that five patients were on levodopa therapy for just two to four years. Of these, three were diagnosed less than five years ago. However, these patients could have presented with more severe symptoms at diagnosis, or diagnosed at a later stage of the disease, therefore requiring higher initial doses of levodopa, which could explain the earlier onset of dyskinesias. A total of four patients were using levodopa for more than 10 years. A Turkish study stated that, in general, of all patients on levodopa therapy, 50% to 90% of them will develop motor complications after five to 10 years of treatment (Benbir, et al., 2006: 732). The results of this study show that less than 50% of patients developed dyskinesias after 10 years of treatment with levodopa. The Turkish study (Benbir, et al., 2006: 729) also reported that the incidence of dyskinesias increased as the duration of levodopa usage increased. Another study stated that dyskinesias have been seen to occur within five years in 50% of patients on chronic levodopa therapy (Kessler and Rezak, 2007: 223). An older study showed that of 50 patients with disease duration of 10 years and longer, 56% developed drug-induced dyskinesias within the first 10 years of the disease (Garret, et al., 1998: 101). The current study showed that of the 25 patients on chronic levodopa therapy for five years and longer, eight (32%) developed dyskinesias. A review stated that it was important to remember that not all patients on levodopa therapy would develop dyskinesias and that there could be certain genetic factors involved in determining its occurrence (Thanvi, et al., 2007: 385).

Figure 6.13 Strengths of levodopa therapies being used by patients with positive incidence of dyskinesias
The majority of patients with dyskinesias were using the 100/25mg strength and only one patient was on levodopa/carbidopa/entacapone. Table 6.4 indicates the initial and current total doses of levodopa for patients reported to experience dyskinesias.

Table 6.4 Initial and current daily doses of levodopa for patients experiencing dyskinesias

<table>
<thead>
<tr>
<th>Patients</th>
<th>Initial prescribed daily levodopa dose</th>
<th>Current prescribed daily levodopa dose</th>
<th>Difference between current and initial daily levodopa dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>100mg</td>
<td>2 000mg</td>
<td>1 900mg</td>
</tr>
<tr>
<td>Patient 2</td>
<td>500mg</td>
<td>1 000mg</td>
<td>500mg</td>
</tr>
<tr>
<td>Patient 8</td>
<td>50mg</td>
<td>400mg</td>
<td>350mg</td>
</tr>
<tr>
<td>Patient 11</td>
<td>Unsure</td>
<td>300mg</td>
<td>_</td>
</tr>
<tr>
<td>Patient 16</td>
<td>200mg</td>
<td>600mg</td>
<td>400mg</td>
</tr>
<tr>
<td>Patient 23</td>
<td>Unsure</td>
<td>400mg</td>
<td>_</td>
</tr>
<tr>
<td>Patient 24</td>
<td>Unsure</td>
<td>1 300mg</td>
<td>_</td>
</tr>
<tr>
<td>Patient 26</td>
<td>Unsure</td>
<td>800mg</td>
<td>_</td>
</tr>
<tr>
<td>Patient 27</td>
<td>300mg</td>
<td>1 250mg</td>
<td>950mg</td>
</tr>
<tr>
<td>Patient 30</td>
<td>Unsure</td>
<td>500mg</td>
<td>_</td>
</tr>
<tr>
<td>Patient 34</td>
<td>Unsure</td>
<td>600mg</td>
<td>_</td>
</tr>
<tr>
<td>Patient 36</td>
<td>300mg</td>
<td>450mg</td>
<td>150mg</td>
</tr>
<tr>
<td>Patient 42</td>
<td>Unsure</td>
<td>1 000mg</td>
<td>_</td>
</tr>
</tbody>
</table>
When comparing the initial and current doses, there is a predictable difference in the values with most being twice as great, or more. Of the six patients who were able to provide both an initial and current dose of levodopa, only two were diagnosed less than five years ago. The patients all showed an increase in the total daily dose of levodopa with the exception of patient 36 who was diagnosed less than five years ago.

Table 6.4 shows that many patients were unsure of the initial levodopa dose. This was expected due to ageing and memory loss. Inaccurate recollection was also expected. However, of the patients who answered, it was seen that most were receiving an initial dose of 200mg or more on a daily basis.

A total of six patients were receiving doses higher than that of the DDD for levodopa. The single patient receiving a relatively low daily dose of 300mg of levodopa was using a combination of levodopa/carbidopa/entacapone. This means that although the levodopa dose was lower, since entacapone extends the half life of levodopa by 50% to 75% (Marin, et al., 2006: 647; Smith, et al., 2005: 307), the potential for developing dyskinesias was greater. According to the WHO, the DDD for levodopa in combination with both a decarboxylase inhibitor and entacapone is decreased to 450mg.

6.3 Medical record review

All 43 patient medical records were reviewed and analysed. According to these records, 44.19% of patients were diagnosed between five and 10 years ago (n = 19), 23.26% were diagnosed fewer than five years before the onset of the study and 27.91% have been diagnosed for more than 10 years.

The medical records show that the majority of patients up to the age of 70 years were diagnosed between five and 10 years ago (n = 10; 23.26%). A total of seven patients were diagnosed fewer than five years before the onset of the study (16.28%) and four patients were diagnosed more than 10 years before the onset of the study (9.30%). When comparing these results to the patient interviews where the
The majority of patients \( (n = 8) \) claimed to be diagnosed fewer than five years ago, it can be seen that memory impairment could have had an influence on their responses. The medical records provide a more accurate date of diagnosis, although the patient would only have presented to the neurologist when the symptoms became bothersome. Figure 6.14 indicates the duration of disease of patients between the ages of 50 to 70 years and Figure 6.15 indicates the disease duration of patients older than 70 years.

Figure 6.14 Disease duration of patients between the ages of 50 to 70 years

![Figure 6.14](image)

Figure 6.15 Disease duration of patients older than 70 years

![Figure 6.15](image)
The majority of patients in the age group 71 to 75 years were diagnosed between five and 10 years ago (n = 9; 20.93%). The rest of the patients aged 70 years and older were mostly diagnosed more than 10 years ago (n = 8; 18.60%). The patient interviews showed that patients over the age of 70 years claimed to be diagnosed more than 10 years ago. This shows that the patients may not be completely relied on when determining date of diagnosis. Figure 6.16 indicates the age at which patients were diagnosed.

Most of the patients were diagnosed between the ages of 56 to 60 years (n = 9; 20.93%) and 61 to 65 years (n = 9; 20.93%). This is in keeping with another study from Singapore, which reported an average age of 64.4±9.9 years. (Tan, et al., 2012: 512). Furthermore, a study conducted in Cardiff in the United Kingdom showed 5.40% and 31.20% of Parkinson’s disease patients had their disease onset before the ages of 50 and 65 years respectively (Wickremaratchi, Perera, O’Loghlen, Sastry, Morgan, Jones, Edwards, Robertson, Butler, Morris and Ben-Shlomo, 2009: 806). This study also showed that the average onset for males was 67.7 years and the average onset for females was 69.7 years (Wickremaratchi, et al., 2009: 806). The majority of patients did not have a disease severity entered into the records. Of those that did (n = 6), five patients were described as having severe disease and one was described as having mild disease at the time of the study.

Figure 6.16 Age at diagnosis
6.3.1 Treatment

This section outlines the therapy being used by patients according to the medical records. The section focuses on the levodopa dosages and medication usage of levodopa, other antiparkinsonian medication and others of the entire study population as well as any co-morbidities with which they have been diagnosed.

6.3.1.1 Levodopa

All patients included in the study were on levodopa therapy. However, it was found that many patients were using other medication as well. Figure 6.17 indicates the current PDDs of levodopa prescribed to patients.

Figure 6.17 Current prescribed daily doses of levodopa according to medical records

![](image)

Figure 6.17 shows that the majority of patients were using 300mg of levodopa daily (n = 7; 16.28%). The patient interviews also showed that the majority of patients received 300mg of levodopa daily (n = 7; 16.28%). According to the SAMF (ed. Rossiter, 2012: 457), the initial dose of levodopa in combination with carbidopa, is 25/100mg three times daily which amount to a total daily dose of 300mg of levodopa.
The second largest group of patients were prescribed 750mg of levodopa daily \((n = 5; 11.63\%)\). Only one patient was receiving a dose of 100mg which was also the lowest dose recorded. The lowest recorded dose from the patient interviews was 200mg. A total of 25 patients (58.14%) were receiving doses higher than the DDD. There were three patients receiving doses of 2 000mg or more with the highest daily dose of levodopa recorded as 2 400mg (patient 33) which is four times that of the DDD. This patient was not experiencing dyskinesias. The maximum daily dose of levodopa according to the SAMF (ed. Rossiter, 2012: 457) is 2 000mg. However, minimum and maximum doses are only guidelines to dosing. If a patient requires higher doses, as long as the patient is able to tolerate the levodopa, a higher dose may be given. The average PDD was 809mg±514mg. This indicates a large range (100mg to 2 400mg) of doses prescribed. The average PDD obtained from the patient interviews was lower (750mg±452mg) than the prescribed dose. Some patients did admit to not adhering to the PDD and increasing or decreasing the dosage according to their preference. This could be a reason for the discrepancy noted between the two sources. Figures 6.18 and 6.19 indicate the total daily dose of levodopa prescribed as a function of disease duration.

Figure 6.18 Prescribed daily doses of levodopa up to 600mg as a function of disease duration

\[ n_{\text{patients}} = 43 \]
Figure 6.18 shows that the majority of patients were diagnosed between five to 10 years ago (n = 7) and were receiving doses of 300mg and above. A total of five patients were diagnosed fewer than 10 years ago and four patients were diagnosed more than 10 years ago.

Figure 6.19 Prescribed daily doses of levodopa 700mg and higher as a function of disease duration

As can be seen from Figure 6.19, the higher doses corresponded with longer disease duration. This is in keeping with Kitagawa and Tashiro (2005: 940). This is due to more severe disease and symptoms requiring higher doses to provide adequate relief. Patients diagnosed fewer than five years ago were receiving a maximum of 800mg of levodopa daily. However, patients diagnosed five years ago or longer, were receiving doses across the range of those identified. A Swedish study (Nyholm, Karlsson, Lundberg and Askmark, 2010: 260) acknowledged that there is no defined dose of levodopa denoting ‘high’ or ‘low’ although in their study a low dose was defined as 400mg or less and a high dose was defined as 1 200mg or more (Nyholm, et al., 2010: 261). The average dose of the population in this study falls in between these two values.
A Japanese study (Kitagawa and Tashiro, 2005: 940) showed that of a total of 92 patients, the average daily dose of levodopa used by patients was 186.40mg. This is a much lower dose compared to those found in this study. American and European guidelines stated that the recommended dose of levodopa/carbidopa be between 400mg to 600mg (VHA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives, 2012: 3). The PDDs according to gender are summarised in Figure 6.20.

Figure 6.20 Prescribed daily doses of levodopa according to gender

It can clearly be seen from Figure 6.20 that males were receiving higher levodopa doses than females. There were more male patients \(n = 16; 37.21\%\) receiving higher doses than the DDD of 600mg with a mean dose of 858mg and median dose of 800mg. More females \(n = 10; 23.26\%\) were receiving doses lower than 600mg with a mean dose of 642.50mg and a median dose of 525mg. This is in keeping with the Swedish study (Nyholm, et al., 2010: 261) which reported that males were receiving higher doses than females. In this study, males were receiving mean and median doses of 494mg and 465mg respectively and females receiving mean and median doses of 408mg and 395mg respectively (Nyholm, et al., 2010: 261).
6.3.1.2 Other antiparkinsonian medication

The following section focuses on all other medication used for Parkinson’s disease such as dopamine agonists, anticholinergics, MAO-B inhibitors, COMT-inhibitors and others prescribed to patients by neurologists for the motor symptoms of Parkinson’s disease.

6.3.1.2.1 Dopamine agonists

The dopamine agonists included bromocriptine, pramipexole and ropinirole prescribed to Parkinson’s patients according to the medical records. A summary of the initial and current PDDs of bromocriptine, pramipexole and ropinirole as well as their duration of therapy is included as Appendix J.

A total of 20 patients were prescribed a dopamine agonist (46.51%). In the cases where ‘NA’ is stated in place of a current dose, it means that the patient is no longer on the therapy. Looking at each individual dopamine agonist, five patients (11.63%) were prescribed bromocriptine, six patients (13.95%) were prescribed pramipexole and 15 patients (34.88%) were prescribed ropinirole. There were also two patients (4.65%) prescribed pergolide, however both were discontinued after a period of six and nine years, respectively.

For bromocriptine, there were two patients for whom the duration of therapy could not be determined, but in the other cases it can be seen that two patients had only been on bromocriptine for one year and less and one patient had been using the drug for eight years. Where the information was available it was noted that bromocriptine was initiated after levodopa therapy. The total daily doses of bromocriptine prescribed were varied, ranging from 2.5mg to 35mg daily. However, according to the WHO, the DDD for bromocriptine, when used in Parkinson’s disease, may be as high as 40mg daily. When looking at the location of each patient in this study, it was seen that four (80%) of the patients were located in the public sector which is the sector in which bromocriptine is more often used in South Africa.
It was stated that in patients who were no longer obtaining satisfactory results with levodopa, bromocriptine could be introduced (Lieberman and Goldstein, 1985: 218). Bromocriptine at low doses of 5mg to 30mg daily in combination with levodopa provided a modest antiparkinsonian effect. Higher doses of 31mg up to 100mg daily in combination with levodopa would result in more adverse reactions including dyskinesias. It was also noted that patients reacted differently to the different dopamine agonists with some improving and others not (Lieberman and Goldstein, 1985: 225). An American study (Pfeiffer, Wilken, Glaeske, Agapito and Lorenzo, 1985: 586) agreed with Lieberman and Goldstein by stating that there were modest but significant improvements in patients receiving bromocriptine at doses 7.5mg to 15mg daily, but with a decline in efficacy seen at doses closer to 20mg. there were adverse effects noted, but they were mild in severity (Pfeiffer, et al., 1985: 588).

However, a study conducted in Ecuador, investigated the benefit of combining bromocriptine with levodopa in early disease (Alarcón, Cevallos and Lees, 1998: 261). The study concluded that there was no statistically significant benefit of combining the two agents in early Parkinson’s disease, nor did it seem to affect the evolution of the disease in any way.

When considering pramipexole it was seen that there were two cases where the duration of therapy could not be determined, but for those which could, three patients (50%) were using pramipexole for fewer than five years and only one patient (16.67%) for 10 years. According to the WHO, the DDD for pramipexole is 2.5mg daily. There were two patients receiving higher doses than this. Patient 12 was receiving 3mg daily and Patient 17 was receiving a total daily dose of 4mg. A review summarising studies done with pramipexole considered two studies using pramipexole only (Piedad and Cavanna, 2012). One study compared four different dosages of pramipexole and the other compared immediate release to extended release. Neither study detected any incidence of dyskinesias. In a study comparing pramipexole with bromocriptine, dyskinesias were found to be more prevalent with pramipexole (Mizuno, Yanagisawa, Kuno, Yamamoto, Hasegawa, Origasa, Kowa and The Japan Pramipexole Study Group, 2003: 1 154).
There were 10 patients using ropinirole for fewer than five years and two using ropinirole for between five and 10 years. Of the 15 patients, 10 are still continuing therapy with ropinirole. Comparing the number of patients using ropinirole to bromocriptine and pramipexole, it appears that ropinirole is the preferred choice of dopamine agonist by South African neurologists, most probably since it is the cheapest agent. There were three patients in whom ropinirole was started in the same year as levodopa or just one year later. According to the WHO, the DDD for ropinirole is 6mg. There were six patients receiving higher doses than this with the highest dose prescribed being 15mg daily.

### 6.3.1.2.2 Anticholinergic agents

This section focuses on the anticholinergic agents benzhexol (also known as trihexyphenidyl), biperidine and orphenadrine prescribed to Parkinson’s patients according to the medical records. A summary of the initial and current PDDs of benzhexol, biperidine and orphenadrine as well as their duration of therapy is included as Appendix K.

There were 11 patients (25.81%) in the patient population prescribed an anticholinergic agent. Focusing on each individual agent, there were six patients (13.95%) prescribed benzhexol, two patients (4.65%) prescribed biperidine and five patients (11.63%) prescribed orphenadrine. Of the two patients prescribed biperidine neither were continued on the medication.

In four of the six cases, benzhexol was discontinued. However, when examining the duration of therapy, it was seen that these drugs were used for several years before being discontinued. Analysis of the dates of when this drug was initiated in relation to levodopa, it was noted that in two cases benzhexol was initial therapy and in one case was initiated the same year as levodopa. It is likely that neurologists are using this drug to provide relief of symptoms of Parkinson’s disease in order to delay the introduction of levodopa. In the early, milder stages of the disease when the patient is not showing many symptoms, therapy with an anticholinergic may be warranted.
(Carr, et al., 2009: 756). As the patient progresses and the symptoms become more obvious, levodopa has a role to play.

Five patients were prescribed orphenadrine and three were still on the medication. The DDD for orphenadrine is 200mg. Only one patient was receiving a higher dose than this. In one instance, orphenadrine was initiated before levodopa and then discontinued. It was most likely that the symptoms were no longer effectively managed by orphenadrine and levodopa was required to provide symptomatic relief.

6.3.1.2.3 MAO-B inhibitors

This section focuses on the MAO-B inhibitors selegiline, also known as eldepryl, and rasagiline prescribed to Parkinson’s patients according to the medical records. A summary of the initial and current PDDs of selegiline and rasagiline as well as their duration of therapy is included as Appendix L.

A total of four patients (9.30%) were prescribed MAO-B inhibitors. Of these, rasagiline was the more popular drug with three patients out of the four being prescribed as such. However, only one of these patients continued therapy of all MAO-B inhibitors prescribed.

6.3.1.2.4 COMT-inhibitors

This section focuses on the COMT-inhibitor entacapone prescribed to Parkinson’s patients according to the medical records. A summary of the initial and current PDDs of entacapone as well as the duration of therapy is included as Appendix M.

Only two patients (4.65%) were prescribed entacapone. One patient discontinued the medication. However, it was not possible to compare the levodopa dose before and after the entacapone was introduced in Patient 21 as the initial dose of levodopa was not available. Theoretically, it should have been decreased.
6.3.1.2.5 Amantadine

This section focuses on amantadine prescribed to Parkinson’s patients according to the medical records. A summary of the initial and current PDDs of amantadine as well as its duration of therapy is included as Appendix N.

A total of eight patients (18.60%) were prescribed amantadine. The DDD of amantadine is 200mg but it can be seen that two patients were receiving higher doses than this.

6.3.1.6 Other medication

There were other agents that were prescribed to the Parkinson’s patients included in the study. Domperidone and metoclopramide were prescribed to two and one patient, respectively. Both these agents are dopamine antagonists used to increase gastric motility (ed. Rossiter, 2012: 43). However, in Parkinson’s disease neurologists may administer domperidone, concurrently with levodopa in order to reduce the incidence of peripheral side effects caused by the dopaminergic drug. Domperidone does not cross the blood brain barrier (Carr, et al., 2009:756). According to Daily Drug Use (ed. Turner, 2010: 446), metoclopramide reduces the effects of levodopa and concurrent use should be avoided.

There were two patients receiving donepezil, an anticholinesterase, and one patient receiving memantine, an NMDA-receptor antagonist and a derivative of amantadine. The primary indication for these drugs in Parkinson’s disease is dementia (ed. Rossiter, 2012: 494).

6.3.2 Co-morbid conditions

The medical records were reviewed to determine any co-morbid conditions the patients may have been diagnosed with and the medication prescribed for these conditions and its impact on the antiparkinsonian medication. The most common conditions noted are summarised in Figure 6.21.
Diagnoses were based on the primary indication of each drug. The group labelled ‘Other’ consists of asthma, congestive heart failure, epilepsy, gout, hypothyroidism, ischaemic heart disease, osteoarthritis, postmenopausal (hot flushes, mood swings) and/or restless legs syndrome. As can be seen from Figure 6.21, many patients were diagnosed with hypertension (n = 18; 41.86%) and constipation (n = 14; 32.56%). When looking at the metabolic conditions, the three most common were hypertension, hyperlipidaemia and diabetes. These conditions are all common diseases experienced by older patients. Considering what can be classified as the NMS of Parkinson’s disease the three most common found in this study include constipation, anxiety and depression (Ceravolo, et al., 2010; Poewe, 2008: 16; Chaudhuri, et al., 2006: 238, 240). Figure 6.22 indicates the other medication used by Parkinson’s patients for co-morbid diseases unrelated to motor symptoms.
The drugs were grouped according to their primary indication. The group labelled ‘Other’ consisted of allopurinol, donepezil, isosorbide mononitrate, levothyroxine, loratadine, promethazine and sodium valproate. One patient was prescribed donepezil.

It can be seen that the most commonly prescribed class of drugs were the antihypertensives \( (n = 19; 44.19\%) \). These included amlodipine, atenolol, carvedilol, enalapril, furosemide, hydrochlorothiazide, indapamide and perindopril. The second most commonly used class of drugs were the laxatives \( (n = 15; 34.88\%) \). This group consisted of bisacodyl, lactulose, senna and sorbitol. This was not a surprising finding, as seen in Figure 6.21, constipation is a NMS experienced by many Parkinson’s patients.

Three patients were found to be taking quetiapine. This is an atypical antipsychotic agent which acts through inhibition of dopamine receptors. Quetiapine has reduced propensity to cause extrapyramidal side effects (ed. Rossiter, 2012: 470). Psychosis is a documented NMS of Parkinson’s disease. The intervention is generally aimed at decreasing the dose of the offending dopaminergic agent and adding an atypical
antipsychotic if necessary (Ceravolo, et al., 2010). Psychosis is also more often seen with the dopamine agonists than with levodopa (Ceravolo, et al., 2010). It is interesting to note that of the three patients in this study receiving quetiapine, two were receiving the dopamine agonist ropinirole as ongoing therapy.

The antidepressants prescribed included amitriptyline and fluoxetine (n = 9; 20.93%). These agents could have been used for their antidepressant effects or for their sedative effects, particularly in the case of amitriptyline. However, depression is also a known NMS of Parkinson’s disease and is seen to affect 10% to 45% of patients although some sources say it can be as many as 70% (Poewe, 2008: 16; Chaudhuri et al., 2006: 238; Cummings, 1992: 444).

6.3.3 Non-dyskinetic patients

This section focuses on non-dyskinetic patients, discussing the disease duration, duration of levodopa therapy as well as the initial and current doses of levodopa being used. Figure 6.23 indicates the disease duration of non-dyskinetic patients.

Figure 6.23 Disease duration of non-dyskinetic patients
The majority of the patients were diagnosed between five and 10 years ago (n = 16; 48.49%). Table 6.5 indicates the initial and current doses of patients not diagnosed with dyskinesias.

Table 6.5 Initial and current prescribed daily doses of levodopa in non-dyskinetic patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Initial prescribed daily levodopa dose</th>
<th>Current prescribed daily levodopa dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 3</td>
<td>150mg</td>
<td>750mg</td>
</tr>
<tr>
<td>Patient 4</td>
<td>300mg</td>
<td>300mg</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Information not available</td>
<td>900mg</td>
</tr>
<tr>
<td>Patient 6</td>
<td>750mg</td>
<td>1 250mg</td>
</tr>
<tr>
<td>Patient 7</td>
<td>300mg</td>
<td>1 250mg</td>
</tr>
<tr>
<td>Patient 9</td>
<td>300mg</td>
<td>700mg</td>
</tr>
<tr>
<td>Patient 10</td>
<td>Information not available</td>
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</tr>
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</tr>
<tr>
<td>Patient 18</td>
<td>Information not available</td>
<td>450mg</td>
</tr>
<tr>
<td>Patient 19</td>
<td>150mg</td>
<td>800mg</td>
</tr>
<tr>
<td>Patient 20</td>
<td>400mg</td>
<td>800mg</td>
</tr>
<tr>
<td>Patient 21</td>
<td>Information not available</td>
<td>700mg</td>
</tr>
<tr>
<td>Patient 22</td>
<td>Information not available</td>
<td>1 200mg</td>
</tr>
<tr>
<td>Patient 24</td>
<td>Information not available</td>
<td>1 300mg</td>
</tr>
<tr>
<td>Patient 25</td>
<td>300mg</td>
<td>750mg</td>
</tr>
</tbody>
</table>
Table 6.5 Initial and current prescribed daily doses of levodopa in non-dyskinetic patients (continued)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Initial prescribed daily levodopa dose</th>
<th>Current prescribed daily levodopa dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 28</td>
<td>300mg</td>
<td>450mg</td>
</tr>
<tr>
<td>Patient 29</td>
<td>Information not available</td>
<td>300mg</td>
</tr>
<tr>
<td>Patient 30</td>
<td>300mg</td>
<td>450mg</td>
</tr>
<tr>
<td>Patient 31</td>
<td>300mg</td>
<td>300mg</td>
</tr>
<tr>
<td>Patient 32</td>
<td>300mg</td>
<td>300mg</td>
</tr>
<tr>
<td>Patient 33</td>
<td>Information not available</td>
<td>2400mg</td>
</tr>
<tr>
<td>Patient 34</td>
<td>600mg</td>
<td>300mg</td>
</tr>
<tr>
<td>Patient 35</td>
<td>450mg</td>
<td>750mg</td>
</tr>
<tr>
<td>Patient 37</td>
<td>Information not available</td>
<td>600mg</td>
</tr>
<tr>
<td>Patient 38</td>
<td>Information not available</td>
<td>400mg</td>
</tr>
<tr>
<td>Patient 39</td>
<td>600mg</td>
<td>750mg</td>
</tr>
<tr>
<td>Patient 40</td>
<td>300mg</td>
<td>800mg</td>
</tr>
<tr>
<td>Patient 41</td>
<td>300mg</td>
<td>750mg</td>
</tr>
<tr>
<td>Patient 42</td>
<td>Information not available</td>
<td>1000mg</td>
</tr>
</tbody>
</table>

It can be seen that non-dyskinetic patients were receiving a wide range of levodopa doses (300mg to 2400mg) with an average dose of 790.91mg±497.88mg. A total of 11 patients were started on a dose of 100/25mg three times daily and increased from there. In almost all cases the total daily doses were increased. Only in two cases were there decreases in the total daily dose of levodopa. This could be due to excessive adverse effects experienced by the patient such as dyskinesias and the dose was decreased in order to provide relief from these effects. Figure 6.24 indicates the age at diagnosis of Parkinson’s disease.
Non-dyskinetic patients did not have an early diagnosis of disease with only seven patients being diagnosed under the age of 55 years. A risk factor for the incidence of dyskinesias is young age at Parkinson’s disease onset (Ha and Jankovic, 2011: 11; Kumar, et al., 2005: 343; Sharma, et al., 2010: 491; Thanvi, et al., 2007: 384). This explains the age of onset distribution of these patients. Figure 6.25 demonstrates the duration of levodopa therapy of non-dyskinetic patients.
Unfortunately there were many incidences where the information was not available due to patients being transferred from one institution to another or one practitioner to another. However, in the cases where the information was recorded, it can be seen that the majority of patients were diagnosed less than five years ago ($n = 14; 32.56\%$). This is in keeping with studies which indicate that a longer duration of levodopa therapy is a risk factor for the development of dyskinesias (Benbir, et al., 2006: 729; Ha and Jankovic, 2011: 10; Schrag and Quinn, 2000: 2297; Thanvi, et al., 2006: 385).

6.3.4 Dyskinesias

The medical records were reviewed for incidence of dyskinesias. It was found that 10 patients (23.26\%) were suffering from dyskinesias. It is important to remember that the review was cross-sectional and only the indication at the patients' last visit was taken into consideration. The number of patients with dyskinesias as indicated by the medical records was less than the number of patients with self-reported dyskinesias ($n = 13$). A reason for this could be that patients did perhaps not fully understand what a dyskinesia was and answered positively. Of the 10 patients who were positively diagnosed with dyskinesias, 50\% ($n = 5$) were males. The severity of the dyskinesias was not specified in five patients. Of the rest of patients, four were diagnosed as having mild dyskinesias (40\%) and one was diagnosed as experiencing severe dyskinesias (10\%). Figure 6.26 indicates the type of dyskinesias experienced by patients as diagnosed by the neurologists.

Figure 6.26 shows that majority of patients experienced a combination of dyskinesias. A total of four patients did not have the information available in the medical records. In general, the most common type of dyskinesia is chorea, followed by dystonia and the two often coexist. The medical records reviewed did not state the types of dyskinesias these patients diagnosed with a combination were experiencing. The onset of levodopa induced dyskinesias is generally associated with maximal effect of levodopa therapy and is known as the peak dose dyskinesia which is most common. Less common is the diphasic dyskinesia (Chong and Lee,
When comparing the medical records to the patient interviews, four patients reported severely disabling dyskinesias, although only two of these patients were identified by the neurologist as experiencing dyskinesias. In both cases the severity was not specified. There were four patients in the interviews who reported that their dyskinesias were only mildly disabling. Of these four patients, three were diagnosed by a neurologist as having dyskinesias and were also all diagnosed with mild dyskinesias. This indicates that patients are relatively accurate when indicating the severity of dyskinesias, but not in identifying the incidence. Figure 6.27 demonstrates the age at diagnosis of patients experiencing dyskinesias according to medical records.
Studies have shown that patients with a younger age at diagnosis are more likely to experience dyskinesias and more severe dyskinesias as well (Ha and Jankovic, 2011: 11; Kumar, et al., 2005: 343; Sharma, et al., 2010: 491; Thanvi, et al., 2007: 384). As seen in Figure 6.24, patients experiencing dyskinesias were diagnosed with Parkinson’s disease earlier than non-dyskinetic patients. One study reported that after five years of levodopa therapy, the incidence of dyskinesias for patients with onset age 40 to 49 years was 80%, decreasing to 26.70% for onset ages 50 to 59 years, 22.70% for onset ages 60 to 69 years and 20% for onset ages 70 to 79 years (Ku and Glass, 2010: 179).

Due to the small number of patients in these age groups, combining them into age groups 40 to 60 years, 61 to 70 years and 70 years and older (Kumar, et al., 2005: 343), it was seen that five patients diagnosed between the ages of 40 to 60 years experienced dyskinesias. The incidence then decreased to two patients who were diagnosed between the ages of 61 to 70 years and one patient experiencing dyskinesias who was diagnosed aged 70 years or older which was shown by the
other study as well (Kumar, et al., 2005: 343). The disease duration of patients positively diagnosed with dyskinesias is demonstrated in Figure 6.28 below.

Figure 6.28 Disease duration of dyskinetic patients according to medical records

It can be seen from Figure 6.28 that 50% of the patients positively diagnosed with dyskinesias were diagnosed more than 10 years ago. Comparing this result to non-dyskinetic patients, the dyskinetic patients had longer disease duration. This is in keeping with the results of other studies which state that there is a positive relationship between disease duration and the risk of dyskinesias (Benbir, et al., 2006: 728; Schrag and Quinn, 2000: 2297).

Other risk factors in the development of dyskinesias are the dose of levodopa, initial and current as well as the duration of therapy (Jankovic, 2005: 12; Schrag and Quinn, 2000: 2297; Sharma, et al., 2010: 492). Table 6.6 indicates the initial and current prescribed daily doses of levodopa according to the medical records.
Table 6.6 Initial and current prescribed daily doses of levodopa according to medical records

<table>
<thead>
<tr>
<th>Patients</th>
<th>Initial prescribed daily dose</th>
<th>Current prescribed daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>300mg</td>
<td>2 000mg</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Information not available</td>
<td>1 000mg</td>
</tr>
<tr>
<td>Patient 8</td>
<td>600mg</td>
<td>1 000mg</td>
</tr>
<tr>
<td>Patient 11</td>
<td>150mg</td>
<td>100mg</td>
</tr>
<tr>
<td>Patient 16</td>
<td>750mg</td>
<td>600mg</td>
</tr>
<tr>
<td>Patient 23</td>
<td>900mg</td>
<td>800mg</td>
</tr>
<tr>
<td>Patient 26</td>
<td>600mg</td>
<td>1 500mg</td>
</tr>
<tr>
<td>Patient 27</td>
<td>Information not available</td>
<td>250mg</td>
</tr>
<tr>
<td>Patient 36</td>
<td>450mg</td>
<td>450mg</td>
</tr>
<tr>
<td>Patient 43</td>
<td>Information not available</td>
<td>1 000mg</td>
</tr>
</tbody>
</table>

In the instances where information was not available, patients had been referred from one institution to another and information was absent from the records. When comparing the initial and current doses, it was seen that the doses were increased in only three cases. In the instances where the dose has been decreased, it is normally done to provide control of dyskinesias. As mentioned above, the Turkish study (Benbir, et al., 2006: 729) showed that patients with an average initial dose of levodopa of 291mg daily resulted in dyskinesias. A total of six patients were receiving initial doses higher than 291mg. Dyskinesias were seen in patients receiving average levodopa doses of 338mg daily (Thanvi, et al., 2007: 384). The results of the current study show that eight patients were receiving daily doses higher than this. Six patients were receiving doses higher than the DDD of 600mg for
levodopa. Figure 6.29 indicates the duration of levodopa in patients positively diagnosed with dyskinesias according to the medical records.

Figure 6.29 Duration of levodopa therapy in patients with dyskinesias according to medical records

It was seen that the majority of patients with dyskinesias were on levodopa therapy for less than five years (n = 4; 40%). A total of four patients did not have the information available in the medical records. Even though the duration of levodopa therapy is considered a risk factor for the development of dyskinesias, the incidence is highly varied and dyskinesias have been seen as early as a few weeks after the initiation of levodopa therapy (Sharma, et al., 2010: 491; Thanvi, et al., 2006: 384). Figure 6.30 indicates the co-morbidities experienced by dyskinetic patients and Figure 6.31 shows the medications prescribed for these co-morbidities unrelated to motor symptoms of Parkinson’s disease.
The majority of patients were suffering from hyperlipidaemia (n = 4; 40%) and constipation (n = 4; 40%). Constipation is a common NMS of Parkinson’s disease, as is depression and urinary incontinence which were both experienced by three patients (30%).

Figure 6.31 Medication used by dyskinetic Parkinson’s patients for co-morbid conditions as prescribed by a medical practitioner
Many dyskinetic patients were receiving lipid lowering agents (atorvastatin, pravastatin and simvastatin) \((n = 5; \text{50\%})\), blood modifying agents (aspirin and warfarin) \((n = 5; \text{50\%})\) and laxatives \((n = 4; \text{40\%})\). There were two patients \((20\%)\) receiving the antipsychotic agent quetiapine. This is the one drug that could have a significant interaction with other antiparkinsonian medications as their mechanisms of action directly antagonise the other. Quetiapine is a dopamine antagonist and could worsen the effects of Parkinson’s disease. In spite of the interaction between antiparkinsonian medications and quetiapine, quetiapine is still used in the management of psychosis in patients with Parkinson’s disease and is, in practice, general well tolerated (Latoo, Mistry and Dunne, 2012: 8-9). Clozapine may also be used, however, the risk of agranulocytosis requires patient blood monitoring. The most promising option has been the cholinesterase inhibitor rivastigmine. Rivastigmine may be used alone or in combination with other antipsychotics (Latoo, et al., 2012: 9).

### 6.4 Summary of major findings

The major findings of both the patient interviews and the medical record review are summarised below. Table 6.7 provides a comparison of common facts obtained from both the patient interviews and medical record review. Table 6.8 compares the major findings of the patient interviews and medical record review in terms of dyskinesias. Patients were able to provide fairly accurate accounts of the disease duration. Patients were also aware of the levodopa dose they were prescribed and using at the time of the study. Patients diagnosed with dyskinesias according to the medical records were diagnosed with Parkinson’s disease earlier than non-dyskinetic patients. There were no proportional gender differences in the incidence of dyskinesias and 50\% of the patients diagnosed with dyskinesias were diagnosed more than 10 years ago. The average PDD of patients with dyskinesias according to the medical records was 870mg. This was higher than the DDD of 600mg for levodopa.
Table 6.7 Comparison of patient interviews and medical record review in terms of general findings

<table>
<thead>
<tr>
<th>Patient interviews</th>
<th>Medical records</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General findings</strong></td>
<td></td>
</tr>
<tr>
<td>A total of 14 patients were found to be between the ages of 71 to 75 years (32.56%) and constituted the largest age group overall</td>
<td></td>
</tr>
<tr>
<td>There was a male to female ratio of 1.15:1</td>
<td></td>
</tr>
<tr>
<td>The male patients were found to be older than the females</td>
<td></td>
</tr>
<tr>
<td>34.88% (n = 15) patients were diagnosed between five and 10 years before the study</td>
<td>44.19% (n = 19) of patients were diagnosed between five and 10 years ago</td>
</tr>
<tr>
<td>The majority (n = 8; 18.60%) of patients up to the age of 70 years were diagnosed less than five years ago</td>
<td>The majority (n = 10; 23.26%) of patients up to the age of 70 years were diagnosed between five and 10 years ago</td>
</tr>
<tr>
<td>90.70% (n = 39) of patients reported that levodopa was the first drug they were prescribed for Parkinson’s disease</td>
<td></td>
</tr>
<tr>
<td>The average PDD of levodopa was 750mg±452mg</td>
<td>The average PDD of levodopa was 809mg±514mg</td>
</tr>
<tr>
<td>The range of PDDs of levodopa was 200mg to 2 000mg</td>
<td>The range of PDDs of levodopa was 100mg to 2 000mg</td>
</tr>
<tr>
<td>The majority (n = 7; 16.28%) of patients were prescribed a daily dose of 300mg of levodopa</td>
<td>The majority (n = 7; 16.28%) of patients were using 300mg of levodopa daily</td>
</tr>
<tr>
<td>There were 36 (83.72%) patients also using other medication such as antihypertensives, hypoglycaemic agents, lipid lowering agents and antidepressants, which were unrelated to the motor symptoms of Parkinson’s disease</td>
<td></td>
</tr>
</tbody>
</table>
Table 6.8 Comparison of patient interviews and medical record review in terms of dyskinesias

<table>
<thead>
<tr>
<th>Patient interviews</th>
<th>Medical records</th>
</tr>
</thead>
<tbody>
<tr>
<td>A positive incidence of dyskinesias was reported by 13 patients (30.23%)</td>
<td>There were 10 patients (23.26%) suffering from dyskinesias</td>
</tr>
<tr>
<td>53.85% (n = 7) were males and 46.15% (n = 6) were females</td>
<td>50% (n = 5) were males</td>
</tr>
<tr>
<td>Fewer than 50% of patients developed dyskinesias after 10 years of treatment with levodopa</td>
<td>50% of the patients diagnosed with dyskinesias were diagnosed more than 10 years ago</td>
</tr>
<tr>
<td>A total of four patients reporting a positive incidence of dyskinesias were using levodopa for more than 10 years</td>
<td>The majority of patients with dyskinesias were on levodopa therapy for less than five years</td>
</tr>
<tr>
<td>The average PDD of patients reporting a positive incidence of dyskinesias was 815.38mg</td>
<td>The average PDD of levodopa prescribed to dyskinetic patients was 870mg</td>
</tr>
<tr>
<td>Patients in the age groups 50 to 60 years, 61 to 70 years and 71 to 80 years demonstrated an incidence of dyskinesias of 45.45%, 16.67% and 31.58% respectively</td>
<td></td>
</tr>
<tr>
<td>The majority of patients presenting with dyskinesias were in the age groups 56 to 60 years and 71 to 75 years</td>
<td></td>
</tr>
<tr>
<td>Of the total number of patients diagnosed longer than 10 years ago, the proportion which reported the presence of dyskinesias was 35.71%</td>
<td></td>
</tr>
<tr>
<td>Of the total number of patients diagnosed between five and 10 years ago, 33.33% reported a presence of dyskinesias</td>
<td></td>
</tr>
<tr>
<td>A total of four patients who reported the presence of dyskinesias were using levodopa for more than 10 years</td>
<td></td>
</tr>
<tr>
<td>Patients experiencing dyskinesias were diagnosed with Parkinson’s disease earlier than non-dyskinetic patients</td>
<td>There were two patients (20%) receiving the antipsychotic agent quetiapine</td>
</tr>
</tbody>
</table>
CHAPTER 7

Conclusion and Recommendations
7.1 Study overview

Parkinson's disease is a progressive neurodegenerative disorder which affects one in every 100 people over the age of 65 years (Singh, et al., 2007: 29). The underlying pathology of Parkinson's disease is a loss of the dopamine producing neurons in the substantia nigra of the brain (Foster and Hoffer, 2003: 177).

There is an approximately 1.5 times higher risk of Parkinson's disease for men than women (Burn, 2007: 78; Fargel, et al., 2007: 208; Miller and Cronin-Golomb, 2010: 2695). Studies have shown there are genetic and environmental links in the aetiology of Parkinson's disease (Schapira and Jenner, 2011: 1050; Nelson, et al., 2005: 1075; Warner and Schapira, 2003: 16).

There is a low reported incidence and prevalence of Parkinson's disease in Africa due to the lack of studies and the short life expectancy of the population (Okubadejo, et al., 2006: 2050). It has been shown, however, that the population aged 60 years and older is expected to double in SSA by 2030 and double again by the year 2050 (Velkoff and Kowal, 2007: 4). In America, approximately 100 000 people are living with Parkinson’s disease (Obeso, et al., 2000: 2) and there is an incidence of 1.8% in people between the ages of 65 to 69 years with the incidence increasing to 2.6% in people aged 85 to 89 years in Europe (De Rijk, et al., 2000: 21), showing that aging is indeed a risk factor to the development of Parkinson’s disease. It is therefore important to determine the incidence and prevalence of Parkinson's disease in SSA and determine the economic burden it does and will place on society and health care resources in the future.

Levodopa is still thought of as the 'gold standard' symptomatic treatment for Parkinson's disease. However, after four to five years of treatment, levodopa efficacy tends to decline even if there was a good initial therapeutic response (Singh, et al., 2007: 30; Stern, 2001: 27; Garret, et al., 1998: 99). Patients tend to experience motor fluctuations and dyskinesias. The major controversy in Parkinson's disease therapy is whether to withhold levodopa as the initial therapy in order to delay the
onset of dyskinesias or to provide the patient with levodopa in order to obtain maximum symptomatic control.

In the early, milder stages of the disease when the patient is not showing many symptoms, therapy with an anticholinergic, a dopamine agonist, amantadine or an MAO-B inhibitor may be useful as first line therapy (Carr, et al., 2009: 756). Once the patient has passed into the moderate to severe stage of Parkinson's disease, other agents such as the dopamine agonists, COMT-inhibitors or MAO-B inhibitors may be of benefit as adjunctive therapy to levodopa with dosage adjustments to obtain maximum symptom relief (Carr, et al., 2009: 756). The NICE guideline also recommends the use of these agents in the later stages of the disease and corresponds with the recommendations of Carr and colleagues (Stewart, 2007: 241). The NICE guideline states that the treatment for Parkinson's disease is open to interpretation as there are no definitive results for studies comparing the effectiveness of one drug class against the other (Stewart, 2007: 241).

There have been numerous global studies into various aspects of Parkinson's disease, but in South Africa, investigation into the treatment of the disease is limited. This study was therefore conducted with the aim of analysing the prescribed treatments for Parkinson's disease in the private and public health care sector as well as the prevalence and risk factors for dyskinesias in the public health care sector. The methodology employed for the realisation of the study objectives included the undertaking of a literature review, the analysis of a prescription database, the administration of a questionnaire survey, and a review of medical records.

The retrospective drug utilisation study was conducted through analysis of a prescription database containing records of prescriptions for antiparkinsonian products captured in a national retail pharmacy group across South Africa during the year 2010. The dataset was analysed to determine the overall demographic information pertaining to the distribution of prescriptions across South Africa, the monthly distribution of prescriptions and the frequencies of antiparkinsonian drugs dispensed. Within these prescriptions, only patients aged 50 years and older were
included in the analyses. Analysis of demographical information, prescribing in different age groups and most commonly identified dosages was conducted.

The questionnaire surveys were verbally administered to patients conclusively diagnosed with Parkinson’s disease and fitted the inclusion criteria. The analysis of the questionnaires included the demographics of patients, the age at which the disease was diagnosed, the duration and dose of levodopa therapy, the use of medication other than levodopa as well as the presence, duration and severity of dyskinesias.

The analysis of the medical record reviews included the date and age at which the disease was diagnosed, the disease severity, the presence, severity and type of dyskinesias, co-morbid conditions, any other medication the patients were using, the specific doses of levodopa and any other antiparkinsonian medication that was being used. In concluding the empirical analysis and achieving the stated research objectives, the following major findings are summarised.

7.2 Summary of major findings

As the study consisted of two parts, a DUR and a questionnaire-based survey, the major findings will be discussed separately. The summary will include a synopsis of the results of the analyses discussed in Chapters 5 and 6.

7.2.1 Major findings of the drug utilisation review

A total of 25 523 antiparkinsonian prescriptions were analysed. There were 5 168 patients identified with 3 058 (59.17%) being female and 2 110 (40.83%) being male, a female to male ratio of 1:0.68.

The average age of the population was 70.74±10.37 years, with the oldest patient being 100 years. Males were shown to be slightly older than females with the average age for males being 71.17±9.88 years and the average age for females being 70.37±10.66 years.
The highest prevalence of Parkinson’s disease was in the age category of 70 years to 79 years for both males and females. The reason for the decrease beyond this age is most likely due to increased mortality.

An average of 4.94 products was dispensed to each patient throughout the year which indicates that patients were on combination therapies. The average number of prescriptions dispensed to male patients was 5.55±6.88 over the year whereas 4.51±5.44 was the average for females. The Chi-squared test shows a statistical significant result \( p<0.05 \) but this is unlikely to be of clinical significance.

The majority of antiparkinsonian products were dispensed to females (54.05%). Patients between the ages of 70 years to 79 years received the highest number of antiparkinsonian products (35.00%) for both genders. This age group constituted a total of 32.28% of the total study population.

It was seen that the majority of antiparkinsonian products dispensed \( n = 11\,875; 46.50\% \) were combination drugs containing levodopa with a decarboxylase inhibitor, and some were combined with a COMT-inhibitor. This was expected as levodopa is considered the gold standard treatment of Parkinson’s disease. The second most dispensed group of drugs were the dopamine agonists which include pramipexole and ropinirole \( n = 10\,164; 39.80\% \). These were followed by the anticholinergic agents benzhexol and orphenadrine \( n = 2\,352; 9.20\% \). The MAO-B inhibitor selegilene and amantadine made up 2.12% and 1.80% of the total products dispensed, respectively. The average age of both males and females did not differ greatly amongst the products which showed that there were no preferred products for particular age groups.

Dopaminergic products include levodopa-containing products and dopamine agonists. It was shown that 3 295 patients received a levodopa-containing product throughout the year while 3 166 patients received a dopamine agonist. This indicates that patients were prescribed combination therapies. It was seen that males were preferentially prescribed levodopa-containing products and females were preferentially prescribed pramipexole.
For the levodopa-containing products, patients in the age group 70 to 79 years held the highest number of prescriptions \((n = 4748)\) with the age group 60 to 69 years holding the second highest proportion of prescriptions \((n = 2988)\). The most commonly identified \((n = 2056)\) PDD was 300mg of levodopa which is half the DDD of 600mg.

The dopamine agonists pramipexole and ropinirole were prescribed more frequently in the younger patient categories. The age group 60 to 69 years held the highest number of prescriptions \((n = 3277)\) and is likely to represent those patients who have been recently diagnosed or are in the early stages of the disease. The most commonly identified PDD of pramipexole was 0.125mg \((n = 2861)\) which is lower than the DDD of 2.5mg for pramipexole. The most commonly identified PDD for ropinirole was 3.73mg \((n = 239)\) which was almost half of the DDD of 6mg for ropinirole.

The monthly dispensing of products remained largely unchanged throughout the year. The average number of prescriptions dispensed for the year was 72.86±58.07 which amounts to 6.07 products per month. There were more female than male patients for each month. However, the average number of prescriptions was higher for males than females for each month. The month of December held the highest number of patients \((n = 1876)\). The slight increase in patients throughout the year did not necessarily indicate an increased incidence of Parkinson’s disease, but could mean that patients transferred their prescriptions from other pharmacies or pharmacy groups to the one under consideration in this study.

The average number of prescriptions per region was 3190.38±1106.44 over the period of one year. The large standard deviation is due to patients travelling throughout the year and obtaining medication in different regions. The Western Cape held the highest proportion of prescriptions, 5799±6.99 (22.72%). The rest of the regions were similar in number of prescriptions. The average number of prescriptions for levodopa-containing products per region was 1484.38±687.96 and the average number of dopamine agonist prescriptions was 1270.50±313.21.
7.2.2 Major findings of the questionnaire-based survey and medical record review

The following section will be divided into two. The first will summarise the major findings of the questionnaire-based survey and the second part will summarise the major findings of the medical record review.

7.2.2.1 Major findings of the questionnaire-based survey

A total of 43 patients were interviewed. Twenty-three males (53.49%) were interviewed which showed an approximate ratio of males to females of 1.15:1 in this study. The majority of participants were coloured (n = 22; 51.16%) and white (n = 16; 37.21%). The coloured patients were found in the public sector while white patients were made up mostly of private sector patients (68.75%).

The majority of patients were in the age group 71 to 75 years (n = 14; 32.56%). This was a similar finding as that shown by the DUR. The male patients were also found to be older than the females; also a finding similar to that of the DUR. The majority of patients (n = 8) up to the age of 70 years were diagnosed less than five years ago. This indicates that some patients had early onset Parkinson’s disease. The patients over 70 years of age were mostly diagnosed more than 10 years ago (n = 6). There were very few patients in the older age groups and this was most likely due to a higher mortality rate in these age groups.

There were 39 (90.70%) patients who reported that levodopa was the first drug they were prescribed for Parkinson’s disease. Fourteen patients were using levodopa for two to four years and 12 for longer than 10 years. A total of 15 patients were using levodopa for the entire duration of their illness.

Most of the patients (90%) diagnosed less than five years ago were receiving doses of levodopa of 600mg or lower. Of the patients diagnosed more than 10 years ago, 66.67% were receiving doses of levodopa higher than 700mg. The majority of patients were prescribed a daily dose of 300mg of levodopa (n = 7; 16.28%). The
second largest group of patients received 600mg (n = 6; 13.95%) which is the DDD for levodopa. The average PDD was 750mg±452mg.

Dyskinesias were reported by 13 patients (30.23%). Of these, seven were males and six were females. 66.67% of patients between the ages of 56 and 60 years developed dyskinesias, as compared to only 28.57% of patients between the ages of 71 to 75 years. Thus, younger patients experienced a higher incidence of dyskinesias (45.45%) compared to older patients (31.58%). A total of 35.71% of patients diagnosed more than 10 years before the study onset reported the presence of dyskinesias. Of the 13 patients with dyskinesias, four were diagnosed more than 10 years ago. The results of this study show that 32% of patients on levodopa therapy for more than five years reported dyskinesias and fewer than 50% of patients reported dyskinesias after 10 years of treatment with levodopa.

Most patients could not remember their initial dose of levodopa. This was to be expected due to ageing and memory loss. However, of the patients who answered, it was seen that most were receiving an initial dose of 200mg or more on a daily basis. A total of six patients were receiving doses higher than that of the DDD for levodopa which is 600mg daily.

7.2.2.2 Major findings of the medical record review

The medical records showed that 44.19% of patients were diagnosed between five and 10 years ago (n = 19), 23.26% were diagnosed less than five years ago and 27.91% have been diagnosed for more than 10 years. The medical records provide a more accurate date of diagnosis, although the patient would only have presented to the neurologist when the symptoms became bothersome.

Males were receiving higher PDDs of levodopa than females. The majority of patients were prescribed a daily dose of 300mg of levodopa (n = 7; 16.28%). The lowest recorded PDD was 100mg and the highest recorded PDD of levodopa was 2400mg. The average PDD was 809mg±514mg. This reflects the large range of
doses prescribed. It was seen that higher doses of levodopa corresponded with longer disease duration.

A total of 20 patients were prescribed a dopamine agonist (46.51%) with five patients (11.63%) being prescribed bromocriptine, six patients (13.95%) prescribed pramipexole and 15 patients (34.88%) prescribed ropinirole. Eleven patients (25.81%) were prescribed an anticholinergic agent. Six patients (13.95%) were prescribed benzhexol, two patients (4.65%) prescribed biperidine and five patients (11.63%) prescribed orphenadrine. A total of four patients (9.30%) were prescribed MAO-B inhibitors. Only two patients (4.65%) were prescribed entacapone. A total of eight patients (18.60%) were prescribed amantadine.

When comparing the private sector analysed in the DUR to the public sector which was the focus of the questionnaire-based survey, it was seen that patients in the private sector had access to a larger range of antiparkinsonian products, particularly auxiliary products usually given in combination with levodopa such as the COMT-inhibitors and the MAO-B inhibitors. This could be due to constraints regarding funding of medication in the public health care sector.

Domperidone and metoclopramide were prescribed to two and one patient, respectively. Domperidone is used in Parkinson’s disease to reduce the incidence of peripheral side effects caused by levodopa. Metoclopramide however, should not be used concurrently with levodopa. Two patients were receiving donepezil and one was receiving memantine for Parkinson’s disease dementia. Three patients were found to be taking quetiapine for psychosis. Two of these three patients were using ropinirole as ongoing therapy. Psychosis is more commonly associated with dopamine agonists than with levodopa. The antidepressants prescribed included amitriptyline and fluoxetine.

Considering what can be classified as the NMSs of Parkinson’s disease the three most common include constipation, anxiety and depression. The most common co-morbidities seen were hypertension, hyperlipidaemia and diabetes. The most
commonly used classes of drugs, other than those used for Parkinson’s disease, were antihypertensives, laxatives and blood modifying agents.

The medical records showed that 10 patients (23.26%) were suffering from dyskinesias. Four patients were diagnosed as having mild dyskinesias (40%) and one was diagnosed as experiencing severe dyskinesias (10%). It is important to remember that the review was cross-sectional and only the indication of dyskinesia severity at the patients' last visit was taken into consideration. This was lower than the number of patients self-reporting a positive incidence of dyskinesias. A reason for this could be that patients did perhaps not fully understand what a dyskinesia was and answered positively.

Patients experiencing dyskinesias were diagnosed with Parkinson’s disease earlier than non-dyskinetic patients. It was seen that five patients diagnosed between the ages of 40 to 60 years experienced dyskinesias. This value then fell to two patients who were diagnosed between the ages of 61 to 70 years and one patient who was diagnosed over the age of 70 years.

The majority (50%) of the patients diagnosed with dyskinesias were diagnosed more than 10 years ago. Comparing this result to non-dyskinetic patients, the dyskinetic patients had longer disease duration. After five years of being diagnosed with Parkinson’s disease, eight patients developed dyskinesias. This gives a rate of 18.60% after five years of disease duration. It was seen that the majority of patients with dyskinesias were on levodopa therapy for less than five years (n = 4; 40%). Even though the duration of levodopa therapy is considered a risk factor for the development of dyskinesias, the incidence is highly varied.

### 7.3 Recommendations

Based on the major findings of the study, certain recommendations regarding the condition, in terms of treatment, can be made. Recommendations for future studies investigating aspects of Parkinson’s disease in both South Africa and internationally can also be made.
7.3.1 Recommendations regarding the study

Parkinson’s disease places an economic burden on society and health care resources. This is a burden that is expected to increase as the population ages in South Africa. It is important that the full extent of the burden be calculated and understood in order to prepare for future incidence.

Patients diagnosed with Parkinson’s disease need to be educated on the condition and what to expect. The medication prescribed to them needs to be explained and the patients need to be warned of any adverse effects they may experience. This will improve patient understanding and adherence to the prescribed regimen.

Although there are guidelines outlining treatment for mild, moderate and severe Parkinson’s disease, specific doses of drugs are not available. This shows that guidelines are recommendations and that clinical experience and the patients’ ability to tolerate the drug have an influence on the prescribing of antiparkinsonian medication.

In terms of dyskinesias, it was seen that patients diagnosed at a younger age and those using levodopa therapy for longer periods of time were most at risk for developing this complication.

7.3.2 Recommendations regarding further research

The results of this study indicate that there is a need for further research into various aspects of Parkinson’s disease in South Africa. Both branches of the study, being the DUR and the questionnaire-based survey, have further applications in research of this disorder. These include:

- Analysis of prescriptions for antiparkinsonian products, especially levodopa-containing products and dopamine agonists, dispensed across South Africa on an interlinked dispensing system, so as to analyse conclusively the prescribing trends in different patients and regions.
• The conducting of a questionnaire-based survey wherein the demographics of the country are reflected in the participants, so as to determine whether the incidence of Parkinson’s disease in South Africa differs between racial or cultural groups.
• Taking into account weight-based dosing of levodopa and determining the effect it has on the incidence of dyskinesias, particularly in female patients.
• The differences in the effectiveness of antiparkinsonian drug classes in terms of gender.
• Further investigation into the effectiveness of the various drug classes used in the treatment of Parkinson’s disease and comparing these classes in order to establish more concrete treatment guidelines.

7.3.3 Concluding statement

There is a large amount of information regarding Parkinson’s disease from various resources. However, this information is largely derived from outside Africa. Given that Parkinson’s disease in South Africa is relatively common, it is important to ensure that research is undertaken so as to allow for better understanding and treatment of this condition. While this study was not a true representation of the incidence of Parkinson’s disease in South Africa, valuable information regarding the total cost of antiparkinsonian products, prescribing patterns and the incidence of dyskinesias was obtained from the DUR and questionnaire-based surveys.

The ideal management of Parkinson’s disease is still a source of much debate. Based on the prescribing trends identified, it can be seen that levodopa is still the preferred first-line treatment for Parkinson’s disease. The value of the dopamine agonists, COMT-inhibitors and MAO-B inhibitors in the management of Parkinson’s disease may yet be realised through further research and gradual increases in prescribing.
REFERENCES


McNamara, P. 2009. Unified Parkinson’s disease rating scale.  
[http://parkinsons.about.com/od/glossary/g/UPDRS.htm](http://parkinsons.about.com/od/glossary/g/UPDRS.htm) [Date accessed: 26/03/2013].

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VHA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives. 2012. Pharmacotherapy recommendations In Parkinson’s


APPENDIX A: ETHICAL APPROVAL - NELSON MANDELA METROPOLITAN UNIVERSITY

Ref: [H11-HEA-PHA-001/Approval]
Contact person: Mrs U Spies
9 June 2011
Prof I Truter
NMMU
Department of Pharmacy
Faculty of Health Sciences

Dear Prof Truter

TREATMENT OF PARKINSON’S DISEASE IN SOUTH AFRICA AND INVESTIGATION OF THE RISK FACTORS CAUSING DYSKINESIA

Your above-entitled application for ethics approval served at the Research Ethics Committee (Human). We take pleasure in informing you that the application was approved by the Committee.

The ethics clearance reference number is H11-HEA-PHA-001, and is valid for three years. Please inform the REC-H, via your faculty representative, if any changes (particularly in the methodology) occur during this time. An annual affirmation to the effect that the protocols in use are still those for which approval was granted, will be required from you. You will be reminded timeously of this responsibility, and will receive the necessary documentation well in advance of any deadline.

We wish you well with the project. Please inform your co-investigators of the outcome, and convey our best wishes.

Yours sincerely

Dr B Pretorius
Chairperson: Research Ethics Committee (Human)

cc: Department of Research Capacity Development
    Faculty Officer, Faculty of Health Sciences
APPENDIX B: ETHICAL APPROVAL - UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

06 May 2011

HREC REF: 154/2011

PROF B KIES,
MEDICINE
NEUROLOGY
E.8
NGSH
Fax: 0214066251

Dear PROF KIES,

PROJECT TITLE: TREATMENT OF PARKINSON’S DISEASE IN SOUTH AFRICA AND INVESTIGATION OF RISK FACTORS CAUSING DYSKINESIA.

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

Approval is granted until 15 May 2012

Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

[Signature]

A/PROF MARC BLOCKMAN

CHAIRPERSON, FHS HUMAN ETHICS

Federalwide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies with the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E9: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 31 and 312.
APPENDIX C: ETHICAL APPROVAL - TYGERBERG HOSPITAL

ETHICS NO: H11-HEA-PHA-001

Treatment of Parkinson’s Disease in South Africa and investigation of the risk factors causing dyskinesia.

Dear Razia Gaida

PERMISSION TO CONDUCT YOUR RESEARCH AT TYGERBERG HOSPITAL

In accordance with the Provincial Research Policy and Tygerberg Hospital Notice No 40/2009, permission is hereby granted for you to conduct the above-mentioned research here at Tygerberg Hospital.

DR D ERASMUS
CHIEF DIRECTOR: TYGERBERG HOSPITAL
Date: 13/06/2012
### APPENDIX D: SAMPLE OF DATA ANALYSED

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| 3+ | ANTI-CHOLINERGICS | AKINETON 2MG TAB 50 |
| 3+ | ANTI-CHOLINERGICS | AKINETON 2MG TAB 50 |
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| 3+ | ANTI-CHOLINERGICS | AKINETON 2MG TAB 50 |
| 3+ | ANTI-CHOLINERGICS | AKINETON 2MG TAB 50 |

175
The data fields included were:

- pharmacy number (a number identifying the specific pharmacy in the national community pharmacy group, for example 253);
- profile number (a number used to identify a specific group of patients, usually a family, for example 10);
- dependant number (a number used to identify each individual person in a profile, for example 1 to 7);
- dependant code (a number used to identify the main member and dependants belonging to a medical aid scheme, for example 001);
- department (indicates whether the drug dispensed is a Schedule 3 or above or below);
- sub-department (indicates which therapeutic class the drug belongs to in relation to its site of action, for example central nervous system);
- class (indicates the type of drug dispensed in relation to its use, for example antiparkinsons);
- sub-class (indicates which specific drug in each class, for example dopaminergics);
- product description (indicates the trade name of the drug dispensed, for example Requip®);
- NAPPI (National Pharmaceutical Product Interface) code (the unique number allocated to specific medicines which allows them to be deducted from medical aid benefits);
- active 1 name (indicates the chemical name of the main active ingredient, for example ropinirole);
- active 2 name (indicates the name of the second active ingredient in the case of combination preparations, for example carbidopa);
- active 1 strength (indicates the strength of the primary active ingredient per dosage unit, for example mg);
- active 2 strength (indicates the strength of the secondary active ingredient in the case of a combination preparation, for example 25mg);
- schedule (the number which indicates the schedule of the drug dispensed, for example 4);
• dosage form (indicates the formulation of the drug, for example tablet);
• dosage type (indicates if the formulation has been modified to prolong the release of the active ingredient from the dosage form, for example CR – controlled release);
• script repeated (indicates whether the drug dispensed was authorised by the prescriber to be repeated on second or multiple subsequent occasions);
• original number of repeats (a number which indicates how many times a drug is to be dispensed on a repeat basis, for example 5);
• current repeat (the number indicating which repeat was being dispensed amongst the total possible number of repeats, for example 4);
• drug schedule (as for schedule);
• units sold (a number indicating the exact number of dosage units dispensed to the patient, for example 30, where 30 would mean tablet or capsules);
• quantity sold (the number indicating the number of pre-packed dosage containers dispensed to the patient, for example 1. If the pack was broken, the quantity sold would be indicated as 0.);
• sales value (a currency value indicating the cost of the drugs sold in South African Rands, for example R153.46);
• gender (indicates whether the patient is male (M) or female (F));
• age category (a number range to group together patients of different ages in years, for example +65);
• relation (a number indicating the relationship of the patient to the primary profile member where ‘2’ indicates spouse, ‘3’ indicates a child and ‘4’ indicates an unspecified relationship);
• age (a number representing the actual age of the patient in years, for example 70);
• area description (geographically determined, identifying the region in which the prescription was dispensed, for example Eastern Cape); and
• calendar month (a number representing which month the prescription was dispensed, for example 9 is September).
APPENDIX E: PATIENT QUESTIONNAIRE

PATIENT QUESTIONNAIRE

Demographic information:

1. Gender
   - Male
   - Female

2. Ethnic group
   - White
   - Coloured
   - Black
   - Indian
   - Other

3. Patient age
   - 50-55 years
   - 56-60 years
   - 61-65 years
   - 66-70 years
   - 71-75 years
   - 76-80 years
   - 81-85 years
   - Over 85 years
4. What is your current body mass?

__________________________________

Clinical Information:

5. When were you diagnosed with Parkinson’s disease?

<table>
<thead>
<tr>
<th>Less than 5 years ago</th>
<th>Between 5 and 10 years ago</th>
<th>More than 10 years ago</th>
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</thead>
</table>

6. How long have you been on levodopa therapy?

<table>
<thead>
<tr>
<th>Two to four years</th>
<th>Five to seven years</th>
<th>Eight to ten years</th>
<th>Longer than 10 years</th>
</tr>
</thead>
</table>

7. What was your initial daily dose of levodopa?

__________________________________

__________________________________

8. What is your current daily dose of levodopa?

__________________________________

__________________________________

9. Was levodopa the first drug you were treated with? If no, which were you started on?

☐ Yes

☐ No, initial treatment was ________________________________________

10. What other medication are you currently using?

__________________________________

__________________________________
Dyskinesias

11. Do you currently experience dyskinesias? If yes, when did they start?
   □ Yes _____________________________________________________________
   □ No
   □ Unsure

12. How disabling are these dyskinesias?

<table>
<thead>
<tr>
<th>Not disabling</th>
<th>Mildly disabling</th>
<th>Moderately disabling</th>
<th>Severely disabling</th>
<th>Completely disabling</th>
</tr>
</thead>
</table>

General:

13. Any other comments regarding medication and its influence on your well-being?

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
APPENDIX F: LETTER SENT TO NEUROLOGISTS

Faculty of Health Sciences, School of Pharmacy
Tel. +2776335589
razia.gaida@live.nmmu.ac.za
Date:__________________

Contact person: Razia Gaida

Dear Doctor

I am a postgraduate Pharmacy student at NMMU conducting a research project in fulfilment of my MPharm.

The topic of my research is “Treatment of Parkinson’s disease in South Africa and investigation of risk factors causing dyskinesia”. The aim of this study is to explore the onset of dyskinesias in patients with Parkinson’s disease who are currently on levodopa and analyse the risk factors involved with the onset. Patient confidentiality will be maintained at all times.

I have obtained consent from the following patients to allow me to review their files and obtain the date of diagnosis, the date of initiation with levodopa treatment, other medication being used, the presence and severity of dyskinesias and any other benefit or side effect the patient experiences:

_____________________
_____________________
_____________________
_____________________

Patients’ names here

I would very much appreciate your co-operation and assistance. If you have any queries please feel free to contact me at the above details.

_________
Yours sincerely,
Razia Gaida
### APPENDIX G: MEDICAL DATA RECORD SHEET

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</tr>
<tr>
<td>Levodopa/Carbidopa/Entacapone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levodopa/Benserazide</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bromocriptine</td>
<td></td>
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</tr>
<tr>
<td>Pramipexole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ropinirole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entacapone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pergolide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisuride</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pregabalin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Date of diagnosis
__________________________________________

Age of patient at diagnosis
__________________________________________

Disease severity
☐ Mild (early)
☐ Moderate
☐ Severe

Presence of dyskinesias
☐ Yes
☐ No

Severity of dyskinesia
☐ Mild
☐ Moderate
☐ Severe

Type of dyskinesia
☐ Peak dose dyskinesia
☐ Diphasic dyskinesias
☐ Off state dystonia
☐ On state dystonia
☐ ‘Yo-yo’ dyskinesia

Co-morbid conditions and medication
__________________________________________________________________________________
__________________________________________________________________________________
__________________________________________________________________________________
__________________________________________________________________________________
Dear Sir/Madam

You are being asked to participate in a research study. The title of the study is ‘Treatment of Parkinson's disease in South Africa and investigation of the risk factors causing dyskinesia’. The study aims to determine the way the medicine is prescribed to patients suffering from Parkinson's disease and to determine the risk factors which are involved in the onset of dyskinesias.

In order to participate, you are required to provide written consent that must include:

- Your name and surname
- The date
- Your signature

Your participation will involve the following: the researcher will extract data from your medical file; and you will be asked to answer a questionnaire. It is important that you understand that participation in this study is completely voluntary; if you choose not to participate, this will not affect your present or future medical care in any way and there will be no penalty to you.

If you agree to participate, you are free to withdraw at any time during the study without any penalty incurred to you. Withdrawing from the study will not affect your current or future medical care in any way. If you wish to withdraw please notify the researcher so that your participation may be ended in an orderly manner.

It is important to remember that participation in this study will not benefit you in any way nor will it cause you any harm. There will not be any experiments conducted on you and your current medication will not be changed in any way. No changes to your medical records will be made. Participation in this study will not incur any additional costs to you as the participant.

This research may be presented at scientific conferences or in scientific publications, but your identity will remain confidential at all times. No information will be able to be tracked back to you.

This study has been approved by the Research Ethics Committee (Human) of the Nelson Mandela Metropolitan University in Port Elizabeth as well as the Faculty of Health Sciences Research Ethics Committee of the University of Cape Town.
If you have any questions, please feel free to contact the researcher using the following details:

**Telephone:** 076 633 5589  
**E-mail:** razia.gaida@live.nmmu.ac.za

If you have any questions regarding your rights and welfare as a participant, please feel free to contact the Chairperson of the Human Research Ethics Committee of the University of Cape Town, Professor Mark Blockman using the following details:

**Telephone:** (021) 406 63388  
Or Dr Blanche Pretorius, Chairperson of the Human Research Ethics Committee of NMMU, using the following details:

**Telephone:** (041) 504 2538

This informed consent statement has been prepared in compliance with current statutory guidelines.

If you understand and accept the conditions and are willing to participate please sign your name and initials below.

_________________________________  ________________________
Participant's name and surname        Participant's signature

Yours sincerely,

__________________________
Razia Gaida  
Researcher
Fakulteit Gesondheidswetenskappe, Departement Farmasie
Razia Gaida
Selfoon: (+27) 76 633 5589
razia.gaida@live.nmmu.ac.za
Datum:________________________

Hoofnavorser: Razia Gaida

NMMU REC-H Verwysingsnommer: H11-HEA-PHA-001
UCT HREC Verwysingsnommer: 154/2011
TYGERBERG REC-H Verwysingsnommer: H11-HEA-PHA-001

Geagte Meneer / Mevrou / Mejuffrou

U word genooi om deel te neem aan ’n navorsingsprojek. Die titel van die studie is ‘Behandeling van Parkinson se siekte in Suid-Afrika en ’n ondersoek na die risikofaktore van diskinesias’. Die studie het ten doel om die wyse waarop die medisyne wat voorgeskryf word aan pasiënte wat aan Parkinson se siekte ly en die risikofaktore wat betrokke is by die aanvang van dyskinesias te bepaal.

Om deel te neem, moet u asseblief skrifelike toestemming gee wat insluit:
• U naam en voorletters
• Die datum
• U handtekening

U deelname sal die volgende behels: die navorser sal ’n uittreksel uit u mediese lêer aanvra, en u sal gevra word om ’n vraelys te voltooi (mondelings). U deelname is volkome vrywillig en dit staan u vry om deelname te weier. U sal op geen wyse hoegenaamd negatief beïnvloed word indien u sou weier om deel te neem nie. U mag ook te eniger tyd aan die navorsingsprojek ontrek, selfs al het u ingestem om deel te neem.

U ontrekking uit die studie sal geen invloed op u huidige of toekomstige mediese sorg op enige wyse hê nie. As u wil ontrek, moet u asseblief die navorser in kennis stel sodat u deelname beëindig kan word.

U sal nie enige direkte voordeel trek uit die studie nie, en ook nie enige skade berokken word nie. Daar sal geen eksperimente op u uitgeoer word nie en u huidige medikasie sal nie verander word nie. Geen veranderinge sal ook in u mediese rekords aangebringword nie. Deelname aan hierdie studie sal ook nie enige bykomende koste vir u inhou nie.
Hierdie navorsing mag in die toekoms (na voltooiing) aangebied word by wetenskaplike konferensies of gepubliseer word in wetenskaplike publikasies, maar u identiteit sal te alle tye vertroulik bly. Geen inligting sal bekend gemaak word wat enige persoon in staat sal stel om u op te spoor of te kontak nie. Hierdie studie is deur die Etiek Komitee (Menslik) van die Nelson Mandela Metropolitaanse Universiteit in Port Elizabeth goedgekeur, sowel as deur die Navorsingsetiekkomitee van die Fakulteit Gesondheidswetenskappe aan die Universiteit van Kaapstad.

As u enige vrae het, is u welkom om die navorser te kontak by:
- Selfoon: 076 633 5589
- E-pos: razia.gaida@live.nmmu.ac.za

As u enige vrae oor u regte as 'n deelnemer het, is u welkom om die Voorsitter van die Navorsingsetiekkomitee van die Universiteit van Kaapstad te kontak, Professor Mark Blockman by:
- Telefoonnommer: (021) 406 63388
OF Dr Blanche Pretorius, Voorsitter van die Navorsingsetiekkomitee van die NMMU, by:
- Telefoonnommer: (041) 504 2538

Hierdie verklaring is opgestel in ooreenstemming met huidige statutêre riglyne. As u die inhoud verstaan en die voorwaardes aanvaar, en bereid is om deel te neem, teken asseblief u naam en voorletters hieronder.

_________________________  _______________________
Naam en voorletters    Handtekening

_________________________  _______________________
Die uwe,

_________________________
Razia Gaida
Navorser
APPENDIX J: INITIAL AND CURRENT PRESCRIBED DAILY DOSES OF BROMOCRIPTINE, PRAMIPEXOLE AND ROPINIROLE AND DURATION OF THERAPY AS PRESCRIBED TO PARKINSON'S PATIENTS BY NEUROLOGISTS

<table>
<thead>
<tr>
<th>Patients</th>
<th>Bromocriptine</th>
<th>Pramipexole</th>
<th>Ropinirole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Current</td>
<td>Duration</td>
</tr>
<tr>
<td>Patient 1</td>
<td>2.5mg</td>
<td>NA*</td>
<td>1 year</td>
</tr>
<tr>
<td>Patient 2</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Patient 9</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Patient 10</td>
<td>7.5mg</td>
<td>7.5mg</td>
<td>8 years</td>
</tr>
<tr>
<td>Patient 12</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Patient 13</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Patient 14</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Patient 15</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Patient 16</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
</tbody>
</table>
INITIAL AND CURRENT PRESCRIBED DAILY DOSES OF BROMOCRIPTINE, PRAMIPEXOLE AND ROPINIROLE AND DURATION OF THERAPY AS PRESCRIBED TO PARKINSON’S PATIENTS BY NEUROLOGISTS (CONTINUED)

<table>
<thead>
<tr>
<th>Patient 17</th>
<th></th>
<th></th>
<th></th>
<th>4mg</th>
<th>4mg</th>
<th>2 years</th>
<th>3mg</th>
<th>NA</th>
<th>4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3mg</td>
<td>4mg</td>
<td>6 years</td>
</tr>
<tr>
<td>Patient 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>INA</td>
<td>15mg</td>
<td>INA</td>
</tr>
<tr>
<td>Patient 21</td>
<td></td>
<td></td>
<td></td>
<td>INA</td>
<td>1.5mg</td>
<td>INA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 23</td>
<td>35mg</td>
<td>20mg</td>
<td>INA</td>
<td>0.125mg</td>
<td>NA</td>
<td>INA</td>
<td>6mg</td>
<td>NA</td>
<td>1 year</td>
</tr>
<tr>
<td>Patient 24</td>
<td>INA</td>
<td>7.5mg</td>
<td>INA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 27</td>
<td>15mg</td>
<td>15mg</td>
<td>&lt;1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3mg</td>
<td>3mg</td>
<td>1 year</td>
</tr>
<tr>
<td>Patient 41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3mg</td>
<td>NA</td>
<td>1 year</td>
</tr>
<tr>
<td>Patient 42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.25mg</td>
<td>1.5mg</td>
<td>2 years</td>
</tr>
<tr>
<td>Patient 43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.5mg</td>
<td>3.75mg</td>
<td>4 years</td>
</tr>
</tbody>
</table>

(*NA – Not applicable; **INA – Information not available)
# APPENDIX K: INITIAL AND CURRENT PRESCRIBED DAILY DOSES OF BENZHEXOL, BIPERIDINE AND ORPHENADRINE AND DURATION OF THERAPY AS PRESCRIBED TO PARKINSON’S PATIENTS BY NEUROLOGISTS

<table>
<thead>
<tr>
<th>Patients</th>
<th>Benzhexol</th>
<th></th>
<th>Biperidine</th>
<th></th>
<th></th>
<th>Orphenadrine</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Current</td>
<td>Duration</td>
<td>Initial</td>
<td>Current</td>
<td>Duration</td>
<td>Initial</td>
<td>Current</td>
</tr>
<tr>
<td>Patient 1</td>
<td>6mg</td>
<td>NA*</td>
<td>5 years</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patient 3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2mg</td>
<td>NA</td>
<td>2 years</td>
<td>100mg</td>
<td>150mg</td>
</tr>
<tr>
<td>Patient 6</td>
<td>3mg</td>
<td>3mg</td>
<td>5 years</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patient 7</td>
<td>2mg</td>
<td>NA</td>
<td>3 years</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patient 11</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100mg</td>
<td>100mg</td>
</tr>
<tr>
<td>Patient 17</td>
<td>6mg</td>
<td>NA</td>
<td>1 year</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Patient 29</td>
<td>6mg</td>
<td>6mg</td>
<td>6 years</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patient 30</td>
<td>1mg</td>
<td>NA</td>
<td>4 years</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
INITIAL AND CURRENT PRESCRIBED DAILY DOSES OF BENZHEXOL, BIPERIDINE AND ORPHENADRINE AND DURATION OF THERAPY AS PRESCRIBED TO PARKINSON’S PATIENTS BY NEUROLOGISTS (CONTINUED)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial Dose Ben</th>
<th>Current Dose Ben</th>
<th>Initial Dose Bip</th>
<th>Current Dose Bip</th>
<th>Initial Dose Orp</th>
<th>Current Dose Orp</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 36</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75mg</td>
<td>NA</td>
<td>2 years</td>
</tr>
<tr>
<td>Patient 38</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>150mg</td>
<td>NA</td>
<td>&lt;1 year</td>
</tr>
<tr>
<td>Patient 39</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3mg</td>
<td>NA</td>
<td>2 years</td>
<td>INA**</td>
</tr>
</tbody>
</table>

(*NA – Not applicable; **INA – Information not available)
APPENDIX L: INITIAL AND CURRENT PRESCRIBED DAILY DOSES OF SELEGILINE AND RASAGILINE AND DURATION OF THERAPY AS PRESCRIBED TO PARKINSON’S PATIENTS BY NEUROLOGISTS

| Patients | Selegiline | | Rasagiline | | |
|----------|------------|----------------|------------|----------------|
|          | Initial | Current | Duration | Initial | Current | Duration |
| Patient 11 | - | - | - | 3mg | NA* | <1year |
| Patient 15 | - | - | - | 1mg | NA | <1 year |
| Patient 16 | - | - | - | 1mg | 1mg | 2 years |
| Patient 17 | INA** | NA | 1 year | - | - | - |

(*NA – Not applicable; **INA – Information not available)
APPENDIX M: INITIAL AND CURRENT PRESCRIBED DAILY DOSES OF ENTACAPONE AND DURATION OF THERAPY AS PRESCRIBED TO PARKINSON’S PATIENTS BY NEUROLOGISTS

<table>
<thead>
<tr>
<th>Patients</th>
<th>Entacapone</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Current</td>
<td></td>
<td>Duration</td>
</tr>
<tr>
<td>Patient 20</td>
<td>600mg</td>
<td>NA*</td>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td>Patient 21</td>
<td>400mg</td>
<td>800mg</td>
<td></td>
<td>4 years</td>
</tr>
</tbody>
</table>

(*NA – Not applicable)
## APPENDIX N: INITIAL AND CURRENT PRESCRIBED DAILY DOSES OF AMANTADINE AND DURATION OF THERAPY AS PRESCRIBED TO PARKINSON’S PATIENTS BY NEUROLOGISTS

<table>
<thead>
<tr>
<th>Patients</th>
<th>Amantadine</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Current</td>
</tr>
<tr>
<td>Patient 1</td>
<td>200mg</td>
<td>200mg</td>
</tr>
<tr>
<td>Patient 2</td>
<td>INA</td>
<td>300mg</td>
</tr>
<tr>
<td>Patient 15</td>
<td>200mg</td>
<td>200mg</td>
</tr>
<tr>
<td>Patient 25</td>
<td>100mg</td>
<td>NA*</td>
</tr>
<tr>
<td>Patient 26</td>
<td>300mg</td>
<td>NA</td>
</tr>
<tr>
<td>Patient 38</td>
<td>400mg</td>
<td>NA</td>
</tr>
<tr>
<td>Patient 42</td>
<td>300mg</td>
<td>300mg</td>
</tr>
<tr>
<td>Patient 43</td>
<td>300mg</td>
<td>NA</td>
</tr>
</tbody>
</table>

(*NA – Not applicable; **INA – Information not available)