Prescribing patterns of medicines used in Parkinson's and other related diseases in the private health care sector of South Africa

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Abstract

Title: Prescribing patterns of medicines used in Parkinson's and other related diseases in the private health care sector of South Africa.

Key words: Parkinson's disease, antiparkinson medicine items, movement disorders, pharmacoeconomics, drug utilisation review, refill-adherence rates.

Parkinson's disease is the most recurrent movement disorder and has a radical effect on the lives of people. This chronic neurological disorder is accompanied by a significant social and financial burden with a negative brunt on sufferers' quality of life. The main cause of Parkinson's disease is still unknown, however, the main goal of existing treatment for Parkinson's disease is to improve the patient's quality of life and ability to go about as normally and easily as possible. The general objective of this study was to investigate the prescribing patterns of medicine items used in Parkinson's disease and other movement disorders associated with Parkinson's disease, as well as the cost associated with the medication in a section of the private health care sector of South Africa.

A quantitative, retrospective drug utilisation review (DUR) study was performed according to data obtained from a medicine claims database, of a South African pharmacy benefit management company (PBM) for four consecutive years (*i.e.* 2005 to 2008).

Of all patients on the total database 0.26% (n = 3 993) were Parkinson's disease patients in 2005 (N = 1 509 621), 0.28% (n = 4 423) in 2006 (N = 1 558 090), 0.34% (n = 4 028) in 2007 (N = 1 178 596) and 0.42% (n = 4 072) in 2008 (N = 974 497). Female Parkinson's disease patients were between 56% and 60% of all Parkinson's disease patients from 2005 to 2008. According to age groups, Parkinson's disease patients had the highest representation in age group five (70 $\geq$ 80 years) and age group six (> 80 years).

In total the number of Parkinson's disease prescriptions claimed through the PMB accounted for 0.3% from 2005 to 2007 and 0.4% in 2008 of all prescriptions claimed on the database. From 2005 (N = R1 819 865 251) to 2008 (N = R1 785 871 013) Parkinson's disease expenditures represented 0.6% (2005, n = R10 459 835; 2006, n = R11 320 616; 2007, n = 11 040 596; 2008, n = 10 697 155) of the total database's prescription expenditure. The female gender and patients of 70 years and older, presented with the highest number of prescriptions claimed and also with the highest costs within the specific age and gender groups.

In 2005 the medicine treatment expenditure for a year's Parkinson's disease treatment was approximately R2 619 $\pm$ R4 179, decreasing with $\pm$ 2% to R2 559 $\pm$ R4 237 in 2006, from

thereon increasing with ± 7% to R2 740 ± R 4 337 in 2007, decreasing again with ± 4% to R 2 627 ± R4 424 in 2008.

Medicine item analyses indicated that dopaminergic medicine items were the most frequently used antiparkinson medicine items from 2005 to 2008. Carbidopa/levodopa containing medicine items were most frequently claimed throughout the study period. The average cost per tablet increased from 2005 to 2008, with the most expensive tablets during the four-year study period indicated as, Tasmar® 100 mg tab and Permax® 1 mg tab. The PDD of all antiparkinson medicine items appeared intact. There were only two medicine items that indicated a PDD, above the maximum daily dosage, namely Permax® 1 mg tablets and Tasmar® 100 mg tablets.

The frequencies of medicine items prescribed in combination decreased rather drastically with an increase of medicine items per prescription throughout the study period. CNS medicine items prescribed together with antiparkinson medicine items per prescription often occurred. The highest frequencies encountered in combination with antiparkinson medicine items were found to include the antidepressants, hypnotics, antipsychotics and anxiolytic medicine items.

A majority of antiparkinson medicine items (53.50%, n = 4 691) had low refill-adherence rates below 90% and were therefore unacceptable. These accounted for 41.62% (n = R16 398 512) of the total cost (N = R39 402 898) of all antiparkinson medicine items included in this study. Only 36.78% (n = 3 225) of antiparkinson medicine items had acceptable refill-adherence rates between 90% and 110%. Those with unacceptably high refill-adherence rates accounted for 9.72% (n = 852) of all antiparkinson medicine items and represented 6.5% (n = R2 574 597) of the total cost.

Conclusion: It can be concluded that even though antiparkinson medicine items are used by only a small percentage of the total patient population in a section of the private health care sector of South Africa, they are expensive and bear implications for the patient as well as medical schemes. Good prescribing patterns were adhered to, with the exception of the poor refill-adherence of antiparkinsons medication items.

Opsomming

Titel: Voorskryfpatrone van medisyne vir Parkinson en ander verwante siektes in die private gesondheidsorgsektor in Suid-Afrika

Sleutelwoorde: Parkinson se siekte, medisyne-items teen parkinsonisme, bewegingsversteurings, farmako-ekonomie, evaluering van medisyneverbruik, hervul-meewerkendheidskoers

Parkinson se siekte is die bewegingsversteuring wat die meeste voorkom en dit het 'n ernstige invloed op mense se lewe. Hierdie chroniese neurologiese versteuring gaan met 'n beduidende sosiale en finansiële las gepaard en het 'n negatiewe uitwerking op die lewensgehalte van pasiënte wat daaraan ly. Die hoofoorsaak van Parkinson se siekte is steeds onbekend, maar die hoofdoel van huidige behandeling is om die pasiënt se lewensgehalte en vermoë om normaal en gemaklik te lewe, te verbeter. Die algemene doelstelling van hierdie studie was om die voorskryfpatrone van medisyne-items vir Parkinson se siekte en ander bewegingsversteurings wat daarmee gepaardgaan, asook die koste daarvan in 'n deel van die private gesondheidsorgsektor in Suid-Afrika te ondersoek.

'n Kwantitatiewe, retrospektiewe studie van die gebruik van medisyne is gedoen op die data van vier opeenvolgende jare (d.i. 2005 tot 2008) in die databasis van medisyne-eise van 'n Suid-Afrikaanse bestuursmaatskappy van farmaseutiese voordele.

Van al die pasiënte in die hele databasis het 0.26% (n = 3 993) van pasiënte in 2005 Parkinson se siekte gehad (N = 1 509 621) met 0.28% (n = 4 423) in 2006 (N = 1 558 090), 0.34% (n = 4 028) in 2007 (N = 1 178 596) en 0.42% (n = 4 072) in 2008 (N = 974 497). Vroulike pasiënte met Parkinson se siekte het van 2005 tot 2008 tussen 56% en 60% van alle pasiënte met Parkinson se siekte uitgemaak. Volgens ouderdom het die grootste aantal pasiënte met Parkinson se siekte in ouderdomsgroep vyf (70 - 80 jaar) en ses (80 jaar) voorgekom.

Die totale aantal voorskrifte vir Parkinson se siekte wat volgens hierdie databasis geëis was, het in die periode van 2005 tot 2007 0.3% en in 2008 0.4% van alle eise in die databasis uitgemaak. Vanaf 2005 (N = R1 819 865 251) tot 2008 (N = R1 785 871 013) het uitgawes aan Parkinson se siekte 0.6% (2005, n = R10 459 835; 2006, n = R11 320 616; 2007, n = R11 040 596; 2008, n = R10 697 155) van die totale uitgawes van die databasis se voorskrifte bedra. Die vroulike geslag en pasiënte van ouer as 70 jaar was verantwoordelik vir die grootste aantal voorskrifte wat geëis is en ook vir die hoogste koste in die spesifieke ouderdoms- en geslagsgroepe.

In 2005 was die uitgawes vir 'n jaar se behandeling van Parkinson se siekte met medisyne ongeveer R2 619 ± R4 179, wat in 2006 met ± 2% na R2 559 ± R4 237 gedaal het, en daarna in 2007 met ± 7% tot R2 740 ± R4 337 gestyg en weer in 2008 met ± 4% tot R2 627 ± R4 424 gedaal het.

Ontleding van die medisyne-items het getoon dat dopaminergiese middels in die periode van 2005 tot 2008 die meeste vir Parkinson se siekte gebruik is. Die meeste eise in die studieperiode was vir medisyne wat karbidopa/levodopa bevat het. Die gemiddelde koste per tablet het van 2005 tot 2008 gestyg en die duurste tablette in die studieperiode van vier jaar was Tasmar® 100 mg en Permax® 1 mg. Dit lyk asof die voorgeskrewe daaglikse dosis (VDD) van alle medisyne vir Parkinson se siekte onveranderd gebly het. Daar was slegs twee medisyne-items met ŉ VDD bo die maksimum daaglikse dosis, naamlik Permax® 1 mg-tablette en Tasmar® 100 mg-tablette.

Die frekwensies van medisyne-items wat tydens die studieperiode in kombinasie voorgeskryf is, het drasties afgeneem soos wat die aantal items per voorskrif toegeneem het. Medisyne vir die SSS is dikwels saam met medisyne vir Parkinson se siekte voorgeskryf. Antidepressante, hipnotika, antipsigotiese en angsiolitiese middels is medisyne wat die meeste in kombinasie met middels vir Parkinson se siekte voorgeskryf is.

Vir die meeste medisyne-items vir Parkinson se siekte (53.50%, n = 4 691) was daar 'n onaanvaarbare hervul-meewerkendheidskoers (onder 90%). Dit het 41.62% (n = R16 398 512) van die totale koste (N = R39 402 898) van alle medisyne vir Parkinson se siekte uitgemaak. Slegs 36.78% (n = 3 225) van medisyne-items vir Parkinson se siekte het ŉ aanvaarbare hervul-meewerkendheidskoers van 90% tot 110% gehad. Dié met onaanvaarbare hervul-meewerkendheidskoers het 9.72% (n = 852) van alle medisyne-items vir Parkinson se siekte en 6.5% (n = R2 574 597) van die totale koste uitgemaak.

Gevolgtrekking: Hoewel medisyne-items vir Parkinson se siekte slegs deur ŉ klein persentasie van die totale pasiëntpopulasie in ‘n deel van die private gesondheidsorgsektor in Suid-Afrika Suid-Afrika gebruik word, is dit duur en het implikasies vir die pasiënt en vir mediese fondse. Met die uitsondering van swak hervul-meewerkendheid van medisyne-items vir Parkinson se siekte is by goeie praktyk vir voorskrifte gehou.

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CHAPTER 1:

Introduction

The purpose of this chapter is to reflect the background and motivation of this study. It will also contain the research questions as well as research objectives, and the methodology followed in this study.

1.1 BACKGROUND AND MOTIVATION FOR THE STUDY

Parkinson's disease is the most recurrent movement disorder (Eggers *et al*., 2009:27) and has a radical effect on the lives of people. Parkinson's disease has a large socio-economic impact as well as a negative brunt on sufferers' quality of life. Parkinson's disease, after Alzheimer's disease, is the second most frequent neurodegenerative disease (Bartels & Leenders, 2008:2).

Characteristic symptoms of Parkinson's disease are known to include extreme trouble in walking normally, an expressionless face, and mutilation in speech (Dodel *et al.,* 1998:300). According to Loenard (2003:319) the clinical condition compromises four main features: bradykinesia, muscular strictness, resting tremors and abnormalities in posture and way of walking. It is a disorder that progresses gradually and results in major disability after a few years (Miyasaki *et al*., 2002:11).

The occurrence of Parkinson's disease affects approximately 1% of the population over the age of 65 (Rodríguez-Molinero *et al.*, 2009:430). In Northern California, a study on the incidence of Parkinson's disease was done on the variation by age, gender and race. For the purpose of this study only the age and gender of the patients will be looked at and not the race. Of the 588 newly identified cases of Parkinson's disease, the adjusted incidence rate by age and gender accounted for 95%, with an escalating frequency over the age of 60 years. Cases diagnosed under the age of 50 years only accounted for 4%. In agreement upon this, Gancher (2010) stated that the prevalence among individuals under the age of 40 years is still an unusual coincidence. According to gender the prevalence of Parkinson's disease is higher in males than in females (Gandey, 2009). Wooten *et al*., (2004:637) conducted a meta-analysis research study determining the incidence between males and females. Results obtained from their study indicated men to be 1.5 more prone to develop Parkinson's disease. In Norway study results showed that men were 1.58 times at higher risk than females, additionally adding that females developed Parkinson's disease at a later

age than males (Alves *et al*., 2009:851). A simple explanation is that female hormones protect women against the development of Parkinson's disease (Gandey, 2009). Fascinatingly the male: female ratio amplifies with age. From this study they also obtained that there is a rapid rise in incidence with an increase in age, especially after the age of 60 years and Parkinson's disease hardly ever occurs before the age of 40 years. The incidence rose after the age of 55 years, with a sharp increase after the age of 60 years (Van Den Eeden *et al.,* 2003:1016, 1022). According to this study it is stated that over 60% of the cases were first diagnosed with Parkinson's disease between the ages of 65 an 79 years, with a small portion of 0.5% diagnosed before the age of 40 years and only 3.4% before the age of 50 years.

Treatment for Parkinson's disease is based on the dopaminergic scarcity. A pharmaceutical pharmacologist came up with the development of levodopa and dopamine agonists. Various medicine items were developed ultimately acting on the dopaminergic mechanisms. These medicine items include dopa-decarboxylase inhibitors, monoamine oxidase inhibitors and catechol-O-methyl transferase inhibitors. Medicine items excluded from working through dopaminergic mechanisms, include anticholinergics and amantadine (World Health Organization, 2006) .

This chronic neurological disorder is accompanied by a significant social and financial burden (Miyasaki *et al*., 2002:11). Apart from this the patients that suffer from this disease, together with their families, indeed are heavily burdened both physically and emotionally. Proper counselling and psychological support contribute to the patients' accepting and facing their future. Appropriate pharmacological treatment will enable the patients to go on with their everyday lives. In considerable time the patients learn to cope with their diagnosis of this chronic disabling disorder and lead a more or less normal life for numerous years (World Health Organization, 2006).

Keränen *et al.* (2003:165) stated that Parkinson's disease has a significant economic burden on the patient. In a study conducted to investigate the financial impact of the disease, a few factors were taken into consideration. Direct costs accounted for 41%, 43% to early retirement due to Parkinson's disease, and informal home care 16%. The direct costs were divided into hospitalisation, medication, formal home care, rehabilitation, other inpatient care and general practitioner (GP) visits. Hospitalisation accounted for 41% of the cost burden, medication 20%, formal home care 14%, rehabilitation 9%, inpatient care 7% and GP visits 9%. Results further obtained showed that 10% of patients with Parkinson's disease were still working full-time, whilst 65% were retired. Parkinson's disease contributed to 46% of early retirement due to their diagnosis. The researchers concluded that there is a significant

correlation between the quality of life and the severity of Parkinson's disease (Keränen *et al.,* 2003:165).

Against this background, it is obvious that research should be carried out regarding the cost implications and utilisation of medical treatment. Above all the prescribing patterns of medicine items used in Parkinson's and other related diseases should be investigated.

1.2 RESEARCH QUESTIONS

The following research questions could be formulated from the problems stated above:

- What does Parkinson's disease entail, and how does it feature in the private health care sector of South Africa?
- How can Parkinson's disease be conceptualised and what are the characteristics of the pharmacological and non-pharmacological treatment thereof?
- Which drug-drug interactions are encountered with the use of Parkinson's medication?
- What is the cost associated with the pharmacological treatment, as well as price differences between innovator and generic products prescribed in Parkinson's disease?
- What is the prevalence as well as the cost associated with additional medicine item therapy other than antiparkinson's medicine items?
- Did the prescribing patterns of medicine items used in Parkinson's disease change from 2005 to 2008 and what was the influence of these changes on medicine cost and prescribing patterns?
- What recommendations can be made regarding the prescribing patterns and costs of medicine items related to Parkinson's disease?

1.3 RESEARCH OBJECTIVES

The research objectives were divided into general and the specific research objectives.

1.3.1 General research objective

The general research objective of this study was to investigate the prescribing patterns of medicine items used in Parkinson's disease and other movement disorders associated with Parkinson's disease, as well as the cost associated with them in a section of the private health care sector in South Africa.

1.3.2 Specific research objectives

The specific research objectives of the study were divided into two sections *i.e.* a literature review and an empirical investigation.

1.3.2.1 Literature review

The specific research objectives of the literature review included the following:

- To conceptualise Parkinson's disease through a literature review in order to form a better understanding of the disease and other movement disorders associated with Parkinson's disease.
- To determine treatment protocols of Parkinson's disease, and reviewing adherence to medicine treatment through previous studies.
- To conceptualise from previous studies what pharmacoeconomics and its specific methods entail.

1.3.2.2 Empirical investigation

The specific research objectives were furthermore divided into the empirical investigation and included the following:

- To analyse the general prescribing patterns of medicine items used in Parkinson's disease and the costs associated, according to demographic factors such as age, gender and prescriber.

- To determine the cost of the different medicine treatment protocols used in Parkinson's disease in order to evaluate prescribing patterns accordingly.
- To determine the comprehensiveness of prescriptions with both antiparkinson and other central nervous system (CNS) medicine items.
- The prescribed daily dosage (PDD) was evaluated accordingly, to determine whether prescribing patterns and treatment protocols were adhered to.
- To determine the refill adherence rates of Parkinson's disease patients.

1.4 RESEARCH METHODS

The research method consisted of a literature phase and the empirical phase.

1.4.1 Literature study phase

The literature study phase of this study contained information on Parkinson's disease and its associated diseases. Another aspect of this phase, focused on the medicines typically used in Parkinson's disease treatment. Furthermore this phase also included a section on the economic impact of Parkinson's disease and pharmacoeconomics as well as a brief overview of a drug utilisation review with special focus on a retrospective drug utilisation review.

1.4.2 Empirical phase

The empirical phase consisted of the data source and study population, the research design followed, descriptive measurements, data analysis, the reliability and validity of the database as well as ethical considerations taken into account.

1.4.2.1 Data source and study population

Data in this study were obtained from a PBM (pharmacy benefit management company) in South Africa. Their goals included to supervise the benefits of different medical schemes to be cost-effective, and to supply reliable solutions and information.

Medicine items were classified according to the MIMS classification system with special reference to section 1.7., the antiparkinson medicine (section 2.7). The antiparkinson treatment was thus divided into its main pharmacological groups, namely

- Dopaminergics;
- Anticholinergics; and
- Others

Referring to the MIMS® classification section 1.7 (Snyman, 2010:42-44) medicine items were analysed according to the National Approved Product Pricing Index (NAPPI) code (Medicover, 2010). This enabled the researcher to distinguish between dosage forms, pack size, strength and manufacturer.

The study population was divided into demographic parameters, namely age, gender and prescribers.

This study's research population consisted of 6 age group divisions starting with the first group being: 0 – 40 years escalating in intervals of 10 year divisions, ending in age group 6 being 80 years and older (section 3.3.2). The researcher decided on these age group divisions, because of the prevalence of Parkinson's disease being more common among the older individual, as a number of studies enlightened in section 1.1.

The gender groups identified in this study were male, female and those that were unidentified. The prescribers consisted of four groups, namely, the general medical practitioners, neurologists, psychiatrists and others.

1.4.2.2 Research design

The main focus of this study was to identify irregularities within the prescribing patterns of medicine items prescribed in Parkinson's disease and other related diseases within a section of the private health care sector of South Africa. In order to accomplish this goal, a retrospective drug utilisation study was implemented. Medicine claims data of a pharmacy benefit management company were used for the study period 1 January 2005 until 31 December 2008 (section 3.2.1).

A retrospective drug utilisation review is a type of method implemented after medication has been administered to a patient (Peterson *et al*., 2007:218-221, Radloff & Jones, 2007:32).

Thus the data were collected after the medication has been administered to the patient. A drug utilisation review assists in detecting, thereafter preventing, inappropriate prescribing patterns (Radloff & Jones, 2007:34).

1.4.2.3 Descriptive measurements

The following descriptive measurements were used and discussed in section 3.4.2.1 of this study:

- Prevalence
- Prescribing patterns
- Cost analysis
- Potential drug-drug interactions on prescriptions
- Prescribed daily dosage
- Refill-adherence rate

1.4.2.4 Data analysis

The data were analysed by employing a specific software programme, Statistical Analysis System® SAS for windows 9.1.3® (SAS institute Inc., 2002-2003). Microsoft (MS) Excel® and Microsoft (MS) Word® were used in order to illustrate results through various graphs and tables throughout this dissertation.

1.4.2.5 Reliability and validity

Data used in this study were obtained from only one South African PBM, and the data were assumed to be valid and reliable.

Attributing to the fact that only one PBM database was used in this study no comparisons of the results obtained from this database could be made according to the cost and prevalence. Only the direct cost per medicine items was used throughout the study. The validation of

results obtained from the data analyses could only be generalised to the specific population and database as external validity limited this study.

1.4.2.6 Ethical considerations

Ethical consent for this study was given by the medicine claims database company, as well as the North-West University (Ethical application number: NWU-0046-08-S5).

1.5 DIVISION OF CHAPTERS

The division of chapters is as follows:

Chapter 1: Introduction

Chapter 2: Literature review

Chapter 3: Research methodology

Chapter 4: Results and discussion

Chapter 5: Conclusions and recommendations

1.6 CHAPTER SUMMARY

In this chapter the background and motivation for this study were given. The research questions, general and specific objectives and the literature study phase and the empirical phase were discussed. The division of chapters also followed. The chapter that follows will entail the literature review concerning the clinical aspects of Parkinson's disease, the treatment of the disease and the economic impact of Parkinson's disease.

CHAPTER 2:

Literature review

Chapter 2 includes the literature review concerning Parkinson's disease, with a brief look at the etiology and physiology and the pharmacological and non-pharmacological treatment thereof. The treatment algorithms for Parkinson's disease will be stipulated and the concept as well as adherence in these patients. A minority of movement disorders will also be discussed in brief, as well as the economic impact that Parkinson's disease has on its patients.

2.1 PARKINSON'S DISEASE

James Parkinson, an English neurologist, described Parkinson's disease in the early 1817s as "shaking palsy" or "paralysis agitans". He referred to shaking palsy as follows:

> *"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured"* (Parkinson, 1817).

Although the cause of the disease is unknown (Bartels & Leenders, 2008:915; Betarbet *et al*., 2000:1301), it can be characterised by the degeneration of neurons on the dopaminergic pathway in the substantia nigra (SN) in the midbrain (Fahn & Sulzer, 2004:139). Apart from the fact that the etiology of the disease is unknown a variety of factors seem to play a role in the development of the disease. Some of these factors are genetic as well as environmental and endotoxin factors (Bartels & Leenders, 2008:915; Calne, 2005:40; Fhan & Sulzer, 2004:139).

2.2 ETIOLOGY OF PARKINSON'S DISEASE

Neurologically the pathways in the brain that are affected by Parkinson's disease have been recognised over the past few years, but evidently the main cause of Parkinson's disease is still unknown. It is feasible to believe that there is a wide range of different causes that can lead to Parkinson's disease. Environmental and genetic factors seem to be the two main features that can result in Parkinson's disease (Tugwell, 2008:12).

2.2.1 Environmental factors

Priyadarshi *et al.* (2001:125) stated that people exposed to various environmental factors, such as living in a rural environment, drinking of well water and the exposure to herbicides or pesticides (Gancher, 2010) can drastically increase the risk of Parkinson's disease. In most cases the exposure to potential neurotoxin in pesticides and herbicides is linked to agricultural living and farming (Petrovitch *et al*., 2002:1787). When Petrovitch *et al*. (2002:1787) assessed men working on a farm in Hawaii exposed to pesticides against those not exposed; there was a considerable increase in the development of Parkinson's disease in those exposed. It is believed that the principal means of pesticide exposure in humans are not only inhalation but also through dermal exposure. Percutaneous inclusion of pesticides differs in every human, seeing that our dermal penetration is all distinctively different (Anon., 2004:168). The environmental assumption that Parkinson's disease is developed from a numerous amount of cell loss in the dopaminergic pathway was theoretically been proved to be linked to an unsafe chemical known as MPTP (Dauer & Przedborski, 2003:892).

MPTP (1-methyl-4-phenyl-1.2.3.6-tetrahydropyridine) is a pyridine, and in structure it is comparable to various farming chemicals (Tugwell, 2008:13). One of these chemicals is the pesticide paraquat, and was used in a study to evaluate the dopaminergic cell deaths, as primary trait in Parkinson's disease diagnosis (McCormack *et al.,* 2002:119). Their findings suggested that paraquat does pose a threat in the in the development of Parkinson's disease, and truly contributes to dopaminergic degeneration. Dick *et al*. (2007:669-670) performed a study on the environmental factors posing a threat on causing Parkinson's disease and also used paraquat dichloride as example in measuring the risk, and came to the same conclusion that the slightest exposure to pesticides might enlarge the risk.

2.2.2 Genetic factors

Through past centuries, genetic studies have grown to higher levels, with new evidence of genetic deficiencies linked to the progress of certain diseases, such as Parkinson's disease (Tugwell, 2008:14-15). Although it is believed that very few cases of Parkinson's disease have a genetic cause, a new concept came to light when a number of genes have been identified as being implicated in this disease (Landsbury & Brice, 2002:653). Some of the identified genes include the following:

- Alpha-nuclein (PARK 1)
- Parkin (parkin)
- Ubiquitin-C-hydrolase-L1 (PARK 5 / UCH-L1)
- DJ – 1 (PARK 7)
- NR4A2

In a study by Periquet *et al*. (2003:1271) the results obtained suggested that almost 15% of cases where patients were diagnosed with Parkinson's disease before the age of 20, the cause was believed to be gene alterations, figures drastically lowering with an increase in age.

2.3 PATHOPHYSIOLOGY

When a closer look is taken at what Parkinson's disease in the human brain entails, it can clearly be stated that various parts of the brain are affected.

Pathophysiological findings expressed two distinct facts regarding this disease:

- The decrease of dopaminergic neurons in the SN is the first concern in the development of Parkinson's disease. The dopaminergic decrease can significantly be seen in the ventral lateral SN. Onset of symptoms usually occurs at a stage where at least 80% of nigrostriatal pathway degeneration had already taken place (Hauser *et al*., 2009). The substantia nigra pars compacta (SNpc) consists of nigrostriatal neurons that venture directly to the putamen. Furthermore these neurons consist of numerous amounts of neuromelanin and other biochemical substances. The

depigmentation of the SNpc can primarily be devoted to these cells (Dauer & Przedborski, 2003:890).

- Secondly the occurrence of Lewy Bodies (LB) (Hauser *et al*., 2009). According to Dauer and Przedborski (2003:890) LB can be defined as "interneuronal proteinacious cytoplamic inclusions" or in the words of Fahn (2003:1) as "cytoplasmic eosinophilic inclusions". Characteristically LB are detected in the SNpc, but it cannot be primarily stated as one of the definite diagnostic features of Parkinson's disease, seeing that it can also be found in various parts of the brain and in other illnesses. In agreement with this statement Burn (2004:177) adds that even though LB is found in a variety of neurological disorders, LB are most frequently related to Parkinson's disease and dementia with LB. Colosimo *et al*. (2003:852-853) also concluded that Parkinson's disease dementia and Lewy body dementia (DLB) cannot firmly be separated from one another. This merely states that the deformities of these two diseases assign them to having similar disease pathophysiologies.

A literature study conducted by Kövari *et al*. (2003:83) confirms that there might be a distinct correlation between the occurrence of cortical LB and dementia in patients with Parkinson's. This study performed in Switzerland consisted of 22 Parkinson's disease patients, and included patients in which Parkinsonism heralded the cognitive degeneration for up to 3 years. This enabled the investigators to distinguish between patients with Parkinson's disease, Alzheimer's disease and LB dementia. Each of the patients' cognitive standings was evaluated according to the clinical dementia rating scale, LB counts and neutrofibrillary tangles. These brain autopsies were done in the Brodmann's areas 9, 21, 24 and 40 and the entorhinal cortex. Respectively to these different areas a distinct relationship was found between the CDR and LB count in the Brodmann's area 24 and the entorhinal cortex. It is also clear to say that the incidence of LB does not always suggest dementia in patients with Parkinson's disease. To conclude, it is safer to say that pathologically classic Parkinson's disease may be impossible to tell apart from cases of reported dementia with LB.

2.4 CLINICAL FEATURES OF PARKINSON'S DISEASE

Parkinson's disease is characterised by the presence of primarily motor symptoms and a variety of non-motor symptoms are also related to this disease (World Health Organization, 2006:140). The four fundamental clinical features that affect the lives of these patients as stipulated by Jankovic (2008:368), Baron (2005:39) and Calne (2005:40) are

- tremor at rest;
- bradykinesia;
- rigidity; and
- postural instability.

The presence of these features, in the absence of any other neurological abnormalities or medicine item induced Parkinsonism, are definite diagnostic principles for Parkinson's disease (Nutt & Wooten, 2005:1026). Together with these four main features there are a few classic non-motor symptoms of Parkinsonism, such as freezing, a bent posture and difficulties in proper speech and swallowing (WHO, 2006:140). In the section to follow the main clinical features linked to Parkinson's disease will be discussed.

2.4.1 Tremor

Deuschl (2008:49) defined tremor as "*a continuous involuntary rhythmical movement sequence of one or several muscles or body segments*".

A tremor at rest is the most familiar symptom of Parkinson's disease which occurs in more or less 70% of patients (Gancher, 2010), and seems to be present throughout rest periods, not always having the tendency to fade away during movement (Duval, 2006:44).

Tremors usually occur at a 4 – 6 Hz frequency, with stress factors and drilled movements of other limbs increasing the amplitude of tremors (Rodriguez-Oroz *et al*., 2009:1129). The tremors' effect is usually maintained as a one-sided effect, but after a number of months or years, the tremor may have an effect on the extremities of the other side of the body (Hauser *et al*., 2009). Tremors commonly affect the hands of the patient (Gancher, 2010), more specifically referring to their fingers, with tremor of the chin, tongue and neck not a distinct phenomenon of Parkinson's disease tremor (Rodriguez-Oroz *et al*., 2009:1129).

Apart from the fact that tremor is the first sign of Parkinson's disease, it is very important to distinguish the difference between essential tremor and parkinsonian tremor. It can be stated that patients with head tremors probably suffer from essential tremors rather than Parkinson's disease. The Table that follows sets apart the various features to distinguish between essential tremor and Parkinson's disease tremor (Jankovic, 2008:370):

Table 2.1 Features separating Parkinson's disease from essential tremor

CHARACTERISTIC	*ESSENTIAL TREMOR*	*PARKINSON'S DISEASE*
Age of commencement	±10-80 years	± 55-75 years
Relatives history	++	+ or -
Tremor regularity (Hz)	5 - 10	4 – 6
Tremor distinctiveness	Flexion – extension	Supination - pronation
Manipulative features:		
Rest	Decline	Amplify
Activity	Amplify	Decline
Intellectual awareness	Amplify	Decline
Writing	Amplify (quivering)	Decline (micrographic)
Walking	Decline	Amplify
Alcohol	Decline	-
Postural tremor	Without latency	Re-emergent
Kinetic tremor	Present	Present or absent
Limb tremor	Symmetric	Asymmetric
Distribution other than limbs	Head, speech	Chin, mouth, jawbone & face
Neuroimigaing-dopaminergic system	Moderate dopaminergic scarcity	Noticeable dopaminergic scarcity
Mid-brain sonography	Moderate hyper-echogenicity	Noticeable hyper-echogenicity
Neuropathology	Moderate cerebellar degeneration, Lewy bodies in substatia nigra, brainstem & cerebellum some cases	Nigrostraital degeneration, Lewy bodies
Treatment	Alcohol, beta-blockers, primidone, topiramate, gabapentin, botulinum toxin, deep brain stimulation	Anticholinergics, amantadine, dopaminergic medicine items, deep brain stimulation

Parkinson's disease patients present with rest tremor as the main characteristic, but additionally postural tremor also occurs. Postural tremor is more well-known and immobilising than rest tremor and may be the first appearance of the disease (Jankovic *et al*., 1999:646). According to Huges *et al*. (1993:140) in a study that was conducted on 100 patients with Parkinson's disease, 69% of these patients had rest tremor at the early stages of their diagnosis, whilst 75% of them had tremor throughout their disease. Asymmetric, quivering onset was ordinary among these patients even though in 23% of the patients no rest tremor occurred (Huges *et al*., 1993:140). A patient's history can often entail much evidence that a little discomfort in executing some activities often precede a trembling hand. In most cases patients endure these signs lacking any complaints. The development of tremor, often leads to patients asking for help, seeing that it gets harder to over look (Tugwell, 2008:7).

2.4.2 Hypokinesia and bradykinesia

Hypokinesia can be defined as decreased movement, whereas bradykinesia can be defined as a decline in naturalness of mobility, whereas akinesia is seen as the lack of controlled

movement (Pugh, 2000:861, 232, 40; Yokochi, 2009:27). Akinesia is divided into principal and secondary akinesia (Yokochi, 2009:27):

- Principal akinesia = Hypokinesia. Even though uncontrolled non-motor movements take place the fundamental motor task is sustained.
- Secondary akinesia = Bradykinesia. Equivalent to rigidity, bradykinesia also takes place as well as weakened skilful motor tasks.

Malfunction in hypokinesia takes place in the limbic striatum/ventral striatum, whereas bradykinesia is a result of malfunction in the SNpc (Yokochi, 2009:29).

Even though bradikinesia's most important scarcity is due to inadequate enrolment of muscle power during the commencement of movement, less significant factors such as muscle limitations, quivering and inflexibility may add to the effect (Berardelli *et al*., 2001:2141). The slowness in performing certain activities, for instance getting dressed, eating, walking and stability impairment, are all consequences of the disease (Gancher, 2010; Montgomery 1995:23). Bradykinesia seems to result first and foremost from the underestimating of movement orders from within, and then the generation of movements follows (Berardelli *et al*., 2001:2141).

2.4.3 Rigidity

Regarding a joint, rigidity refers to a raise in resistance to submissive movement. Resistance to this movement can be even or it can be a cogwheel-type resistance (Gancher, 2010; Hauser *et al*., 2009). The series of movement during a specific activity is regarded as being consistent, and can be evident in the absence or presence of tremor (Samii *et al*., 2004:1784).

In a study conducted by Riley *et al*. (1989:65) in Toronto, Canada they discovered that frozen shoulder occurs in 12.7% of patients with Parkinson's disease. A remarkable observation that had not yet been documented was the fact that frozen shoulder is the general incidence as the presenting feature of Parkinson's disease. Evidently their study also proved that frozen shoulder has the tendency to occur within a few years preceding to the onset of Parkinson's disease symptoms (Riley *et al*., 1989:65).

The occurrence of muscular inflexibility with Parkinson's disease aggravates problems with movement and it escalates to all muscle groups being affected (Tugwell, 2008:6).

2.4.4 Postural instability

This is a symptom that generally arises after the onset of all the additional clinical features (Jankovic, 2008:371) or very late stages of Parkinson's disease (Benatru *et al*., 2008:459). Parkinson's disease patients are burdened with a distinctive bent posture as an outcome of flexed knees and hands. Because of the progressive nature of this disease, postural instability becomes a bothersome feature (Tugwell, 2008:7).

Postural instability suggests unevenness and loss of righting impulses (Hauser *et al*., 2009). The capability to maintain balance during daily tasks for instance sitting, standing and walking around, are severely compromised by this clinical feature. Patients with postural instability are incapable to balance their body's mass correctly and are destined to fall at some stage or another of their disease (Morris *et al*., 2000:205).

Apart from the fact that dopaminergic medicine items have little influence on lessening this symptom, physiotherapy is the desirable way to recover postural reactions (Baron, 2005:42). A patient's quality of life is strongly impaired by the vast possibility of falling, and bearss great risk for the patient. Jöbges *et al.* (2004:1686) concluded their investigation and stated that monotonous training has a great influence on the steadiness and mobility of a patient. Finally, after complying with the physiotherapeutic training, the patient's quality of life was enhanced (Jöbges *et al.*, 2004:1685-1686; Benatru *et al*., 2008:459).

2.5 MOVEMENT DISORDERS

2.5.1 Introduction

A reduction or time-consuming focused movement or an extreme controlled or abnormal uncontrolled movement altering your day to day activities can be described as a movement disorder (Beers, 2006a:1879).

It has come to our attention that movement disorders is one of the most disabling neurological disorders that affects the middle-aged and elderly population. These diseases bestow a burden on the patients affecting their day to day activities. Wenning *et al*., (2005:815) conducted a study on men and women in the semi-urban area of northern Italy. The population consisted of men and women between the age of 50 and 89. A total of 706 patients formed the study population. There were numerous similarities in the gender based groups with a significant increase in the 50 – 59 years age group with a 19% prevalence up

to 51% prevalence in the in the 80 – 89 year group. Combinations of movement disorders were taken into consideration, for example Parkinsonism and restless legs syndrome, Parkinsonism and secondary dystonia/ dyskinesia. A group set apart from the others because of the large incidence rate was the group with Parkinsonism and Parkinson's disease. In this group 5% had a family history of Parkinson's disease. The total of those who received treatment accounted for 20%. The group that presented the second largest incidence were medicine item induced parkinsonism, with almost no reported cases of Lewy body dementia, supranuclear palsy and multiple system atrophy. In this community on which the study was done results obtained suggested that tremor was the most frequent movement disorder, while restless legs syndrome, Parkinsonism, dystonia, tics and chorea followed. Apart from the fact that movement disorders have this degrading effect on people's lives many patients do not receive sufficient treatment. Research also came to the conclusion that a fifth of movement disorders are medicine item induced, and can thus be avoided in future (Wenning *et al.*, 2005: 815-819).

A similar study was done in a nursing home in New York City, with a study population consisting of 397 patients with an average age of 86 years (Tse *et al*., 2008:359). Several types of movement disorders were identified, distinctly pointing out that essential tremor (8.8%), and Parkinsonism (7.1%) have the highest prevalence. Movement disorders such as dystonia (1.3%), myoclonus (0.5%), dyskinesias (0.3%) and medicine item-induced tremor (3%) all accounted for the 21% of the study population being affected by movement disorders.

Against this background knowledge was gathered that even the slightest movement that we make, is a complex process in the brain that also involves all your nerves and muscles. Failure in any of these mechanisms might add up to some sort of movement disorder. Movement disorders can be categorised into a range of different diseases. The categories of this study were based on the classification of the Merck Manual (Eidelberg & Pourfar, 2007):

- Chorea, athetosis and hemiballismus
- Coordination disorders
- Dystonia
- Huntington's disease
- Fragile X-associated tremor/ataxia syndrome
- Multiple system atrophy
- Myclonus
- Progressive supranuclear palsy
- Tics
- Tremor

In the sections to follow a brief overview on each of these movement disorders and its preferred treatment will be given in order to make a correlation between a more general way of treatment and the treatment for Parkinson's disease specifically, which is the main focus of this study.

2.5.2 Chorea, Athetosis and Hemiballismus

2.5.2.1 Chorea

Chorea is a movement that starts in one part of the body or in one limb and can move hastily, impulsively, and often constantly to another part or limb. The type of movement can be described as: recurring, short, jumpy, swift and unintentional (Jankovic, 2009:845).

Against the background of the basal ganglia's susceptibility and its associations to a wide range of pathologies, it is quite difficult to distinguish between the diagnosis of acute and chronic chorea. There are various factors to be taken into consideration that can result in chorea, for instance inherited and metabolic diseases, endocrine disorders, autoimmune disorders, infections, cerebrovascular disease, neoplasm, neurodegenerative diseases, toxins, and trauma (Gilbert, 2009:71). In addition and in conjunction with Gilbert (2009:71), the following Table (Table 2.2) outlines a view causes of chorea as well as an example of a type of chorea as a result thereof (Cardoso *et al*., 2006:592,594):

Table 2.2 Causes and types of chorea

Causes of Chorea	Types of Chorea
Hereditary chorea	*Huntington's disease*
	Ataxia telengiectasia
Structural basla-ganlia lesions	*Multiple sclerosis plagues*
	Vascular chorea in stroke
Parainfectious and autoimmune disorders	*Sydenham's chorea*
	Chorea gravidarum
Transmittable chorea	*HIV encephalopathy*
	Viral encephalitis
Metabolic or deadly encephalopathy	*Hyperthyroidism*
	Hypocalcaemia
Drug-induced chorea	*Dopamine receptor blocking agents*
	Antiparkinsonian medicine items
	Antiepileptic medicine items
	Psychostimulants
	Calcium-channel blockers
	Others e.g. Lithium, Baclofen, Digoxin

It is clear that differentiation between numerous types of chorea is possible, but for the purpose of this study, a detailed review on the entire spectrum of these diseases will not be taken into account.

When chorea is caused by a disease or a medicine item it can be treated by treating the disease or terminating of treatment of the medicine item that caused the chorea. Otherwise dopaminergic medicine items like reserpine and tetrabenazine, that decrease dopamine, will reduce uncharacteristic movement. Antipsychotic medicine items such as fluphenazine, risperidone and haloperidol will also help to block the action of dopamine (Eidelberg & Pourfar, 2007). Carbamazepine also showed effectiveness in the treatment of chorea (Yilmaz, 2006:29).

2.5.2.2 Athetosis

Athetosis is a permanent stream of slow, smooth, writhing instinctive movements. It is said to believe that this is not a disease but a symptom of another disorder. The signs of athetosis are commonly noticeable in the hands and feet of patients, causing jumpy, dance-like actions. In the brain the basal ganglia is responsible for coordinating movements

projected from nerve impulses. If unnecessary motions are detected in this area of the brain it might result in chorea and athetosis. When athetosis and chorea occur together the term choreoathetosis can be used. The treatment for athetosis is similar to that of chorea (Eidelberg & Pourfar, 2007).

2.5.2.3 Hemiballismus

Hemiballismus, a type of chorea is seen as a very uncommon movement disorder and the effects can only be seen unilateral in the extremities, also involving the subthalamic nucleus (STN) (Postuma & Lang, 2003:661). Characteristically when a choreic movement has additional brutal effects, and involves aggressive, hurling unconscious movements it is referred to as ballism (Cardoso *et al*., 2006:589; Jankovic, 2009:845). For this disorder treatment is usually not needed, because of the fact that it will disappear after a few days (Postuma & Lang, 2003:661), at the most it will be present for up to 6-8 weeks. Antipsychotic medicine items will have the needed effect on the patient, restraining the symptoms (Eidelberg & Pourfar, 2007).

2.5.3 Coordination disorders

In this disorder the cerebellum is mainly affected, and leads to the loss in coordination, making a person's day to day activities quite difficult. The most common cause of coordination disorders is believed to be excessive intake of alcohol, ultimately leading to damaging the cerebellum. Another cause is anticonvulsants taken in high doses, but the symptoms can then fade away when the medicine item treatment has been discontinued. Causes that are uncommon are: Hypothyroidism, tumours in the brain and Vit. E (Eidelberg & Pourfar, 2007).

When a person suffers from coordination disorders, other disorders tend to develop. Irregularities that may arise would, *inter alia*, include dysmetria (uncontrolled series of body movements), dysathria (vocal cords and speech are affected, as well as mouth muscles), scrutinising speech (speaking with uncertainty and in one tone), nystagmus (eyes missing an object), tremor (Eidelberg & Pourfar, 2007).

The preferred way to treat coordination disorders is by reducing the cause. For example stopping the excessive intake of alcohol, or decreasing the dosage of anticonvulsant medicine items. When doing so is not possible, alternative treatment should be used, merely treating the symptoms (Eidelberg & Pourfar, 2007).

2.4.5 Friedreich's ataxia

Friedreich's ataxia is a disorder prevalent in both children and adults, associated with cerebellar ataxia, and is known to be a mitochondrial syndrome (Dürr, 2002:370). Neurodegeneration as well as gene alterations are both trademarks of Friedreich's ataxia (Hou & Jankovic, 2003:29). Primarily gene mutations take place when there is meddling with the copying of the specific gene and this then leads to reduced expression of the genes (Grabczyk *et al*., 2001:367). This is also a very progressive disorder, impairing muscle movement, making it difficult to walk properly (Eidelberg & Pourfar, 2007). Regarding the treatment, antioxidant therapy (Dürr, 2002:373) as well as Idebenone, iron-chelating therapies, erythropoietin and histone deacetylase inhibitors (Shultz *et al*., 2009:232) are among the various treatment strategies that are still being tested and improved for the relieve of symptoms.

2.5.5 Dystonia

Dystonia is a movement disorder recognised by whichever mutilation of muscle tendency, and often occurs as a side-effect of certain medication, generally affecting the tongue, neck and head (Meyer, 2006:606). The occurrence of uncharacteristic postures or torsion movements as a result of continuous muscular tightening is a hallmark of dystonia (Cardoso *et al*., 2006:589). Although a disease usually occurs because of a specific reason, many patients are diagnosed with primary dystonia in the absence of a specific cause (Jankovic, 2006:864).

It is possible to distinguish between numerous different types of dystonia with various causes and characteristics (De Carvalho Aguiar & Ozelius, 2002:316). To achieve the purpose of this study, the different types will only be set apart briefly without any further discussion. Through contributions of many researchers (De Carvalho Aguiar & Ozelius, 2002:316; Eidelberg & Pourfar, 2007; Geyer & Bressman, 2006:780-781; Jankovic, 2006:864) the following is a broad classification of different types and causes of dystonia:

⇒ Primary dystonia

⇒ Secondary dystonia:

- Generalised (muscle diminution throughout the whole body).
- Focal (only one body part is affected) e.g.:

        - Eyes (blepharospasm),
        - Neck/head (cervical dystonia).
    - Segmental (two or more neighbouring parts are affected) e.g.:
        - Miege syndrome (eyes and jaw are affected, resulting in jaw grinding and flickering of the eyes),
    - Multifocal (two or more non-contiguous body regions are effected).
    - Hemidystonia (dystonia restricted to a single body region).
    - Heredodegenerative (associated with inheritance).

Regarding the treatment of dystonia Jankovic (2006:870) stipulated the following treatment algorithm (Adapted from Jankovic, 2006:870):

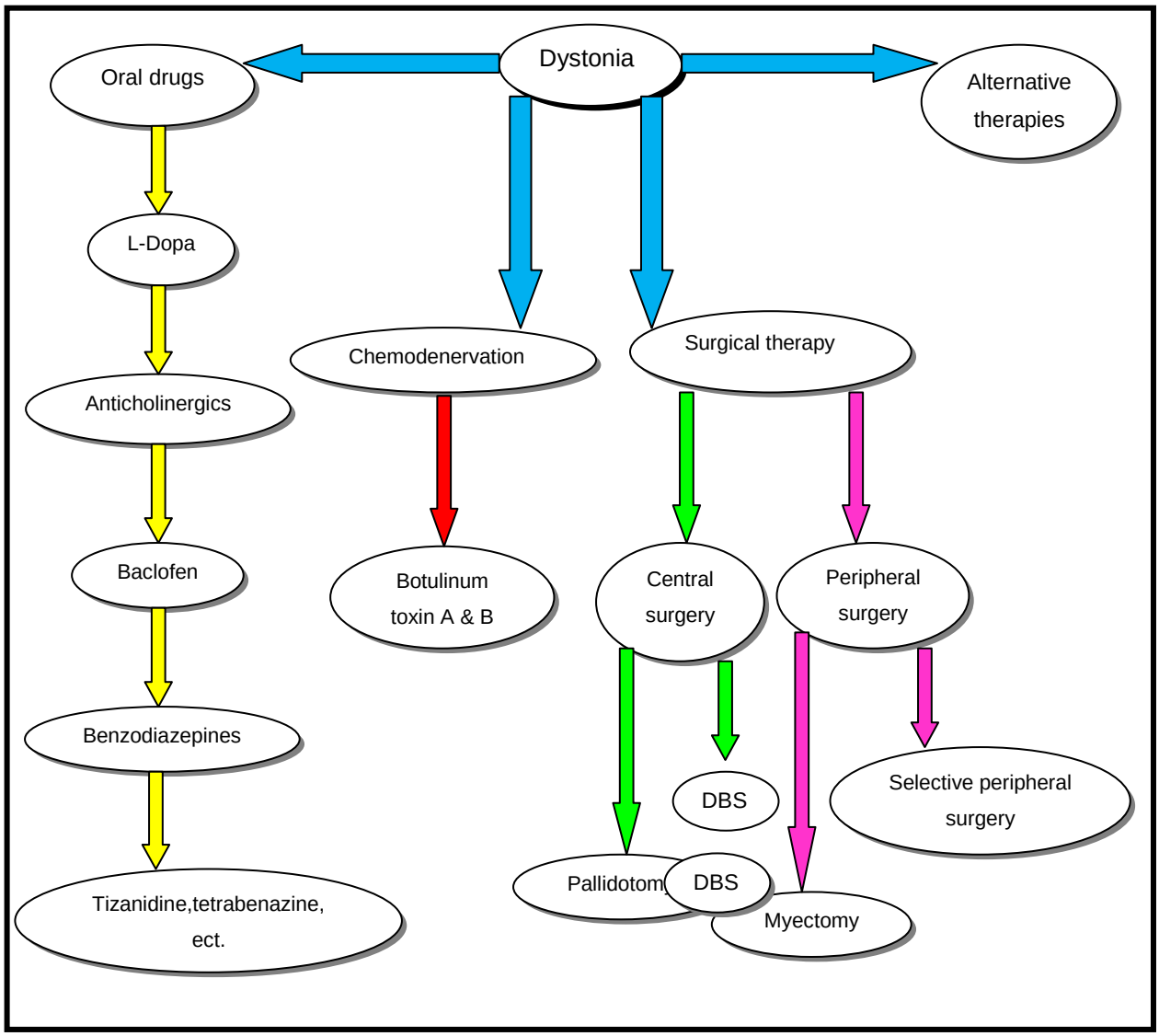

Figure 2.1 Treatment algorithm for dystonia

In conjunction with Jankovic's findings spasms can primarily be prevented or treated by reducing the cause of dystonia. When generalised dystonia is so stern that medicine item treatment, such as anticholinergics, benzodiazepines or baclofen, does not give any alleviation and alternative measures, such as electrode implants in the basal ganglia can be taken into account. Levodopa-carbidopa combination can be given to patients with dopa-responsive dystonia, alongside botulinum toxin injections as a relatively new method in the treatment of dystonia (Eidelberg & Pourfar, 2007). Adams and Jankovic (2007:363) also agree with the different types of medication in the treatment of dystonia.

2.5.6 Fragile X-associated tremor/ataxia syndrome (FXTAS)

This is a very recently acknowledged degenerative disorder, and it is also believed to be a genetic disorder that has great affinity for the FMR1 X-linked gene where mutation ultimately occurs (Loesch *et al*., 2007:245). Quivering, ataxia with walking and white substance irregularities on MRI, are clinical features that escort fragile X-associated tremor/ataxia syndrome (Greco *et al*., 2006:243).

The pattern this disease takes on can be described as rather interesting. In aged men, over the age of 50, at least 1 out of 3000, are affected by fragile X-associated tremor/ataxia syndrome. It is known to us that women have two X chromosomes, and men on the contrary have only one X chromosome and a Y chromosome (Eidelberg & Pourfar, 2007). An extreme mutation on the X-chromosome leads to fragile X syndrome (Grabczyk *et al*., 2001:367; Hou & Jankovic, 2003:59). Men as the primarily affected party, carry the mutation, and may transfer it to their daughters, and not to their sons. Women with the mutation hardly ever show any signs of this disease, and only a small percentage of 5% are being infected. These women tend to pass it on to their sons, who then end up inheriting fragile X syndrome. In this sense it is of utmost importance for women to know whether they are carriers of the mutation, so that counselling and prenatal testing in the case of pregnancy can take its course (Eidelberg & Pourfar, 2007).

Medicine items used in treating Parkinson's disease can be used to relieve the signs and symptoms of FXTAS, seeing that most medicine items for the treatment thereof correspond with other disorders. Although difficult, the main focus of treatment should target gene expression and crossing the blood brain barrier (Hagerman *et al*., 2008:251-262).

2.5.7 Huntington's disease (HD)

Branded by continual progressive chorea and psychological weakening that result in dementia, are the main characteristics by which this degenerative disease is labelled as an unusual irregular inherited condition (Myer, 2006:907; Pugh, 2000:343). Neurologically the targeted areas are the putamen and caudate nucleus, with gene mutations detected on chromosome 4. Patients affected by this disease are usually maturely aged and prognosis is believed to be no longer than 15 years.

The first and most important steps in the treatment of Huntington's disease is making the correct diagnosis according to several clinical tests conducted, thereafter the patient must have a support group consisting of family members present when receiving the news. It is essential for the physician to make this encounter as pleasant as feasible, conquering all the possible questions, mythologies and negativity clinging to the disease (Walker, 2007: 224).

Up to date there is no definite treatment for Huntington's disease, but several attempts in treating the symptoms have somewhat alleviated the burden of the disease. For instance, medicine items such as reserpine and tetrabenazine, act by the mechanism of impairing the dopaminergic neurotransmission through reducing central monoamines, and phenothiazines and butyrophenones, by blocking the dopamine receptor, often lessening the symptoms of chorea. In contrast to this, medicine items such as dopaminergic medicine items seem to aggravate the unwanted symptoms (Aminoff, 2009a:480). Banaie *et al*. (2008:364-366) proposed in their study that further research should be done, on medicine item treatment in the revival of the basal ganglia route lifting the verge of GABA output, with medicine items like gabapentin and diazepam.

2.5.8 Multiple system atrophy (MSA)

Multiple system atrophy is an irregular, degenerative, α-synuclein disorder (Wenning *et al*., 2004:93), recognised by influencing several regions of the central nervous system like the cerebellum, autonomic nervous system and the pyramidal pathways (Beers, 2006a:1768; Stefanova *et al*., 2009:1172). This can lead to loss of synchronisation in movements and internal body procedures ultimately failing, for example bladder control and blood pressure (Eidelberg & Pourfar, 2007), resulting in hypotension, constipation, stiffness, ataxia, postural wavering and dystonia (Beers, 2006a:1768).

The first notable group of symptoms is so-called Parkinsonism (Colosimo & Pezzella, 2002:195). These symptoms are similar to those of Parkinson's disease and other movement disorders, thus difficulty in diagnosis arises (Ghaemi *et al*., 2002:517; Wenning *et al*., 2004:93; Rehman, 2001:382). The difference between a patient with Parkinson's disease and that of a patient with multiple system atrophy, is the fact that they are less likely to experience tremors during periods of rest, this in contrast to Parkinson's disease patients who experience tremor during rest periods. Secondly loss of coordination can also arise. This can be a very embarrassing condition that a patient needs to deal with, seeing that he or she finds it difficult to perform simple tasks. Last but not least, malfunction of internal body processes occur. Different effects on the blood pressure can manifest, constipation is

ordinary in these patients and problems with not urinating normally can arise as well (Eidelberg & Pourfar, 2007).

Reversing the manifestation or the condition, is easier said than done, therefore only momentary symptomatic treatment relating to that of Parkinson's disease is available (Colosimo & Pezzella, 2002:195; Rehman, 2001:382). Levodopa is the medicine item of choice, with proved effectiveness although variability in the diseases is evident. Future prospective therapies relating to neuroprotective strategies are being researched in ongoing clinical trials (Wenning *et al*., 2004:93).

2.5.9 Myoclonus

Myoclonus is a movement disorder originated from dysfunction in the central nervous system when a single muscle or a group of muscles is affected unpredictably and unintentional, leading to swift, shock-like, tiny movements (Lees, 2002:20; Vercueil, 2006:327; Schlaggar & Mink, 2003:40,48).

There are a few things from which myoclonus can result, including *inter alia*, other neurodegenerative disorders (e.g. Alzheimer's disease), brain damage or head injuries, epilepsy, metabolic disorders as well as other medicine item treatment regimens (Caviness & Brown, 2004:598). Various causes and classifications of myoclonus do exist, but appropriate detailed layout is outside the scope of this dissertation. However, differentiation is very important for a correct diagnosis (Schlaggar & Mink, 2003:48)

The treatment concerns the right diagnosis, and correcting the cause wherever possible (Vercueil, 2006:327). Whether myoclonus has an epileptic basis or not, anticonvulsant medication like; clonazepam, carbamazepine, and valproate produces great response to symptoms (Schlaggar & Mink, 2003:48; Beers, 2006). There is a desperate need for medicine item treatment development specifically for myoclonus as a movement disorder, with hereditary factors and patophysiology taken into account (Caviness & Brown, 2004:606), consequently not using medicine item treatment indicated for other diseases.

2.5.10 Progressive supranuclear palsy (PSP)

Characteristically collapsing, fixed eye palsy or the inability to move their eyes, subcortical forgetfulness and Parkinsonism are main traits of the disease (Warren *et al*., 2005:239). This is a very uncommon disease in contrast to Parkinson's disease and affects about 5 out of

100 000 people (Karceski, 2008:71). Progressive supranuclear palsy has various differential diagnoses, because of the overlapping of detected symptoms alike to those of Parkinson's disease and multiple system atrophy (Kimber *et al*., 2000:1422; Rehman, 2000:333). Apart from the basal ganglia being the most affected brain area in most movement disorders, increased focus is now placed upon the thalamus (Halliday *et al*., 2005:2272), as well as the brain stem, responsible for all the critical body functions, is also affected. Kimber *et al*. (2000:1428) stresses cardiovascular autonomic impairment as eliminating criteria for diagnosis in the first stages of the disease, but could refer to another movement disorder like multiple system atrophy. Ondo and his team of researchers (2000:1467-1468) performed a computerised posturography test on patients with early Progressive supranuclear palsy and Parkinson's disease, in order to differentiate between balance impairment in these patients. Their results showed that the patients suffering Progressive supranuclear palsy suffered more severe postural control compared to the Parkinson's disease patients. Therefore, referring to the above statements, it is very important for neurologists to take into account the distinct differences between the disease symptoms throughout various stages of the disease (Sakamoto *et al*., 2010:33) in order to make the correct diagnosis.

The gloomy part of this disease is that no effective treatment for the isolated disease (Rehman, 2000:335) exists. As a result of the different symptoms presented by progressive supranuclear palsy, a combination of medicine is needed to alleviate the symptoms (Karceski, 2008:72). The treatment regimen can therefore consist of medicine items used in Parkinson's disease for example levodopa, as well as medicine items in the treatment of Alzheimer's disease for memory impairment. Other mainstays to contribute to sufficient relief involve physiotherapy that helps restore muscle potency and movement.

2.5.11 Tremor

Tremor can be divided into two categories. Firstly it is a distinct clinical feature of Parkinson's disease, as described earlier in this chapter in section 2.3.1, and secondly it is seen as a movement disorder unaccompanied by critical features as in Parkinson's disease.

A tremor can then be defined as a spontaneous, recurring, trembling movement, created when muscles repetitively contract and loosen up (Eidelberg & Pourfar, 2007).

Differentiating between different types of tremor, by means of a simple classification will clarify diagnostic features of this movement disorder. The classification of tremor can be set apart as follows (Bain, 2007:369; Abdo *et al*., 2010:33 as quoted by Deuchl *et al*.):

Table 2.3 Classification of tremor

Rest tremor	Usually occurs when limbs are relaxed, often seen in the hands, arms or head, and disappears with muscle movement (Pugh, 2000:1867).
Action tremor:	Takes place during deliberate muscular movements (Chen & Swope, 2007:459).
Postural tremor	Visually present when the limbs or trunk are moved after being kept still and in position (Pugh, 2000:1867).
Kinetic tremor	A type of action tremor, for example present when putting a key into a keyhole or writing (Chen & Swope, 2007:459).
Intention tremor	The cerebellum is mainly responsible, and is evident when a specific muscle movement is performed (Pugh, 2000:1867).
Task-specific tremor	A tremor that takes place when a precise task is performed e.g. when writing or speaking (Miles *et al*., 1997:252-254).
Isometric tremor	An action tremor resulting from muscular tightening against an inflexible static entity (Chen & Swope, 2007:459).

There are numerous factors that can contribute to making a tremor more evident, such as exhaustion, tension and nervousness. Several withdrawal symptoms can lead to tremor, e.g. abstaining from alcohol and drugs like opioids. Medicine items like anticonvulsants, corticosteroids, and medicine items used in the treatment of asthma can lead to the same symptoms, as well as the intake of caffeine. Hyperthyroidism may also contribute (Eidelberg & Pourfar, 2007).

Pharmacologic treatment concerning the different types of tremor adds up to the following: propranolol is the first medicine item of choice to use, other medicine item treatment such as gabapentin, zonisamide, promidone and topiramate are all medicine items that show efficiency to some extent, not forgetting surgical intercessions for severe disabilities (Baron, 2005:48; Chen & Swope, 2007;467; Lees *et al*., 2010:251).

2.5.12 Tic disorders and Tourette's syndrome

Fast, typecast, irregular, unexpected movements varying in ruthlessness and easily mimicked are only one way of describing tics (Lees, 2002:18; Schlaggar & Mink, 2003:40). It has been reported to take effect in the facial region, like the head and neck, with characteristic movements like eye twitching, blinking, frowning and head throwing (Gilbert,

2006:692). Tic disorders are the hallmark characteristic for Tourette's syndrome, in addition to other neurological and psychiatric components (Gaze *et al*., 2006:657; Gilbert, 2006:690).

Children between the ages of 7 and 18 years are the most frequently affected by this disease, whereas 5% of these children are affected by tics and roughly 1% are affected with Tourette syndrome (Srour *et al*., 2008:150). The incidence of diseases such as ADHD (attention deficit hyperactivity disorder), OCD (obsessive compulsive disorder), depression, anxiety, behavioural and sleep disorders are all conditions that are frequently encountered upon and in association with tics and Tourette syndrome (Gaze *et al*., 2006:657), thus approximations are exceptionally inconsistent due to this wide range of severity (Srour *et al*., 2008:150).

Although the precise cause of Tourette's syndrome is not known it is believed to have an overload of dopamine leading to the one-sidedness and unconstrained movements (Baym *et al*., 2008:165). Clonidine or guanfacine are medicine items that can be used for the treatment of tics in Tourette's syndrome (Eidelberg & Pourfar, 2007; Gilbert, 2006:697; Srour *et al*., 2008:156). Medicine item treatment for bothersome tics includes clonazepam and diazepam as mild sedative medicine items and can bring relief for some tics. Depending on the severity of the tics antipsychotic medicine items can be very affective, and a specific muscle can be injected with BoNT, and this will lead to paralysis of that muscle, putting a stop to the tics (Eidelberg & Pourfar, 2007). Tic disorders do not always require medication, but when necessary in conjunction with behavioural therapy dopamine modulators, and tetrabenazine are affective (Srour *et al*., 2008:156).

2.6 DISORDERS RELATED TO THE CENTRAL NERVOUS SYSTEM

The section to follow will briefly outline two central nervous system disorders that are commonly found among Parkinson's disease patients. These disorders all contribute to numbing the patient's enthusiasm to life, therefore it could be better to acknowledge it and treat it accordingly.

2.6.1 Sleep disorders

When a person ages it is known to all that with this unstoppable process of life, it may be normal that ageing would be accompanied by several age-related diseases, for example Parkinson's disease. Sleep patterns are also commonly affected by ageing (Pal *et al*.,

1999:1) and occurs frequently among Parkinson's disease patients, negatively affecting their quality of life (Lökk, 2010:96; Jahan *et al*., 2009:538; Dhawan *et al*., 2006:227). Causes other than normal ageing, such as chemical changes in the brain, central nervous system variations and simultaneous disorders and their medicine item therapies can contribute to sleep disorders. With Parkinson's disease being the main focus of this study, it is also known that there are numerous brain implications as well as chemical processes and neuron damaging that may have taken place, and that may contribute to sleep disorders (Pal *et al*., 1999:1).

A few reasons for sleep disturbances in Parkinson's disease were acknowledged (Korczyn, 2006:163-164; Pal *et al*., 1999:7):

- Age-associated sleep alterations in the sense that people of matured age ultimately require a reduced amount of sleep. Parkinson's disease also occurs more or less at retirement age. Less substantial activity is yet another reason for less sleep needed, also due to increased napping during daytime. In this case of such age-related causes sleeplessness should not be mistaken for insomnia.

- Effects of Parkinson's disease:

    - Sleep being affected due to neuronal loss in Parkinson's disease.

    - Interruption of sleep because of motor symptoms of Parkinson's disease.

- Atypical night-time motor activities frequently seen in Parkinson's disease.

- Simultaneous medical and psychiatric circumstances, for example the presence of depression and anxiety.

- Undesirable effects of medicine item therapy:

    - Dopaminomimetic medicine items have the tendency to cause awakening, dramatic dreams or nightmares, jerky movements, disturbance of sleep rhythm.

    - Medicine items leading to insomnia includes caffeine, decongestants, bronchodilators, antihypertensives, theophylline, hormones, anticholinergics, phenytoin and nicotine.

    - Medicine items leading to adjustment in the manner of sleeping antidepressants have the tendency to enhance the stage of motor activities

during sleep, as well as restraining REM sleep, with the latter also connected to anticholinergic medicine items. Antipsychotic medicine items enhance REM sleep while benzodiazepines suppress it, with a further affect of extreme daytime drowsiness.

Oerlemans and his colleague, de Weerd (2002:148), conducted a community-based survey on Parkinson's disease patients and the prevalence of sleep disorders. Main figures from their survey indicated 82% of the patients complained about sleep and being awake during the night, as well as 16% indicated that they experienced sleep initiation as their main concern. Regardless of all the complaints they observed through their questionnaire the overall impression regarding sleeping patterns is believed to be good. They came to an interesting conclusion stating that Parkinson's disease related to sleep disorders can be linked to a precise sleep disorder. These precise sleeping disorders include apnoea, OSAS (obstructive sleep apnoea syndrome) and snoring, and it also had relevance to 12% of the study population. This proves that not only Parkinson's disease can indicate sleeping disorders (Oerlemans & De Weerd, 2002:148).

Pal *et al.* (2004:166-167) conducted a study on 40 Parkinson's disease patients as well as 23 of their caregivers. They all had complaints of disrupted or poor sleeping patterns. After intense evaluation they came to the conclusion that almost 40% of the patients' sleep disorders were before the onset of Parkinson's disease, or during the time of diagnosis. The same percentage was obtained with the intake of dopamimetic medicine items. Another interesting result obtained was that 84% of the patients had been poor sleepers. Other significant statistics that were identified was that 51, 5% of the patients were depressive and 63,1% suffered from anxiety. Apart from the fact that there were no clear associations between the patients suffering from sleep disorders and Parkinson's disease, the severity increased with the intensity of Parkinson's disease and had a magnificent effect on a number of patients with added depression and anxiety (Pal *et al*., 2004:166-167).

Parkinson's disease itself places much tension on the patients, and therefore they forget to mention that they also suffer a type of sleep disorder, because of their motor symptoms being much more severe. The most general cause of the inability to sleep is depression, especially in the elderly patients, and therefore also in Parkinson's disease patients. Antidepressants are very effective in the treatment of depression and also have an added tranquilising affect (Korczyn, 2006:164-165). The key rule is to start with the lowest dose possible (10 mg), and from there onwards to increase the dose gradually. Antidepressants have not yet been fully tested in Parkinson's disease, but are very sufficient and a dose higher than 50 mg is hardly ever needed (Korczyn, 2006:164-165).

Based on these outcomes and general knowledge the assumption were made, that a patient with Parkinson's disease would probably have some indication of deprived sleep, merely because of the fact that sleep disorders are also linked to being an age-related deficit, and not that the sleep disorder is solely because of the Parkinson's disease.

2.6.2 Depression

The next disorder that has a contributing disabling effect on the frame of mind of Parkinson's disease patients in conjunction with sleep disturbances is depression (Suzuki *et al*., 2009:15). General knowledge leads to believing that the cause of the depression in these patients can merely be because of the fact that it decreases the quality of life for these patients and places a heavy emotional burden upon them. Depression in Parkinson's disease is much more ordinary than the credit that it has been given, and thus leads to being ineffectively treated (Chen & Cheng, 2008:179).

The prevalence of patients suffering from depression as well as Parkinson's disease simultaneously accounts for 34%, in a study conducted at an outpatient clinic in Brazil (Stella *et al*., 2008:160). Stella *et al.* (2008:160) showed that patients with a high score on the *Hoehn and Yahr* Parkinson's disease rating scale, revealing the intensity of their Parkinson's disease status, also had the highest rates of depression on its rating scale. Through the various statistics obtained from their study they came to the conclusion that patients with higher scores of depression also had a more severe degree of Parkinson's disease. Depression in itself contributes to a Parkinson's disease patient's constantly feeling unable and later unwilling to perform certain physical tasks, and in some ways even validate the rapid disease progression of the patients (Stella *et al*., 2008:160-162).*(Hoehn and Yahr: a scale developed for Parkinson's disease, that puts the disease into five stages/categories. The first stage/category is the mildest stage of the disease, and stage/category five being the worst).*

Another study conducted on a group of Parkinson's disease patients led the researchers to the observation that 64.9% of the patients suffered from depression. In all statistical analyses it is very important to keep in mind that the outcomes of a study can never be 100% correct. In the case of this study, as in many, the percentage deviation can be allocated to the fact that the patients themselves completed the questionnaires and sometimes they might even exaggerate their clinical and physical state (Suzuki *et al*., 2009:17-18).

Health-related quality of life (HrQol) is a measurement that is used by researchers in order to personalise and indicate the patients' perspective of their illness (Scharg, 2006:155). Depression is also recognised as one of the main factors that indicate reduced HrQoL. Apart

from the fact that depression contributes largely to impaired HrQoL, little is known of its treatment in conjunction with Parkinson's disease (Scharg, 2006:155). Scharg based his treatment outcomes of tricyclic antidepressants, SSRIs and selective norepinephrine reuptake inhibitors as well as antiparkinson's medication for the treatment of depression in Parkinson's disease, on the evidence in accordance with his study, as successful treatment (Scharg, 2006:155). Jones *et al.* (2009:339) also stress the substantial burden of other contributing factors on the HrQol of Parkinson's disease patients, such as depression and stress. Non-motor symptoms and figures such as 9% of Parkinson's disease patients suffering from major depression and 35.7%, who describe their lives as tremendously stressful, will be less significantly when efficiently managed, and in the end a noticeable improvement in HrQoL will be evident (Jones *et al*., 2009:339).

Through these various studies conducted it can clearly be noticed that the occurrence of depression in Parkinson's disease is a given. Therefore it is very important for a Parkinson's disease patient to undergo adequate assessment in order to determine whether depression is present. There are numerous metabolic disorders that can masquerade the signs of depression and because of this proper screening tests are very important (Sawabini & Watts, 2004:40). The foundation for depression treatment is SSRIs and tricyclic antidepressants, and in the case of refractory depression electroconvulsive treatment will be effective, but should be used with caution, regarding the fact that drug-drug interactions can occur (Waters, 2002:19). Adding up to an improved quality of life dopamine agonists as well as an exercise programme, in combination with antidepressants will profit the lives of Parkinson's disease patients with depression (Sawabini & Watts, 2004:40).

2.7 PHARMACOLOGICAL TREATMENT FOR PARKINSON'S DISEASE

2.7.1 Introduction

As mentioned in the first few pages of this chapter it is known that Parkinson's disease is a neurodegenerative disorder and that there is nothing that can be done to stop the degeneration or to reverse the already existing damage.

The main goal of existing treatment for Parkinson's disease is to improve the patient's quality of life and ability to go about as normally and easily as possible. However, there is no guarantee that the treatment will alter the development of the degenerative course of action (Singh *et al*., 2007:29).

2.7.2 Classification of treatment

The MIMS classification system will be used in this study to illustrate the different medication items that can be used to treat Parkinson's disease. The main pharmacological classification will be done from section 1.7. and would indicate the different groups (Snyman, 2010:42-44). The different groups include the following:

1.7.1. Dopaminergics

1.7.2. Anticholinergics

1.7.3. Other

The Tables to follow (Table 2.4 to 2.6) consist of the specific active ingredients and trade names available in South Africa for the treatment of Parkinson's disease (Snyman, 2010:42-44):

Table 2.4 Antiparkinson agent: Dopaminergic medicine items

Active ingredient/s	Trade name available in South Africa
Carbidopa 25 mg / levodopa 100 (250)mg[1,2,3,4]	Carbilev ®
Levodopa 200 mg/ benserazide HCl 50 mg[1,2,3,4]	Madopar ®
Pramipexole dihydrochlor.monohydr. [1, 2, 3, 4]	Pexola ®
Ropinirole [1, 2, 3, 4]	Requip ®
Carbidopa 25 mg / levodopa 250 mg [1, 2, 3, 4]	Sinemet 25/250®
Levodopa 50 mg / carbidopa 12,5 mg / entacapone 200 mg [1, 2, 3, 4]	Stalevo ®
Amantadine HCl [1, 2, 3, 4]	Symmetrel ®
Pergolide mesylate [1]	Permax®
Bromocriptine*	Aspen Bromocriptine®
Bromocriptine mesylate*	Parlodel®

(Snyman, 2006:50-51 [1]; Snyman, 2007:47-48 [2]; Snyman, 2009:41-42[3]; Snyman, 2010:42-44[4])
* Medicine indicated for the treatment of Parkinson's disease, but is not in group 1.7. of the MIMS classification system, but rather section 19.8. (Snyman, 2010:331,334).

The absence of pergolide (Permax®) from the MIMS as of 2007, could be as a result of the FDA withdrawing it from the US market, because of increased reports of Permax® causing serious heart valve damage (FDA, 2007).

Table 2.5 Antiparkinson agent: Anticholinergics

Active ingredient/s	Trade name available in South Africa
Orphenadrine HCl [1, 2, 3, 4]	Disipal ®
Biperidine HCl [1, 2]	Akineton®
Trihexyphenidyl HCl [1]	Artane®

*(Snyman, 2006:51-52 [1]; Snyman, 2007:48-49 [2]; Snyman, 2009:42[3]; Snyman, 2010:42-44[4])

Table 2.6 Antiparkinson agent: Other

Active ingredient/s	Trade name available in South Africa
Entacapone [1, 2, 3, 4]	Comtan ®
Selegiline HCl [1, 2, 3, 4]	Eldepryl® (original) Parkilyne ® (generic)
Tolcapone [1, 2, 3, 4]	Tasmar ®
Rasagiline [3, 4]	Azilect®

*(Snyman, 2006:51-52 [1]; Snyman, 2007:48-49 [2]; Snyman, 2009:42-43[3]; Snyman, 2010:42-44[4])

A brief explanation for using not only the most up to date source of Snymans' MIMS classification system, is because of medicine changing from time to time. Furthermore not only the MIMS consists of the medicine used in the prescribing of Parkinson's disease, thus other out dated versions of this source are also referenced in this chapter onwards in order to cover the broadest spectrum with regard the MIMS in particular. Another reason for using outdated versions is that data from the 2005 to 2008 will be used to evaluate the prescribing patterns of medicine items used in Parkinson's and other movement-related disorders. The methodology of this study will be outlined and discussed in detail in chapter 3.

2.7.3 ANTIPARKINSON AGENTS

Three antiparkinson agent groups are identified for the treatment of Parkinson's disease. This segment of the thesis primarily focuses on the mechanism of action, recommended use, adverse effects of these medicine items as well as their contraindications and interactions. The following illustration (Figure 2.2) shows the various sites of action of the currently prescribed pharmacological medicine items used in the treatment regimen of Parkinson's disease.

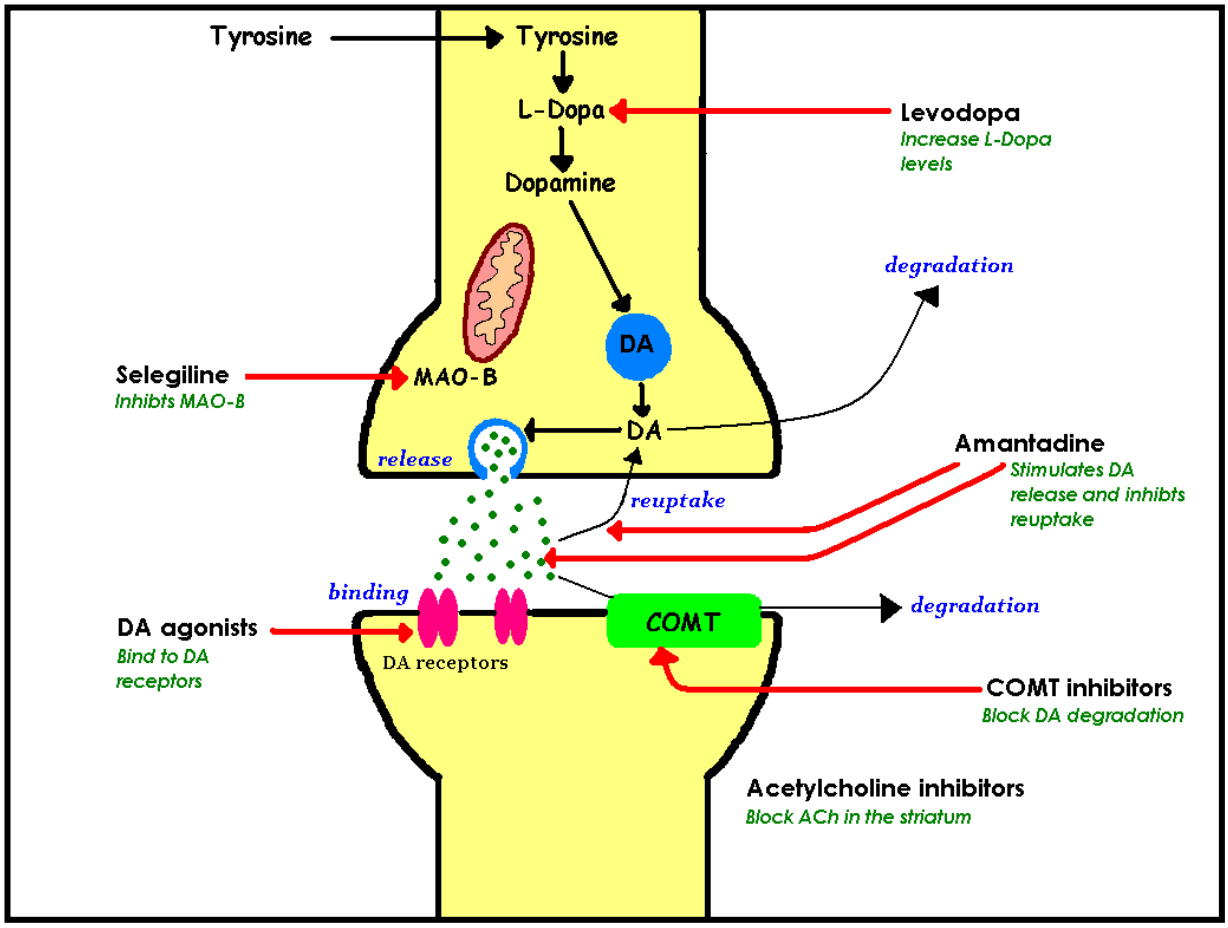

Figure 2.2 Site of action of antiparkinson's medicine item therapy (Adapted from Singh *et al*., 2007:31)

2.7.4 DOPAMINERGICS

2.7.4.1 LEVODOPA

Through many years of research it has been made clear that levodopa is the medicine item of choice for the treatment of Parkinson's disease (Clarke, 2002:23; LeWitt, 2009:31). In particular it shows effective relief for the akinetic symptoms that accompany this disease, but is rather ineffective in situations where there is being referred to Parkinsonism as being medicine item induced (Rossiter, 2010:454).

2.7.4.1.1 Mechanism of action

Levodopa is the most important metabolic antecedent of dopamine. In the metabolism of dopamine, levodopa is decarboxylazed to dopamine ultimately leading to an increased amount of dopamine, thus ideal for the treatment of Parkinson's disease (Eidelberg & Pourfar, 2007). Dopamine, however, cannot cross the blood brain barrier, and therefore, as a single administration, it would be ineffective in the treatment of Parkinson's disease (Aminoff, 2009a:470; Yokochi, 2009:27). According to this levodopa is always administered in combination with either carbidopa or benserazide. Carbidopa and benserazide both acting as aromatic L-amino acid decarboxylase inhibitors, which then enable levodopa to reach the CNS and not end up being decarboxylased in the intestinal mucosa (Beers, 2006a:1883; Clarke, 2002:23).

2.7.4.1.2 Recommended use

Levodopa is always given in combination with carbidopa, the reason set apart in the section above. The preferred way of treatment is to keep the levodopa /carbidopa combination as low as possible, gradually increasing the dose and then adding a dopamine agonist to the treatment regimen (Aminoff, 2009a:471). The preferred way of treatment is to start with an initial dose of 25/100 (250) mg combination (e.g. Carbilev®), set apart as 25 mg carbidopa and 100 (250) mg levodopa, given twice daily (bd) or in some case three times daily (tds) (Baron, 2005:41). Thereafter the dose can be increased gradually (not exceeding 8 tablets a day), with adverse effects taken into consideration (Beers, 2006a:1883; Snyman, 2010:42). With the prolonged use of levodopa it is common to see an "on – off" period where the dose response starts to decline, and therefore it is important for a slowly upwards titrating of levodopa. With patients on chronic levodopa treatment it can be beneficial to take a dopamine agonist or a COMT inhibitor that will prevent these "on – off" periods (Schwinghammer, 2003:556).

2.7.4.1.3 Adverse effects

When large doses of levodopa are taken a few unpleasant side-effects tend to rise to the occasion (Rossiter, 2010:456-457):

- *Gastrointestinal effects*: Nausea and vomiting as well as anorexia are very common side-effects that occur in the absence of a decarboxylase inhibitor in combination with

levodopa. To reduce these side-effects it will help a patient to take the medicine after a meal as well as in divided doses (Aminoff, 2009a:472). This will also lessen gastrointestinal bleeding as well as peptic ulceration that commonly occur (Rossiter, 2010:456).

- *Cardiovascular effects*: This is a side-effect that tends to happen more commonly in people with myocardial ischemia (Rossiter, 2010:457). A range of arrhythmias have been portrayed in patients using levodopa. Tachycardia and ventricular extrasystoles are included among these. As with the gastrointestinal side-effects, the cardiovascular effects are outweighed when given in conjunction with a decarboxylase inhibitor. Postural hypotension fades away with concurrent use, and in some patients hypertension is also evident but to a small extent (Aminoff, 2009a:473; Lennon medicines, 2004).

- *Dyskinesias*: As discussed in-depth in section 2.3.2 of this chapter, can be described as a state of unnecessary and unusual unintentional movements. Dyskinesias can be observed in patients at different stage of their dopamine levels, thus describing it as an effect being dose-related (Eidelberg & Poufar, 2007; Lennon medicines, 2004; Obeso *et al*., 2000:4). If levodopa-induced dyskinesias is visible, simultaneous use of MAO-B and COMT inhibitors with levodopa should immediately be stopped, as well as a reduction in levodopa dose should take effect (Yokochi, 2009:26).

- *Behavioural effects*: Levodapa-induced psychoses is also very common among Parkinson's disease patients. The cause of these mental deficits can simply be because of the fact that higher levels of dopamine are reached in the brain. Typical effects like hallucinations, depression, nightmares, anxiety as well as insomnia have been reported (Aminoff, 2009a:473; Baron, 2005:41; Lennon medicines, 2004). In addition to that, disorders associated with a person's behaviour, include: gambling and hyper sexuality (Obeso *et al*., 2000:4). When these effects are persistent, the dose of levodopa is slowly titrated downwards, with the treatment of motor symptoms closely observed (Yokochi, 2009:26).

- *Miscellaneous adverse effects*: Effects that may also occur may include mydriasis, hemolysis, brownish colouring of secretions (Aminoff, 2009a:473), and urinary infrequencies as well as increased levels of liver enzymes (Rossiter, 2010:457).

2.7.4.1.4 Contraindications

The concurrent use of levodopa is absolutely contraindicated in the following situations and should be carefully monitored e.g. angle-closure glaucoma, psychotic patients, peptic ulcer patients, melanoma, as levodopa is a precursor of skin melanin (Aminoff, 2009a:473; Lennon medicines, 2004), and patients younger than 25 years (Rossiter, 2010:456).

2.7.4.1.5 Interactions

Various types of interactions can be detected when taken into consideration, the various factors that play a role. Interactions in this situation can be divided into medicinal interactions as well as food interactions with levodopa itself.

The Table (refer to Table 2.7) that follows will set apart the drug-drug interactions that occur simultaneously with levodopa, although differentiation between the severities of the interactions will not be given (Turner, 2006:452[1]; Rossiter, 2010:456[2]; Lennon medicines, 2004[3]):

Table 2.7 Drug-drug interactions with levodopa and the implications thereof

Medication interactions	Implications of medicine interactions
Anaesthetics[1, 2,]	Possibility of arrhythmias
Anticholinergics[1]	Reduced levels of L-Dopa, when used in combination
Antihypertensives[1, 2]	Increased effect of hypotension
Bupropion[1]	Amplifies L-Dopa side-effects
MAOI's[1, 2, 3,]	Hypertensive crisis
Papaverine[1]	Reduce response to L-Dopa
Phenothiazines[1, 2, 3,]	Antagonises L-Dopa effect
Phenytoin[1]	Impedes with L-Dopa's therapeutic effects
Tricyclic antidepressants[1]	Can be used. Increased postural hypotension

Levodopa's absorption is the main feature that is compromised by the intake of food (Snyman, 2010:43). The absorption is either delayed or reduced by food. The levodopa concentrations in the blood are reduced by food that consists of high protein content.

It is therefore recommended that levodopa be taken with or after a light meal, the reason being to establish slow absorption and decrease the effects of nausea (Lennon medicines, 2004) and gastric intolerance (Rossiter, 2010:457). Eidelberg and Pourfar (2007) also state that adverse effects could be decreased with or after food, but the importance of protein enriched meals that might reduce the absorption of levodopa is also highlighted.

2.7.4.2 DOPAMINE RECEPTOR AGONISTS

This specific group of medicine items directly works on the different dopamine receptors, and there is no need for any enzymatic conversion to take place in order for them to be effective, as in the case of levodopa (Rossiter, 2010:458). Dopamine agonists tend to have fewer side-effects than levodopa. Certain medicine items work on certain receptors making them a little more specific, but then patient variation must also be taken into consideration, seeing that some respond more aggressively to a certain medicine items than anothers. Dopamine receptor agonists can briefly be divided into two categories:

- *Ergot derivatives*: Bromocriptine and pergolide (Aminoff, 2009a:474) and carbergoline (Rossiter, 2010:458),
- *Non ergot derivatives*: Pramiprexole and ropinirole (Aminoff, 2009a:472).

2.7.4.2.1 Mechanism of action

Bromocriptine and pergolide have the same adverse effect and their actions are more or less the same, but their pharmacological properties are fairly diverse. Bromocriptine has the stronger affinity acting on the D_2 receptors, with limited antagonist effects on the D_1 receptor. On the other hand pergolide acts as a D_1 and D_2 receptor agonist. Both these medicine items have excellent outcomes in the treatment of Parkinson's disease (Standaert & Young, 2009). Parmipexole on the other hand acts as a D_3 receptor agonist (Aminoff, 2009a:474), while ropinirole is more effective as a D_2 and D_3 receptor agonist (Aminoff, 2009a:474) while in Parkinson's disease its effect is seen on stimulation of the D_2 receptor in the caudate-putamen in the brain (GlaxoSmithKline, 2007).

2.7.4.2.2 Recommended use

The safest way to use any medicine item is by starting at the lowest dose possible and from there on increasing the dosage very slowly with great precaution to the adverse effects.

- With pergolide the desired dose to start with is usually 0.05 mg (Beers, 2006a:1884; Standaert & Young, 2009), then reaching a dose of 3 mg within a period of 4 weeks.

- Bromocriptine on the other can have a little more complex dosage, seeing that the daily dose required can differ between 7,5 mg and 30 mg or even 40 mg (Standaert & Young, 2009). Although the recommended dose to start with would be 1.25 mg twice daily (Standaert & Young, 2009), it would be wise to slowly increase the daily dose of the patient over a 2- to 3-month period, in order to minimise the adverse effects (Aminoff, 2009a:474).

- For pramipexole to be sufficient the recommend daily dose varies between 0,5 mg and 1,5 mg three times a day (Baron, 2005:41). Seeing that patients have different responses and sensitivity to pramipexole, 0,125 mg is the starting dose, with an increase of double 0,125 mg every week (Aminoff, 2009a:475). Snyman (2010:42) recommends the first week's dosage to be 0.375 mg per day (Standaert & Young, 2009), 0.75 mg per day for week two and the third week the dosage should be increased to 1.5 mg per day.

- The other non-ergot derivate, ropinirole is started at a dose of 0,25 mg three times daily (Baron, 2005:41), and the end result of its treatment in order to be effective, needs to peak between 2 mg and 8 mg three times daily, increasing the dose gradually. After incrementally increasing the dose, a final dose of 24 mg per day should not be exceeded (GlaxoSmithKline, 2007; Standaert & Young, 2009). It is very important when working with dosage forms to take patient variation into consideration (Aminoff, 2009a:475).

All of these medicine items were known for their status as add-on therapy in Parkinson's disease, but as efficacy has been established they are now also being used as first-line therapy (Rossiter, 2010:458). Dopamine agonists are now being used in initial treatment of Parkinson's disease, because of the benefit of reducing motor complications on the long run (Caraceni & Musicco, 2001:113). Adding to this, in some cases other adverse reactions could occur, consequently the patient should outweigh the benefits.

2.7.4.2.3 Adverse effects

- *Gastrointestinal effects*: Nausea is a very common side-effect when taking dopamine agonists, with lower occurrence of vomiting (Schwinghammer, 2003:559), although anorexia can frequently occur. To a smaller extent it has also been reported in some cases that reflux esophagitis, constipation and bleeding op peptic ulcerations may occur (Aminoff, 2009a:475).

- *Cardiovascular effects*: These side-effects are uncommon with the use of dopamine agonists, but postural hypotension is evident in some cases (Schwinghammer, 2003:559).

- *Dyskineasias*: This type of abnormal movements are documented in some cases, but are believed to be dose dependent and therefore the effects can easily be reversed (Aminoff, 2009a:475).

- *Mental disturbances*: When dopamine agonists and levodopa are used simultaneously the risk for psychiatric disturbances increases (Clarke, 2002:24). Consequently the occurrence of hallucinations, nightmares and delusions are a common phenomenon, with great results when the medicine items are partially withdrawn (Rossiter, 2010:459).

- *Miscellaneous effects*: Signs of sinusitis, rhinitis, oedema, urinary infrequencies, and headaches are a few of the reported side-effects of ergot derivates (Rossiter, 2010:459).

2.7.4.2.4 Contraindications

Special precautions need to be taken into consideration in patients that suffer peripheral vascular disease, myocardial infarction, psychotic illnesses and peptic ulceration (Aminoff, 2009a:475).

Persons showing hypersensitivity to any ingredient should avoid the use thereof (GlaxoSmithKline, 2007; Snyman, 2010:42).

2.7.4.2.5 Interactions

In the following Table reference is made to dopamine agonists' interactions with regard to a few medicine items; pergolide (Permax®) (Eli Lilly and Company, 2003[1]; Turner, 2006:454[2]), pramipexole (Pexola®) (Rossiter, 2010:458[3]; Snyman, 2010:43[7]), ropinirole (Requip®) (GlasoSmithKline, 2007[4]; Rossiter, 2008:459[5]; Snyman, 2010:43[6]) as well as bromocriptine (Aspen bromocriptine® and Parlodel®) (Snyman, 2010:331,334[8]):

Table 2.8 Drug-drug interaction with pergolide, pramipexole, ropinirole and bromocriptine

Medication interactions	Implications of medicine interaction
ACE inhibitors [2] e.g. Lisinopril	Monitor patients for hypotension
Antipsychotics [1, 2, 4, 6]	Pergolide's effect can be antagonised
Dopamine antagonists [1, 2, 3, 4, 6, 7, 8] e.g. Domperidone and Metoclopramide	Antagonises the effect of pergolide, pramipexole and ropinirole
P_{450} Interactions [4, 5, 6] e.g. Theophylline, ciprofloxacin	Interaction with substrates of inhibitors of the enzyme (CYP1A2) responsible for metabolism
Levodopa [3, 4]	Increased C_{max} values of levodopa when administered with pramipexole or ropinirole
Oestrogens [4,5, 6]	Variations in plasma levels can occur
Alcohol[8] and CNS depressants [5, 6, 7]	Additional effect of sedation
Cimetidine [3, 7]	AUC and $T_{½}$ will increase
Erithromycin and macrolide antibiotics[8]	Plasma levels will increase

2.7.4.3 AMANTADINE

Amantadine has shown efficacy in working against the mild symptoms of Parkinson's disease, and although it was only detected by chance, this antiviral agent illustrates promising results (Rossiter, 2010:454; Clarke, 2002:23).

2.7.4.3.1 Mechanism of action

Even though the precise mechanism of action for amantadine is not known, clinicians believe that its promising effect on relieving Parkinson's disease symptoms has something to do with it either manipulating the synthesis, the discharge of dopamine in the striatum (Standaert & Young, 2009) or altering the reuptake mechanism of dopamine, and either way it dramatically increases the dopamine levels (Aminoff, 2009:477). Another theory opposed to the mechanism of action of amantadine related to Parkinson's disease, is the possible anticholinergic characteristics (Endo pharmaceuticals inc., 2009; Standaert & Young, 2009) as well as its ability to block the NMDA glutamate receptor (Endo Pharmaceuticals inc., 2009).

2.7.4.3.2 Recommended use

Amantadine can be used as the first-line therapy in mild Parkinson's disease (Standaert & Young, 2009), and recommended daily dose to start with amantadine treatment is an initial dose of 100mg in the morning, after one week increasing it to 100 mg twice daily never exceeding a dose of 400 mg daily (Baron, 2005:41; Rossiter, 2010:458; Snyman, 2010:44; Endo Pharmaceuticals inc., 2009).

2.7.4.3.3 Adverse effects

A number of side-effects are detected with the use of amantadine, but are divided into commonly, less commonly, and rarely:

- ✓ *Commonly*: Skin discolouration and irritation (Rossiter, 2010:458), nausea, dizziness and sleeplessness (Endo Pharmaceuticals inc., 2009; Rossiter, 2010:458).

- ✓ *Less commonly*: Dry mouth, headaches, gastrointestinal disturbances, psychosis, hallucinations, vivid dreams and anxiety (Aminoff, 2009:477; Clarke, 2002:23; Endo Pharmaceuticals inc., 2009; Rossiter, 2010:458).

- ✓ *Rarely*: Convulsions and postural hypotension (Rossiter, 2010:458; Endo Pharmaceuticals inc., 2009).

2.7.4.3.4 Contraindications

Heart failure and the occurrence of epileptic episodes are the main concerns for patients taking amantadine (Aminoff, 2009:477). Snyman (2010:44) also indicates concern towards patients with hepatic and renal dysfunction. It would be wise for a patient with hypersensitivity towards amantadine to rather avoid or discontinue the use thereof (Endo Pharmaceuticals inc., 2009).

2.7.4.3.5 Interactions

With reference to a specific medicine item Symmetrel® with active ingredient amantadine, medicine item interactions are listed in the Table below (Endo Pharmaceuticals inc., 2009 [1]; Rossiter, 2010:458[2]; Turner, 2006:453-454 [3]):

Table 2.9 Drug-drug interactions associated with amantadine

Medication interactions	Implications of medicine interactions
Central Nervous System (CNS) stimulants[1, 2, 3]	Additional stimulation of the CNS
Co-trimoxazole[3]	Inadequate renal clearance leading to toxic frenzy
Anticholinergic effect [1, 2, 3]	Additional anticholinergic & CNS effects
Quinidine, quinine [1, 3]	Inadequate renal clearance of Amantadine
Sedative antihistamines [3]	Increase CNS effects
Thioridazine [1, 2, 3]	Aggravating tremor in elderly patients
Alcohol [2]	Might increase on CNS

2.7.5 ANTICHOLINERGICS

According to the MIMS classification system (Snyman, 2010:44; Snyman, 2009:41-43; Snyman, 2006:51-52; Snyman, 2007:48-49) the following are all medicine items that can be used as anticholinergic medicine items in the treatment of Parkinson's disease:

- Orphenadrine, biperidine, and trihexyphenidyl,

- Benztropine mesylate, procyclidine, diphenhydramine and ethopropazine (Aminoff, 2009a:477; Brocks, 1999:39).

Anticholinergic medicine items, however, are not favourable for use in elderly patients, because of the adverse effects associated with these medicine items (Beers, 2006b).

2.7.5.1 Mechanism of action

Brocks (1999:39) stipulated the mechanism of action of anticholinergic medicine items to simply being agonists of the muscarinic receptors (Clarke, 2002:23) acting in the neostriatum in the brain (Standaert & Young, 2009). This simple explanation can be attributed to the fact that the real mechanism of action for this specific use of anticholinergic medicine items is yet unknown (Brocks, 1999:39).

2.7.5.2 Recommended use

The preferred daily dose for the specific medication is:

Orphenadrine: 50 – 100 mg, taken in divided doses of three to four times daily as sufficient for the treatment of Parkinson's disease, with a total daily dose not more than 400 mg (Aminoff, 2009a:477; Snyman, 2010:44; Pharmacare limited, 2005).

Biperiden HCl: 1 – 2 mg, taken three to four times daily (Snyman, 2007:48).

Trihexyphenidyl: on day one, 1 mg, thereafter increasing with 2 mg daily within three to five days, that does not exceed a total dose of 6-10 mg a day (Baron, 2005:41; Snyman, 2006:52; Standaert & Young, 2009).

2.7.5.3 Adverse effects

The following are common side-effects stumbled upon with the use of anticholinergic medicine items (Aminoff, 2009b:881; Baron, 2005:41; Clarke, 2002:23; Schwinghammer, 2003:554): dryness of the mouth, disturbed vision, constipation, urinary retention, arrhythmias and mydriasis.

In more severe cases the following have been reported (Schwinghammer, 2003:554): forgetfulness, depression, anxiety, vomiting and sedation (Rossiter, 2010:455).

2.7.5.4 Contraindications

With reference to the following sources the following are contraindicated situations (Aminoff, 2009:881[1]; Beers, 2006b[2]; Pharmacare limited, 2005[3]; Rossiter, 2010:455-456[4]; Schwinghammer, 2003:554[5]):

- Closed angle glaucoma [1, 2, 3, 4] and myasthenia gravis[4]
- Prostatic hyperplasia [1, 2, 3] and dementia[3]
- Gastrointestinal obstructions [1, 4] and urinary infrequencies [4]
- Patients with matured aged are more susceptible to anticholinergic medicine items and it should be used with caution in these cases[1, 5]

2.7.5.5 Interactions

Interactions encountered will presented with reference to three specific individual medicine items; Trihexyphenidyl (Artane®), Biperiden (Akineton®) and Orphenadrine (Disipal®/Norflex®).

Table 2.10, indicates the drug-drug interactions with trihexyphenidyl (Rossiter, 2010:455[1]; Turner, 2006:450[2]):

Table 2.10 Drug-drug interactions encountered with trihexyphenidyl

Medication interactions	Importance of medicine interactions
Antacids[2]	Reduced absorption
Corticosteroids[2]	Probability of worsening intraocular pressure
Anticholinergics[1, 2]	Amplified anticholinergic effects
Ketoconazole[2]	Reduced absorption of Ketoconazole in GIT
Levodopa[1, 2]	Decreased absorption and less effectiveness

The following sources (Snyman, 2007:491; Turner, 2006:452[2]) were used in order to compile Table 2.11, indicating drug-drug interactions with biperidine:

Table 2.11 Drug-drug interactions encountered with biperidine

Medication interactions	Importance of medicine interactions
Anticholinergics[1, 2]: • Antihistamines • Antipsychotics • Quinidine • Phenothiazines • Tricyclic antidepressants	Amplified anticholinergic effects.

To follow is a Table of drug-drug interactions stumbled upon with the use of orphenadrine (Rossiter, 2010:455[1]; Turner, 2006:452[2]):

Table 2.12 Drug-drug interactions encountered with orphenadrine

Medication interactions	Importance of medicine interactions
Chlorpromazine[2]	Hypoglycaemia in a non-diabetic patient
Medicine items with effects similar to anti-cholinergics[1, 2] e.g. Antipsychotics, tricyclic antidepressants, antihistamines and amantadine	Amplified effect of anticholinergic
Propoxyphene[2]	Increased CNS depression
Levodopa[1]	Amplified effect of levodopa

2.7.6 OTHERS

In this category the following subdivisions of medicine items will be focused upon:

- Monoamine oxidase (MAO) inhibitors
- Catechol – O – methyltransferase (COMT) inhibitors.

2.7.6.1 MONOAMINE OXIDASSE INHIBITORS (MAOI)

In this category the medicine item that will be focused on is selegiline, also known as deprenyl. Selegiline is a selective irreversible monoamine oxidase inhibitor B (Aspen Pharmaceuticals, 2007; Schwinghammer, 2003:558). A relatively new MAO-B inhibitor, rasagaline, is successfully used for the early as well as late stages of Parkinson's disease. It is still a mystery whether its properties are solely symptomatic or also neuroprotective (Eidelberg & Pourfar, 2007).

2.7.6.1.1 Mechanism of action

Monoamine oxidase is an enzyme that is characterised for metabolising dopamine. Two types of monoamine oxidase enzymes can be distinguished, i.e. MAO-A and MAO-B. MAO-B dominates brain metabolism of dopamine (Standaert & Young, 2009). Selegiline improves the dopamine action by dynamically blocking the breakdown of dopamine, thus increasing the dopamine levels in the brain ultimately treating the symptoms of Parkinson's disease (Aminoff, 2009a:476). Through this mechanism of action selegiline and rasagiline (Rascol *et al*., 2005:952) extend the ability to reduce the levodopa dosage because of the effect of extending the duration of levodopa action (Schwinghammer, 2003:558).

2.7.6.1.2 Recommended use

The preferred daily dosage for selegiline is 5 mg in the morning, thereafter escalating it to 10 mg if required (Aspen Pharmaceuticals, 2007; Eidelberg & Pourfar, 2007). It is said to be best to initiate therapy in conjunction with levodopa therapy and then slowly to decrease the levodopa dosage, but without discontinuing it (Rossiter, 2010:460). Furthermore selegiline can be given as a single medicine item to initiate therapy, and if used early enough the need for levodopa are postponed considerable (Ives *et al*., 2004:595-596).

Rasagiline can be given in conjunction with levodopa, or as single medicine item treatment at a dose of 1 mg daily (Aminoff, 2009:476; Rascol *et al*., 2005:952; Rossiter, 2010:461).

2.7.6.1.3 Adverse effects

No severe adverse effects are detected with the use of this monoamine oxidase inhibitor B, but the only noticeable effect of selegiline is to aggravate the existing side-effects of levodopa, with special regard to the dyskinesias and psychotic hallucinations (Aspen Pharmaceuticals, 2007; Schwinghammer, 2003:558). Other side-effects that occur frequently, with special reference to selegiline, are nausea, vomiting and a dry mouth (Aspen Pharmaceuticals, 2007).

2.7.6.1.4 Contraindications

The following patients should steer clear of using selegiline:

- Record of peptic ulcers, using serotonin receptor agonists (Aspen Pharmaceuticals, 2007), other movement disorders and mental disturbances (Rossiter, 2010:460).

Rasgaline on the other hand should be avoided in circumstances such as

- Patients using other MAOI or pethidine (Aminoff, 2009a:476), or who suffer from hepatic deficiencies (Rossiter, 2010:460).

2.7.6.1.5 Interactions

Aspen Pharmaceuticals[1] (2007) that manufactured the generic medicine item of Eldepryl®, Parkilyne®, as well as Turner[2] (2006:454) set apart drug-drug interactions with selegiline, as illustrated in Table 2.13.

Table 2.13 Drug-drug interactions with selegiline

Medication interactions	Importance of medicine interactions
Levodopa[2]	Intensifies dyskinesias
Opiate agonist, e.g. pethidine [1, 2]	Hallucinations, agitation and fatal reports with reference to pethidine.
Tricyclic antidepressants, SSRIs[1, 2]	Serotonin syndrome. Discontinue use 2 weeks before starting selegiline treatment.
Sympathomimetic medicine items as well as ephedrine & pseudoephedrine containing medicine items[2]	Hypertensive crisis might occur

Any food product containing tyramine should be avoided (Aspen Pharmaceuticals, 2007), and patients must be warned that a hypertensive crisis can occur when precaution is not taken. Headache, heart palpitations and neck inflexibility are the main warning signs for a hypertensive crisis. The following food contains tyramine and should be avoided (Turner, 2006:483):

- × Biltong
- × Buttermilk
- × Pickled herring
- × Bovril® / Oxo® / Marmite®
- × Chicken liver
- × Red wine
- × Broad bean pods
- × Cheese
- × Yoghurt

2.7.6.2 CATECHOL – O – METHYLTRANSFERASE INHIBITORS

In this group there are two medicine items that will be referred to, namely

- Tolcapone and
- Entacapone.

2.7.6.2.1 Mechanism of action

These medicine items are effective in their treatment of Parkinson's disease, seeing that they prevent levodopa from being completely metabolised to its 3OMD form. Levodopa is metabolised by the enzyme COMT to its metabolite 3-OMD (3-O-methyltransferas) and 3-methoxytyramine, when it reaches this form, its effect is altered, and it starts wearing off (Aminoff, 2009a:476; Novartis, 2000; Standaert & Young, 2009). A COMT inhibitor boosts the quantity of levodopa that crosses the blood brain barrier (Clarke, 2002:26). Because of this it is very effective to use a COMT inhibitor in conjunction with a levodopa / carbidopa combination, in order for its full potential to be reached.

2.7.6.2.2 Recommended use

Tolcapone is ideally used three times a day in a dosage of 100 mg (Aminoff, 2009a:476). In contrast to this entacapone in 200 mg dosage forms (Baron, 2005:41), should be taken up to a maximum dose of 800 mg daily with a maximum range of not more than 1600 mg once daily (Eidelberg & Pourfar, 2007; Novartis, 2000).

2.7.6.2.3 Adverse effects

The following sources reported a variety of adverse effects with the use of a COMT inhibitor:

- Aggravation of levodopa toxicity with regard to dyskinesias, nausea and confusion (Aminoff, 2009:476; Standaert & Young, 2009).
- Abdominal pain and diarrhoea due to hepatotoxicity (Aminoff, 2009b:883; Clarke, 2002:26; Standaert & Young, 2009).
- Sleep disturbances, hallucinations, and orthostatic hypotension (Aminoff, 2009a:476; Novartis, 2000; Standaert & Young, 2009).
- Brownish – orange colouring of secretions (Clarke, 2002:26; Schwinghammer, 2003:558).

2.7.6.2.4 Contraindications

Liver impairment and concurrent use with MAO inhibitors are the only contraindicated circumstances for the use of COMT inhibitors (Novartis, 2000; Snyman, 2010:44), as well as the use of entacapone in children under the age of 18 years.

2.7.6.2.5 Interactions

As set apart in 2.6.6.2, entacapone and tolcapone are the two COMT inhibitors that are referred to in this paper, and Table 2.14 indicates the various drug-drug interactions that occur the most commonly among the use of COMT inhibitors (Novartis[1], 20001; Turner, 2006:456[2]):

Table 2.14 Drug-drug interactions come across with entacapone

Medication interactions	Importance of medicine interactions
Central Nervous System depressants[2]	Increased sedative effects
Medicine items metabolised by COMT[1, 2]; • Apomorphine, • Dobutamine, • Isoprenaline and • Methyldopa	Dosage should be decreased when taken with tolcapone

Table 2.15 Drug-drug interactions come across with tolcapone

Medication interactions	Importance of medicine interactions
Warfarin and other anticoagulants[1]	Plasma concentration of warfarin might increase

2.8 NON-PHARMACOLOGICAL TREATMENT

2.8.1 Introduction

Apart from the traditional and in some cases the first option, medicine item treatment is not always the only option. In the section to follow there will only briefly be looked at the non-

medicine item treatment of Parkinson's disease, seeing that a detailed description hereof has no significance to the current study.

2.8.2 Surgery

In very advanced cases of Parkinson's disease, where medicine item treatment is no longer sufficient, surgery, and deep brain stimulation in particular would seem to be the answer (Aminoff, 2009b:883). Although it is the most recent trend to follow in severe cases there is also much controversy about the type of surgery that can be regarded as the surgery of choice.

The different types of surgery with reference to the National Parkinson's Foundation (2009) include, *inter alia*, the following:

- Pallidal (globus pallidus) stimulation:
  - GPi (Globus pallidus interna stimulation)
  - STN (Subthalamic nucleus stimulation),
- Thalamic (thalamus) stimulation:
  - Vim Deep brain stimulation.

Stover *et al*. (2005:141) also mentioned internal globus pallidus or STN as well as thalamic subnucleas intermedius as the surgery of choice for essential tremor. Deep brain stimulation not only assists in minimising the symptoms of essential tremor in Parkinson's disease, but also the occurrence of rigidity, bradykinesia and gout (Tabbal *et al*., 2008:234).

In comparison the criteria for the different procedures can be set apart as revealed in Table 2.16 (National Guidelines Clearinghouse, 2009):

Table 2.16 Surgical treatment comparisons

Globus pallidus stimulation (STN and GPi)	Thalamic stimulation (Vim DBS)
Motor complications, unmanageable by medicine item treatment.	Primarily rigorous immobilising tremor and STN not performable.
Physically fit	
Levodopa reactive	
Absence of dynamic mental problems	

Krause and colleagues performed a study on a small group of Parkinson's disease patients comparing the benefits of these two types of surgical procedures, STN (Subthalamic nucleus stimulation) and GPi (Globus pallidus interna stimulation). They were of opinion that STN is the preferred procedure because the existence of bothersome symptoms can be eliminated and recoil tremor effects can be restrained (Krause *et al*., 2001:469). Benabid and his team also concluded by referring to STN as the suitable and foremost surgery in highly developed cases of Parkinson's disease (Benabid *et al*., 2000:287). Although various benefits from the GPi procedures were produced, STN dramatically reduced the need for pharmacological treatment, and therefore it might have a promising future with regard to pharmacoeconomics and reducing the financial burden upon the patients (Green *et al*., 2004:833; Krause *et al*., 2001:469).

Although interventions focused on alleviating the disabling symptoms associated with this disease, not a single one treatment goes beyond limitations, thus pointing out that up-and-coming treatment options would always be new and emerging, as Singh *et al*. (2007:29) only pointed out an additional few:

- ✓ Neuroprotective agents:
    - Nicotine
    - Anti-inflammatory agents
    - Melatonin
    - Selenium
    - Iron-chelators
    - Vitamins A, C and E
- ✓ Parkinson's disease vaccine
- ✓ Cell transplantation
- ✓ Gene therapy.

On the other hand, Waters (2002:20) adds that maintaining a protein-restricted diet, physical and psychological therapy and appropriate support groups would help in making the disease bearable.

2.9 TREATMENT ALGORITHMS

This section of the study describes the preferable treatment regimen to be used for the treatment of Parkinson's disease. In order to evaluate the prescribing patterns of physicians on various prescriptions on the database, various treatment algorithms were consulted. An overview from 1999 to 2009 was used in order to make a final conclusion.

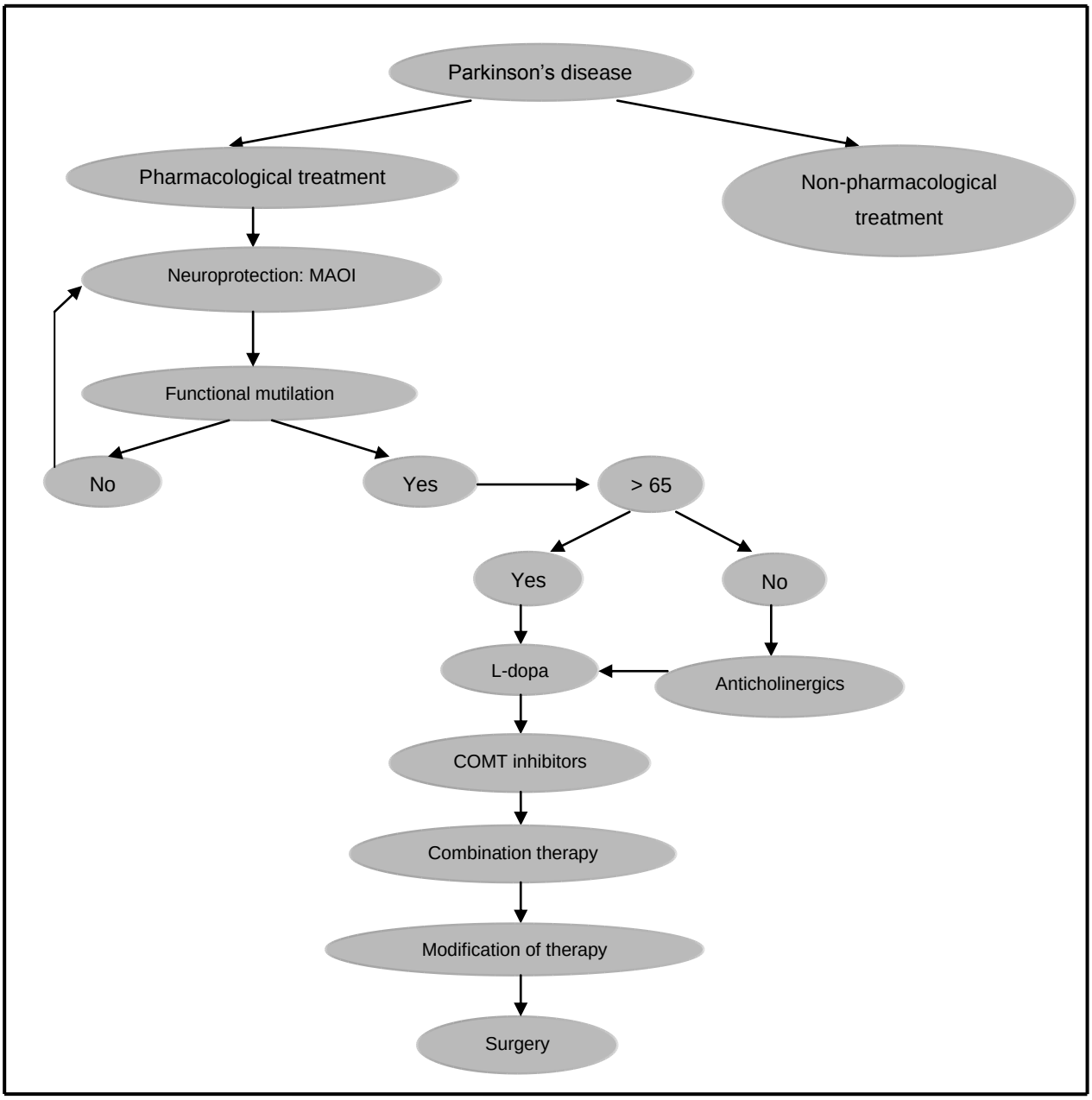

Figure 2.3 Treatment algorithm for the year 1999 (Adapted from Jankovic, 1999:789)

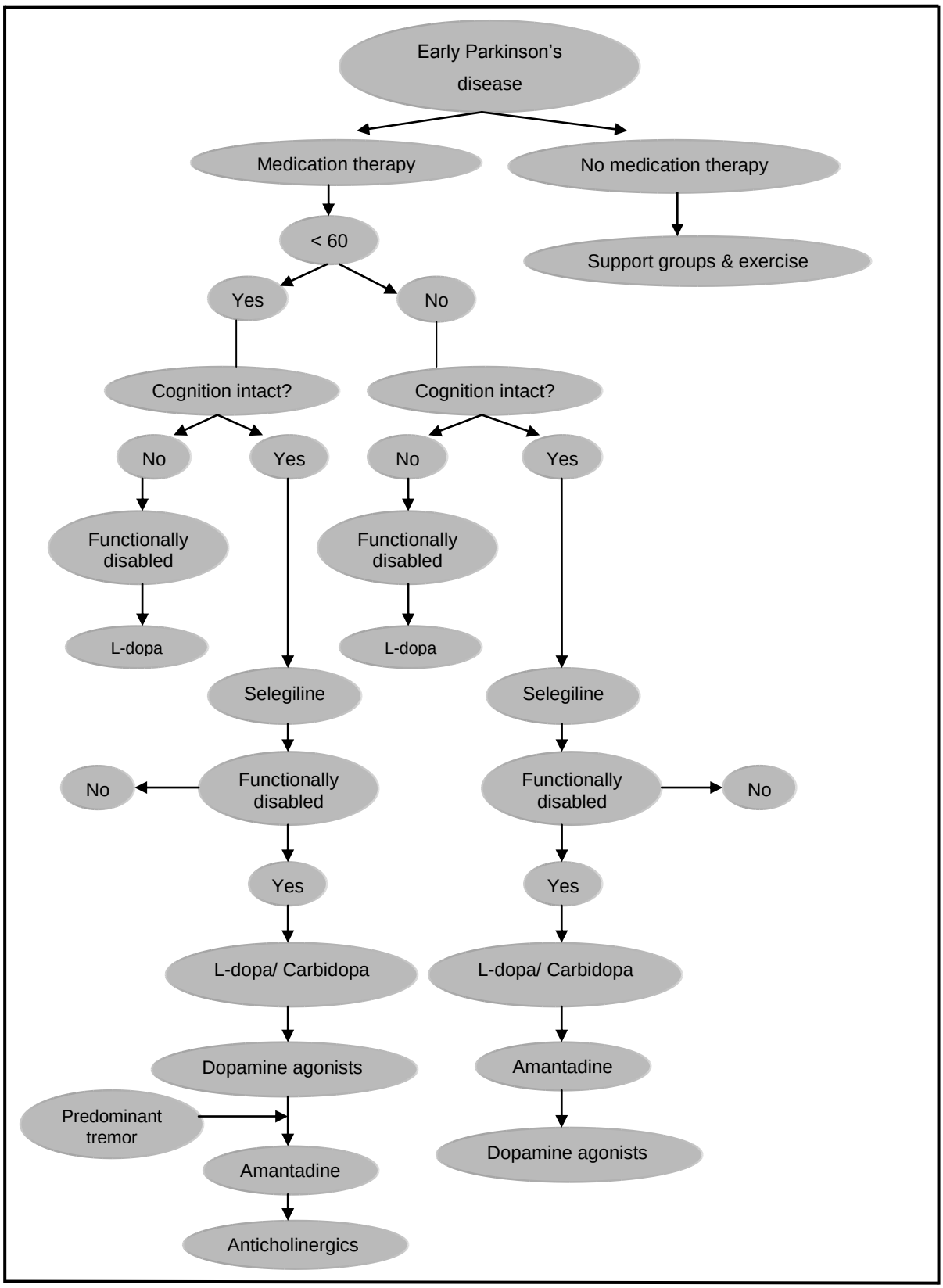

Figure 2.4 Treatment algorithm for the year 2003 (Adapted from Schwinghammer, 2003:553)

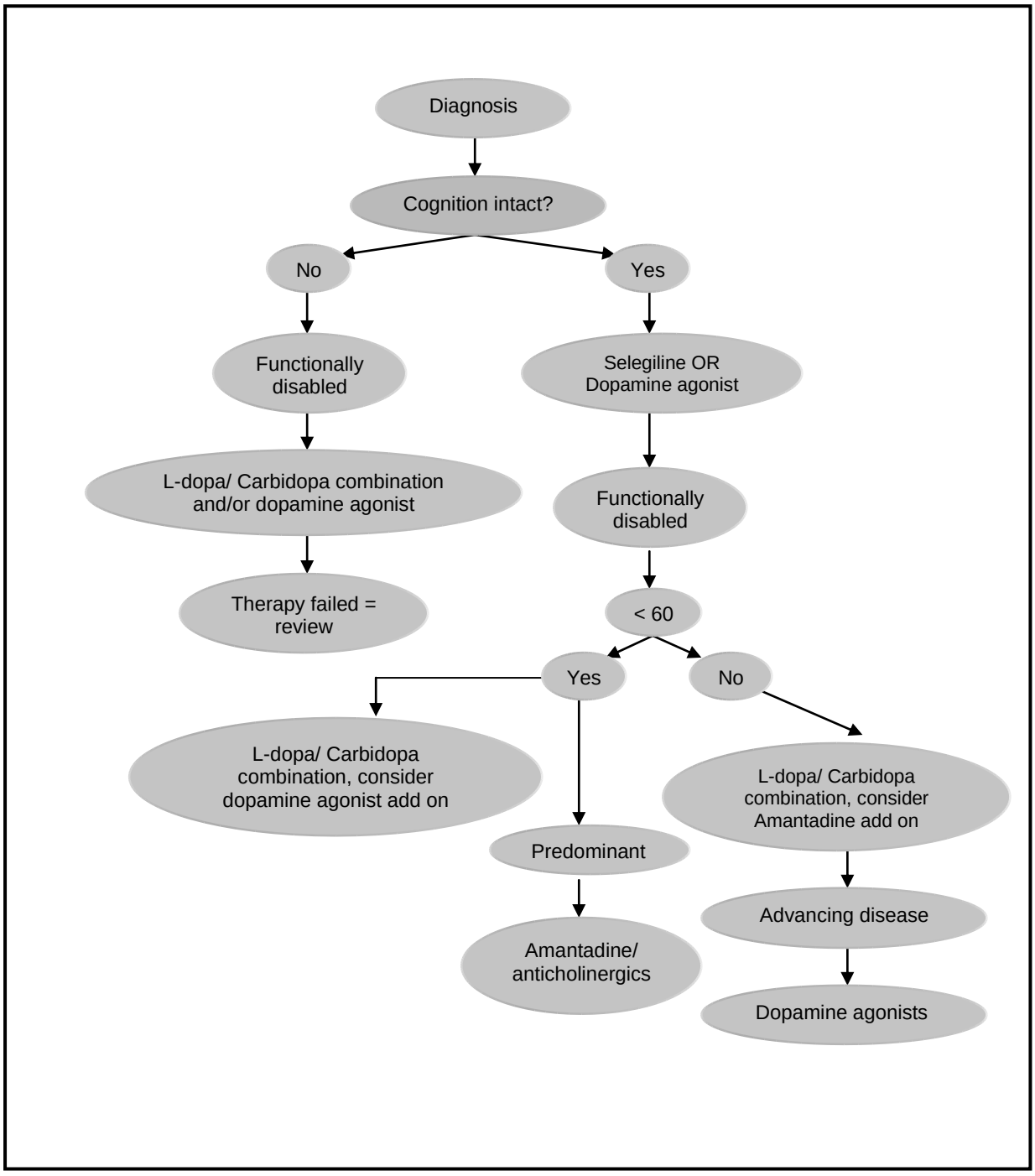

Figure 2.5 Treatment algorithm for the year 2009 (Adapted from Council for Medical Schemes, 2009)

When taken into consideration, it is clear that a very distinct pattern of similarity is present throughout the various illustrations (Figure 2.3 to Figure 2.5). With reference to the databases, as mentioned in chapter 1, data from the year 2005 to 2008 were used. Taken into perspective, after evaluating the treatment algorithms of 2003 and 2009, there seemed to be no diverse differences between these regimens, therefore the 2009 treatment algorithm will be used. In conclusion to this it has been thought best to use the 2009 adaptation of the treatment algorithm for Parkinson's disease, seeing that no significant treatment algorithm was found within the period of 2005 to 2008.

2.10 ADHERENCE IN PARKINSON'S DISEASE PATIENTS

In general adherence can be defined as being obedient to or to follow certain principles or rules (Myer, 2006:43; Pugh, 2000:27) With reference to the medical dictionary a patient's adherence is the degree to which he or she continues to take his or her medication according to the pre-arranged schedule under restricted control or custody, even when confronted with contradictory burdens (Pugh, 2000:27).

Poor obedience to treatment schedules adds up to aggravation of the disease leading to death and amplified health care costs (Osterberg & Blaschke, 2005:494). The sub-optimal use of medicine in Parkinson's disease largely contributes to clinical consequences (Grosset, 2010:118). With Parkinson's disease being a neurodegenerative disorder, emphasis is placed on the importance of taking the medication as prescribed by a health care professional, in order to optimise the outcomes by lessening the symptoms, seeing that nothing can be done to undo the degeneration that has already taken place (Faulkner, 2009).

This kept in mind, Grosset and his colleagues (2006:250) proved that most Parkinson's disease patients do try their best at keeping to medication schedules. General or basic methods of measuring adherence were identified (Grosset, 2010:115). In Table 2.17, Osterberg and Blaschke (2005:489) stipulated 2 methods in order to measure adherence in patients taking chronic medication:

Table 2.17 Methods in measuring adherence in patients

Indirect methods	Direct methods
× Questionnaires and self-reports × Pill counts × Refill rates of prescriptions × Clinical response assessment × Electronic medication monitors × Physiologic markers × Diaries of patients	× Directly observed therapy × Measurement of medicine levels in the blood × Measurement of biologic markers in the blood

In agreement with this, Grosset *et al.* (2006:250) also distinguished between two techniques used in order to measure the adherence rates in Parkinson's disease patients. The first method that was used was manual tablet counts, and secondly electronic monitoring of tablet counts was done. With regard to the first method, a 97% adherence rate was obtained and 96% with electronic devices. Patients reporting missed doses accounted for 57% and those that took extra doses 23% (Grosset *et al*., 2006:250).

Although adherence does not project to be a major concern for Parkinson's disease patients, it is very important for pharmacists together with health care professionals and caregivers to promote adherence and the importance thereof (Osterberg & Blaschke, 2005:494), seeing that noncompliance goes about fairly unrecognised these days (Huges *et al*., 2001:1195).

A few easy steps are stipulated in order to promote adherence:

- ✓ Strongly advise the use of pill boxes (Faulkner, 2009; Osterberg & Blaschke, 2005:494).
- ✓ Design a medicine item treatment calendar (Faulkner, 2009; Osterberg & Blaschke, 2005:494).
- ✓ Alarms can be set in order to remind a patient to take the medicine items (Faulkner, 2009).
- ✓ Direct a patient towards support groups (Faulkner, 2009).
- ✓ Imply specific lifestyle adjustments to help manage certain side-effects (Faulkner, 2009).
- ✓ Create a mechanical system that will notify or remind a patient of refills, and when the refills are ready (Faulkner, 2009).

Finally it can be concluded that the treatment of Parkinson's disease adds up to more than merely the treatment of visual symptoms. It is very important to maintain a good communicative relationship between the patient, the caregiver and other health care

professionals in order to obtain the best results with minimum adherence difficulties (Buetow *et al*., 2009:5; Faulkner, 2009).

2.11 ECONOMIC IMPACT OF PARKINSON'S DISEASE

As mentioned in chapter 1 the social and financial burden upon a Parkinson's disease patient has a great effect and impact on his or her quality of life (Keränen *et al.,* 2003:165; Miyasaki *et al*., 2002:11). Although a great proportion of chronic patients rely on private health care insurance and the government's contributions for their medicine item treatment costs, a substantial amount is still to be paid by the purchasers themselves. According to these costs of all health care expenditures for instance pharmaceuticals and related services would have to be reviewed and reduced to the minimum, seeing that not only the government and insurance parties are affected, but most certainly the patients as well (Bootman *et al*., 2005:1).

Cost and expenses of a disease like Parkinson's disease are not only associated with medicine item treatment but also hospitalisation costs, care givers, inpatient care, general practitioners' visits and rehabilitation. Parkinson's disease disables the individual patient to such an extent that early retirement is forced upon him or her, therefore increasing the financial burden, as well as the impact that it has on insurance parties and society (Findley, 2007:8).

Schenkman (2001:44-45) and his research team performed a 3-year investigation in the USA on the burdens of Parkinson's disease on patients, focusing on financial and physical burdens. Their study consisted of 70 patients who were requested to classify their overall health status as "excellent, very good, good, fair or poor". The average age for the study population was 71,2 years, with 5,6 years from their first diagnosis, and largely consisting of educated male patients. Figure 2.6, illustrates the first year of research data with a definite incline in cost from a good to poor health prospective. As a result of the degenerative and disabling effect of this disease it can be concluded that the financial implications of Parkinson's disease only escalate with a progression in time and disease deterioration.

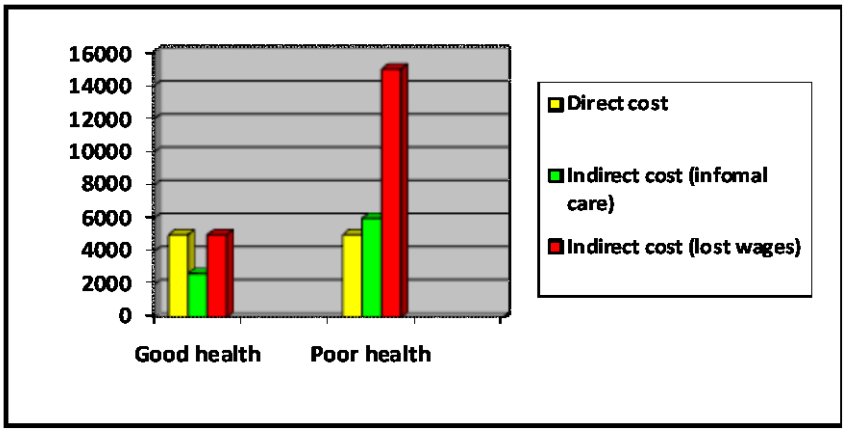

Figure 2.6 Direct and indirect cost associated with health status

Knowing the financial burden and quality of life impairments that Parkinson's disease contributes to a patient's health, the World Health Organization (WHO, 2006) took a more in-depth look at the burden that Neurological disorders have globally. The study of WHO followed the approach of the Global Burden of Diseases (GBD) and Parkinson's disease, among other diseases, has been grouped under the broad term of Neurological diseases within the neuropsychiatric category. The umbrella term of globally can be set apart including the following nations: Africa, Americas, South-East Asia, Europe, Eastern Mediterranean and Western Pacific. The outcomes of the global burden of diseases were measured in terms of DALYs (disability-adjusted life years) and YLDs (years of healthy life lost as a result of disability). Not only were assessments made, but projections on the future also took up a great proportion of this study. Results obtained significantly showed an increase in DALYs from 1 617 000 in 2005, 1 762 000 in 2015 and 2 015 000 in 2030, merely supporting facts that Parkinson's disease has a disabling effect on a patient. In contrast the YDLs decrease in future projections from 17.7/100 000 population in 2005 to 17.3/100 000 population in 2015 and 17.1/100000 population in 2030 (WHO, 2006).

These statistics on the global burden that neurological diseases have cannot but appears frightening for future health, unless instant steps are taken to improve this health issue. It is also evident that the financial burden is much larger in lower income countries, even more so escalating in underprivileged populations. This in itself poses a threat for South African individuals with Parkinson's disease, whose disease only progresses with time, adding to the financial load of caregivers, medicine item treatment and hospitalisation costs (WHO, 2006).

2.11.1 Pharmacoeconomics applicable to Parkinson's disease

Pharmacoeconomics is a relatively new concept that started during the early 1970s and with great expectations it promises to improve health care worldwide with optimum use of finances and services (Bootman & Harrison, 1997:178).

In addition to this agreement with Cantor's statement can be reached. He pointed out that although limitations in health care resources exist, the importance of new interventions should be analysed from the financial aspect and burden it places upon individuals. In the decades passed, there has been significant increase in pharmacoeconomic research (Cantor, 2002:28). Crawford and Evans stated that most of the studies that have been conducted had focused purely on the analysis or the design of data. Most of the evaluations were done with regard to medicine item cost or one mechanism in comparison with other medicine items (Evans & Crawford, 2000:545).

According to Reeder (1995:5) the act of finding equilibrium between the cost of a certain outcome and the pharmaceutical services applied can be classified as pharmacoeconomics. In addition the concept of pharmacoeconomics can solely be based on the medical reimbursements and financial costs with reference to the recognition, extent and assessment of pharmaceutical goods and services (Cantor, 2002:29).

Therefore pharmacoeconomics can be seen as the instrument in achieving the best outcomes in medicine item therapy with the least expensive services in the most cost-effective manner (Bootman & Harrison, 1997:178).

Pharmacoeconomic research can further be divided into different methods of research and consists of cost-minimisation analysis, cost-benefit analysis, cost-of-illness analysis, cost-utility analysis, cost-effectiveness analysis, as well as quality of life evaluations and assessment studies (Bootman & Harrison, 1997:178). For the purpose of this study only the four main methods (Walley *et al*., 2004:12) will shortly be discussed with relevant examples if possible.

2.11.2 Pharmacoeconomics

Pharmacoeconomic methods (as mentioned in section 2.11.1) are briefly discussed in this section with applicable examples where possible.

Foreign exchange rates as in the section to follow was done based on rates supplied by South African travel on 8 April 2010 (South African travel, 2010).

2.11.2.1 Cost-effectiveness analysis (CEA)

Bootman *et al*. (2005:8) stated that a CEA assists in choosing the best possibility after a sequence of options have been carefully revised through logical and numerical events. A CEA can only be applied to health issues where the contributions are measurable in terms of cost and the produced effects evident in life years gained (Bootman *et al*., 2005:8).

A CEA was done in Japan in order to establish whether dopamine agonists, as additional treatment in Parkinson's disease, are cost-effective (Shimbo *et al*., 2001:875-884). The analysis took place using the Hoehn-Yahr (HY) model for Parkinson's disease for the stages 2 to 5. When dopamine agonists were used in conjunction with levodopa the incremental cost-effectiveness, during HY stage 2, estimated to ¥18 610 000 (R1 488 800) and ¥19 320 000 (R1 545 600)/QALY. During HY stage 3 the levodopa therapy with added dopamine agonists produced outcomes that were more effective with reduced expenses. The total cost can be divided into the cost per medicine item, hospitalisation cost and cost needed for care. During the HY stage 2 levodopa treatment accounted for ¥10 650 (R825), levodopa and bromocriptine calculated to ¥12 140 (R971.20) and ¥13 220 (R1 057.60) for treatment with levodopa and pergolide. By comparing these statistics with HY stage 3, the following results were documented: levodopa treatment alone = ¥20 340 (R1 627.20), levodopa and bromocriptine treatment = ¥19 900 (R1 592) and levodopa and pergolide treatment = ¥19 760 (R1 580.80). In conclusion Shimbo *et al*. (2001:875-844) noted that levodopa treatment in conjunction with bromocriptine and pergolide are only more cost-effective in the HY stage 3 than levodopa treatment alone, with the opposite being true for HY stage 2.

A similar study conducted in the United States also proved that it would be more cost-effective and would increase the QALYs when adding etacapone to standard Parkinson's disease treatment (Palmer *et al*., 2002:617). Pramipexole also proved to be more cost-effective, but only when used over a time period longer than 2 years, compared to levodopa treatment (Noyes *et al*., 2004:472; Noyes *et al*., 2005:1258).

2.11.2.2 Cost-utility analysis (CUA)

The number of life years and the value of life years gained define the measurement according to which to conduct a CUA evaluation of various intercessions. A CUA is more or less equivalent to a CEA (Vogenberg, 2001:70), but can be set apart from a CEA because of the fact that the patients' view contributes an additional facet to this type of analysis (Bootman *et al*., 2005:8-9).

In Finland Hudry *et al*. (2006:652,653-655) used rasagiline and entacapone in Parkinson's disease patients to evaluate standard treatment with levodopa to perform a cost-utility analysis. This study performed by them took place over a period of 2 years with the following as measurement tools: "25% or less off-time/day", "greater than 25% off-time/day" and "dead". The efficacy was measured in terms of "quality-adjusted life years (QALYs) and months with 25% or less off-time/day". They obtained the following results:

Table 2.18 Results comparing rasagiline and entacapone costs in a cost-utility analysis

Medicine compared in the study	QALYs/months	25% or less off-time days	Cost savings per patient treated*	ICER#
Rasagiline	0.13 / 5.2	> 55%	€930 (R9 011.70)	€17 800 (R172 482)
Entacapone	0.12 / 5.1	55%	€830 (R8 042.70)	€18 600 (R180 234)

* The amount saved compared to levodopa treatment

Incremental cost-effectiveness ratio (Struwig, 2008:51): this ratio evaluates additional cost required to gain additional benefits.

Hudry *et al*. (2006:651,653-655) came to the conclusion that rasagiline treatment works as the most effective option compared to standard treatment in terms of the total cost spent on treatment.

2.11.2.3 Cost-benefit analysis (CBA)

CBA aims at distinguishing between the benefits of a treatment strategy and the economic cost associated with the treatment (McCloskey, 2001:148; Vogenberg, 2001:69). For a CBA to be compiled successfully, it is necessary for the same conversion to monetary terms to take place in all applicable aspects of a disease treatment as a whole (Bootman *et al*., 2005:7; Walley, 2004:13-14). Although difficulties are sometimes experienced when

conversions to monetary terms take place (Bootman *et al*., 2005:7), CBA is of importance in comparing existing services (McCloskey, 2001:149).

Yianni *et al*. (2005:155-161) constructed a cost-utility analysis simultaneously with a cos-benefit analysis in the UK in order to evaluate the cost and benefit of treatment with deep brain stimulation to those not receiving deep brain stimulation in patients with dystonia (a movement disorder discussed in section 2.5.4). The measurement units of the benefit of treatment were quality-adjusted life-years (QALYs) and the effectiveness of the treatment was measured through the willingness to pay (WTP). The study results suggested a 0.94 QALYs gained with deep brain stimulation treatment over patients not receiving this type of treatment, and an incremental cost per QALYs gained of 33 980 UK pound sterling (R375 479). This suggests that deep brain stimulation is cost-effective in dystonia patients, to whom medicine treatment is not sufficient.

2.11.2.4 Cost-minimisation analysis (CMA)

A CMA is the most basic methodology that can be performed, and the specific intercessions can only be evaluated in terms of costs with the assumption that the results between two or more alternatives are equal in effect (Bootman *et al*., 2005:7; McCloskey, 2001:141). Every cost-analysis has its limitations. This type of analysis produces much more, purely because of the equal units of measurement that are required (Walley *et al*., 2004:12), therefore limiting the quantity of studies that could be done through a cost-minimisation analysis. Examples of cost-minimisation analysis, done on Parkinson's disease medicine items are consequently also limited (Rascati, 2009:36). Furthermore it was not possible to conduct a cost-minimisation analysis within this study.

The most ordinary example would be to evaluate two or more generic comparable medicine items. These generic medicine items should be FDA (Food and Drug Administration) approved, which would indicate that the generic compounds are counterpart to the original medicine item, indicating identical dosages, chemical compounding as well as pharmaceutical characteristics. This suggests that the only difference in the generic products would be the cost, therefore being the only measurable component of the medicine item therapy (Rascati, 2009:36).

2.12 CHAPTER SUMMARY

In this chapter the clinical aspects of Parkinson's disease with respect to the etiology, pathophysiology and the clinical features of the disease, as well as various movement disorders were discussed. Disorders related to the central nervous system, in particular sleep disorders and depression, were also briefly discussed.

Furthermore the pharmacological treatment of Parkinson's disease was discussed with special reference to the three main pharmacological classification groups according to the MIMS classification system i.e. the dopaminergics, anticholinergics and others. Each individual medicine was discussed with the focus on the mechanism of action, recommended use, adverse effects, contraindications and drug-drug interactions. Non-pharmacological treatment, i.e. surgery, was also acknowledged. The treatment algorithms for Parkinson's disease were briefly outlined, as well as the concept of adherence in these patients.

Aspects of the economic impact of Parkinson's disease were discussed through the concept of pharmacoeconomics and a few types of pharmacoeconomic analyses were explained.

These discussions have provided answers to the research questions applicable up to this point in the investigation of this study.

CHAPTER 3:

Research methodology

In this chapter the empirical investigation will be set apart, consisting of the following concepts: the general and specific objectives, research design, the research methodology and the data analysis

3.1 RESEARCH OBJECTIVES

The research objectives can further be divided into general and specific research objectives. Only the specific objectives that relate to the empirical investigation will be discussed in this chapter.

3.1.1 General research objectives

The general research objective of this study was to review and analyse the prescribing patterns of medicine items used in Parkinson's disease and movement disorders associated with Parkinson's disease, as well as the cost associated with their usage in a section of the private health care sector of South Africa.

3.1.2 Specific research objectives

The specific research objectives were divided into a literature review and an empirical study. The specific research objectives of the literature review were taken care of in chapter 2, and the empirical study will follow briefly. The specific research objectives of the empirical study included the following:

- To analyse the general prescribing patterns of medicine items used in Parkinson's disease and the costs associated, according to demographic factors such as age, gender and prescriber.
- To determine the cost of the different medicine treatment protocols used in Parkinson's disease in order to evaluate prescribing patterns accordingly.

- To determine the comprehensiveness of prescriptions with both antiparkinson and other central nervous system (CNS) medicine items.
- The prescribed daily dosage (PDD) was evaluated accordingly, to determine whether prescribing patterns and treatment protocols were being adhered to.
- To determine the refill adherence rates of Parkinson's disease patients.

3.2 RESEARCH DESIGN

The main focus of the research was to identify the prescribing patterns of medicine items used in Parkinson's disease and other related diseases in the private health care sector of South Africa. In order to meet these expectations a retrospective drug utilisation review was done, seeing that data (refer to section 3.2.1) used in the study were collected after patients had received their medication.

3.2.1 Drug utilisation review (DUR)

Health care systems worldwide are all highlighting the fact that finding equilibrium between the value and cost of care is an acknowledged problem, as well as the proper use of medicine (Peterson 2007:215). A drug utilisation review is only one technique that can be used in assessing medicine use.

Drug utilisation review was defined by the WHO (2003:8) in 1997 as "*the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences*".

Perez (2001) defined DUR as being a programme that evaluates and identifies data on medicine use alongside precise and probable standards and in order to produce specific outcomes, curative strategies are implemented where needed.

Wettermark *et al*. (2008:160) described DUR as having an investigative as well as an evocative component, with regard to the understanding and assessing of prescriptions, dispensing and medicine use thereof, with appropriate interventions beforehand to improve the quality of care.

DUR is needed because it helps to improve the quality of care, protect economic interest of all applicable parties, as well as keep the integrity of the programme intact by helping

patients to the correct and rational in their use of medicine. It also guides prescribers towards responsible prescribing (Perez, 2001; Weber, 1999; WHO, 2003). Randloff and Jones (2007:32) emphasise the use of DUR in PBM companies, to encourage medicine use that is harmless, successful and suitable.

DUR can be classified in three different categories: Prospective DUR, concurrent DUR and retrospective DUR. The following definitions were compiled from Peterson *et al*. (2007:218-221; Radloff & Jones, 2007:32):

- *Prospective DUR*: This type of review takes place before a patient receives the medication.

- *Concurrent DUR*: This type of review takes effect in intervening while the patient is receiving the medication.

For the purpose of this study only a retrospective DUR study was discussed, because the data that were received from the database, only contained data of the medicines already dispensed to a patient. Consequently an appropriately detailed description of prospective and concurrent DUR studies was beyond the scope of this study.

- *Retrospective DUR*: This type of review takes effect after the medication has been administered to the patient.

Retrospective drug utilisation review is a type of study that suggests that data are collected after events have occurred, thus suggesting that after a patient has received his/her medication the analysis of the prescription will take place (Perez, 2001; Strom, 1994:698; Webber, 1999). Through this the extent to which a patient adheres to his/her medicinal instructions is measured, i.e. patient usage patterns (Radloff & Jones, 2007:34).
A retrospective DUR is helpful in detecting, thereafter preventing, inappropriate prescribing patterns, as well as adverse effects and the misuse of medicine (Radloff & Jones, 2007:34; Webber, 1999). Lyles *et al*. (2001:78) also pointed out the following areas that a retrospective DUR will enlighten:

- ✓ Identifying use of costly medicine

- ✓ Comparing specific medicine item classes used by specific services of suppliers

- ✓ Monitoring adherence to refill prescriptions (Radloff & Jones, 2007:34)

With this kept in mind as aspiring objectives a retrospective drug utilisation review was done in order to evaluate the prescribing patterns of medicine items used in Parkinson's disease

and other medicine items prescribed for related movement disorder, as well as the usage patterns of patients with emphasis on their refill adherence rates.

3.3 RESEARCH METHODOLOGY

3.3.1 Data source

The data used in this study were obtained from a medicine claims database of a pharmacy benefit management company, for the period of four years from 1 January 2005 to 31 December 2008. The specific company is a PBM company that holds itself responsible for assuring cost-effective management of benefits of their medical schemes, to provide medicine solutions that are consistent, to supply appropriate assurance and capacity of performance and provide consistent information.

3.3.2 Study population

The study population was selected according to all the prescriptions analysed on the PMB database (as mentioned in section 3.3.1). All the prescriptions that contained medicine items classified under the MIMS classification 1.7 of antiparkinson's medicine items (as mentioned in section 2.7.2) were selected for the analysis. This ensured the researcher that no prescriptions could be excluded from the analysis.

The following Table (Table 3.1) consists of the total number of prescriptions and patients on the database in comparison to all the prescriptions and patients associated with antiparkinson's medication for the four-year period selected (as mentioned in section 3.3.1).

Table 3.1 Total prescriptions on database in contrast to antiparkinson's prescriptions

		2005	2006	2007	2008
Total database	Prescriptions	8 391 836	8 906 348	7 911 096	6 775 873
	Patients	1 509 621	1 558 090	1 178 596	974 497
	Medicine items	19 500 774	21 113 422	19 075 724	16 439 253
Antiparkinson's medication	Prescriptions	25 011	27 324	25 513	24 404
	Patients	3 993	4 423	4 028	4 072
	Medicine items	30 950	33 768	31 455	30 040

3.4 DATA ANALYSIS

The data were analysed by employing a specific software programme, Statistical Analysis System® SAS for windows 9.1.3® (SAS institute Inc., 2002-2003). Microsoft (MS) Excel® and Microsoft (MS) Word® were used in order to illustrate results through various graphs and tables throughout this dissertation.

3.4.1 Classification system

The classification system of this study was divided into the medication used to treat the disease as well as demographic parameters.

3.4.1.1 Medication classification system

To compile this study the MIMS® (Monthly Index of Medical Specialties) classification system (as mentioned in section 2.7.2) was used to identify the specific medication. The MIMS® divides the antiparkinson treatment into three main pharmacological groups, namely

- → Dopaminergics;
- → Anticolinergics; and
- → "Other".

Referring to the MIMS classification section 1.7, medication was then analysed according to the National Approved Product Pricing Index (NAPPI) code, which enables researchers to distinguish between dosage forms, pack size, strength and manufacturer.

3.4.1.2 Demographic parameters classification system

Different classification systems according to demographic parameters were used during this study, which will be discussed subsequently.

3.4.1.2.1 Gender

Controversy exists in setting apart the terms sex and gender, and therefore the WHO indicated that an individual's sex is the physiological and biological features that define a man and a woman; whereas gender designates socially assembled activities and roles that humanity considers suitable for a man and a woman (WHO, 2010).

To differentiate between gender on a prescription, in order to indicate prevalence differences, gender and sex were seen as synonyms.

The prescribing patterns of Parkinson's disease were evaluated according to gender, because of the statement made (see section 1.1) that males are more drastically affected than females.

3.4.1.2.2 Age

Age is commonly referred to as the period of time that has passed since birth (Pugh, 2000:34). The date of birth that was indicated on the prescriptions dispensed was used in order to determine the age of the patients on the last day of the specific year of the study.

The researcher divided the age distribution across the database into six specific groups (see section 3.3.2). Age as a measuring tool was also chosen because of certain age groups being more drastically affected, as well as different treatment protocols followed for different age groups (see section 1.1. and 2.9). These aspects served as motivation for the division into different age groups.

For the purpose of the study data from the medicine claims database were divided into the following age groups:

Table 3.2 Age group divisions throughout the study

AGE GROUP	CRITERIA
Age group 1	0 ≥40 years
Age group 2	40 ≥ 50 years
Age group 3	50 ≥ 60 years
Age group 4	60 ≥ 70 years
Age group 5	70 ≥ 80 years
Age group 6	80 > years

In chapter 1 (section 1.1) the age groups 4 to 6 would be expected the groups most commonly affected by Parkinson's disease, and as indicated in chapter 2 (section 2.9) different treatment protocols are followed for patients of groups 1 to 3 and groups 4 to 6. Evaluations will take place accordingly.

3.4.1.2.3 Prescriber

Parkinson's disease and other movement disorders are of neurological origin and therefore the specialist in this field is a neurologist. General practitioners and neurologist are equally entitled to prescribing antiparkinson's agents. In some cases a psychiatrist is also indicated to have prescribed antiparkinson's agents. In this study the prescribers were divided into four groups *i.e.* GP (General practitioner), N (neurologist), P (psychiatrist) and O (other). The term "other" indicates any other specialist or party that prescribed these medicines. This study will evaluate the prescriptions with active ingredients indicated for the use of Parkinson's disease (section 2.7.3) and related movement disorders, with reference to the specific prescribers, as indicated on the database in order to

- ⇒ evaluate medicine items prescribed by the four different entities; and
- ⇒ evaluate whether the treatment protocols were followed.

3.4.2 Descriptive measures and statistical analysis

The descriptive measures and statistical analysis are discussed in the following section.

3.4.2.1 Descriptive measures

The following were elements identified against which the quality assessment and prescriptions were compared:

3.4.2.1.1 Prevalence

Myer (2006:1523) defined prevalence as being the total of all the new as well as old cases of an illness or incidence of an event, reported in a particular period. As mentioned in chapter 1 the incidence of Parkinson's disease among the elderly patients, over the age of 60 years

is of great significance and therefore prevalence was used as a measuring instrument in the data analysis to determine the following:

- ✓ The prevalence of antiparkinson's medicine on the database for the years 2005 to 2008, including such to demographic parameters as age, gender and prescriber.
- ✓ The prevalence of central nervous system medicines prescribed together with antiparkinson's medicine (as differentiated in section 2.6).
- ✓ The prevalence of drug-drug interactions between antiparkinson's medicine and co-administered CNS medicine items.
- ✓ The prevalence of the usage of different combinations of antiparkinson's medicine (evaluating against treatment algorithm as described in section 2.9).

3.4.2.1.2 Prescribing patterns

All of the prescriptions on the database that were identified with antiparkinson's medicine items were analysed according to the prescribing patterns with regard to the following aspects:

- × Medicine prescribed (section 2.7.3).
- × Evaluating whether treatment protocols were followed (referring to section 2.9).
- × Other CNS medicines prescribed with antiparkinson's medicine items (referring to section 2.6).
- × Prescribed daily dosage of the antiparkinson's medicine items (section 3.4.2.1.8).
- × Refill adherence rates of individual antiparkinson's medicine items according to the trade name (section 3.4.2.1.9).

3.4.2.1.3 Cost analysis

In this study the costs were determined from the database in order to evaluate the results in Rand values for the specific items associated with Parkinson's disease. The cost was calculated for the following purposes:

- Total cost of all the medicine items on the database.
- Total cost of all the antiparkinson's medicine on the database.
- Total cost per tablet per medicine item.
- Total cost per prescription.
- Total cost per treatment protocol.
- Total cost of the medical aid vs. cost contribution of the patient.

3.4.2.1.4 Potential drug-drug interactions on prescriptions

All the potential drug-drug interactions were compiled throughout the literature review of the pharmacological treatment of Parkinson's disease (see section 2.7.3). Each individual active ingredient was discussed and part of this brief discussion consisted of a Table of potential drug-drug interactions. The Tables were compiled according to various references that are appropriately indicated within each Table. See Tables 2.7 to 2.15 for drug-drug interactions with active ingredients linked to the treatment of Parkinson's disease. In brief, the tables consisted only of the active ingredients available in South Africa and the importance of the interaction to the patient as well as prescriber.

3.4.2.1.5 Prescribed daily dosage (PDD)

The typically prescribed dose of a particular ingredient on a sample of a prescription is seen as the prescribed daily dosage (WHO, 2003:39). The reason for using the prescribed daily dosage in this study and not the defined daily dosage, is that the dosage on a prescription can fluctuate according to the specific illness treated (Parkinson's disease or another movement disorder), the severity thereof, as well as patient individuality that differs (WHO, 2003:39).

The prescribed daily dosages were evaluated according to

- treatment algorithms (see section 2.9); and
- registered daily dosages, according to active ingredients or specific medicine product (see section 2.7 and section 4.5, Table 4.51).

3.4.2.1.6 Refill-adherence rate

The measure to which a patient's medicinal and physical condition's counselling corresponds with his/her actions is defined by Haynes (as quoted by Hess *et al*., 2006:1280) as adherence. Using the data provided by the database as set apart in section 3.3.1 and calculating the refill-adherence in accordance, assisted the researcher in evaluating the extent to which Parkinson's disease patients were adherent to their medication regimens, in recognition of limitations at hand (Hess *et al*., 2006:1285).

Calculations of refill-adherence rates of an individual trade name in the project will take place according to the following equation, as adapted from Ren *et al*. (2002:50):

$$AR = \frac{(Total\ days\ of\ antiparkinson's\ items\ supplied - days\ supplied\ at\ the\ last\ refill)}{(last\ dispensing\ date - first\ dispensing\ date)}$$

Osterberg and Blaschke (2005:487) evaluated several clinical trials and stated that no satisfactory value can be awarded to being compliant, seeing that some regard greater than 80% as compliant and others regard serious diseases' compliance to be greater than 95%. The researcher of this study will accept 100% as the standard of adherence to medicine, seeing that the disease has a great disabling affect on the patient (see section 1.1 and 2.7) and being less that 100% compliant to treatment regimens will only aggravate the disease symptoms.

Non-adherence further contributes to treatment regimens failing specific outcomes, severe unfavourable medicine reactions also leading to needless medical costs (Huges *et al*., 2001:1195), thus the more reason for investigation of adherence to medicine treatment among Parkinson's disease patients.

The following figure illustrates the number of medicine items that was used in order to calculate the refill adherence rates from 2005 to 2008:

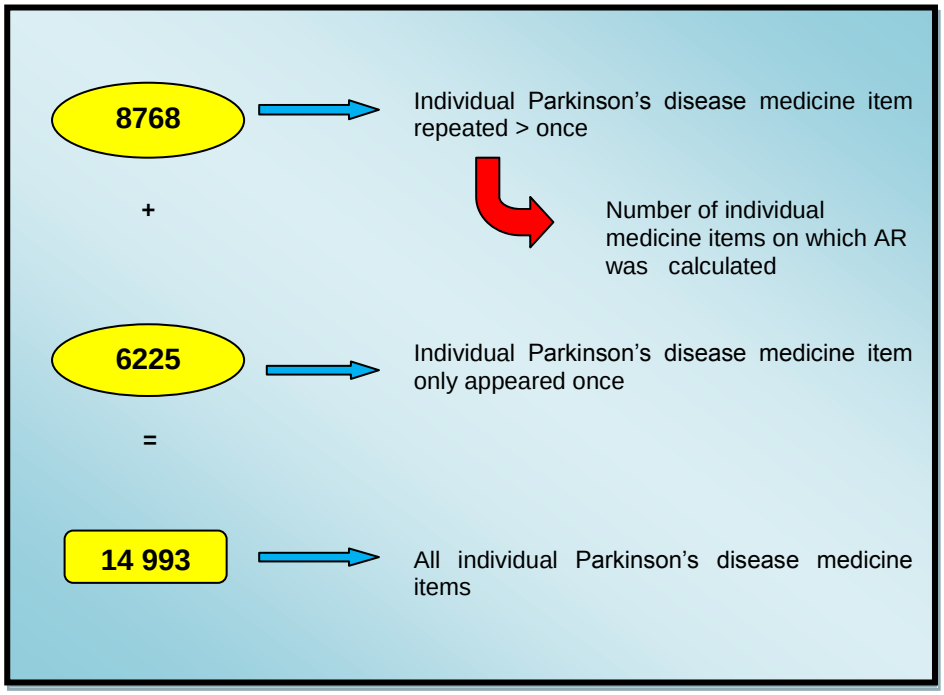

Figure 3.1: Diagramme illustrating the individual number of medicine items used for AR calculations

In order to evaluate the cost implications of the AR the following equation was used:

Final cost = Cost per medicine item[#] – Cost of medicine items of the last refill[*]

[#]Cost per medicine item = cost per medicine item received + cost per medicine item of 1st refill + cost per medicine item of 2nd refill + cost per medicine item of 3rd refill +....etc.

[*]indicating that the cost of the last refill was subtracted

The following Tables respectively stipulate the adherence rates (AR) and the days supply criteria that were used in this study:

Table 3.3: Refill-adherence rate criteria

Adherence rate (AR)category	*Criteria*
1	AR ≤ 90%
2	90% < AR ≤ 110%
3	AR > 110%

Table 3.4: Days supplied criteria

Total days supplied category	*Criteria (days)*
1	≤ 60
2	> 60 ≤ 90
3	> 90 ≤ 120
4	> 120 ≤ 180
5	> 180 ≤ 360
6	> 360 ≤ 720
7	> 720 ≤ 1080
8	> 1080

Furthermore the section that follows contains brief discussions on the statistical analysis that took place in this study.

3.4.2.2 Statistical analysis

The following are statistical methods that were used to analyse the data:

3.4.2.2.1 Arithmetic mean

The mean can be defined as an average that uses the precise value of each entry (Brase & Brase, 1999:94) or all observations present in a study added together then divided by the sum of all observations present in the study (Banerjee, 2003:3), and can simply be illustrated by the following:

$$\text{Mean} = \frac{sum\ of\ all\ entries}{number\ of\ entries}$$

Mathematically, it is articulated as:

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

Where:

- $\bar{x}$ = sample arithmetic mean
- $\sum x$ = the sum of all given *x* values
- n = number of observations

Throughout the study “mean” and “average” were used as synonyms.

3.4.2.2.2 Standard deviation

The standard deviation is a value that assists a researcher in understanding to what extent an individual data set differs from the mean (Doane & Seward, 2007:131), and is described as follows in the equation below (Brase & Brase, 1999:104):

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

Where:

- s = Standard deviation
- x = Any entry in the distribution
- $\bar{x}$ = Mean
- n = number of entries
- $\sum$ = sum of

3.4.2.2.3 Cost prevalence index

The cost prevalence index (CPI) was defined by Serfontein (1989:180) as the percentage cost divided by the percentage frequency:

$$Cost\ prevalence\ index = \frac{Cost\ \%}{Prevalence\ \%}$$

For the purpose of this research study the cost prevalence index was interpreted as follows:

- If cost index < 1 then the therapy utilised is relatively inexpensive
- If cost index = 1 then there is equilibrium between the cost and prevalence of the therapy.
- If cost index > 1 then the therapy utilised is relatively expensive.

The CPI was used as a descriptive measure in order to evaluate the cost associated with Parkinson's disease. The assumption could then be made, whether or not the treatment cost of this disease could be regarded as viable.

3.4.2.2.4 Effect size (d-values)

In 1988, Cohen, defined the effect size (d) to be the "*degree to which the phenomenon is present in the population*" (Cohen, 1988:9). Thalheimer and Cook (2002:3) defined it as "*the difference between two means divided by the standard deviation of two conditions*" and Cohen and Lea (2004:125) also agreed upon the fact that the effect size indicated "how many standard deviations apart two population means are". The effect size (d) can be calculated as follows:

$$d = \frac{\overline{x_t} - \overline{x_c}}{s_{max}}$$

Where:

- d = effect size
- $\overline{x_t}$ = mean (average cost of treatment)
- $\overline{x_c}$ = mean (average cost of comparison treatment)
- s_{max} = maximum standard deviation between t and c.

The d value can further be interpreted as follows (Cohen, 1988:25-26; Steyn, 1999:3):

- d = 0.2 Small effect size, and indicates no practical significance.
- d = 0.5 Medium effect size, might be significant.
- d = 0.8 Large effect size, and indicates great practical meaning.

In this study the d value was used in the following circumstances:

- Calculate the difference in average cost per medicine item between the total database and Parkinson's disease data where applicable.

3.5 ETHICAL CONSIDERATIONS

In order to perform this study permission was needed, and successfully granted by the PBM as well as the NWU Ethical Committee (Ethical application number: NWU-0046-08-S5).

3.6 RELIABILITY AND VALIDITY

Data used in this study were directly obtained from the medicine claims database, and no manipulation of data was done by the researcher. Reliability and validity are two key aspects to be taken into consideration in a research study. The PMB's standpoint is that of supplying data that would be reliable and valid, thus in this study, also the perspective of the researcher, not questioning their views.

3.7 RESULTS AND DISCUSSION

The results and discussion referring to the empirical investigation of this study will be discussed in Chapter 4.

3.8 CONCLUSIONS AND RECOMMENDATIONS

The conclusions and recommendations of this study with specific reference to the objectives set apart will be documented in Chapter 5.

3.9 CHAPTER SUMMARY

This chapter focused on the empirical investigation of this study that was outlined by the research objectives, the research design and research methodology. The chapter also included the specific descriptive measures and statistical analyses that were used. Also discussed in this chapter are ethical considerations and reliability and validity of the research.

CHAPTER 4:

Results and discussion

In this chapter the results of the empirical investigation will be discussed, obtained from the data provided by a PBM company, for the period 1 January 2005 to 31 December 2008.

4.1 ANNOTATIONS CONCERNING THE ANALYSIS OF THE DATA:

- The quantities in the data Tables have been rounded off to the nearest two decimal places. This explains why the collective sum not always adds up to 100 per cent.
- The cost used in the data Tables is divided into the three different amounts: "Total prescription cost"/ "Total medicine item cost", which presents the total cost of the prescription or medicine item, "Medical scheme contribution", which represents the cost attributed by the medical scheme and "Patient contribution", which represents the amount the patients themselves have to pay.
- Tables referring to the different age groups were only portrayed as "age group 1 – 6", with precise layout of the age group categories found in section 3.3.2.
- Gender was categorised into three groups: the symbols "F", "M" and "U" were used in some Tables to display F (female), M (male) and U (unidentified). The unidentified group will, however, not be discussed throughout this dissertation.
- Different types of medicine were illustrated abbreviations/symbols throughout the study: M (the original product with patent), N (original product without any generic), O (original product with generic) and Y (generic product).
- Prescribers were divided into four main groups relevant to this study. The following symbols were used to portray the various prescribers: GP (general practitioner), N (neurologist), P (psychiatrists) and O (other).
- "Trade name product/s" in this study would refer to a medicine item or a registered medicine product that is used to treat a disease or condition.
- The pharmacological groups of antiparkinson medicine items were divided into three categories namely, the dopaminergics, the anticholinergics and other (see section 2.12.2).

- Frequency, prevalence and incidence were used interchangeably and refer to the number of times that a trend occurred.
- Throughout the study “mean” and “average” were used as synonyms.
- The medicine cost does not include expenses such as injections, gloves or medicine instruments.
- Due to the extent of the use of trade name products and trade mark products, the ® is not shown throughout appendix A, although in the discussion of this chapter.
- Abbreviations used to describe the different dosage forms throughout the study were as follows: cap (capsules); tab (tablets); inj (injections); SRT (slow release tablets); XL (extended release) and CR (controlled release).

4.2 PRESENTATION OF THE DATA ANALYSIS

Figure 4.1 illustrates through a flow diagram, how the results of this study will be presented.

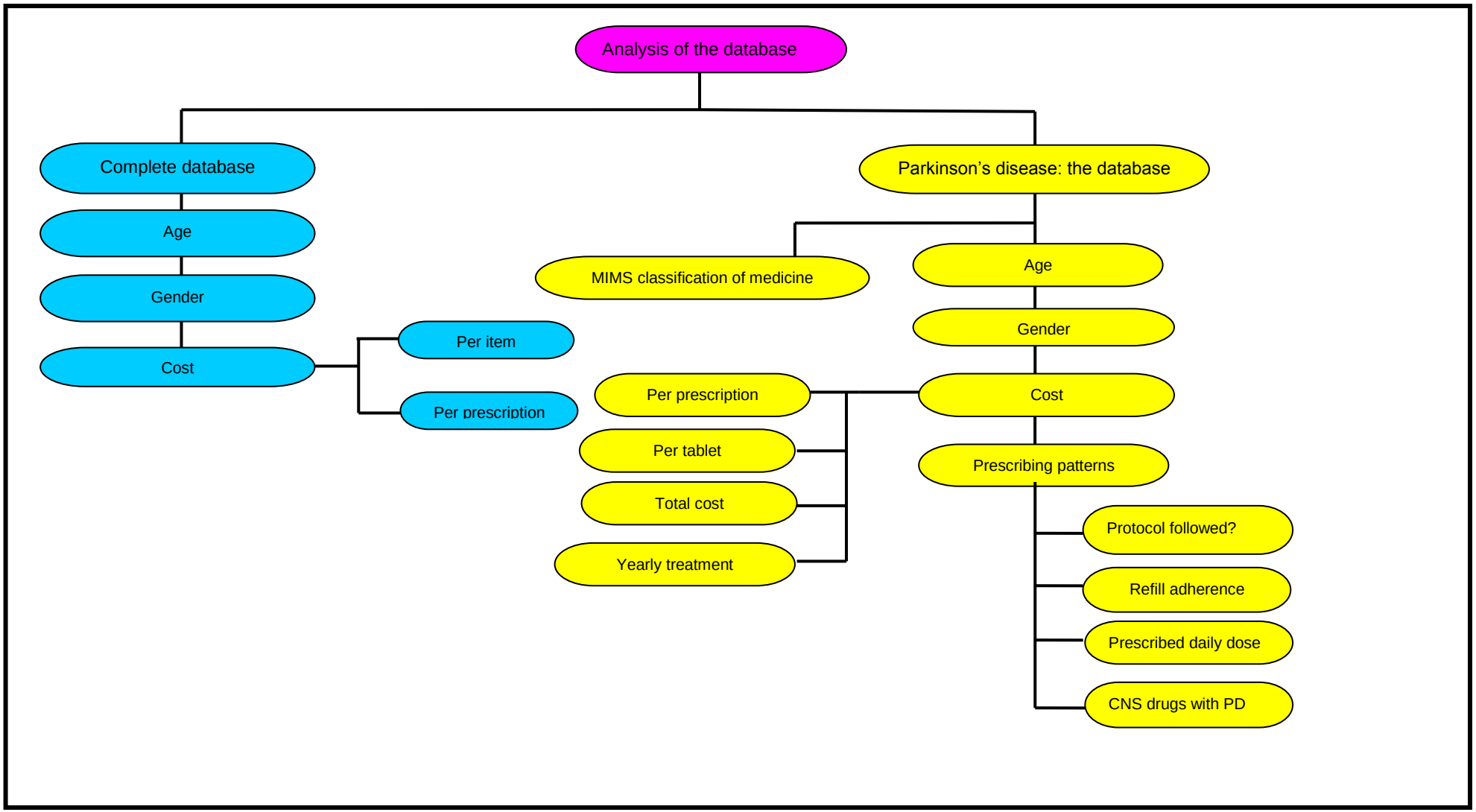

Figure 4.1 Flow diagram illustrating the general analysis of the data

4.3 GENERAL ANALYSIS OF THE DATA

To start with, this section contains an overall analysis of the complete database in comparison to medicines used in Parkinson's and other related diseases. Thereafter a brief discussion follows with regard to the relevant demographic parameters; age and gender, and differentiation between specific prescribers is also made with regard to the antiparkinson's medicine.

Variables portray the division of cost in this section namely: Total prescription cost which represents the total cost of the prescription, and consists of the medical scheme contribution and patient contribution. Medical scheme's contribution embodies the amount paid by the medical scheme of the patient and the patient contribution represents the amount paid by the patients themselves.

4.3.1 General analysis of the total database and Parkinson's disease medicine

Tables 4.1 and 4.2 are compiled from Tables A.1; A.5; A.9 and A.10 in appendix A, and reflect data of the complete database, as well as medicines used in Parkinson's disease and other related disorders for the four study years. These two Tables compare the average cost per item, average cost per prescription, the average number of medicine items per prescription and the average number of prescriptions per patient per year as well as the total database and antiparkinson's medicine.

Table 4.1a: Analysis of the total database

Year	Variable	Frequency (n)	Mean ± Std Dev (R)	Total cost (R)
Cost per medicine items				
2005	Total medicine item cost	-	- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
2006	Total medicine item cost	-	- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
2007	Total medicine item cost	-	- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
2008	Total medicine item cost	-	- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
Cost per prescription				
2005	Total prescription cost	-	- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
2006	Total prescription cost	-	- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
2007	Total prescription cost	-	- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
2008	Total prescription cost	-	- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	- ± -	-
2006		-	- ± -	-
2007		-	- ± -	-
2008		-	- ± -	-
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		-	- ± -	-
2006		-	- ± -	-
2007		-	- ± -	-
2008		-	- ± -	-

Table 4.1b: Analysis of the total database (continued)

Average cost per medicine item on total database according to generic indicator						
Year	**Generic indicator**	**Variables**	**Frequency (n)**	**%**	**Mean ± Std Dev (R)**	**Total cost (R)**
2005	**M**	Total medicine item cost	136 529	0.7	86.62 ± 86.36	11 825 895.65
		Medical scheme contribution			78.13 ± 79.73	10 666 835.04
		Patient contribution			8.49 ± 26.71	1 159 060.61
	N	Total medicine item cost	8 328 268	42.71	136.26 ± 227.00	11 34 806 272.48
		Medical scheme contribution			121.26 ± 218.80	1 009 848 021.92
		Patient contribution			15.00 ± 57.48	124 958 250.57
	O	Total medicine item cost	2 678 727	13.74	99.45 ± 132.89	266 399 728.78
		Medical scheme contribution			81.07 ± 126.08	217 151 755.41
		Patient contribution			18.38 ± 40.64	49 247 973.37
	Y	Total medicine item cost	8 357 250	42.86	48.68 ± 60.00	406 833 354.71
		Medical scheme contribution			43.65 ± 56.87	364 781 037.06
		Patient contribution			5.03 ± 16.14	42 052 317.65
2006	**M**	Total medicine item cost	32 387	0.13	95.50 ± 38.19	3 093 081.05
		Medical scheme contribution			82.35 ± 43.04	2 666 981.24
		Patient contribution			13.16 ± 26.16	426 099.81
	N	Total medicine item cost	7 983 562	32.66	139.88 ± 287.68	1 116 715 653.50
		Medical scheme contribution			122.72 ± 280.45	979 751 640.27
		Patient contribution			17.16 ± 63.62	136 964 013.24
	O	Total medicine item cost	3 224 378	13.19	101.92 ± 152.09	328 623 621.75
		Medical scheme contribution			81.40 ± 144.54	262 474 041.93
		Patient contribution			20.52 ± 45.84	66 149 579.82
	Y	Total medicine item cost	98 73 095	40.39	51.79 ± 67.28	511 306 377.79
		Medical scheme contribution			45.97 ± 64.24	453 817 287.92
		Patient contribution			5.82 ± 18.44	57 489 089.86
2007	**M**	Total medicine item cost	12 811	0.07	59.49 ± 69.29	762 063.88
		Medical scheme contribution			40.75 ± 67.46	522 049.81
		Patient contribution			18.73 ± 34.99	240 014.07
	N	Total medicine item cost	6 998 781	36.69	153.53 ± 509.44	1 074 554 517.96
		Medical scheme contribution			131.76 ± 478.62	922 144 828.59
		Patient contribution			21.78 ± 160.90	152 409 689.37
	O	Total medicine item cost	3007375	15.77	102.26 ± 177.95	307 532 420.50
		Medical scheme contribution			76.10 ± 167.03	228 857 332.44
		Patient contribution			26.16 ± 53.03	78 675 088.06
	Y	Total medicine item cost	9 056 757	47.48	59.12 ± 79.26	535 435 174.32
		Medical scheme contribution			51.18 ± 74.99	463 482 822.08
		Patient contribution			7.94 ± 22.84	71 952 352.24
2008	**M**	Total medicine item cost	13 318	0.08	65.45 ± 47.64	871 710.14
		Medical scheme contribution			52.70 ± 43.51	701 811.62
		Patient contribution			12.76 ± 28.67	169 898.52
	N	Total medicine item cost	5 773 344	35.12	170.42 ± 712.01	983 898 369.62
		Medical scheme contribution			144.53 ± 686.66	834 400 983.12
		Patient contribution			25.89 ± 172.05	149 497 386.50
	O	Total medicine item cost	2 544 252	15.48	103.66 ± 208.77	263 742 507.88
		Medical scheme contribution			74.06 ± 194.69	188 433 455.69
		Patient contribution			29.60 ± 66.03	75 309 052.19
	Y	Total medicine item cost	8 108 339	49.32	66.27 ± 86.98	537 358 426.21
		Medical scheme contribution			56.12 ± 81.42	455 011 978.49
		Patient contribution			10.16 ± 26.24	82 346 447.72

Table 4.2 Analysis of Parkinson's disease medicine

Cost per medicine item				
Year	**Variable**	**Frequency (n)**	**Mean ± Std Dev (R)**	**Total cost (R)**
2005	Total medicine item cost	-	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2006	Total medicine item cost	-	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2007	Total medicine item cost	-	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2008	Total medicine item cost	-	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
Cost per prescription				
2005	Total prescription cost	25 011	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2006	Total prescription cost	27 324	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2007	Total prescription cost	25 513	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2008	Total prescription cost	24 404	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	±	-
2006		-	±	33 768
2007		25 513	±	31 455
2008		24 404	±	30 040
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		3 993	±	-
2006		-	±	-
2007		-	±	-
2008		-	±	-

For the study period analysed, a total number of 1 509 621 **patients** were represented in 2005, 1 558 090 in 2006, 1 178 596 in 2007 and 974 497 in 2008. Of all these patients 0.26% (n = 3 993) were Parkinson's disease patients in 2005 (N =1 509 621), 0.28% (n = 4 423) in 2006 (N = 1 558 090), 0.34% (n = 4 028) in 2007 (N = 1 178 596) and 0.42% (n = 4 072) in 2008 (N = 974 497) (Refer to Tables 4.1 and 4.2).

Prescriptions claimed through the PBM indicated that, 8 391 836 were claimed in 2005, 8 906 348 in 2006, 7 911 096 in 2007 and 6 775 873 in 2008. Parkinson's disease medicine prescriptions accounted for only 25 011 prescriptions in 2005, 27 324 in 2006, 25 513 in 2007 and 24 404 in 2008. These figures already indicated that Parkinson's disease prescriptions represented a small percentage of all prescriptions on the database. Parkinson's disease prescriptions accounted for 0.3% from 2005 - 2007 and 0.4% in 2008 of all prescriptions claimed on the database (Refer to Tables 4.1 and 4.2).

Tables 4.1 and 4.2 particularly stipulate the **prescription expenditures** for each of the study periods for both the total database statistics as well as the Parkinson's disease data. From 2005 (N = R1 819 865 251.63) to 2008 (N = R1 785 871 013.85) Parkinson's disease represented 0.6% (2005, n = R10 459 835.93; 2006, n = R11 320 616; 2007, n = R11 040 596.32; 2008, n = R10 697 155.54) of the total database's prescription expenditure. Table 4.3 indicates the medical schemes' and patients' contributions for each year of both the total database and Parkinson's disease.

Table 4.3: Percentage division of medical scheme and patient contribution per prescription per year

TOTAL DATABASE					
Year	**Total prescription cost (R)**	**Medical scheme contribution (R)**	**Medical scheme contribution (%)**	**Patient contribution (R)**	**Patient contribution (%)**
2005	1 819 865 251.63	1 602 447 649.43	**88.05**	217 417 602.20	**11.95**
2006	1 959 738 734.09	1 698 709 951.36	**86.68**	261 028 782.73	**13.32**
2007	1 918 284 176.66	1 615 007 032.92	**84.19**	303 277 143.73	**15.81**
2008	1 785 871 013.85	147 858 228.92	**82.79**	307 322 784.93	**17.21**
PARKINSON'S DISEASE DATA					
2005	10 459 835.93	9 323 689.32	**89.14**	1 136 146.61	**10.86**
2006	11 320 616.71	10 015 330.71	**88.47**	1 305 286.00	**11.53**
2007	11 040 569.32	98 074 475.17	**88.83**	1 233 094.15	**11.17**
2008	10 697 155.54	9 266 962.73	**86.63**	1 430 192.81	**13.37**

Patient contributions were significantly smaller than medical scheme contributions on both accounts, but apart from this the patients' contribution increased with more or less 5% from 2005 to 2008 on the total database, and the Parkinson's disease patients' contribution increased with ±2.5% from 2005 to 2008 (Refer to Table 4.3).

Reasons that could be inflicted for this might have been: PBM take more control over the treatment regime, regimes that changed, patients receiving more medicine items and global economy's impact on South Africa. The average patient contribution per prescription on the total database increased with 75.07% from 2005 (R25.91 ± R81.07) to 2008 (R45.36 ± R181.31). In contrast to this an increase of only 4% per Parkinson's disease prescription was found from 2005 (R 418.21 ± R 397.63) to 2008 (R 438.34 ± R 426.45). The *d-value* indicated that the cost per Parkinson's disease prescription had intermediate practical significance to the prescription cost on the total database in 2005 (d = 0.5) and 2006 (d= 0.5), although 2007 (d = 0.3) and 2008 (d = 0.2) did not share the same connotation (Refer to Tables 4.1 and 4.2).

The total number of **medicine items** on the complete database for 2005 to 2008 was: 19 500 774, 21 113 422, 19 075 724 and 16 439 253. Parkinson's disease medicine items contributed to an average of 0.16% of the total number of medicine items in 2005 (n =30 950), 2006 (n = 33 768) and 2007 (n = 31 455), with 0.18% in 2008 (n = 30 040) (Refer to Tables 4.1 and 4.2).

Average **medicine item costs were** evaluated against the *d*-value. The *d*-value gave an indication of the difference in cost per medicine item on the total database, in contrast to that of the Parkinson's disease medicine item cost. The *d-value* decreased slightly from 2005 (d = 1) and 2006 (d = 1) to 2007 (d = 0.8) and 2008 (d = 0.6), still all values were of great practical significance. This indicated that the medicine item cost per Parkinson's disease medicine item was rather expensive in comparison to the medicine items of the total database (Refer to Table 4.1 and 4.2).

Each prescription on the total database had an average of between 2.32 ± 1.52 and 2.43 ± 1.64 medicine items over the period, in contrast to an average number of 1.23 ± 0.54 and 1.24 ± 0.55 medicine items on a antiparkinson's prescription from 2005 to 2008. On both accounts the number of medicine items per prescription was rather consistent

Each patient received between 5.56 ± 6.75 and 6.95 ± 7.85 prescriptions per year over the study period on the complete database. Antiparkinson's prescriptions were, however, between 5.99 ± 5.38 and 6.33 ± 5.47 prescriptions per patient per year from 2005 to 2008 (Refer to Tables 4.1 and 4.2).

Table 4.4 illustrates the CPI (see section 3.4.2.2.3) of Parkinson's disease according to data in Tables 4.1 and 4.2.

Table 4.4: CPI on Parkinson's disease medicine items

Year	Number of Items			Cost per item			CPI
	Total database	Parkinson's disease	%	Total database	Parkinson's disease	%	
2005	19 500 774	30 950	0.16	1 819 865 251.63	10 459 835.93	0.57	**3.62**
2006	21 113 422	33 768	0.16	1 959 738 734.09	11 320 616.71	0.58	**3.61**
2007	19 705 724	31 455	0.16	1 918 284 176.66	11 040 569.32	0.57	**3.49**
2008	16 439 253	30 040	0.18	1 785 871 013.85	10 697 155.54	0.60	**3.28**

According to criteria (as set apart in section 3.4.2.2.3), a CPI value of more than 1, indicates treatment of a disease to be relatively expensive. Thus according to Table 4.4 values indicated great practical significance in expenditures of Parkinson's disease treatment.

The subsequent section entails the analysis of demographic parameters.

4.3.2 Analysis according to demographic parameters

The demographic parameters that were discussed in this section were based on only two parameters, *i.e*. gender and age. Each of these two parameters was divided into sub-categories as specified in section 3.3.2 (age) and 4.1 (gender).

Firstly the main focus was on the two gender groups, female and male, thereafter the six different age groups were discussed.

4.3.2.1 Analysis according to gender groups

The section to follow will contain the discussion of this study more closely related to the two gender entities, female and male. Although the gender of the study population was initially divided into three individual groups namely; female, male and unidentified, the unidentified groups' data will only be presented in appendix A (Tables A.2., A.6., A.9. and A.10.).

Table 4.5: Analysis of the total database according to the female gender

Cost per medicine item				
Year	**Variable**	**Frequency (n)**	**Mean ± Std Dev (R)**	**Total cost (R)**
2005	Total medicine item cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Cost per prescription				
2005	Total prescription cost	5 036 494	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	5 336 203	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	4 754 911	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	4 062 385	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	12 699 707
2007		4 754 911	-	11 509 346
2008		4 062 385	-	9 893 928
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		842 386	-	-
2006		-	-	-
2007		-	-	-
2008		-	-	-

Table 4.6: Analysis of Parkinson's medicine according to the female gender

Cost per medicine item				
Year	**Variable**	**Frequency (n)**	**Mean ± Std Dev (R)**	**Total cost (R)**
2005	Total medicine item cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Cost per prescription				
2005	Total prescription cost	13 433	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	14 979	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	13 906	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	13 735	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	17 883
2007		13 906	-	16 645
2008		13 735	-	16 260
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		2 251	-	-
2006		-	-	-
2007		-	-	-
2008		-	-	-

4.3.2.1.1 Analysis according to the female gender

The discussion that follows is based on the female gender represented on the database. Tables 4.5 and 4.6 provide data for all female patients in the total database as well as data applicable to the female gender that used Parkinson's disease related medicines. Table 4.5 and Table 4.6 are compiled from Tables A.2, A.6, A.9 and A.10 in appendix A.

Female **patients** represented 55.80% (n = 842 386) of all patients on the total database in 2005 (N = 1 509 621), although in the same year female Parkinson's disease patients accounted for only 0.15% (n = 2 251) of the total database. In 2006 (N = 1 558 090), 55.77% (n = 868 891) of the complete databases' claims were claims for female patients and 0.17% (n = 2 591) were female Parkinson's disease patients. Following more or less the same trend, female patients consisted of 55.52% (n = 654 348) of all patients in 2007 (N = 1 178 596), with a small proportion of 0.20% (n = 2 369) of female Parkinson's disease patients. Similarly in 2008 (N = 974 497), the female patients were 55.23% (n = 538 254) and only 0.25% (n = 2 446) were Parkinson's disease patients (Refer to Table 4.1, 4.5 and 4.6). Female patients on the total database, however, decreased with 56.5% from 2005 to 2008 (Refer to Table 4.2). Focusing on the total number of Parkinson's disease patients, female Parkinson's disease patients represented 56.37% (n = 2 251) of them in 2005 (N = 3 993), 58.58% (n = 2 591) in 2006 (N = 4 423), 58.81% (n = 2 369) in 2007 (N = 4 028) and 60.07% (n = 2 446) in 2008 (N = 4 072). Female Parkinson's disease patients increased with 8.7% from 2005 to 2008 (Refer to Tables 4.2, 4.5 and 4.6).

The number of **prescriptions claimed** for female patients represented 60.02% (n = 5 036 494) in 2005 (N = 8 391 836) of which 0.27% (n = 13 433) were for female Parkinson's disease patients. With figures differing slightly, more or less the same was true for 2006, 2007 and 2008. Prescription claims for females in 2006 (N = 8 906 348) amounted to 59.91% (n = 5 336 203), 60.01% (n = 4 754 911) in 2007 (N = 7 911 096) and 59.95% (n = 4 062 385) in 2008 (N = 6 775 873). In 2006, 0.28% (n = 14 979) of all female claims were female Parkinson's prescription claims, as were 0.29% (n = 13 906) in 2007 and 0.34% (n = 13 735) in 2008 (Refer to Tables 4.1, 4.5 and 4.6).

Prescription cost for a female patient in 2005 (N = R1 819 865 251.63) represented 59.60% (n = R1 084 626 865.29) of the total database's prescription cost. Similarly, 59.31% (n = R1 162 254 536.29) in 2006 (N = R1 959 738 734.09), and 59.33% (n = R1 138 188 990.86) in 2007 (N = R1 918 284 176.66) and 59.20% (n = R1 057 274 453.63) in 2008 (N = R1 785 871 013.85) were for female patients. Female Parkinson's disease patients' total prescription cost accounted for 47.53% (n = R4 971 131.04), 48.42% (n = R5 481 072),

48.70% (n = R5 377 298.17) and 49.20% (n = R5 262 661.83) of the total Parkinson's disease prescription cost respectively to 2005 (N = R10 459 835.93), 2006 (N = R11 320 616.71), 2007 (N = R11 040 569.32) and 2008 (N = R10 697 155.54). These figures could further be divided into the medical scheme contribution and that of the patient. On both the total database, as well as Parkinson's disease data, the contribution that the patient had to make increased noticeably (Refer to Tables 4.1, 4.2, 4.5 and 4.6). The following Tables stipulate both the medical scheme and patient contribution (in Rand) per prescription per year:

Table 4.7: Percentage division of medical scheme and patient contribution per prescription per year according to the female gender

TOTAL DATABASE					
Year	**Total prescription cost (R)**	**Medical scheme contribution (R)**	**Medical scheme contribution (%)**	**Patient contribution (R)**	**Patient contribution (%)**
2005	1 084 626 865.29	947 688 793.44	**87.37**	136 938 071.85	**12.63**
2006	1 162 254 536.29	999 015 475.00	**85.95**	163 239 061.29	**14.05**
2007	1 138 188 990.86	949 029 333.61	**83.38**	189 159 657.25	**16.62**
2008	1 057 274 453.63	865 959 792.23	**81.90**	191 314 661.40	**18.10**
PARKINSON'S DISEASE DATA					
2005	4 971 131.04	4 364 037.05	**87.79**	607 093.99	**12.21**
2006	5 481 072.03	4 786 849.50	**87.33**	694 222.53	**12.67**
2007	5 377 298.17	4 724 307.72	**87.86**	652 990.45	**12.14**
2008	5 262 661.83	4 510 443.40	**85.71**	752 218.43	**14.29**

On the total database the patients' contribution per prescription increased with an average of 73% from R27.19 ± R80.87 in 2005 to R47.09 ± R195.17 in 2008 (Refer to Table 4.5). The increase for Parkinson's disease data was smaller, but also notable, with an average increase of 21% from R45.19 ± R92.12 in 2005 to R54.77 ± R114.46 in 2008 (Refer to Table 4.6). Medical scheme contributions were reasonably consistent when focusing on Parkinson's disease data, only increasing with 1% from 2005 (R324.87 ± R307.02) to 2008 (R328.39 ± R336.16), in comparison to a 13% increase on the complete database for the same period (Refer to Table 4.5 and 4.6). Calculating the *d*-value for females, only 2005 (d = 0.5) indicated moderate practical significance regarding prescription cost of the Parkinson's disease female data and the total database's female data. The other study periods indicated no practical significance in prescription cost (2006: d = 0.4, 2007: d = 0.3, 2008: d = 0.2).

Medicine items consumed by women accounted for 60.25% (n = 11 750 190) of all medicine items on the total database in 2005 (N = 19 500 774), essentially the figures for 2006 (N = 21 113 422), 2007 and 2008 were more or less equal with 60.15% (n = 12 699 707), 60.34% (n= 11 509 346) and 60.18% (n = 9 893 928) respectively. In 2005 (N = 11 750 190), 2006 (N = 12 699 707) and 2007 (N = 11 509 346) 0.14% (n = 12 140, n = 17 883, n = 16 645) and

0.16% (n = 16 260) in 2008 (N = 9 893 928) of all medicine items that were used by females were in fact Parkinson's disease medicine items. In contrast to these figures, medicine items used by Parkinson's disease women were 52.15% (n = 16 140) in 2005 (N = 30 950), 52.96% (n = 17 883) in 2006 (N = 33768), 52.92% (n = 16 645) in 2007 and 54.13% (n = 16 260) in 2008 (N = 30 040) of all Parkinson's disease medicine items claimed (Refer to Table 4.4 and 4.5).

Medicine item cost for female Parkinson's disease patients was exceptionally higher than the total database female patients' item cost. The *d*-value indicated immense practical significance in medicine item cost for Parkinson's disease females in contrast to females on the total database. The *d-value* decreased slightly from 2005 (d = 1), to 2006 (d = 0.9), 2007 (d = 0.8), and 2008 (d = 0.5) (Refer to Table 4.5 and 4.6)

Female antiparkinson's prescriptions were between 5.62 $\pm$ 5.20 and 5.97 $\pm$ 5.17 prescriptions per year, and had an average number of 1.18 $\pm$ 0.48 and 1.20 $\pm$ 0.50 medicine items per prescription over the study period. In contrast, women on the total database had an average of 5.98 $\pm$ 7.16 and 7.55 $\pm$ 8.32 prescriptions with 2.33 $\pm$ 1.54 and 2.44 $\pm$ 1.67 medicine items per prescription in the same period (Refer to Table 4.5 and 4.6).

4.3.2.1.2 Analysis according to the male gender

The section that follows will briefly entail a discussion on the medicine usages as well as the medicine cost, applicable to the male gender.

Table 4.8: Analysis of the total database according to the male gender

Cost per medicine item				
Year	**Variable**	**Frequency (n)**	**Mean ± Std Dev (R)**	**Total cost (R)**
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Cost per prescription				
2005	Total prescription cost	3 348 219	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	3 565 331	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	3 154 367	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	2 713 488	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	8 403 158
2007		3 154 367	-	7 562 466
2008		2 713 488	-	6 545 325
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		665 505	-	-
2006		-	-	-
2007		-	-	-
2008		-	-	-

Table 4.9: Analysis of Parkinson's medicine according to the male gender

Cost per medicine item				
Year	**Variable**	**Frequency (n)**	**Mean ± Std Dev (R)**	**Total cost (R)**
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Cost per prescription				
2005	Total prescription cost	11 559	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	12 333	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	11 607	-	-
	Medical scheme contribution		-	-
	Patient contribution		±	-
2008	Total prescription cost	10 669	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	15 873
2007		11 607	-	14 810
2008		10 669	-	13 780
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		1 740	-	-
2006		-	-	-
2007		-	-	-
2008		-	-	-

Table 4.8 and Table 4.9 are summarised Tables, with all relevant information regarding the male gender on the total database as well as male Parkinson's disease patients, compiled from Tables A.2, A.6, A.9 and A.10 for the individual study periods.

Male **patients** among the total database represented 44.08% of all patients in 2005 (N = 1 509 621), 44.16% in 2006 (N = 1 558 090), 44.45% in 2007 (N = 1 178 596) and 44.77% in 2008 (N = 974 497) (Refer to Tables 4.1 and 4.8). Male Parkinson's disease patients on the other hand represented only 0.12% (2005, n = 1 740; 2006, n = 1 827) of patients in 2005 (N = 1 509 621) and 2006 (N = 1 558 090), 0.14% (n = 1 659) in 2007 (N = 1 178 596) and 0.17% (n = 1 625) in 2008 (N = 974 497), compared to the complete database (Refer to Tables 4.1 and 4.9). When looking at only the Parkinson's disease patient data, 43.58% (n = 1 740) in 2005 (N = 3 993), 41.31% (n = 1 827) in 2006 (N = 4 423), 41.18% (n = 1 659) in 2007 (N = 4 028) and 39.91% (n = 1 625) in 2008 (N = 4072) were men (Refer to Table 4.2 and 4.9). From 2005 to 2008, male Parkinson's disease patients decreased with 7.1% (Refer to Table 4.9), whereas male patients on the total database decreased with 52.6% (Refer to Table 4.8)

Of all the **prescriptions claimed** through the PBM, male patients' prescriptions represented 39.90% (n = 3 348 219), 40.03% (n = 3 565 331), 39.87% (n = 3 154 367) and 40.05% (n = 2 713 488), respectively for 2005 (N = 8 391 836), 2006 (N = 8 906 348), 2007 (N = 7 911 096) and 2008 (N = 6 775 873). Furthermore of these prescriptions, 0.35% were prescriptions for male Parkinson's disease patients in 2005 and 2006, with 0.37% and 0.39% being for male Parkinson's disease patients in 2007 and 2008 (Refer to Table 4.1, 4.8 and 4.9). Prescriptions claimed for male Parkinson's disease patients were 46.22% (n = 11 559) in 2005 (N = 25 011), 45.14% (n = 12 333) in 2006 (N = 27 324), 45.49% (n = 11 607) in 2007 (N = 25 513) and 43.72% (n = 10 669) in 2008 (N = 24 404) of all the Parkinson's disease prescriptions (Refer to Tables 4.2 and 4.9).

The total **prescription expenditure** for a male patient in contrast to that of the total database was very consistent over the four-year study period. In 2005 (N = R1 819 865 251.53) the prescription expenditure for a male patient was 40.32% (n = R733 769 633.85) of the total prescription cost per year. Comparable statistics could be observed for 2006 (N = R1 959 738 734.09), where 40.64% (n = R796 360 101.04) of the total prescription expenditure was for male patients, with 40.64% (n = R779 598 488.81) in 2007 (N = R1 918 248 176.66) as well, and 40.80% (n = R728 596 560.22) in 2008 (N = R1 785 871 013.85) (Refer to Tables 4.1 and 4.8). Comparing the total cost per male Parkinson's disease patient prescription with that of the total Parkinson's disease data prescription cost, the male Parkinson's disease patient had to pay 52.38% (n = R5 479 205.15) in 2005 (N = R10 459 835.93), 51.53% (n = R5 833 515.93) in 2006 (N = R11 320 616.71), 51.30% (n = R5 663 271.15) in 2007 (N =

R11 040 569.32) and 50.80% (n = R5 434 493.71) in 2008 (N = R10 697 155.54) (Refer to Tables 4.2 and 4.9). Male Parkinson's disease patients' total prescription cost per year decreased with 0.8 % from 2005 to 2008. Evaluating the figures in Tables 4.8 and 4.9, the medical scheme and patient contribution per prescription per year can be set apart as follows in Table 4.10:

Table 4.10: Percentage division of medical scheme and patient contribution per prescription per year according to the male gender

TOTAL DATABASE					
Year	**Total prescription cost (R)**	**Medical scheme contribution (R)**	**Medical scheme contribution (%)**	**Patient contribution (R)**	**Patient contribution (%)**
2005	733 769 633.85	653 370 941.06	**89.04**	80 398 692.92	**10.96**
2006	796 360 101.04	698 682 181.29	**87.73**	97 678 219.75	**12.27**
2007	779 508 488.81	665 466 500.10	**85.37**	114 041 988.71	**14.63**
2008	728 596 560.22	612 588 436.69	**84.01**	116 008 123.53	**15.92**
PARKINSON'S DISEASE DATA					
2005	5 479 205.15	4 950 152.53	**90.34**	529 052.62	**9.66**
2006	5 833 515.93	5 222 626.27	**89.53**	610 889.66	**10.47**
2007	5 663 271.15	5 083 167.45	**89.76**	580 103.70	**10.24**
2008	5 434 493.71	4 756 519.33	**87.52**	677 974.38	**12.48**

Comparing these figures, the Parkinson's disease male patient's levy was consistent over the study period, and only increased with about 3% from 2005 to 2008, in contrast to the total database's male patient contribution that increased with more or less 5% from 2005 to 2008. Per prescription, the total prescription cost per male patient increased with 22.5% from 2005 to 2008, compared to an increase of 7.5% from 2005 to 2008 of male Parkinson's disease patients' prescription costs (Refer to Table 4.8. and 4.9). The *d-value* indicated that the average prescription cost for a male Parkinson's disease patient was relatively higher than that of a male patient on the total database in 2005 (d = 0.56) and 2006 (d = 0.55). In 2007 (d = 0.37) and 2008 (d = 0.29) the values decreased, which indicated a smaller practical significance than the other two study periods.

The number of **medicine items claimed** for male patients remained relatively consistent at 39% for 2005 (N = 19 500 774), 2006 (N = 21 113 422), 2007 (N = 19 075 724) and 2008 (N = 16 439 253) (Refer to Tables 4.1 and 4.8). In 2005, 7 734 461 medicine items were claimed for male patients, of which 0.19% (n = 14 791) medicine items were for Parkinson's disease male patients. The same was true for the other three study periods, where 0.19% (n = 15 873) of the total database's medicine items in 2006 (N = 8 403 158) were for male Parkinson's disease medicine items, 0.20% (n = 14 810) of 7 562 466 medicine items for male patients were for male Parkinson's disease patients in 2007 and 0.21% (n = 13 780) in 2008 (Refer to Table 4.8 and 4.9).

Per medicine item the *d-value* indicated greater significance regarding the **cost per medicine item**. Male Parkinson's disease patients' medicine item cost in 2005 (d = 1.04) and 2006 (d = 1.03) was much higher than the male patients' on the total database, with smaller, although also practical significant values in 2007 (d = 0.78) and 2008 (d = 0.61).

Men on the total database received roughly between 5.03 ± 6.16 and 6.22 ± 7.15 prescriptions with between 2.31 ± 1.47 and 2.41 ± 1.59 items per prescription from 2005 to 2008. Male antiparkinson's prescriptions were roughly between 3.71 ± 4.19 and 4.27 ± 4.67 prescriptions per year with between 2.29 ± 1.33 and 2.34 ± 1.37 medicine items on each prescription in 2005 to 2008. This indicated that male patients on the total database roughly received more prescriptions with more medicine items per prescription.

4.3.2.1.3 Summary of the gender groups

The following paragraphs will enclose a short overview of section 4.3.2.1.1 and section 4.3.2.1.2.

On the total database the patient population was not evenly distributed. Females on the total database represented 55% of all patients and males 44% over the study period (Refer to Tables 4.5 and 4.8). Females were 11% more than male patients. The patient population on the database was the complete population of the PBM, and patients had equal chances to diagnosis, although it should be noted that the database only represents 35% of the higher income group. Furthermore statistics South Africa indicated that in the census of 2001, approximately 52% of the population were females (Statistics South Africa, 2001). In addition midyear estimates indicated that in 2009, 52% of the population were females (Statistics South Africa, 2009) and in 2010, 51% (Statistics South Africa, 2010). This implies no foregone conclusion occurs and that accurate comparisons of the gender groups in the patient population could be made.

Female Parkinson's disease patients were between 56% and 60% of all Parkinson's disease patients from 2005 to 2008. Male Parkinson's disease patients were between 39.9% and 43.6%, decreasing from 2005 to 2008. Male: female ratios for Parkinson's disease patients were 1:1.3 in 2005, 1:1.4 in 2006 and 2007 and 1:1.5 in 2008. Female Parkinson's disease patients increased from 2005 to 2008 with 8.7% with males decreasing with 7.1%.

Literature in chapter one, research studies indicated that men were 1.5 to 1.58 times more prone to develop Parkinson's disease than women (Alves *et al*., 2009:851; Wooten *et al*., 2004:637). This study's results, however, indicated the other way round. On the total

database females also dominated. The latest census information in South Africa indicated that 52% of the population were females.

On the total database a male: female ratio of 1:1.5 was consistent in every study period, with reference to the number of prescriptions claimed, the number of medicine items and the total medicine cost. Male: female ratios on the Parkinson's disease data presented the following results (Refer to Table 4.6 and 4.9):

- Number of prescriptions claimed - 1:1.2 from 2005 to 2007 and 1:1.3 in 2008,
- Number of medicine items claimed - 1:1.1 for 2005 -2008
- Total cost - 1: 0.9 for 2005 -2008.

These three parameters indicated little to any difference between the two genders with Parkinson's disease.

The following charts (figures 4.2 and 4.3) illustrate the medical scheme and patient contribution for each gender group on both the total database and Parkinson's disease data with data from Tables 4.7 and 4.10:

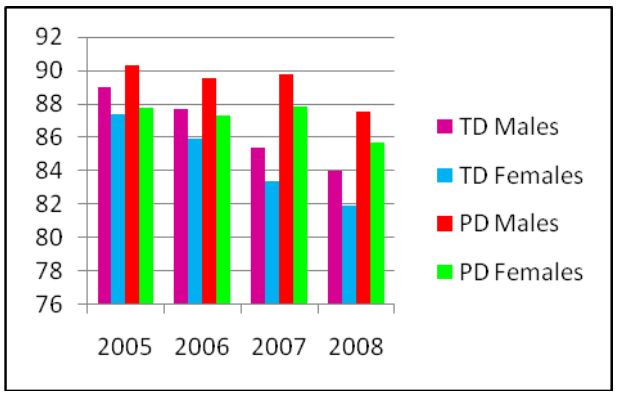

Figure 4.2: Medical scheme contributions on the total database (TD) and Parkinson's disease (PD) data according to gender

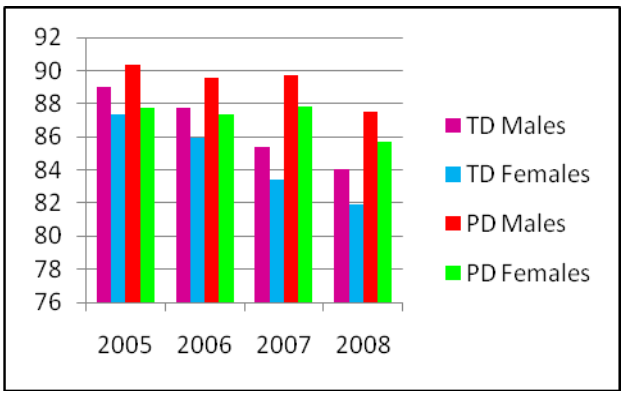

Figure 4.3: Patient contributions on the total database (TD) and Parkinson's disease (PD) data according to gender

Parkinson's disease is a chronic disease, and also appears on the standardised chronic disease list of South Africa. Medical schemes are obligated to cover expenditures of chronic diseases that appear on the chronic disease list (Council for Medical Schemes, 2005). On the total database, not only chronic disease prescriptions were claimed, but acute prescriptions as well. This implies a reason for the medical scheme contributions that were much higher than those of Parkinson's disease patients on the total database.

The section that follows contains the analysis of the next demographic parameter, the various age groups.

4.3.2.2 Analysis according to age groups

For this study patients on the database were divided into six different age groups (Refer to section 3.3.2). The discussions in the subsequent sections were done per age group whereas the total database's specific age group was compared to the same specific Parkinson's disease age group.

Table 4.11: Analysis of the total database according to age group one

Year	Variable	Frequency (n)	Mean ± Std Dev (R)	Total cost (R)
Cost per medicine item				
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Cost per prescription				
2005	Total prescription cost	3 018 239	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	3 155 000	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	2 644 361	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	1 975 494	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	7 337 330
2007		2 644 361	-	6 192 279
2008		1 975 494	-	4 543 368
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		814 222	-	-
2006		-	-	-
2007		-	-	-
2008		-	-	-

Table 4.12: Analysis of Parkinson's medicine according to age group one

Cost per medicine item				
Year	**Variable**	**Frequency (n)**	**Mean ± Std Dev (R)**	**Total cost (R)**
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Cost per prescription				
2005	Total prescription cost	846	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	1 103	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	1 012	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	810	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	1 169
2007		1 012	-	1 054
2008		810	-	858
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		399	-	-
2006		-	-	-
2007		-	-	-
2008		-	-	-

4.3.2.2.1 Analysis according to age group one (0 ≥ 40 years)

Age group one represents all the patients 40 years and younger on the total database and Parkinson's disease data. Tables 4.11 and 4.12 are summarised Tables, compiled from Tables A.3, A.7, A.9 and A.10 in appendix.

Patients of age group one represented 53.94% (n = 814 222) of all patients on the total database in 2005 (N = 1 509 621), 53.19% (n = 828 715) in 2006 (N = 1 558 090), 52.57% (n = 619 630) in 2007 (N = 1 178 596) and 47.60% (n = 463 830) in 2008 (N = 974 497) (Refer to Table 4.1 and 4.11). Parkinson's disease patients of this group only represented 0.03% (2005: n = 399, 2006: n = 524) of the total database's patients in 2005 (N = 1 509 621) and 2006 (N = 1 558 090), with 0.04% (2007: n = 464, 2008: n = 374) representation in 2007 (N = 1 178 596) and 2008 (N = 974 497) (Refer to Tables 4.1 and 4.12). With values increasing slightly, age group one Parkinson's disease patients represented 9.99% (n = 399) of all Parkinson's disease patients in 2005 (N = 3 993), 11.85% (n = 524) in 2006 (N = 4 423), 11.52% (n = 464) in 2007 (N = 4 028) and 9.18% (n = 374) in 2008 (N = 4 072) (Refer to Tables 4.2 and 4.12).

Prescriptions claimed for this group represented 35.97% (n = 3 018 239) in 2005 (N = 8 391 836), 35.42% (n = 3 155 000) in 2006 (N = 8 906 348), 33.43% (n = 2 644 361) in 2007 (7 911 096) and 29.15% (n = 1 975 494) in 2008 (N = 6 775 873) of all prescription claimed on the total database. Furthermore, of all prescriptions claimed only 0.01% were for Parkinson's disease patients in age group one throughout the four study periods (Refer to Table 4.1, 4.11 and 4.12). Of the total of 25 011 Parkinson's disease prescriptions claimed in 2005, 3.38% (n = 846) were for age group one, 4.04% (n = 1 103) in 2006 (N = 27 324), 3.97% (n = 1 012) in 2007 (N = 25 513) and 3.32% (n = 810) in 2008 (N = 24 404) (Refer to Tables 4.2 and 4.12).

Age group one patients on the total database had a total **prescription expenditure** of R 492 879 458.92 (27.08%) in 2005 (N = R1 819 865 251.63). In 2006 (N = R1 959 738 732.09), 2007 (N = R1 918 284 176.66) and 2008 (N = R1 785 571 013.85) the cost of this group patients on the total database's was 26.37% (n= R516 805 384.07), 24.08% (n = R461 983 661.27) and 20.97% (n = R374 478 882.90) respectively. Of the total Parkinson's disease prescription expenditure, 1.18% (n = R123 386.43) was the expenditure of this group in 2005 (N = R10 459 835.93). In 2006 (N = R11 320 616.71), 2007 (N = R11 040 569.32) and 2008 (N = R10 697 155.54) this group's Parkinson's disease patients' prescription costs were respectively 1.46% (n = R164 732.42), 1.33% (n =R147 305.10) and 1.18% (n = R125 837.05) (Refer to Tables 4.1, 4.2, 4.11 and 4.12). Table 4.13 stipulates the medical scheme

and patient contribution for the age group one patients on the total database and the Parkinson's disease data.

Table 4.13: Percentage division of medical scheme and patient contribution per prescription per year according to age group one

TOTAL DATABASE					
Year	**Total prescription cost (R)**	**Medical scheme contribution (R)**	**Medical scheme contribution (%)**	**Patient contribution (R)**	**Patient contribution (%)**
2005	492 879 458.92	444 247 202.53	**90.13**	48 632 256.39	**9.87**
2006	516 805 384.07	455 658 665.24	**88.17**	61 146 718.83	**11.83**
2007	461 983 661.27	390 140 961.78	**84.45**	71 842 699.49	**15.55**
2008	374 478 882.90	311 199 495.15	**83.10**	63 279 387.75	**16.90**
PARKINSON'S DISEASE DATA					
2005	123 386.43	110 506.81	**89.56**	12 879.62	**10.44**
2006	164 732.42	147 037.81	**89.23**	17 694.61	**10.74**
2007	147 305.10	130 642.27	**88.69**	16 662.83	**11.31**
2008	125 837.05	101 892.18	**80.97**	23 944.87	**19.03**

Through these figures set apart here it is seen that on both total database and Parkinson's disease data, the medical scheme contribution decreases from 2005 to 2008 with ± 7-8%, thus leading to the same percentage increase in patient contribution.

The cost per prescription increased with16.08% for this age group's patients on the total database from 2005 to 2008. This was more than twice the increase of 6.51% per prescription for a Parkinson's disease patient of this age group in the same period (Refer to Tables 4.11 and 4.12). The *d-value,* however, indicated no practical significance between the cost per prescription for this age group's patients on the Parkinson's disease and total database respectively (2005 – 2008; d = 0.1).

With regard to **medicine items** claimed, 35.48% (n = 6 919 565), 34.75% (n = 7 337 330), 32.46% (n = 6 192 279) and 27.64% (n = 4 453 368) of all the medicine items were for age group one patients in 2005 (N = 19 500 774), 2006 (N = 21 113 422), 2007 (N = 19 075 724) and 2008 (N = 16 439 253) respectively (Refer to Tables 4.1 and 4.11). Age group one Parkinson's disease patients' medicine item claims were 2.87% (n = 887) of all Parkinson's disease items in 2005 (N = 30 950), 3.46% (n = 1 69) in 2006 (N = 33 768), 3.35% (n = 1 054) in 2007 (N = 31 455) and 2.86% (n = 858) in 2008 (N = 30 040) (Refer to Tables 4.2 and 4.12).

On the total database the **medicine item cost** per prescription per age group one patients increased with 15.71% from 2005 (R71.23 ± R126.29) to 2008 (R82.42 ± R284.83). This group's Parkinson's disease patients experienced an increase of 5.43% from 2005 (R139.11

± R135.27) to 2008 (R146.66 ± R132.37). Practical significance in cost difference per medicine item was detected between the two sets of data for age group one, with a *d-value* of 0.5 in 2005 and 2006, after decreasing in 2007 (d = 0.3) and 2008 (d = 0.2) showing smaller practical significance.

An age group one patient on the total database received between 3.71 ± 4.19 and 4.26 ± 4.79 prescriptions per year with between 2.29 ± 1.33 and 2.34 ± 1.37 medicine items per prescription from 2005 to 2008. This age group's antiparkinson's prescriptions were between 2.10 ± 2.69 and 2.18 ± 2.72 prescriptions per year with between 1.04 ± 0.21 and 1.6 ± 0.25 medicine items per prescriptions per year (Refer to Tables 4.11 and 4.12).

The section that follows contains the discussion of the second age group 40 ≥ 50 years.

4.3.2.2.2 Analysis according to age group two (40 ≥ 50 years)

This age group represents the patients between the age of 40 and 50 years. Tables 4.14 and 4.15 were compiled from Tables A.3, A.7, A.9 and A.10 in appendix A.

Age group two **patients** represented 18.17% (n= 274 288) of all patients in 2005 (N = 1 509 621) and Parkinson's disease patients of the same age group were 0.2% (n = 354) of all patients. For 2006 (N = 1 558 090), 2007 (N = 1 178 596) and 2008 (N = 974 497) age group two' patients represented 18.55% (n = 289 947), 18.46% (n = 217 605) and 19.04% (n = 185 572) respectively of all patients. Parkinson's disease age group two patients represented 0.02% (n = 389), 0.03% (n = 336) and 0.04% (n = 365) of all patients respectively to 2006 - 2008 (Refer to Table 4.1, 4.14 and 4.15).

Table 4.14: Analysis of the total database according to age group two

Cost per medicine item				
Year	**Variable**	**Frequency (n)**	**Mean ± Std Dev (R)**	**Total cost (R)**
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Cost per prescription				
2005	Total prescription cost	1 555 030	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	1 687 320	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	1 484 105	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	1 251 445	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	3 912 429
2007		1 484 105	-	3 505 609
2008		1 251 445	-	2 958 642
Average number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		274 288	-	-
2006		-	-	-
2007		-	-	-
2008		-	-	-

Table 4.15: Analysis of Parkinson's medicine according to age group two

Year	Variable	Frequency (n)	Mean ± Std Dev (R)	Total cost (R)
Cost per medicine item				
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Cost per prescription				
2005	Total prescription cost	1 341	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	1 401	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	1 159	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	1 208	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	1 579
2007		1 159	-	1 316
2008		1 208	-	1 345
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		354	-	-
2006		-	-	-
2007		-	-	-
2008		-	-	-

Evaluating only the Parkinson's disease patients, this age group's patients, represented 8.87% (n = 354) of all Parkinson's disease patients in 2005 (N = 3 993). Differing slightly, the same was true for the other three study periods. In 2006 (N = 4 423) 8.9% (n = 389) were age group two Parkinson's disease patients, and 8.34% (n = 336) in 2007 (N = 4 028) and 8.96% (n = 365) in 2008 (N = 4 072) (Refer to Tables 4.2 and 4.15). With detailed figures in Tables 4.14 and 4.15, the number of patients in age group two on the total database decreased with 47.81% from 2005 (274 288) to 2008 (185 572) compared to a 3.11% increase in Parkinson's disease patients in age group two from 2005 (354) to 2008 (365) after fluctuating over the four-year period.

In 2005 (N = 8 391 836) 18.53% (n= 1 555 030) of all **prescriptions claimed** were for age group two patients, maintaining a percentage of 18% (n = 1 687 320, n = 1 484 105, n = 1 251 445) in 2006 (N = 8 906 348), 2007 (N = 7 911 096) and 2008 (N = 6 775 873) (Refer to Tables 4.1 and 4.14). Parkinson's disease age group two prescriptions claimed were 0.02% of all prescriptions from 2005 (N = 8 391 836) to 2008 (N = 6 775 873), the same age group represented 5.36% (n = 1 341) of all Parkinson's disease prescriptions claimed in 2005 (N = 25 011), 5.13% (n = 1 401) in 2006 (N = 27 234), 4.54% (n = 1 159) in 2007 (N = 25 513) and 4.95% (n = 1 208) in 2008 (N = 24 404) (Refer to Tables 4.1, 4.2 and 4.15).

Prescription expenditure for age group two patients indicated that 16.60% (n = R302 079 245.67) in 2005 (N = R1 819 865 251.63), 16.86% (n = R330 3434 409.54) in 2006 (N = R1 959 738 734.09), 16.57% (n = R317 879 932.08) in 2007 (N = R1 918 284 176.66) and 16.07% (n = R286 943 374. 17) in 2008 (N = R1 785 871 013.85) of the total prescription expenditures were for this group's patients (Refer to Table 4.1 and 4.14). Age group two Parkinson's disease patients' expenditure amounted to 3.45% (n = R361 078.24) in 2005 (N = R10 459 835.93), 3.56% (n = R403 046.76) in 2006 (N = R11 320 616.71), 3.27% (n = R360 474.70) in 2007 (N = R11 040 569.32) and 3.32% (n = R355 441.44) in 2008 (N = R10 697 155.54) of the total Parkinson's disease prescription expenditure (Refer to Tables 4.2 and 4.15). For each year the final prescription cost is divided into the medical scheme contribution and patient contribution, as set apart in Table 4.16:

Table 4.16: Percentage division of medical scheme and patient contribution per prescription per year according to age group two

TOTAL DATABASE					
Year	**Total prescription cost (R)**	**Medical scheme contribution (R)**	**Medical scheme contribution (%)**	**Patient contribution (R)**	**Patient contribution (%)**
2005	302 079 245.67	271 471 414.16	**89.87**	30 607 831.51	**10.13**
2006	330 434 409.54	293 219 526.05	**88.74**	37 214 883.49	**11.26**
2007	317 879 932.08	273 761 801.66	**86.12**	44 118 130.42	**13.88**
2008	286 943 374.17	243 396 847.08	**84.82**	43 546 527.09	**15.18**
PARKINSON'S DISEASE DATA					
2005	361 078.24	314 344.65	**87.06**	46 733.59	**12.94**
2006	403 046.76	344 772.09	**85.54**	58 274.67	**14.46**
2007	360 474.70	303 326.64	**84.15**	57 148.06	**15.85**
2008	355 441.44	280 501.16	**78.92**	74 940.28	**21.08**

In contrast to previous figures where the Parkinson's disease data showed the lowest increase in patient contribution from 2005 to 2008, in this age group Parkinson's disease data showed an increase of about 8% from 2005 to 2008. The total database' data showed a more or less 5% increase in patient contribution from 2005 to 2008, self explanatory meaning that the medical schemes contributions lessened with the same percentages.

The **cost per prescription** for this age group of patients on the total database, increased with 18.03% from 2005 (R194.26 $\pm$ R325.49) to 2008 (R229.29 $\pm$ R654.79). Parkinson's disease patients in this group, experienced an increase of 9.28% in the cost per prescription from 2005 (R269.26 $\pm$ R348.38) to 2008 (R294.24 $\pm$ R443.66) (Refer to Table 4.14 and 4.15). Although the difference in figures seems to drastically differ, the *d*-value indicated the difference in cost per prescription between the total database and the Parkinson's disease data, for age group two, to have very little practical significance with a *d*-value of 0.2 for 2005 to 2007, and even smaller value of 0.1 for 2008.

Medicine items claimed on the total database indicated that in 2005 (N = 19 500 774), 18.10% (n = 3 529 839) of all medicine items were for this age group's patients. Furthermore in 2006 (N = 8 906 348) 18.53% (n = 3 912 429), in 2007 (N = 7 911 096) 18.38% (n = 3 505 609) and 18% (n = 2 958 642) were for this age group's patients (Refer to Tables 4.1 and 4.14). In 2005 (N = 30 950), 1 495 (4.83%) of all Parkinson's disease medicine items claimed were for age group two patients. More or less the same percentages were encountered in 2006 (N = 33 768), 2007 (N = 31 455) and 2008 (N = 30 040) where 4.68% (n = 1 579), 4.18% (n = 1 316) and 4.48% (n = 1 345) respectively were medicine items claimed for age group two Parkinson's disease patients (Refer to Tables 4.2 and 4.15).

The average **cost per medicine item** for this age group's patients increased with 13.32% from 2005 (R85.58 $\pm$ R161.40) to 2008 (R96.98 $\pm$ R368.36). Parkinson's disease patients of this age group experienced a 9.42% increase in the average cost per medicine item from

2005 (R241.52 ± R247.49) to 2008 (R264.27 ± R325.22) (Refer to Tables 4.14 to 4.15). From 2005 (d = 0.6) to 2008 (d = 0.5) the *d-value* indicated intermediate practical significance in the cost per medicine item between the this age group's patients, respectively to the total database and the Parkinson's disease data (Refer to Table 4.14 and 4.15).

A patient of age group two on the total database roughly received between 5.67 ± 6.31 and 6.82 ± 7.01 prescriptions per year with between 2.27 ± 1.41 and 2.36 ± 1.48 medicine items per prescription. In comparison antiparkinson's prescriptions for this age group were between 3.31 ± 3.98 and 3.79 ± 4.26 prescriptions with more or less 1.11 ± 0.41 and 1.14 ± 0.51 medicine items (Refer to Tables 4.14 and 4.15). This indicated that the patients of this age group of the total database received more prescriptions and medicine items per year, compared to the Parkinson's disease patients of this age group.

The discussion of age group three follows in section 4.3.2.2.3.

4.3.2.2.3 Analysis according to age group three (50 ≥ 60 years)

Age group three of this study represents all the patients between the age of 50 years and 60 years. Tables 4.17 and 4.18 contain data from Tables A.3, A.7, A.9 and A.10 in appendix A.

In 2005 **patients** on the database accounted for 1 509 621, of which 13.14% (n = 198 312) were patients in age group three, and 0.03% (n = 447) were Parkinson's disease patients aged between 50 years and 60 years. In 2006 (N = 1 558 090), 2007 (N = 1 178 596) and 2008 (N = 974 497) patients between 50 years and 60 years represented 13.57% (n = 211 477), 13.85% (n = 163 288) and 15.87% (n = 154 659) respectively of all patients. The Parkinson's disease patients of this age group however represented 0.03% (n = 543) of all patients in 2006, 0.04% (n = 460) in 2007 and 0.06% (n = 539) in 2008 (Refer to Tables 4.1, 4.17 and 4.18). In 2005 (N = 3 993), 11.19% (n = 447) of all Parkinson's disease patients were of this age group. Similarly, in 2006 (N = 4 423) 12.18% (n = 543), and 11.42% (n = 460) in 2007 (N = 4 028) and 13.24% (n = 539) in 2008 (N = 4 072) (Refer to Tables 4.2 and 4.18).

Table 4.17: Analysis of the total database according to age group three

Cost per medicine item				
Year	**Variable**	**Frequency (n)**	**Mean ± Std Dev (R)**	**Total cost (R)**
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Cost per prescription				
2005	Total prescription cost	1 478 562	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	1 594 842	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	1 456 421	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	1 355 480	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	3 722 515
2007		1 456 421	-	3 481 411
2008		1 355 480	-	3 288 346
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		198 312	-	-
2006		-	-	-
2007		-	-	-
2008		-	-	-

Table 4.18: Analysis of Parkinson's medicine according to age group three

Year	Variable	Frequency (n)	Mean ± Std Dev (R)	Total cost (R)
Cost per medicine item				
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Cost per prescription				
2005	Total prescription cost	2 424	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	2 782	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	2 442	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	2 546	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	3 310
2007		2 442	-	2 904
2008		2 546	-	3 016
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		447	-	-
2006		-	-	-
2007		-	-	-
2008		-	-	-

Claimed prescriptions for age group three accounted for 17.62% (n = 1 478 562), 17.91% (1 594 842), 18.41% (n = 1 456 421) and 20% (n = 1 355 480) of all prescriptions claimed in 2005 (N = 8 391 836), 2006 (N = 8 906 348), 2007 (N = 7 911 096) and 2008 (N = 6 775 873) respectively. Prescriptions claimed for Parkinson's disease patients age group three represented 0.03% (n = 2 424) of all prescriptions claimed in 2005 (N = 8 391 836). In 2006 (N = 8 906 348; n = 2 782) and 2007 (N = 7 911 096; n = 2 442) 0.03% and 0.04% (n = 2546) in 2008 (N = 6 775 873) represented claims for this age group's Parkinson's disease patients (Refer to Tables 4.1, 4.17 and 4.18). Prescriptions for Parkinson's disease age group three patients, represented 9.69% (n = 2 424) of all Parkinson's disease prescriptions claimed in 2005 (N = 25 011), 10.18% (n = 2 782) in 2006 (N = 27 824), 9.57% (n = 2 442) in 2007 (N = 25 523) and 10.43% (n = 2 564) in 2008 (N = 24 404) (Refer to Tables 4.2 and 4.18).

Prescription expenditure per year for patients in age group three represented 19.26% (n = R350 548 696.47) of the total prescription expenditure in 2005 (N = R1 819 865 251.63). Total prescription expenditures decreased with 1.9% from 2005 to 2008. In 2006 (N = R1 959 738 734.09), 2007 (N = R1 918 284 176.66) and 2008 (N = R1 785 871 013.85) representation of the expenditures for this group's patients were 19.60% (n = R384 013 712.92), 20.03% (N = R348 265 598.69) and 21.30% (n = R380 433 225.13) (Refer to Tables 4.1 and 4.17).

Of the total prescription expenditure per year for Parkinson's disease prescriptions, in 2005 (N = R10 459 835.93) 9.09% (n = R950 944.34) represented the expenditure per patient aged between 40 years and 50 years. Furthermore Parkinson's disease age group three patents' cost represented 9.01% (n = R1 020 038.59) in 2006 (N = R11 320 616.71), in 2007 (N = R11 040 569.32) 8.48% (n = R936 258.26) and 9.21% (n = R985 444.53) in 2008 (N = R10 697 155.54) of all Parkinson's disease prescription expenditures (Refer to Table 4.2 and 4.18). The division of what the medical scheme and patients themselves had to contribute per prescription per year can be seen in Table 4.19 that follows below.

Table 4.19: Percentage division of medical scheme and patient contribution per prescription per year according to age group three

TOTAL DATABASE					
Year	**Total prescription cost (R)**	**Medical scheme contribution (R)**	**Medical scheme contribution (%)**	**Patient contribution (R)**	**Patient contribution (%)**
2005	350 548 696.47	309 958 669.11	**88.42**	40 590 027.36	**11.58**
2006	384 013 712.92	335 414 305.66	**87.34**	48599 407.26	**12.66**
2007	384 265 598.69	327 913 290.70	**85.34**	56 352 307.99	**14.66**
2008	380 433 225.13	319 230 366.04	**83.91**	61 202 859.09	**16.09**
PARKINSON'S DISEASE DATA					
2005	950 944.34	855 660.32	**89.98**	95 282.02	**10.02**
2006	1 020 038.59	917 754.08	**89.97**	102 284.51	**10.03**
2007	936 258.26	844 603.89	**90.21**	91 655.03	**9.79**
2008	985 444.53	874 542.26	**88.75**	110 902.27	**11.25**

A similar trend followed with patients in age group three compared to the previous two age groups, whereas the patient contribution increased from 2005 to 2008, consequently meaning a decrease in the medical scheme payments. Parkinson's disease patients' contribution in this age group increased with 1.23% from 2005 (10.02%) to 2008 (11.25%). Patients of the same age on the total database experienced an increase of 4.51% from 2005 (11.58%) to 2008 (16.09%) (Refer to Table 4.19). According to the *d*-value calculated for each of the study periods, no practical significance was found in the difference between the average prescription cost of a patient in age group three on the total database or Parkinson's disease database. The only study periods that showed some practical significant differences in the average prescription cost were 2005 and 2006 (d = 0.3) from thereon onwards only decreasing to d = 0.2 in 2007 and d = 0.1 in 2008. Contrary to this, on the total database the average prescription cost for patients in age group three increased with 18.38% from 2005 (R237.09 $\pm$ R372.74) to 2008 (R280.66 $\pm$ R961.86), in contrast to that a decrease of 1.35% for the same age Parkinson's disease patient was identified from 2005 (R392.30 $\pm$ R493.43) to 2008 (R387.06 $\pm$ R456.48) (Refer to Tables 4.17 and 4.18).

The number of **medicine items claimed** by the PBM for age group three patients calculated as 17.20% (n = 3 354 209) of all medicine items for 2005 (N = 19 500 774) and 17.63% (n = 3 722 515) in 2006 (N = 21 113 422), 18.25% (n = 3 481 411) in 2007 (N = 19 075 724) and 20% (n = 3 288 346) in 2008 (N = 16 439 253) (Refer to Tables 4.1 and 4.17). The number of medicine items for patients of age group three on the total database decreased with 2% from 2005 (3 354 209) to 2008 (3 288 346). Of all Parkinson's disease medicine items claimed in 2005 (N = 30 950) 9.46% (n = 2 927) represented this age group's Parkinson's disease patients. In 2006 (N = 33 769) 9.80% (n = 3 310) of all Parkinson's disease

medicine items were for this group and 9.23% (n = 2 904) in 2007 (N = 31 455) and 10.04% (n = 3 016) in 2008 (N = 30 040) (Refer to Tables 4.2 and 4.18). Claimed medicine items for Parkinson's disease patients in this age group increased with 3% from 2005 (2 927) to 2008 (3 016).

The average cost per **medicine item** for a person between 40 years and 50 years of age on the total database increased with 10.70% from 2005 (R104.51 ± R185.62) to 2008 (R115.69 ± R530.13), while the Parkinson's disease medicine item cost increased with a small percentage of 0.6% from 2005 (R324.89 ± R307.75) to 2008 (R326.74 ± R298.34) (Refer to Tables 4.17 and 4.18). The d-value for the average cost per medicine item between this age group's patients on the total database and the Parkinson's disease data was calculated. The d-value indicated great practical significant differences in the average cost per medicine item in 2005 (d = 0.7), 2006 (d = 0.7) and 2007 (d = 0.6), slightly decreasing in 2008 (d = 0.4) (Refer to Tables 4.17 and 4.18).

Results revealed that a patient in age group three received between 7.46 ± 7.96 and 8.92 ± 8.47 prescriptions per year which had between 2.27 ± 1.51 and 2.43 ± 1.63 medicine items per prescrition. In contrast to Parkinson's disease patients of the same age received between 4.72 ± 4.96 and 5.42 ± 5.32 antiparkinson's prescriptions with between 1.18 ± 0.49 and 1.21 ± 0.56 medicine items per prescription (Refer to Tables 4.17 and 4.18).

Patients aged between 60 years and 70 years will be discussed in the subsequent section.

4.3.2.2.4 Analysis according to age group four (60 ≥ 70 years)

Patients discussed in the subsequent section are between the age of 60 and 70 years. Summarised data for this group are found in Tables 4.20 and 4.21 and are compiled from Tables A.3, A7, A9 and A10 in appendix A.

Table 4.20: Analysis of the total database according to age group four

Cost per medicine item				
Year	**Variable**	**Frequency (n)**	**Mean ± Std Dev (R)**	**Total cost (R)**
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Cost per prescription				
2005	Total prescription cost	1 119 445	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	1 190 704	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	1 085 239	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	1 024 773	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	2 893 615
2007		1 085 239	-	2 684 068
2008		1 024 773	-	2 585 064
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		118 000	-	-
2006		-	-	-
2007		-	-	1 085 239
2008		-	-	1 024 773

Table 4.21: Analysis of Parkinson's medicine according to age group four

Cost per medicine item				
Year	**Variable**	**Frequency (n)**	**Mean ± Std Dev (R)**	**Total cost (R)**
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Cost per prescription				
2005	Total prescription cost	5 317	.±.	-
	Medical scheme contribution		.±.	-
	Patient contribution		.±.	-
2006	Total prescription cost	5 879	.±.	-
	Medical scheme contribution		.±.	-
	Patient contribution		.±.	-
2007	Total prescription cost	5 266	.±.	-
	Medical scheme contribution		.±.	-
	Patient contribution		.±.	-
2008	Total prescription cost	5 139	.±.	-
	Medical scheme contribution		.±.	-
	Patient contribution		.±.	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	7 970
2007		5 266	-	7 021
2008		5 139	-	6 644
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		770	-	-
2006		-	-	-
2007		-	-	5 266
2008		-	-	5 139

Age group four **patients** represented 7.82% (n = 118 000), and Parkinson's disease age group four patients represented 0.05% (n = 770) of all the patients on the database in 2005 (N = 1 509 621). Patients of this age group represented 7.9% (2006: n = 123 093, 2007: n = 93 045) of all patients in 2006 (N = 1 558 090) and 2007 (N = 1 178 596) and 9.19% (n = 89 570) in 2008 (N = 974 497). Furthermore Parkinson's disease patients represented 0.05% (n = 828) of all patients in 2006, 0.06% (n = 746) in 2007 and 0.08% (n = 800) in 2008. Of all the Parkinson's disease patients in 2005 (N = 3 993), 19.28% (n = 770) were between 60 and 70 years, 18.72% (n = 828) in 2006 (N = 4 423), 18.52% (n = 746) in 2007 (N = 4 028) and 19.45% (n = 800) in 2008 (N = 4 072) (Refer to Table 4.1, 4.2, 4.20 and 4.21).

Prescriptions claimed for this age group accounted for 13.33% (n = 1 119 445) of all prescriptions claimed for 2005 (N = 8 391 836), 13.37% (n = 1 190 704) in 2006 (N = 8 906 348), 13.72% (n = 1 085 239) in 2007 (N = 7 911 096) and 15.12% (n = 1 024 773) in 2008 (N = 6 774 873), showing increases of small increments from the first to last study period (Refer to Tables 4.1 and 4.20).

In 2005 (N = 8 391 836), 5 317 (0.06%) of all prescriptions claimed on the database were for Parkinson's disease patients in age group four, and for both 2006 (N = 8 906 348) and 2007 (N = 7 911 096) 0.07% (2006: n = 5 879, 2007: n = 5 266), and 0.08% (n = 5 139) in 2008 (N = 6 775 873) respectively (Refer to Tables 4.1. and 4.21). Relative consistency could be seen on the Parkinson's disease data representing age group four, with 21.26% (n = 5 417) of all Parkinson's disease prescriptions being for this specific group in 2005 (N = 25 011), 21.52% (n = 5 879) in 2006 (N = 27 324), 20.64% (n = 5 266) in 2007 (N = 25 513) and 21.06% (n = 5 139) in 2008 (N = 24 404) (Refer to Tables 4.2 and 4.21).

Prescription expenditures per age group four patient increased from 17.27% (n = R314 226 050.43) in 2005 (N = R1 819 865 251.63) to 17.54% (n = R343 825 122) in 2006 (N = R1 959 738 734.09) to 17.93% (n = R343 9633 853.04) in 2007 (N = R1 918 284 176.65) finally reaching 19.19% (n = R324 790 861.99) in 2008 (N = R1 785 871 913.85) (Refer to Tables 4.1 and 4.20). The total prescription cost for this age group increased with 9% from 2005 (n = R314 226 050.43) to 2008 (n = R324 790 861.99). Growing from the previously discussed age groups, the total prescription costs per year for Parkinson's disease patients of age group four presented with the second highest percentage. In 2005 (N = R10 459 835.93) the prescription cost for Parkinson's disease patients of this age group accounted to 26.41% (n = R2 762 198.26) of the total Parkinson's disease expenditure per year, with 25.73% (n = R2 912 762.33) in 2006 (N = R11 320 616.71), 23.78% (n = R2 625 177.49) in 2007 (N = R11 040 569.32) and 22.85% (n = R2 444 261.41) in 2008 (N = R10 697 155.54) (Refer to Tables 4.2 and 4.21). Parkinson's disease total prescription cost decreased with 13% from 2005 (R2 762 198.26) to 2008 (R2 444 261.41).

Table 4.22 that follows indicated that the patient contribution for a patient of age group four on the total database, increased with 4.2% from 2005 to 2008. Parkinson's disease patients of this age group had a patient contribution increase of more or less 3% over the same period of time. The medical scheme contributions respectively decreased in the study periods.

Table 4.22: Percentage division of medical scheme and patient contribution per prescription per year according to age group four

TOTAL DATABASE					
Year	**Total prescription cost (R)**	**Medical scheme contribution (R)**	**Medical scheme contribution (%)**	**Patient contribution (R)**	**Patient contribution (%)**
2005	314 226 050.43	273 295 510.80	**86.97**	40 930 539.63	**13.03**
2006	343 825 122.00	295 728 687.03	**86.01**	48 096 435.00	**13.99**
2007	343 963 853.04	289 974 364.31	**84.30**	53 989 488.73	**15.70**
2008	342 790 861.99	283 688 150.76	**82.76**	59 102 711.23	**17.24**
PARKINSON'S DISEASE DATA					
2005	2 762 198.26	2 483 051.22	**89.89**	279 147.04	**10.11**
2006	2 912 762.33	2 624 503.28	**90.10**	288 259.05	**9.90**
2007	2 625 177.49	2 372 323.03	**90.37**	252 854.46	**9.63**
2008	2 444 261.41	2 122 684.73	**86.84**	321 576.68	**13.16**

Age group four patients on the total database had a greater financial burden than those of the same age for their antiparkinson's medication. The average prescription expenditure for a patient between 60 and 70 years increased with 19.17% from 2005 (R280.70 $\pm$ R422.99) to 2008 (R334.50 $\pm$ R1 037.40). Parkinson's disease patients of this age group experienced a decrease of 9.22% in the average prescription cost from 2005 (R519.50 $\pm$ R486.58) to 2008 (R475.63 $\pm$ R487.66). The *d*-values were calculated to indicate a difference in the average prescription cost between the two sets of data. The only study period that showed relative practical significance was 2005, with a *d*-value of d = 0.5, thereafter decreasing with small increments from 2006 (d = 0.4) to 2008 (d = 0.1).

Medicine items claimed for age group four patients represented 13.65% (n = 2 662 019) in 2005 (N = 19 599 774) of all medicine items claimed through the PBM, 13.71% (n = 2 893 615) in 2006 (N = 21 113 422), 15.01% (n = 2 684 068) in 2007 (N = 19 075 724) and 15.72% (n = 2 585 064) in 2008 (N = 16 439 253). Although decreasing slightly, 23.64% (n = 7 316) in 2005 (N = 30 950), 23.60% (n = 7 970) in 2006 (N = 33 768), 22.32% (n = 7 021) in 2007 (N = 31 455) and 22.1.2% (n = 6 644) in 2008 (N = 30 040), of all Parkinson's disease medicine items claimed were for patients aged between 60 and 70 years (Refer to Tables 4.1, 4.2, 4.20 and 4.21).

The **average medicine item cost** showed an increase for patients in this age group, compared to other age groups. The average medicine item cost increased with 12.33% from

2005 (R188.04 ± R197.64) to 2008 (R332.60 ± R573.79) for patients of this group on the total database. Parkinson's disease patients of this age group had a decrease of 2.63% in average medicine item cost from 2005 (R377.56 ± R282.77) to 2008 (R367.89 ± R305.59) (Refer to Tables 4.1, 4.2, 4.20 and 4.21). The *d*-value, however, indicated great practical significance between average medicine item cost for the two sets of data in 2005 (d = 0.9) and 2006 (d = 0.9), decreasing from thereon, 2007 (d = 0.6) and 2008 (d = 0.4) (Refer to Tables 4.20 and 4.21).

On average an age group four patient received between 9.49 ± 9.23 and 11.66 ± 9.75 prescriptions per year with between 2.38 ± 1.70 and 2.52 ± 1.83 medicine items per prescriptions. In comparison, antiparkinson's prescriptions of this age group had between 6.42 ± 5.52 and 7.10 ± 5.42 with between 1.29 ± 0.59 medicine items (Refer to Tables 4.20 and 4.21). The Parkinson's disease patients had a more consistent average of prescriptions and medicine items per year.

4.3.2.2.5 Analysis of age group five (70 ≥ 80 years)

Patients between the age of 70 and 80 years on the database were represented by age group five and were discussed in the section that follows. Compiled from Tables A.3, A.7, A.9 and A.10 in Appendix A, Tables 4.23 and 4.24 give a summary of all age group five's data on the total database and Parkinson's disease data respectively.

Table 4.23: Analysis of the total database according to age group five

Year	Variable	Frequency (n)	Mean ± Std Dev (R)	Total cost (R)
Cost per medicine item				
2005	Total medicine item cost		±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2006	Total medicine item cost		±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2007	Total medicine item cost		±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2008	Total medicine item cost		±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
Cost per prescription				
2005	Total prescription cost	799 577	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2006	Total prescription cost	827 593	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2007	Total prescription cost	785 089	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2008	Total prescription cost	726 905	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-

		Number of prescriptions	Average number of medicine items per prescription	Total number of medicine items
Number of medicine items per prescription				
2005		-	-	-
2006		-	-	2 121 016
2007		785 089	-	2 055 639
2008		726 905	-	1 929 653

		Number of patients	Average number of prescriptions per patient	Total number of prescriptions
Number of prescriptions per patient				
2005		70 854	-	-
2006		-	-	-
2007		-	-	785 089
2008		-	-	726 905

Table 4.24: Analysis of Parkinson's medicine according to age group five

Year	Variable	Frequency (n)	Mean ± Std Dev (R)	Total cost (R)
Cost per medicine item				
2005	Total medicine item cost		±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2006	Total medicine item cost		±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2007	Total medicine item cost		±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2008	Total medicine item cost		±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
Cost per prescription				
2005	Total prescription cost	8 386	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2006	Total prescription cost	8 680	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2007	Total prescription cost	8 482	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2008	Total prescription cost	8 134	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	11 027
2007		8 482	-	10 829
2008		8 134	-	10 543
Number of prescriptions per patient				
		Number of patients	**Average items per prescription**	**Total number of prescriptions**
2005		1 126	-	-
2006		-	-	-
2007		-	-	8 482
2008		-	-	8 134

Patients of this age group, represented 4.69% (n = 70 854) of all patients on the database in 2005 (N = 1 509 621), 4.58% (n = 71 416) in 2006 (N = 1 558 090), 4.72% (n = 55 591) in 2007 (N = 1 178 596) and 5.37% (n = 52 301) in 2008 (N = 974 497). Furthermore, of all the patients, Parkinson's disease patients in this age group represented only 0.07% (n = 1 126, n = 1 167) in both 2005 and 2006, slightly increasing to 0.09% (n = 1 088) and 0.11% (n = 1 050) in 2007 and 2008 (Refer to Tables 4.1, 4.23 and 4.24). Of all the Parkinson's disease patients in 2005 (N = 3 993), 28.20% (n = 1 126) were of age group five, likewise for 2006 (N = 4 423) with 26.38% (n = 1 167), 27.01% (n = 1 088) in 2007 (N = 4 028) and 25.79% (n = 1 050) in 2008 (N = 4 072) (Refer to Tables 4.2 and 4.24).

Prescriptions claimed for patients of age group five through the PBM for this study period were reasonably consistent with 9.53% (n = 199 577) of all prescription in 2005 (N = 8 391 836), 9.29% (n = 827 593) of all prescriptions in 2006 (N = 8 906 348) and 9.92% (n = 785 089) in 2007 (N = 7 911 096) and 10.73% (n = 726 905) in 2008 (N = 6 775 873) (Refer to Tables 4.1 and 4.23). Prescriptions claimed for Parkinson's disease patients in this age group represented only 0.1% of all prescriptions claimed on the database in each of the study periods. In comparison 33.53% (n = 8 386) of all the Parkinson's disease prescriptions claimed in 2005 (N = 25 011), 31.77% (n = 8 680) in 2006 (N = 27 324), 33.25% (n = 8 482) in 2007 (N = 25 513) and 33.33% (n = 8 134) in 2008 (N = 24 404) were for this age group's patients (Refer to Tables 4.1, 4.2 and 4.24).

The final **prescription cost** for 2005 was R1 819 865 251.63 of which R241 473 684.43 (13.27%) indicated the cost contributed by age group five patients. In 2006 (N = R1 959 738 734.09) 13.08% (n = R256 283 882.06), in 2007 (n = R1 918 284 176.66) 14.02% (n = R268 955 271.37) and 14.54% (n = R259 683 970.57) of 2008' (R1 785 871 013.85) final prescription costs were the costs that this age group's patients paid (Refer to Tables 4.1 and 4.23). The part of the final Parkinson's disease prescription cost that the age group five Parkinson's disease patients had to pay, was almost three times more than that of the total database, 35.22% (n = R3 684 440.91). In 2005 (N = R10 459 835.93), 35.71% (n = R4 042 272.32) in 2006 (N = R11 320 616.71), 37.69% (n = R 4 161 183.72) in 2007 (N = R11 040 569.32) and finally increasing with ± 3.8% from 2005 to 2008, 39.04% (n = R4 175 353.08) of 2008 (N = R10 697 155.54) prescription costs were for age group five Parkinson's disease patients' prescription expenditure (Refer to Tables 4.2 and 4.24). The patient contribution and medical scheme contributions for each study period are given in Table 4.25 below:

Table 4.25: Percentage division of medical scheme and patient contribution per prescription per year according to age group five

TOTAL DATABASE					
Year	**Total prescription cost (R)**	**Medical scheme contribution (R)**	**Medical scheme contribution (%)**	**Patient contribution (R)**	**Patient contribution (%)**
2005	241 473 684.43	206 388 877.35	**85.47**	35 084 807.08	**14.53**
2006	256 283 882.06	215 944 958.47	**84.26**	40 338 923.59	**15.74**
2007	268 955 271.37	223 112 869.31	**82.96**	45 842 402.06	**17.04**
2008	259 683 970.57	212 259 297.03	**81.74**	47 424 673.54	**18.26**
PARKINSON'S DISEASE DATA					
2005	3684440.91	3 302 880.88	**89.64**	381 560.03	**10.36**
2006	4042272.32	3 586 996.35	**88.74**	455 275.97	**11.26**
2007	4161183.72	3 718 545.68	**89.36**	442 638.04	**10.64**
2008	4175353.08	3 688 128.68	**88.33**	487 224.40	**11.67**

Although the total patient contribution per prescription increased with only 3.7% on the total database's data for age group five from 2005 (14.53%) to 2008 (18.26%), the average cost per prescription increased with 18.29% from 2005 (R302 ± R438.90) to 2008 (R357.25 ± R968.22). The cost per prescription for Parkinson's disease patients increased with 16.83% from 2005 (R439.36 ± R361.63) to 2008 (R513.332 ± R450.26), compared to the patient contribution increasing with only 1.3% in the same period (Refer to Tables 4.23, 4.24 and 4.25). When comparing the difference in average prescription cost between the two sets of data for a patient in age group five, a slight to almost no practical significance was indicated by the *d*-value for all the study periods (2005: d = 0.3, 2006: d = 0.3, 2007: d = 0.2, 2008: d = 0.2).

The number of **medicine items claimed** for a person aged between 70 and 80 years represented 10.26% (n = 2 000 692) of all medicine items claimed in 2005 (N = 19 500 774), 10.05% (n = 2 121 016) in 2006 (N = 21 113 422), 10.78% (n = 2 055 639) in 2007 (N = 19 075 724) and 11.74% (n = 1 929 653) in 2008 (N = 16 439 253) (Refer to Tables 4.1 and 4.23). Age group five Parkinson's disease patients had the highest percentage of medicine items claimed of all Parkinson's disease medicine items, with 33.82% (n = 10 467) in 2005 (N = 30 950), 32.66% (n = 11 027) in 2006 (N = 33 768), 34.43% (n = 10 829) in 2007 (N = 31 455) and 35.10% (n = 10 534) in 2008 (N = 30 040) (Refer to Tables 4.2 and 4.24).

The average **medicine item cost** increased from 2005 (R120.70 ± R201.36) with 11.50% to 2008 (R134.58 ± R507.88) on the total database data for this age group, compared to an increase of 12.51% from 2005 (R352.01 ± R224.62) to 2008 (R396.03 ± R277.022) on the Parkinson's disease data. Opposing *d*-value statistics differing from any of the other age groups, showed that immense practical significance in average medicine item cost was found

in 2005 (d = 1.03) and despite decreasing the same was true for 2006 (d = 0.8) and 2007 (d = 0.7), leaving 2008 (d = 0.5) with the smallest *d*-value (Refer to Tables 4.23 and 4.24).

On average the age group five patients received between 11.28 ± 11.28 and 14.12 ± 10.67 prescriptions per year. These prescriptions contained between 2.50 ± 1.86 and 2.65 ± 2.00 medicine items per prescription. Antiparkinson's prescriptions for this age group represented between 7.45 ± 5.49 and 7.80 ± 5.48 prescriptions per year, with 1.25 ± 0.54 and 1.30 ± 0.60 medicine items per prescription (Refer to Tables 4.23 and 4.24). The Parkinson's disease data showed more consistency in the number of prescriptions and medicine items throughout the study period.

The last age group will be discussed in the section that follows.

4.3.2.2.6 Analysis according to age group six (80 > years)

This section contains the discussion of the last age group of this study. Patients that are 80 years and older were in this age group. Tables 4.25 and 4.26 include summarised data from Tables A.3, A.7, A.9 and A.10.

Table 4.26: Analysis of the total database according to age group six

Year	Variable	Frequency (n)	Mean ± Std Dev (R)	Total cost (R)
Cost per medicine item				
2005	Total medicine item cost	-	- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
2006	Total medicine item cost		- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
2007	Total medicine item cost		- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
2008	Total medicine item cost		- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
Cost per prescription				
2005	Total prescription cost	420 983	- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
2006	Total prescription cost	450 889	- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
2007	Total prescription cost	455 881	- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
2008	Total prescription cost	441 776	- ± -	-
	Medical scheme contribution		- ± -	-
	Patient contribution		- ± -	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	1 126 517
2007		455 881	-	1 156 718
2008		441 776	-	1 134 180
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		33 945	-	-
2006		-	-	-
2007		-	-	455 881
2008		-	-	441 776

Table 4.27: Analysis of Parkinson's medicine according to age group six

Year	Variable	Frequency (n)	Mean ± Std Dev (R)	Total cost (R)
Cost per medicine item				
2005	Total medicine item cost		±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2006	Total medicine item cost		±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2007	Total medicine item cost		±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2008	Total medicine item cost		±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
Cost per prescription				
2005	Total prescription cost	6 697	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2006	Total prescription cost	7 479	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2007	Total prescription cost	7 152	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
2008	Total prescription cost	6 567	±	-
	Medical scheme contribution		±	-
	Patient contribution		±	-
Number of medicine items per prescription				
		Number of prescriptions	**Average number of medicine items per prescription**	**Total number of medicine items**
2005		-	-	-
2006		-	-	8 713
2007		7 152	-	8 331
2008		6 567	-	7 634
Number of prescriptions per patient				
		Number of patients	**Average number of prescriptions per patient**	**Total number of prescriptions**
2005		897	-	-
2006		-	-	-
2007		-	-	7 152
2008		-	-	6 567

Patients older than 80 years represented only 2.25% (n = 33 945) of all patients on the database in 2005 (N = 1 509 621), 2.20% (n = 34 342) in 2006 (N = 1 558 090), 2.50% (n= 29 437) in 2007 (N = 1 178 596) and 2.93% of all patients in 2008 (N = 974 497) (Refer to Tables 4.1 and 4.26). Parkinson's disease patients in the same age group, however, represented only 0.06% (n = 897, n = 972) of all patients in 2005 (N = 1 509 621) and 2006 (N = 1 558 090), and only 0.08% (n = 934) and 0.1% (n = 944) in 2007 (N = 1 178 596) and 2008 (N = 974 497) respectively (Refer to Tables 4.1 and 4.27). Despite Parkinson's disease age group six patients' poor representation on the complete database, they represented 22.46% (n = 879) of all Parkinson's disease patients in 2005 (N = 3 993). Furthermore in 2006 (N = 4 423) Parkinson's disease patients of this age group represented 21.98% (n = 972), 23.19% (n = 934) in 2007 (N = 4 028) and 23.44% (n = 944) in 2008 (N = 4072) (Refer to Tables 4.2 and 4.27).

Data supplied by the PBM showed that the number of **prescriptions claimed** for age group six represented 5.12% (n = 420 983) of all prescriptions claimed in 2005 (N = 8 391 836). In 2006 (N = 8 906 348) this age group's prescription claims represented 5.06% (n = 450 889) of all prescriptions and 5.76% (n = 455 881) in 2007 (N = 7 911 096) and 6.52% (n = 441 776) in 2008 (6 775 873) (Refer to Tables 4.1 and 4.26). Prescriptions claimed for Parkinson's disease patients in this age group were 0.08% (n = 6 697, n = 7 479) of all prescriptions in 2005 and 2006, and 0.09% (n = 7 152) in 2007 and 0.1% (n = 6 567) in 2008. The number of prescriptions claimed for Parkinson's disease patients 80 years and older in 2005 (N = 25 011) represented 26.78% (n = 6 697) of all Parkinson's disease prescriptions claimed for that year. In 2006 (N = 27 324) however 27.37% (n = 7 479), 28.03% (n = 7 152) in 2007 (N = 25 513) and 26.91% (n = 6 567) in 2008 (N = 24 404) of all Parkinson's disease prescriptions belonged to this age group (Refer to Tables 4.2 and 4.27).

Even though the final **prescription expenditure** only increased with 1.4% from 2005 to 2008 for age group six patients, in 2005 (N = R1 819 865 251.62) this age group's share that was paid, accounted for 6.52% (n = R118 658 115.71) of the total prescription expenditures for that year. This was also true for 2006 (N = R1 959 738 734.09), 2007 (N = R1 918 284 176.66) and 2008 (N = R1 785 871 013.85), where these patients' contribution to the final prescription cost amounted to 6.55% (n = R128 376 223.47), 7.36% (n = R141 235 860.21) and 7.93% (n = R141 540 699.09) respectively (Refer to Tables 4.1 and 4.26). Figures four times higher compared to the total database's equivalent group, stipulated the part that Parkinson's disease patients in the same group had to pay of the total Parkinson's disease prescription expenditures per year to be 24.62% (n = R2 577 787.75) in 2005 (N = R10 459 835.93), 24.54% (n = R2 777 764.29) in 2006 (N = R11 320 616.71), 25.45% (n = R2 810 169) in 2007 (N = R11 040 469.32) and 24.41% (n = R2 610 818) in 2008 (N = R10 697

155.54) (Refer to Tables 4.2 and 4.27). Table 4.28 gives detailed figures for the total medical scheme contribution of each year, as well as the total patient contribution per year.

Table 4.28: Percentage division of medical scheme and patient contribution per prescription per year according to age group six

TOTAL DATABASE					
Year	**Total prescription cost (R)**	**Medical scheme contribution (R)**	**Medical scheme contribution (%)**	**Patient contribution (R)**	**Patient contribution (%)**
2005	118 658 115.71	97 085 975.48	**81.82**	21 572 140.23	**18.18**
2006	128 376 223.47	102 743 808.91	**80.03**	25 632 414.56	**19.97**
2007	141 235 860.21	110 103 745.16	**77.96**	31 132 115.05	**22.04**
2008	141 540 699.09	108 774 072.86	**76.85**	32 766 626.23	**23.15**
PARKINSON'S DISEASE DATA					
2005	2 577 787.75	2 257 243.44	**87.57**	320 544.31	**12.43**
2006	2 777 764.29	2 394 267.10	**86.19**	383 497.19	**13.81**
2007	2 810 169.39	2 438 033.66	**86.76**	372 135.73	**13.24**
2008	2 610 818.03	2 199 213.72	**84.23**	411 604.31	**15.77**

From 2005 to 2008 the patient contribution increased parallel to a decrease in medical scheme contribution with 4.97% on the total database, compared to an increase of 3.34% on the Parkinson's disease data (Refer to Table 4.28). On the total database the average prescription expenditure per year increased from 2005 (R281.86 $\pm$ R354.95) with 13.67% to 2008 (R320.39 $\pm$ R536.86). The average prescription cost increased with 3.29% for a Parkinson's disease patient 80 years and older form 2005 (R384.92 $\pm$ R316.06) to 2008 (R397.57 $\pm$ R306.00). The *d*-value was calculated for the average prescription cost between the total database and Parkinson's disease data. The only study periods that indicated slight practical significance between the average prescription cost between the total database and Parkinson's disease data were 2005 (d = 0.3) and 2006 (d = 0.2). The remainder of the study periods, 2007 (d = 0.1) and 2008 (d = 0.1) indicated little to no practical significant difference in average prescription cost (Refer to Tables 4.26 and 4.27).

The number of **medicine items claimed** for patients of 80 years and older, represented 5.3% (n = 1 034 450, n = 1 126 517) of all medicine items claimed in 2005 (N = 19 500 774) and 2006 (N = 21 113 422), but only 6.06% (n = 1 156 718) in 2007 (N = 19 075 724) and 6.9% (n = 1 134 180) in 2008 (N = 16 439 253) (Refer to Tables 4.1 and 4.26). Medicine items claimed for Parkinson's disease patients in 2005 were 30 950 of which 7 858 (25.39%) were for age group six Parkinson's disease patients. In 2006 (N = 33 768), 25.80% (n = 8 713) and 26.49% (n = 8 331) in 2007 (N = 31 455) were for this groups Parkinson's disease patients leaving only 2008 (N = 30 040) of which 25.41% (n = 7 634) of all Parkinson's disease prescription were for these patients (Refer to Tables 4.2 and 4.27).

The **cost per medicine item** increased with 8.8% per year on the total database for age group six patients from 2005 (TD: R114.71 ± R167.71, PD: R328.05 ± R203.71) to 2008 (TD: R124.80 ± R275.29, PD: R342 ± R218.05), 4.25% however was the increase experienced by the Parkinson's disease patient of the same age group (Refer to Tables 4.26 and 4.27). Incomparable to any other age group, this group shows enormous practical significance in terms of average medicine item cost difference between the total database and Parkinson's disease data. The *d*-values were calculated, and indicated in 2005 (d = 1.05) and 2006 (d = 1.08) the highest *d-value*s not differing much from 2007 (d = 0.7) and 2008 (d = 0.8) (Refer to Tables 4.26 and 4.27)

A person aged 80 years and older received more or less 12.40 ± 11.06 and 15.49 ± 11.65 prescriptions per year with between 2.46 ± 1.85 and 2.57 ± 1.96 medicine items on a prescription, whereas the same aged Parkinson's disease patient received roughly between 6.96 ± 5.05 and 7.69 ± 4.29 antiparkinson's prescriptions per year with 1.16 ± 0.44 and 1.17 ± 0.46 medicine items per prescription (Refer to Tables 4.26 and 4.27). The chronic Parkinson's disease patient had a consistent number of prescriptions and medicine items received over the study period, compared to the total database patient.

In the subsequent section a summary of the second demographic parameter is given.

4.3.2.2.7 Summary of the age groups

The **patients** on the database were divided into these specific age groups. After evaluating the two data sets for the six different age groups, the distinct conclusion could be made that in each study period there was a decrease of patient representation on the total database from age group one to six. For the Parkinson's disease data set, the exact opposite was true where the increase was found from age group two to five, only slightly decreasing again to age group six. Literature indicated that the prevalence of Parkinson's disease among individuals 40 years and younger (age group one) was not an ordinary phenomenon (Gancher, 2010). Furthermore the literature proved the Parkinson's disease data of this study correct, which claimed, that the incidence of Parkinson's disease rises with an increase of age. Thus a higher prevalence from 50 to 60 years was encountered (Van Den Eeden *et al.,* 2003:1016; Rodríguez-Molinero *et al.*, 2009:430).

Figure 4.4 illustrates the patient representation on the total database and Parkinson's disease data respectively to each age group, compiled from Tables 4.11 to 4.27. On the total database patients in age groups one to three were ± 83% compared to Parkinson's disease patients of age groups one to three being ± 32% of each study period, thus age

groups four to six on the total database representing ± 15% compared to the majority of Parkinson's disease patients representing ± 68% per year. This proves literature mentioned in section 1.1 of this study to be true, which states the patients affected by Parkinson's disease usually occur from the age of ± 60 years.

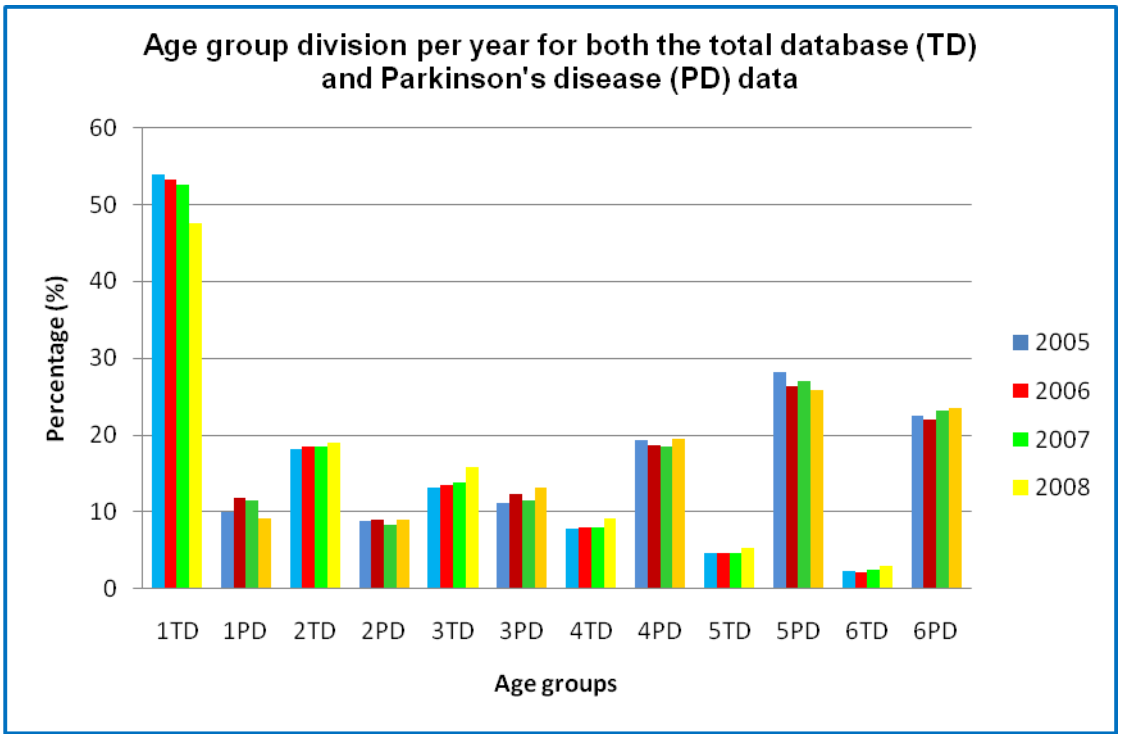

Figure 4.4: Age group divisions per year for total database (TD) and Parkinson's disease (PD) data

When taking a closer look at the number of **prescriptions claimed** through the PBM, the majority of prescriptions on the total database were claimed each year for age group one with an average of 33% (2005 = 35.97%, 2006 = 35.42%, 2007 = 33.43%, 2008 = 29.15%) over the study period (Refer to Tables 4.1 and 4.11). On the Parkinson's disease data, the largest number of prescriptions was claimed for age group five representing more or less 33% (2005 = 33.53%, 2006 = 31.77%, 2007 = 33.25%, 2008 = 33.33%) of all antiparkinson prescriptions claimed over the study period (Refer to Table 4.2 and 4.24). The smallest number of prescriptions claimed was for age group six on the total database representing more or less 5.5% (2005 =5.12%, 2006 = 5.06%, 2007 = 5.76%, 2008 = 6.52%) per year (Refer to Tables 4.1 and 4.26). Antiparkinson prescriptions claimed were the least for age group one representing more or less 3.5% (2005 = 3.38%, 2006 = 4.04%, 2007 = 3.97%, 2008 = 3.32%) per year (Refer to Tables 4.2 and 4.12). On the total database the ratio of age groups one to three against age groups four to six is 2:1, compared to the Parkinson's disease data that showed a 1:4 ratio for the same age group division, as shown in Table 4.29 below (Table 4.29 is compiled from Tables 4.11, 4.12, 4.14, 4.15, 4.17, 4.18, 4.20, 4.21, 4.23, 4.24, 4.26 and 4.27).

Table 4.29: Percentage division of claimed prescriptions for age groups one to three and age groups four to six

Year	Total database		Ratio	Parkinson's disease data		Ratio
	Age group 1 to 3 (%)	Age group 4 to 6 (%)		Age group 1 to 3 (%)	Age group 4 to 6 (%)	
2005	72.12	27.98	**2:1**	18.43	81.57	**1:4**
2006	72.28	27.72	**2:1**	19.35	80.66	**1:4**
2007	70.60	29.40	**2:1**	18.08	81.92	**1:4**
2008	63.03	32.37	**2:1**	18.70	81.30	**1:4**

The economic impact of the total **prescription expenditure** per year was throughout the study period the largest for age group one patients on the total database with an average of 24% per year (2005 = 27.08%, 2006 = 26.37%, 2007 = 24.08%, 2008 = 20.97%) respectively to each period's total expenditure (Refer to Tables 4.1 and 4.11). Age group five patients on the Parkinson's disease data had the largest total prescription expenditures with an average of 37% (2005 = 35.22%, 2006 = 35.71%, 2007 = 37.69%, 2008 = 39.03%) per year respectively to the total Parkinson's disease expenditures (Refer to Tables 4.2 and 4.24). With figures fluctuating slightly from year to year in each age group, no distinct pattern of a specific study period with the largest expenditure could be pinned down. The ratio for age groups one to three against age groups four to six patients still shows the largest for the aged Parkinson's disease patient group, with a more or less 20:80 per year contradictory to the total database ratio of 60:40 per year. Prescription costs per year showed rather little to no practical significant difference to any of the age groups.

The number of **medicine items** per prescription was more or less consistent for each Parkinson's disease age group every year, with $\pm$ 1 to 2 medicine items per prescription, of all the medicine items claimed. The largest percentage of medicine items claimed was for that of age group five Parkinson's disease patients representing more or less 34% (2005 = 33.82%, 2006 = 32.66%, 2007 = 34.43%, 2008 = 35.10%) throughout the study period (Refer to Tables 4.2 and 24). Secondly, more or less 26% (2005 = 25.39%, 2006 = 25.80%, 2007 = 26.49%, 2008 = 25.41) of antiparkinson medicine item claimed were for age group six (Refer to Tables 4.2 and 4.27). The total database's figures for medicine items claimed was the highest for age group one with an average of 33% (2005 = 35.48%, 2006 = 34.75%, 2007 = 32.46%, 2008 = 27.64%) per year over the study period (Refer to Tables 4.1 and 4.11). The number of medicine items claimed gradually declined with the increase in age on the total database (Refer to Tables 4.11, 4.14, 4.17, 4.20, 4.23 and 4.26). The number of medicine items per prescription per age group per year was also relatively consistent on the total database, with an average of between 1 to 4 medicine items per prescription.

Medicine item expenditure increases were felt mainly by age group one patients on the total database, with an increase of 15.71% from 2005 to 2008 (Refer to Table 4.11), with

Parkinson's disease patients in age group five with an increase of 12.51% from 2005 to 2008 (Refer to Table 4.24). In most cases practical significant differences were indicated regarding medicine item cost, showing the largest economic impact to be on the Parkinson's disease age groups.

In general the pattern repeated itself, showing that the age group affected the most on the total database was age group one, and on the Parkinson's disease data, age group five stood out the most, closely followed by age groups six and four. This, however, confirms other studies (Gancher 2010; Rodríguez-Molinero *et al.*, 2009:430; Van Den Eeden *et al.,* 2003:1016, 1022) mentioned in chapter one, stating that Parkinson's disease affects patients from 60 years the most, not often affecting patients of 40 years and younger. An insightful discovery also confirmed by this study was that the incidence of Parkinson's disease rose with an increase in age.

The section to follow contains a discussion on the prescribers relevant to only Parkinson's disease data as to prescriptions and medicine items cost.

4.3.3 Analysis of Parkinson's disease data according to prescribers

In the subsequent section four sets of prescriber data were discussed per medicine item cost and prescription cost for Parkinson's disease. The prescribers that were assed were: General Medical Practitioners (GP), Neurologists (N), Psychiatrists (P) and Other (O). Tables 4.30 and 4.31 contain the summarised data for the prescribers mentioned, compiled from Tables A.4 and A.8 in Appendix A.

Table 4.30: Analysis of Parkinson's medicine according to prescribers

Cost per medicine item				
Year	**Variables**	**Frequency (n)**	**Mean ± Std Dev (R)**	**Total Cost (R)**
General medical practitioner				
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Neurologist				
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		473.45 ± 304.63	3 665 419.86
	Medical scheme contribution		-	-
	Patient contribution		-	-
Psychiatrist				
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Other				
2005	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total medicine item cost		-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-

Table 4.31: Analysis of Parkinson's medicine according to prescribers

Average cost per prescription				
Year	**Variables**	**Frequency (n)**	**Mean ± Std Dev (R)**	**Total Cost (R)**
General medical practitioner				
2005	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Neurologist				
2005	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Psychiatrist				
2005	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
Other				
2005	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2006	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2007	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-
2008	Total prescription cost	-	-	-
	Medical scheme contribution		-	-
	Patient contribution		-	-

The **medicine items claimed** as prescribed by a general medical practitioner were 55.58% (n = 17 203) in 2005 (N = 30 950), 56.79% (n = 19 177) in 2006 (N = 33768), 54.17% (n = 17

040) in 2007 (N = 31 455) and 55.74% (n = 16 743) in 2008 (N = 30 040) of all medicine items claimed for each year. Following with second highest percentages, the number of medicine items claimed as prescribed by a neurologist in 2005, represented 25.56% (n = 7912), then 25.03% (n = 8 452) in 2006, increasing to 26.95% (n = 8 477) in 2007 and 25.77% (n = 7 7442) in 2008. The prescriber group denoted as "other" were responsible for 14.48% (n = 4 481) of all medicine items claimed in 2005 as prescribed by them, as was the case in 2006 with 13.75% (n = 4 643), 14.37% (n = 4 521) in 2007 and 14.28% (n = 4 290) in 2008. Psychiatrists were responsible for more or less a 5th of all claimed medicine items in 2005 to 2008, with 4.37% (n = 1 353), 4.43% (n = 1 496), 4.50% (n= 1 417) and 4.21% (n = 1 265) respectively (Refer to Table 4.2 and 4.30).

In this process of focusing on the number of **prescriptions claimed** as prescribed by a specific prescriber the majority represented prescriptions prescribed by general medical practitioners, followed by neurologists, others and with the smallest proportion for psychiatrists. With detailed figures in Tables 4.30 and 4.31, Table 4.32 gives the percentage of prescriptions claimed as prescribed by the specific prescriber for each of the study periods.

Table 4.32: Percentage division of prescriptions claimed as prescribed by prescriber

Percentage of prescriptions prescribed by prescriber									
Year	**All prescriptions claimed (N)**	**GP**		**N**		**P**		**O**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
2005	25 011	14 734	**58.91**	5 386	**21.53**	1 240	**4.96**	3 651	**14.60**
2006	27 324	16 389	**59.98**	5 647	**20.67**	1 376	**5.04**	3 912	**14.32**
2007	25 513	14 653	**57.43**	5 704	**22.36**	1 281	**5.02**	3 875	**15.19**
2008	24 404	14 385	**58.95**	5 193	**21.28**	1 133	**4.64**	3 693	**15.13**

Parkinson's disease's **total expenditures** per year could be divided between the four prescriber groups, for 2005 (N = R10 459 835.93), the proportion claimed by each prescriber represented the following, GP: 49.62% (n = R5 190 194.10), N: 33.81% (n = R3 536 814.46), P: 2.63% (n = R274 318.61) and O: 13.94% (n = R1 458 508.76). In 2006 (N = R 1 320 616.71) the part of the total expenditure by each prescriber represented more or less the same ratio as in 2005 with general medical practitioners' final expenditures being 51.16% (n = R5 791 609.90) of the total expenditure for that year, neurologists' expenditures represented 32.86% (n = R3 719 820.50), others' 13.45% (n= R1 522 708.32) and psychiatrists' 2.53% (n = R286 477.86). For 2007 (N = R11 040 569.32) 49.67% (n = R5 483 853.06) represented general medical practitioners' expenditures for the year, 34.29% (n = R3 786 342.62) made out the neurologists' claims, leaving 13.11% (n = R1 447 462.41) and 2.92% (n = R322 910.45) the cost for prescriptions prescribed by others and psychiatrists respectively. With the pattern repeating itself in 2008 (N = R10 697 155.54) the part claimed

as prescribed by general medical practitioners represented 49.3% (n = R5 280 477.68), 34.26% (n = R3 665 419.86) represented neurologists, 13.57% (n = R1 451 680.73) represented others and 2.80% (n = R299 577.27) psychiatrists (Refer to Table 4.2, 4.30 and 4.31). Table 4.33 gives the medical aid, as well as patient contributions for each year, for prescriptions prescribed by specific prescribers.

Table 4.33: Medical scheme and patient contributions per prescriber per year

Year	GP		N		O		P	
	Medical scheme contribution (%)	Patient contribution (%)	Medical scheme contribution (%)	Patient contribution (%)	Medical scheme contribution (%)	Patient contribution (%)	Medical scheme contribution (%)	Patient contribution (%)
2005	88.67	11.33	90.65	9.35	88.25	11.75	83.30	16.70
2006	88.27	11.73	90.31	9.69	86.42	13.58	79.57	20.43
2007	89.08	10.92	89.82	10.18	86.77	13.23	82.27	17.73
2008	86.57	**13.43**	88.43	**11.57**	84.94	**15.06**	73.93	**26.07**

From Table 4.33 it can be seen that parallel to a decrease in the contribution from the medical schemes from 2005 to 2008, there was an increase in patient contribution. Patient contributions per prescriptions as prescribed by a general medical practitioner increased with 2.1% from 2005 to 2008, 2.2% for prescriptions by neurologists, 3.3% for prescriptions by others with the highest increase from 2005 to 2008 with 9.4% for prescriptions by psychiatrists.

Average prescription cost as prescribed by general medical practitioners, increased with 4.21% from 2005 (R352.26 ± R319.77) to 2008 (R367.08 ± R351.09). Neurologists' prescription cost increased with 7.49% compared to a 16.80% increase of psychiatrists' prescriptions cost from 2005 (N: R656.67 ± R526.71, P: R221.22 ± R288) to 2008 (N: R705.84 ± R514.70, P: R264.41 ± R327.10). In contrast, prescriptions by the 'other' group showed a decrease in prescription cost from 2005 (R399.48 ± R343.82) to 2008 (R393.09 ± R429.76) of 1.63% (Refer to Table 4.31).

Medicine item cost followed the same trend as the cost per prescription. Over the study period a 4.5% increase was observed in the cost per medicine item from 2005 to 2008 as prescribed by a general medical practitioner, 5.91%, 16.8% and 3.99% respectively were the increases in medicine item cost for the same period for neurologists, psychiatrists and other prescribers (Refer to Table 4.30).

The section to follow contains a short summary on the prescribers.

4.3.3.1 Summary of the prescribers

General medical practitioners had the highest percentage of *medicine items* prescribed in every study period with an average of 56%, followed by neurologists with an average of 26%, with an average of 14% of medicine items per year prescribed by other prescribers and the smallest average of 4% prescribed by psychiatrists.

Regarding the number of *prescriptions prescribed* by each prescriber group gave roughly a 12:4:3:1 ratio per year, which also pointed in favour of the general medical practitioners with the highest percentage, followed by neurologists, other prescribers and psychiatrists.

The total expenditures per year also showed to be indistinguishable with the majority of prescriptions prescribed by general medical practitioners and neurologists with more or less 85% of the cost for each year, although on average the patient contributions were the highest for other prescribers and psychiatrists (Refer to Table 4.33). The highest average cost per prescription and per medicine item had, however, been on average those prescribed by neurologists (Refer to Tables 4.30 and 4.31).

4.3.4 Analysis of medicine items

In the section that follows the various medicine items according to their classification will be discussed.

According to the literature as set apart in chapter two, section 2.7 stipulates the pharmacological classification for Parkinson's disease. The MIMS classification system was the classification system of choice in this study (see section 2.7.2).

Figure 4.4 was compiled from Table A.11 in appendix A, and gives a summarised illustration of the three various subgroup classifications, and their popularity of use throughout the four-year study period.

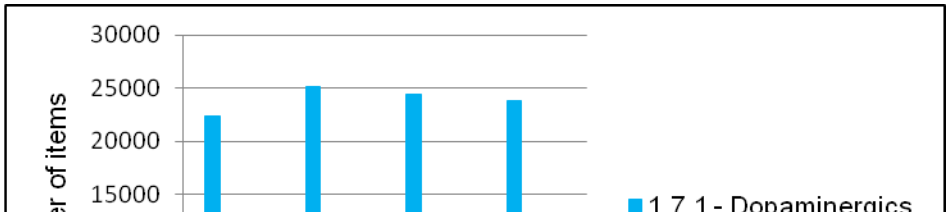

Figure 4.5: Division of various medicines used in the different subgroups of the MIMS classification system

In all four study periods results showed that group 1.7.1, the dopaminergics were the most frequently used antiparkinson medicine items, with 72.44% in 2005, 74.51% in 2006, 77.55% in 2008 and 79.54% in 2008. From 2005 to 2008 there was an increase of 7.1% in the use of dopaminergic medicine items, subsequently leading to a decrease in the use of medicine items in categories 1.7.2 and 1.7.3. In each of the study periods, the second most frequently products used were those of group 1.7.2, the anticholinergics with 19.13%, 17.99%, 15.49% and 14.39% respectively from 2005 to 2008, followed by the smallest number of medicine items used in the other category, 1.7.3 with 8.43% in 2005, 7.50% in 2006, 6.96% in 2007 and 6.07% in 2008.

The three different categories of the pharmacological treatment further consisted of the various medicine items with their assorted active ingredients and combinations (see section 2.7.2). When excluding the different trade names and strengths available there were more or less 7 groups of active ingredients within category 1.7.1. with 3 groups in 1.7.2 and 1.7.3. Table 4.34 was compiled from Tables A.11 and A.12 in appendix A. This Table illustrates the percentage of each active ingredient used each year within its specific category of the MIMS classification system.

Table 4.34: Percentage division of active ingredients used in a sub-category group

MIMS subgroup classification	Active ingredient/s	2005 (%)	2006 (%)	2007 (%)	2008 (%)
1.7.1	Bromocriptine	0.5	2	2	1
	Carbidopa/Levodopa	72	71	69	62
	Carbidopa/Levodopa/Ent			1	2
	Levodopa/Benserazide	8	8	7	5
	Pergolide	3	2	0.3	
	Pramipexole	11	11	14	21
	Ropinirole	6	7	11	8
Total number of medicine items in group 1.7.1		***22 421***	***25 150***	***24 389***	***23 883***
1.7.2	Biperiden	67	66	76	76
	Orphenadrine	14	14	21	24
	Trihexyphenidyl	19	20	3	0.02
Total number of medicine items in group 1.7.2		***5 920***	***6 073***	***4 870***	***4 322***
1.7.3	Entacapone	18	19	18	14
	Selegiline	81	80	81	85
	Tolcapone	1	1	0.5	1
Total number of medicine items in group 1.7.3		***2 609***	***2 531***	***2 190***	***1 822***

According to Table 4.34 the carbidopa/levodopa containing products in category 1.7.1 were mostly claimed during all study years and represented on average 69% per year. Pramipexole proved to be the second most popular medicine item used for Parkinson's disease with an average of 14%, followed by ropinirole with 8% and the levodopa/benserazide combination with 7%. Bromocriptine and pergolide were used the least in this group both with an average of 1%. The combination of carbidopa/levodopa/entacapone only appeared on the market in 2007 and a precise comparison was therefore ruled out. The reasons for the decline in pramipexole use and absence in 2008 are explained in section 2.7.2.

When looking at category 1.7.2, more or less the same trend persisted in each of the study periods. Biperiden was used most frequently representing 71% from 2005 to 2008, followed by trihexyphenidyl with 19.5% and orphenadrine with 14% in 2005 and 2006, and a majority of more or less 23% of orphenadrine items used in 2007 and 2008 followed by an average of 1.5% trihxyphenidyl usage for the same period.

Category 1.7.3 showed that from 2005 to 2008 selegiline was used mainly, representing 82% followed by entacapone and tolcapone, with 17% and 1% respectively.

Possible explanations for the percentage divisions in which these medicines were used are set apart in sections 2.7.4 – 2.7.6 explaining the preferred way to treat Parkinson's disease (Jankovic, 1999:789; Schwinghammer, 2003:553; Council for Medical Schemes, 2009), with

the treatment algorithms stipulated in section 2.9 of this thesis. The figures given here also confirm the preferred way of treatment in literature studies done over centuries, varying slightly with new found research and developments, also taking patient variability into account.

4.3.5 Analysis of the average cost per tablet

Table 4.35 below was compiled from Table A.13 in appendix A, with the targeted group being the items identified in the MIMS® classification system (see section 3.4.1.1). Table 4.35 contains the top 10 trade names arranged according to the most expensive medicine item according to the average cost per tablet for each of the study periods.

Table 4.35: Top ten trade names according to average cost per tablet

2005			2006		
Trade Name	**Active ingredient/s**	**Mean ± Std Dev (R)**	**Trade Name**	**Active ingredient/s**	**Mean ± Std Dev (R)**
Akineton® 5mg/ml inj	Biperiden	36.27 ± 5.56	Akineton® 5mg/ml inj	Biperiden	32.26 ± 8.26
Tasmar® 100mg tab	Tolcapone	13.65 ± 0.39	Tasmar® 100mg tab	Tolcapone	14.10 ± 0.27
Permax® 1mg tab	Pergolide	13.64 ± 0.61	Permax® 1mg tab	Pergolide	13.79 ± 0.91
Eldepryl®	Selegiline	11.88 ± 0.74	Eldepryl®	Selegiline	11.80 ± 0.86
Comtan® 200mg tab	Entacapone	11.79 ± 0.30	Comtan® 200mg tab	Entacapone	11.73 ± 0.66
Pexola® 1mg tab	Pramipexole	10.94 ± 0.56	Pexola® 1mg tab	Pramipexole	10.85 ± 0.40
Requip® 5mg tab	Ropinirole	8.54 ± 0.09	Requip® 5mg tab	Ropinirole	8.55 ± 0.20
Aspen Bromocriptine® 2.5mg	Bromocriptine	6.88 ± 0.46	Aspen Bromocriptine® 2.5mg	Bromocriptine	6.70 ± 1.13
Sinemet® CR tab	Carbi-/Levodopa	5.87 ± 0.47	Sinemet® CR tab	Carbi-/Levodopa	5.89 ± 0.41
Pexola® 0.25mg tab	Pramipexole	5.56 ± 0.40	Pexola® 0.25mg tab	Pramipexole	5.56 ± 0.55
2007			**2008**		
Trade Name	**Active ingredient/s**	**Mean ± Std Dev (R)**	**Trade Name**	**Active ingredient/s**	**Mean ± Std Dev (R)**
Akineton® 5mg/ml inj	Biperiden	33.84 ± 10.78	Akineton® 5mg/ml inj	Biperiden	39.70 ± 3.77
Permax® 1mg tab	Pergolide	14.71 ± 1.21	*Requip® XL 8mg SRT	Ropinirole	17.19 ± 0.31
Tasmar® 100mg tab	Tolcapone	14.08 ± 0.20	Tasmar® 100mg tab	Tolcapone	14.50 ± 0.39
Eldepryl®	Selegiline	12.27 ± 1.56	Eldepryl®	Selegiline	12.73 ± 2.63
Pexola® 1mg tab	Pramipexole	11.20 ± 1.07	Pexola® 1mg tab	Pramipexole	11.74 ± 1.35
Comtan® 200mg tab	Entacapone	9.30 ± 2.27	*Requip® XL 4mg SRT	Ropinirole	10.52 ±0.36
*Stalevo® 150/37.5 mg tab	Carbi-/levodopa/ent	8.91 ± 1.40	*Stalevo® 50/12.5 mg tab	Carbi-/levodopa/ent	9.11 ± 0.39
*Stalevo® 50/12.5 mg tab	Carbi-/levodopa/ent	8.71 ± 2.62	*Stalevo® 100/25 mg tab	Carbi-/levodopa/ent	9.03 ± 0.94
*Stalevo® 100/25 mg tab	Carbi-/levodopa/ent	8.58 ± 2.01	*Stalevo® 150/37.5 mg tab	Carbi-/levodopa/ent	8.84 ± 1.56
Requip® 5mg tab	Ropinirole	8.56 ± 0.83	Requip® 5mg tab	Ropinirole	8.73 ± 0.24

* New tablets on the market

Frequencies (n) for each medicine item are indicated in Table A.13 in appendix A

For 2005 and 2006 the top 10 lists contained of the same trade names although the average cost per tablet differed slightly between the two study periods. On a continuous basis, research and development are being done, new tablets appear on the market, and others leave the market. This seemed to be true in 2007 and 2008 whereas evidently other more recent medicine items appeared on the top ten lists.

Table A.13 in appendix A gives a clear indication of whether or not there are generic products available for the medicine items. The majority of antiparkinson's disease medication does not have any generic equivalent. With reference to the data source used and information assembled there are only 3 medicine items over this study period that had a generic equivalent. These medicine items were:

- ✓ Original product: Sinemet® 25/100 Tab Sinemet® 25/250 Tab Eldepryl® 5mg Tab
- ✓ Generic product: Carbilev® 25/100 Tab Carbilev® 25/250 Tab Parkilyne® 5mg Tab

Because of the fact that there are only three products with comparative equivalents, no effective evaluation in cost differences between the original and generic product was done in this study. Therefore in means of the average cost per tablet the cost variation for each medicine item on the top ten lists was assessed within the four years of this study.

The evaluations of the average cost per tablet are discussed in the subsequent section according to active ingredients of those medicine items on the top ten list for each year.

4.3.5.1 Biperiden (Akineton® 5mg/ml injection)

In each of the four study periods the Akineton® 5mg/ml injection was the most expensive medicine item used. The cost for one millilitre vile was R36.27 ± R5.56 in 2005, after decreasing slightly in 2006 and 2007 to R32.26 ± R8.26 and R33.84 ± R10.78 respectively. The average cost for a millilitre vile was R39.70 ± R3.77 in 2008 (Refer to Table 4.35). There was on average a 23% increase on the average cost per millilitre vile from 2006 to 2008.

According to Rossiter (2010:455) this form of intravenous or intra-muscular injection gives an advantage in the quick management of dystonic reactions provoked by other medicines. This form of medicine item treatment is rather expensive but is not used on chronic basis, but rather in the management of Parkinson's disease related symptom crises.

4.3.5.2 Tolcapone (Tasmar® 100 mg Tablet)

Tasmar® 100 mg tablets had the second highest average cost per tablet in 2005 and 2006, moving down to the third highest average cost per tablet in 2007 and 2008. In the first study period Tasmar® 100 mg tablets started with an average cost per tablet of R13.65 ± R0.39, thereafter increasing slightly with more or less 3% to R14.10 ± R0.27 in 2006, fluctuating with

small increments to R14.08 ± R0.20 and R14.50 ± R0.39 in the last two study periods (Refer to Table 4.35). Altogether the average cost per tablet increased with roughly 6% from 2005 to 2008.

In section 2.7.6.2.2 the desired dosage of tolcapone is set apart as 100 mg tablets to be taken three times a day (Aminoff, 2009a:476). In conjunction with section 2.7.6.2.2, section 2.9 clearly states that tolcapone is considered to be add-on therapy in increasing the effectiveness of a levodopa/carbidopa combination (see section 4.3.8). This consequently also means that the cost implication of this tablet would not be the only tablet a Parkinson's disease patient would be taking, but would rather be an added expense.

4.3.5.3 Pergolide (Permax® 1 mg tablet)

The average cost per Permax® 1 mg tablet increased throughout the study period. The increase took place gradually from an average cost per tablet of R13.64 ± R0.61 in 2005, increased with ± 7% to 2007, with average costs of 13.79 ± R0.91 and R14.71 ± R1.21 in 2006 and 2007 (Refer to Table 4.35). In 2008 Permax® 1 mg tablets were not on the top ten list of the highest average cost per tablet, because the product had been withdrawn from the market by the FDA with reasons documented in section 2.7 (FDA, 2007).

Before withdrawing Permax® 1mg tablets from the market, the desired dose was a dose of 3 mg daily as given in section 2.7.4.2.2 (Beers, 2006a:1884). This means that the average cost per tablet could more or less be tripled in calculating the financial burden on the patient. In most cases this would not be the only therapy a Parkinson's disease patient would receive, but would rather be part of a treatment regimen (see section 2.9 and section 4.3.8).

4.3.5.4 Selegiline (Eldepryl® 5 mg tablet)

This tablet pertained a consistent fourth position on the list of top ten most expensive products based on the average cost per tablet over the four-year study period. The average cost per tablet increased with more or less 7% from 2005 to 2008, from R11.88 ± R0.74 in 2005 to R12.73 ± R2.63 in 2008. In 2006 the average cost per tablet slightly decreased to R11.80 ± R0.86 thereafter increasing again with about 4% to R12.27 ± R1.56 in 2007 (Refer to Table 4.35).

The recommended dose of selegiline is referred to as being 10 mg in the morning (Aspen pharmaceuticals, 2007; Eidelberg & Poufar, 2007) (see section 2.7.6.1.2) in conjunction with levodopa (see section 4.3.8), which also gives the impression of an added expense to a Parkinson's disease patient.

4.3.5.5 Entacapone (Comtan® 200 mg tablet)

After being consistently in the fifth place of the top ten lists in both 2005 and 2006, Comtan® 200 mg moved down a place in 2007, while not appearing at all on the list in 2008. Up and till now Comtan® 200 mg is the first tablet that showed a rather drastic decrease of about 26% from 2005 to 2007, form an average cost per tablet of R11.79 ± R0.30 in 2005, to R11.73 ± R0.66 in 2006 and R9.30 ± R2.27 in 2007 (Refer to Table 4.35).

These tablets' cost however decreased quite drastically over the study period, but as stated in section 2.7.6.2.2 a maximum dose of 800 mg (4 tablets) (Baron, 2005:41) could be used not exceeding a dose of 1 600 mg (8 tablets) per day (Eidelberg & Poufar, 2007; Norvartis, 2000). Entacapone is usually used in conjunction with levodopa (see section 4.3.8) thus the cost hereof would not be the only expense a patient has.

4.3.5.6 Pramipexole (Pexola® 1 mg tablet, Pexola® 0.25 mg tablet)

- Pexola® 1 mg tablet

In 2005 and 2006 Pexola® 1 mg tablets were the 6th most expensive tablets. In these two periods the average cost per tablet appeared to decrease but increased again, all in all with more or less 7% from 2005 to 2008. The average cost per Pexola® 1 mg tablet thus fluctuated from R10.94 ± R0.56 in 2005; R10.85 ± R0.40 in 2006 to R11.20 ± R1.07 in 2007 and R11.74 ± R1.35 in 2008 (Refer to Table 4.35).

- Pexola® 0.25 mg tablet

Pexola® 0.25 mg tablets were last on the top ten lists of expensive tablets in 2005 and 2006, not appearing on the list in 2007 and 2008. This was the tablet that showed the best consistency from one period to another from R5.56 ± R0.40 in 2005 to R5.56 ± R0.55 in 2006 (Refer to Table 4.35).

According to literature the sufficient end dose of pramipexole is 1.5 mg three times daily (Standeart & Young, 2009) depending on patient variation (see section 2.7.4.2.2), thus

meaning that one strength tablet could not be used alone. Consequently, apart from the tablets being used in conjunction with levodopa (see section 4.3.8), the 1 mg and 0.25 mg Pexola® tablets alone are not sufficient in the treatment of the symptoms in some patients, all adding up to escalating costs.

4.3.5.7 Ropinirole (Requip® 5 mg tablet, Requip® XL 4 mg SRT, Requip® 8 mg SRT)

- Requip® 5mg tablet

Although the average cost per tablet has been relatively consistent across the four-year study period it was the seventh most expensive tablet in 2005 and 2006, but due to other more recent tablets and formulations entering the market, moved to the tenth place in 2007 and 2008. From 2005 the average cost per tablet increased from R8.54 ± R0.09 with 2% to R8.73 ± R0.24 in 2008; being rather steady in 2006 and 2007 with R8.55 ± R0.20 and R8.56 ± R0.83 (Refer to Table 4.35).

- Requip® XL 4 mg SRT

Requip® XL 4 mg SRT made its first appearance on the database in 2008. The average cost per tablet is R10.52 ± R0.36 (Refer to Table 4.35). This average cost per tablet seems relatively pricy; a reason could be the formulation process of formulating a tablet into the slow release form.

- Requip® XL 8 mg SRT

In addition to the Requip® XL 4 mg SRT, this Requip® XL 8 mg SRT were even more expensive with an average cost per tablet of R17.19 ± R0.31, securing it to the second spot on the most expensive list of tablets in 2008 (Refer to Table 4.35). Requip® XL 8mg SRT were encountered for the first time on the dataset in 2008.

In section 2.7.4.2.2 the recommended usage of ropinirole has already been clearly stated, specifying that in addition to a treatment regimen of levodapa (see section 4.3.8), and depending on patient variations, the maximum dosage of ropinirole should not exceed 24 mg daily (GlaxoSmithKline, 2007; Standeart & Young, 2009) in divided doses. The slow release tablets are only to be taken once daily, although more than one tablet might be necessary to be effective.

4.3.5.8 Bromocriptine (Aspen bromocriptine® 2.5 m tablet)

The average cost per tablet of a bromocriptine tablet was relatively stable from 2005 to 2006, being the only two periods in which this tablet was rated as one of the expensive tablets. With an average cost per tablet of R6.88 ± R0.46 in 2005 the average cost per tablet decreased with more or less 2% to R6.70 ± R1.13 in 2006 (Refer to Table 4.35).

Bromocriptine has a complex dosage regimen that could vary drastically according to the patients' response (see section 2.7.4.2.2). The recommended dose could increase to a maximum of 30 mg to even 40 mg per day in divided doses (Standaert & Young, 2009), meaning that the cost implications could be more according to the number of tablets that would be needed in addition to levodopa (see section 4.3.8).

4.3.5.9 Carbidopa/Levodopa (Sinemet® CR tablet)

This controlled release tablet only appeared to be on the top ten lists of expensive tablets in 2005 and 2006. The average cost per tablet was consistent over the two periods increasing with not even one percent from R5.87 ± R0.47 in 2005 to R5.89 ± R0.41 in 2006 (Refer to Table 4.35).

The adverse effects as well as the patient variations play an important role in deciding the precise number of tablets needed (see section 2.7.4.1.2). This indicates that not only one tablet would control the symptoms (Aminoff, 2009a:471), increasing the financial implications for the patient.

4.3.5.10 Carbidopa/Levodopa/Entacapone (Stalevo® 50/12.5 mg tablet, Stalevo® 100/25 mg tablet, Stalevo® 150/37.5 mg tablet)

This tablet became visible on the database in 2007 for the first time. Not only was this a new product, but its formulation also contained an interesting combination of more than two active ingredients.

- Stalevo® 50/12.5 mg tablet

This strength of the new formulation experienced a more or less 4% increase in cost from R8.71 ± R2.62 in 2007 to R9.11 ± R0.39 in 2008 moving from 8th to 7th position on the top ten

list of expensive tablets for the treatment of Parkinson's disease from 2007 to 2008 (Refer to Table 4.35).

- Stalevo® 100/25 mg tablet

The average cost per tablet had a 5% increase from R8.58 ± R2.01 in 2007 to R9.03 ± R0.94 in 2008 (Refer to Table 4.35), moving up a spot from 9th position in 2007 to 8th position in 2008.

- Stalevo® 150/37.5 mg tablet

From 2007 to 2008 this strength of Stalevo® tablets had a decrease in the average cost per tablet even though it might seem unnoticeable, from R8.91 ± R1.40 in 2007 to R8.84 ± R1.56 in 2008 (Refer to Table 4.35). This small decrease also led to this medicine item moving from the 7th place on the top ten lists in 2007 to 9th position in 2008.

According to Snyman (2009:42) the maximum dose could not exceed a number of 10 tablets daily, meaning that only one tablet might not be sufficient, escalating the total cost.

The subsequent section contains the summary of the average cost per tablets according to their specific trade names.

4.3.5.11 Summary of the average cost per tablet as per trade name

The investigation showed that on average the majority of trade names, on the top 10 list of the highest average cost per tablet, experienced an increase in the average tablet cost from 2005 to 2008.

Akineton® 5mg/ml injection revealed the highest increase of 23% from 2006 to 2008. On average Requip® 5mg tablets had a cost increase per tablet of 2% whereas Stalevo® 50/125mg and Stalevo® 100/25 mg tablets had an increase of between 4% and 5%. The following medicine items all displayed an increase of between 6% - 7%: Tasmar® 100 mg tablets, Permax®1 mg tablets, Eldepryl® 5 mg tablets and Pexola® 1 mg tablets. Sinemet® CR tablets and Stalevo® 150/37.5 mg tablets showed consistency over the study period, although Aspen Bromocriptine® 2.5 mg tablets had a 2% decrease in cost and a 26% decrease in Comtan® 200 mg tablets was experienced from 2005 to 2007.

Table 4.36 stipulates the d-values (see section 3.4.2.2.4 for criteria) for each of the trade names represented on the top 10 lists of average cost per tablet for the four-year study period:

Table 4.36: D-values for cost per tablet according to trade names

Period	Trade name	d-value	Significance [small/medium/large]
2005 - 2008	Tasmar® 100 mg tab	2.33	Very large
	Eldepryl® 5 mg tab	0.3	Small
	Pexola® 1 mg tab	0.6	Medium
	Requip® 5 mg tab	0.8	Large
2005 - 2007	Permax® 1 mg tab	0.9	Large
	Comtan® 200 mg tab	1.1	Large
2005 - 2006	Pexola® 0.25 mg tab	0	None
	Aspen Bromocriptine® 2.5 mg tab	0.2	Small
	Sinemet® CR tab	0	None
2006 - 2008	Akineton® 5mg/ml inj	0.9	Large
2007 -2008	Stalevo® 50/12.5 mg tab	0.2	Small
	Stalevo® 100/25 mg tab	0.2	Small
	Stalevo® 150/37.5 mg tab	0	None

In comparison to the other medicine items (see Table A.13), these medicine items analysed here were rather expensive. In most cases, these medicine items discussed here only make out a proportion of the total cost of the financial burden of a Parkinson's disease patient, as these medicine items are all used in combination with others in order to improve effectiveness (see section 4.3.8).

The average cost per tablet according to trade names, was set apart according to gender, age and prescribers, but will not be discussed in this study (see Tables A.14 – A.24 in appendix A).

The section that follows contains the average cost per yearly treatment for a Parkinson's disease patient.

4.3.6 Analysis of the average cost per yearly medicine treatment

The subsequent section contains a brief discussion on the average cost for a year's treatment for a patient with Parkinson's disease (Refer to Table 4.37).

Table A.27 contains the final medicine treatment expenditure, medical scheme cost and the patient contribution per year for each of the study periods.

The final medicine expenditure per year for 2005, 2006, 2007 and 2008 respectively were; R10 459 835.93, R11 320 616.71, R11 040 569.32 and R10 697 155.54.

Table 4.37: Medical scheme and patient contributions per yearly treatment

Year	Total prescription cost (R)	Medical scheme contribution (R)	Medical scheme contribution (%)	Patient contribution (R)	Patient contribution (%)
2005	10 459 835.93	9 323 689.32	**89.14**	1 136 146.61	**10.86**
2006	11 320 616.71	10 015 330.71	**88.47**	1 305 286.00	**11.53**
2007	11 040 569.32	9 807 475.17	**88.83**	1 233 094.15	**11.67**
2008	10 697 155.54	9 266 962.73	**86.63**	1 430 192.81	**13.37**

From 2005 to 2008 the medical schemes' contribution decreased with about 2.5% consequently meaning an increase in the patient contribution per year. This increased the financial burden growing from one year to another for a patient with this chronic disease.

The average medicine treatment expenditure per year varied slightly between the study periods. In 2005 the medicine treatment expenditure for a year's Parkinson's disease treatment was approximately R2 619.54 ± R4 179.72, decreasing with about 2% to R2 559.49 ± R4 237.23 in 2006, from thereon increasing with more or less 7% to R2 740.96 ± R4 337 in 2007, decreasing again with about 4% to R2 627 ± R4 424.53 in 2008. The medical scheme and patient contributions per prescription were also set apart in Table A.27 in appendix A.

In appendix A Tables A.28 and A.29 the average expenditure for a year's treatment is specified according to gender and various age groups for the study periods.

4.3.7 Prescription containing Parkinson's disease medicine items

In this section the prescriptions with only Parkinson's disease medicine items were discussed. As mentioned in chapter 3, this was done to evaluate the prescribing patterns of prescribers as well as the combination in which medicine items were prescribed. Tables A.30 to A.36 in appendix A have detailed figures of all the prescriptions with Parkinson's disease medicine items in combination. The discussion was done according to the number of repeated prescriptions with the specified number of medicine items in combination, according to the top ten highest frequencies of occurrence throughout the four-year study period.

This section starts with a discussion of all the prescriptions with only one Parkinson's disease medicine item.

4.3.7.1 Prescriptions with one Parkinson's disease medicine item

Table A.30 in Appendix A contains information on prescriptions with only one Parkinson's disease medicine item, for each of the study periods. Table 4.38 is a summary of the top ten medicine items according to the highest occurrence in each period.

Throughout the study period, there was a remarkable trend showing that more or less the same medicine items were used each year, according to the top ten lists of the highest frequencies in Table 4.38.

Table 4.38: Prescription with one Parkinson's disease medicine item according to frequency and average cost

Trade name	Frequency (n)	Average cost per prescription (R)	Total cost (R)
2005			
CARBILEV® 25/100 TAB	4367	270.76 ± 141.98	1182395.33
AKINETON® 2MG TAB	3272	135.37 ± 76.95	442928.19
SINEMET® 25/100 TAB	3251	331.67 ± 161.99	1078262.78
SINEMET® CR TAB	1566	361.41 ± 165.85	565966.93
CARBILEV® 25/250 TAB	1543	354.23 ± 153.83	546569.70
MADOPAR® TAB	987	319.25 ± 142.62	315096.64
SINEMET® 25/250 TAB	886	432.42 ± 194.35	383119.88
ARTANE® 2MG TAB	759	76.51 ± 69.26	58067.91
DISIPAL® 50MG TAB	683	38.76 ± 22.28	26473.09
ELDEPRYL® 5MG TAB	661	461.83 ± 194.31	305267.26
2006			
CARBILEV® 25/100 TAB	5360	267.38 ± 148.55	1433146.55
AKINETON® 2MG TAB	3333	132.47 ± 75.19	441517.87
SINEMET® 25/100 TA®B	3239	328.73 ± 165.34	1064764.34
CARBILEV® 25/250 TAB	1695	362.11 ± 159.92	613775.21
SINEMET® CR TAB	1601	377.39 ± 180.14	604195.83
MADOPAR® TAB	1149	312.52 ± 144.14	359086.54
SINEMET® 25/250 TAB	806	433.33 ± 194.26	349266.82
ARTANE® 2MG TAB	780	75.99 ± 70.43	59272.29
DISIPAL® 50MG TAB	757	40.27 ±22.08	30485.52
ELDEPRYL® 5MG TAB	669	469.80 ± 228.40	314295.08
2007			
CARBILEV® 25/100 TAB	5137	283.35 ± 162.10	1455591.80
AKINETON® 2MG TAB	2992	156.22 ± 110.24	467399.52
SINEMET® 25/100 TAB	2895	348.10 ± 179.16	1007756.04
CARBILEV® 25/250 TAB	1670	392.64 ± 187.53	655708.56
SINEMET® CR TAB	1464	384.58 ± 163.04	563020.50
MADOPAR® TAB	1067	316.97 ± 150.94	338202.98
DISIPAL® 50MG TAB	876	43.08 ± 24.08	37734.52
PEXOLA® 0.25MG TAB	789	458.23 ± 308.13	361543.17
SINEMET® 25/250 TAB	718	416.42 ± 200.11	298993.05
PEXOLA® 0.125MG TAB	610	175.04 ± 108.81	106773.54
2008			
CARBILEV® 25/100 TAB	4941	295.93 ± 153.24	1462193.59
AKINETON® 2MG TAB	2606	160.79 ± 115.08	419008.02
SINEMET® 25/100 TAB	2248	356.57 ± 187.32	801569.30
PEXOLA® 0.125MG TAB	1570	134.67 ±87.61	211430.76
CARBILEV® 25/250 TAB	1444	394.07 ± 200.59	569035.98
PEXOLA® 0.25MG TAB	1348	366.92 ± 287.60	494614.11
SINEMET® CR TAB	1185	366.98 ± 174.52	434875.98
DISIPAL® 50MG TAB	874	44.57 ± 25.14	38957.93
MADOPAR® TAB	754	356.11 ± 156.22	268510.32
SINEMET® 25/250 TAB	546	424.15 ± 206.41	231584.25

Medicine items that had the highest frequencies throughout were the following as given in Table 4.39 below:

Table 4.39 Trade names of one medicine item most frequently found on Parkinson's disease prescriptions

Trade names of medicine items	Category division of medicine items, in accordance with the MIMS classification system		
Carbilev® (generic product)/ Sinemet® (original product)	RED	-	Levodopa combinations
Madopar®	YELLOW	-	Dopamine agonists
Artane®	BLUE	-	Anticholinergics
Akineton®	GREEN	-	MAOI
Disipal®			
Eldepryl®			
Pexola®			

According to literature (see section 2.7) the golden standard for Parkinson's disease treatment is believed to be levodopa (Clarke, 2002:23; LeWitt, 2009:31), in combination with carbidopa or benserazide (Beers 2006a:1883; Clarke, 2002:23) according to motivations discussed in section 2.7. In addition to this the treatment algorithm (see section 2.9) also indicates that for many patients the initial medicine item to start therapy with would be a levodopa combination. A Carbilev® and Sinemet® tablet contains a combination of levodopa and carbidopa, whereas another combination of levodopa with benserazide is formulated in Madopar® tablets. This gives a rather justified explanation for these medicine items having the highest frequency of individual medicine items on a prescription. In each of the study periods, levodopa containing medicine items represented 60% of medicine items on the top ten list of highest frequencies (Refer to Table 4.39).

According to treatment algorithms (see figure 2.5 in section 2.9), the initiation of therapy in a Parkinson's disease patient starts after the state of cognition had been determined. If a patient's cognition is intact that indicated that therapy should start with Eldepryl® (selegiline) (Jankovic, 1999:789; Schwinghammer, 2003:553) or a dopamine agonist in this case Pexola® (Council for Medical Schemes, 2009). Both of these medicine items occur rather frequently as a single item on a prescription. These medicine items can be used as initial therapy and in combination with other medicine items when treating Parkinson's disease.

Ives *et al*. (2004:595-596) justify the statement that selegiline can be given as a single medicine item or in conjunction with levodopa. Furthermore Ives and her research team stated that when selegiline was used early the need for levodopa was postponed considerably. Dopamine agonists on the other hand were also administrated alone. A reason for that might be that when treatment is started with a dopamine agonist, on the long run motor complication can be reduced (Caraceni & Musicco, 2001:113). However, patients should outweigh the benefits thereof, as other adverse effects could worsen.

Additionally another group of medicine items, the anticholinergics, were also well represented among the top ten most frequently used items. These items were Akineton®,

Artane® and Disipal®. According to treatment algorithms anticholinergic medicine items are not indicated in the individual treatment or initiative treatment of Parkinson's disease (Jankovic, 1999:789; Schwinghammer, 2003:553; Council for medical schemes, 2009). However, these medicine items are also not preferable to be used by elderly patients, because of the adverse effects associated with these medicines (Aminoff, 2009b:881). Patients on the Parkinson's disease data also indicated that the majority of patients, with ± 68% were 60 years and older (see section 4.3.2.2.7). Reasons for the high frequency as a single medicine item per prescription could be that these medicine items were:

- Used by younger patients to whom the adverse effects were not as disabling,
- An addition to a treatment regimen already followed by a patient.
- Because of ICD 10 codes not supplied, the exception of these medicine items being indicated for Parkinson's disease alone could not be made. Therefore, these anticholinergic medicine items' high frequency could also be the result of them being used for another indication other than Parkinson's disease (Snyman, 2007:48-49), such as dystonia (Eidelberg & Pourfar, 2007).
- The sole exclusion of these medicine items being used in the treatment of other movement disorders cannot be made either, because of the lack of the diagnoses or ICD 10 codes (see section 2.5), on the database.

The subsequent section contains the brief evaluation of two medicine items on one Parkinson's disease prescription.

4.3.7.2 Prescriptions with two Parkinson's disease medicine items

Table 4.40 was compiled from Table A.31 in Appendix A, containing only the top ten prescriptions with two Parkinson's disease medicine items, according to the highest frequencies, from 2005 to 2008.

Table 4.40: Prescriptions with two Parkinson's disease medicine items according to frequency and average cost

Trade name		Frequency (n)	Average cost per prescription (R)	Total cost (R)
2005				
CARBILEV® 25/100 TAB	ELDEPRYL® 5MG TAB	259	748.25 ± 222.06	193795.51
SINEMET® 25/100 TAB	SINEMET® CR TAB	201	706.62 ± 174.14	142031.45
CARBILEV® 25/100 TAB	SINEMET® CR TAB	168	695.70 ± 219.71	116878.01
CARBILEV® 25/250 TAB	ELDEPRYL® 5MG TAB	149	869.76 ± 236.87	129594.60
AKINETON® 2MG TAB	CARBILEV® 25/100 TAB	145	449.01 ± 147.72	65106.82
ELDEPRYL® 5MG TAB	SINEMET® CR TAB	144	742.47 ± 198.95	106915.63
ELDEPRYL® 5MG TAB	SINEMET® 25/100 TAB	141	803.88 ± 206.34	113346.51
AKINETON® 2MG TAB	SINEMET® 25/100 TAB	119	580.31 ± 209.46	69056.85
ELDEPRYL® 5MG TAB	MADOPAR® TAB	114	691.76 ± 128.07	78861.06
ARTANE® 2MG TAB	CARBILEV® 25/100 TAB	75	382.37 ± 115.99	28677.71
2006				
CARBILEV® 25/100 TAB	ELDEPRYL® 5MG TAB	320	750.59 ± 209.44	240188.01
SINEMET® 25/100 TAB	SINEMET® CR TAB	255	707.65 ±195.07	180450.80
CARBILEV® 25/100 TAB	SINEMET® CR TAB	162	707.69 ± 236.91	114644.98
AKINETON® 2MG TAB	CARBILEV® 25/100 TAB	137	500.47 ± 175.51	68563.87
ELDEPRYL® 5MG TAB	SINEMET® CR TAB	137	738.87 ± 196.85	101224.75
ELDEPRYL® 5MG TAB	SINEMET® 25/100 TAB	134	802.07 ± 192.25	107477.58
CARBILEV® 25/250 TAB	ELDEPRYL® 5MG TAB	131	883.87 ± 243.21	115787.04
ARTANE® 2MG TAB	CARBILEV® 25/100 TAB	129	382.40 ± 116.33	49329.10
ELDEPRYL® 5MG TAB	MADOPAR® TAB	112	730.58 ±183.87	81825.13
AKINETON® 2MG TAB	SINEMET® 25/100 TAB	110	504.29 ± 178.38	55471.56
2007				
SINEMET® 25/100 TAB	SINEMET® CR TAB	258	786.08 ± 218.62	202808.93
CARBILEV® 25/100 TAB	ELDEPRYL® 5MG TAB	234	822.28 ± 250.42	192414.13
CARBILEV® 25/100 TAB	SINEMET® CR TAB	191	732.35 ± 203.57	139878.95
AKINETON® 2MG TAB	CARBILEV® 25/100 TAB	166	546.30 ± 182.45	90686.51
ELDEPRYL® 5MG TAB	SINEMET® CR TAB	134	772.28 ± 207.81	103485.06
CARBILEV® 25/250 TAB	PEXOLA® 1MG TAB	123	1329.41 ± 386.69	163516.86
ELDEPRYL® 5MG TAB	SINEMET® 25/100 TAB	118	815.42 ± 183.43	96220.09
AKINETON® 2MG TAB	SINEMET® 25/100 TAB	85	490.94± 242.87	41730.21
CARBILEV® 25/100 TAB	PEXOLA® 1MG TAB	77	1342.13 ± 322.44	103344.01
CARBILEV® 25/100 TAB	PEXOLA® 0.25 MG TAB	75	963.44 ± 434.29	72257.67
2008				
AKINETON® 2MG TAB	CARBILEV® 25/100 TAB	225	518.56 ± 188.33	116674.88
CARBILEV® 25/100 TAB	SINEMET® CR TAB	185	737.60 ± 168.34	136456.10
SINEMET 25/100 TAB	SINEMET® CR TAB	163	812.81 ± 253.59	132488.70
CARBILEV® 25/100 TAB	ELDEPRYL® 5MG TAB	154	874.97 ± 274.16	134745.16
CARBILEV® 25/100 TAB	PARKILYNE® 5MG TAB	140	626.93 ± 130.53	87770.71
CARBILEV® 25/100 TAB	PEXOLA® 0.25 MG TAB	130	1049.59 ± 386.79	136446.89
CARBILEV® 25/100 TAB	PEXOLA® 1MG TAB	89	1490.73 ± 442.85	132674.84
AKINETON® 2MG TAB	CARBILEV® 25/250 TAB	84	642.45 ± 197.40	53966.19
ELDEPRYL® 5MG TAB	SINEMET® CR TAB	80	747.34 ±203.70	59787.39
ELDEPRYL® 5MG TAB	SINEMET® 25/100 TAB	78	859.75 ± 180.42	67060.37

Throughout the study period, a trend of certain combinations emerged from the data. With reference to Table 4.40, the most popular combinations were found to be the following, as set apart in Table 4.41:

Table 4.41: Trade names of two medicine items most frequently found together on Parkinson's disease prescriptions

Trade names of medicine items		Number of different categories present
Carbilev® / Sinemet®	Sinemet® CR	1
	Artane®	2
	Akineton®	2
	Pexola®	2
	Eldepryl®/Parkilyne®	2
Medopar®	Eldepryl®	2
Category division of medicine items, in accordance with the MIMS classification system		
RED - Levodopa combinations		
YELLOW - Dopamine agonists		
BLUE - Anticholinergics		
GREEN - MOAI		

Research (see section 2.7) quite clearly indicates a levodopa combination with carbidopa (Carbilev® / Sinemet®) or benserazide (Madopar®) to be the choice medicine items in treating Parkinson's disease (Clarke, 2002:23; LeWitt, 2009:31). The dose of levodopa should preferably be increased gradually (Beers, 2006a:1883; Snyman, 2010:42) depending on the patient response, adverse effects and severity of the disease. This indicates a reason for the occurrence of two levodopa containing products on one prescription.

Selegiline (Eldepryl®/ Parkilyn®) containing medicine items were also used rather often in conjunction with levodopa combinations. Selegiline also increases dopamine levels (Aminoff, 2009a:476), thus assisting in treating the symptoms. In another research study Ives *et al*. (2004:596) also indicated that selegiline containing products in addition to levodopa, reduced the need for levodopa. The addition of these products might depend on the cognition and functional abilities of the patient (Schwinghammer, 2003:553). These, however, are valid reasons for the high frequency of these combination occurrences on prescriptions throughout the study period.

Other frequently seen combinations on the data were those of anticholinergic medicine items (Akineton® and Artane®) and a dopaminergic agonist (Pexola®) in combination with levodopa/carbidopa. The reason for an anticholinergic medicine item in conjunction with levodopa/carbidopa according to the treatment algorithms (section 2.9), could be that patients were 60 years or younger with impaired functional abilities (Council for Medical Schemes, 2009). More or less the same could be true for the combination with dopaminergic agonist, with the difference being that patients were older than 60 years. Dopamine agonists are also the preferred "add-on" medicine item to levodopa treatment (Aminoff, 2009a:471). There are various types of dopamine receptor agonists (see section 2.7.4.2). The choice of

dopamine agonist solely depends on the patients' response to the medicine item, the severity of the disease and adverse effects associated.

After evaluating the prescriptions with only two Parkinson's disease medicine items on, no major irregularities were found. The following section entails a brief discussion on prescriptions with three Parkinson's disease medicine items.

4.3.7.3 Prescriptions with three Parkinson's disease medicine items

This specific section contains a discussion on Parkinson's disease prescriptions with three medicine items. The figures hereof were compiled from Table A.32 in Appendix A, and were summarised in Table 4.42. This was done according to the top ten medicine items found in combination according to the highest frequency. Table 4.43 contains a summarised version of all the possibilities of three Parkinson's disease medicine items in combination on that occurred on prescriptions from 2005 to 2008.

Table 4.42: Prescriptions with three Parkinson's disease medicines items according to frequency and average cost

Trade Name			Frequency (n)	Average Cost per prescription (R)	Total cost (R)
2005					
AKINETON® 2MG TAB	PEXOLA® 0.125MG TAB	SINEMET® 25/100 TAB	33	765.02 ± 18.17	25245.75
AKINETON® 2MG TAB	ELDEPRYL® 5MG TAB	SINEMET® 25/250 TAB	29	1255.14 ± 261.93	36399.08
ELDEPRYL® 5MG TAB	PEXOLA® 1MG TAB	SINEMET® 25/100 TAB	22	1449.92 ± 259.42	31898.25
PEXOLA® 1MG TAB	SINEMET® 25/100 TAB	SINEMET® CR TAB	22	1539.83 ± 155.88	33876.29
COMTAN® 200MG TAB	ELDEPRYL® 5MG TAB	MADOPAR® TAB	20	1490.74 ± 123.05	29814.74
AKINETON® 2MG TAB	ELDEPRYL® 5MG TAB	SINEMET® CR TAB	18	1208.18 ± 190.42	21747.18
CARBILEV® 25/100 TAB	ELDEPRYL® 5MG TAB	PEXOLA® 1MG TAB	18	1328.80 ± 329.04	23918.35
AKINETON® 2MG TAB	CARBILEV® 25/100 TAB	ELDEPRYL® 5MG TAB	16	662.01 ± 75.85	10592.12
CARBILEV® 25/100 TAB	CARBILEV 25/250 TAB	ELDEPRYL® 5MG TAB	16	1090.51 ± 226.55	17448.11
COMTAN® 200MG TAB	ELDEPRYL® 5MG TAB	MADOPAR® HBS CAP	15	1555.94 ± 25.74	23339.04
2006					
CARBILEV® 25/100 TAB	ELDEPRYL® 5MG TAB	SINEMET® CR TAB	37	1075.78± 159.73	39803.85
COMTAN® 200MG TAB	SINEMET® 25/100 TAB	SINEMET® CR TAB	21	1562.03 ± 224.92	32802.57
CARBILEV® 25/100 TAB	REQUIP® 1.0MG	REQUIP® 2.0MG	20	1122.36 ± 309.94	22447.25
ELDEPRYL® 5MG TAB	PERMAX® 1MG TAB	SINEMET® CR TAB	20	2193.14 ± 253.69	43862.78
AKINETON® 2MG TAB	ELDEPRYL® 5MG TAB	SINEMET® 25/250 TAB	19	1303.04 ± 267.47	24757.72
AKINETON® 2MG TAB	ELDEPRYL® 5MG TAB	SINEMET® CR TAB	19	1203.06 ± 207.11	22858.22
AKINETON® 2MG TAB	PEXOLA® 0.125MG TAB	SINEMET® 25/100 TAB	19	767.81 ± 34.77	14588.48
CARBILEV® 25/100 TAB	PEXOLA® 0.125MG TAB	PEXOLA® 0.25MG TAB	19	1163.58 ± 110.48	22108.06
ARTANE® 2MG TAB	CARBILEV® 25/100 TAB	COMTAN® 200MG TAB	18	1487.04 ± 69.45	26766.79
ARTANE® 2MG TAB	CARBILEV® 25/100 TAB	SINEMET® CR TAB	17	1068.65 ± 164.09	18167.10
2007					
CARBILEV® 25/100 TAB	ELDEPRYL® 5MG TAB	SINEMET® CR TAB	30	1408.79 ± 1526.14	42263.81
CARBILEV® 25/250 TAB	COMTAN® 200MG TAB	PEXOLA® 1MG TAB	27	2941.61 ± 6284.05	79423.41
PEXOLA® 0.25MG TAB	SINEMET® 25/100 TAB	SINEMET® CR TAB	22	1628.19 ± 2430.72	35820.26
CARBILEV® 25/100 TAB	PEXOLA® 0.25MG TAB	SINEMET® CR TAB	19	1807.02 ± 2165.73	34333.39
CARBILEV® 25/100 TAB	REQUIP® 1.0MG	REQUIP® 2.0MG	18	1397.40 ± 1479.93	25153.19
COMTAN® 200MG TAB	SINEMET® 25/100 TAB	SINEMET® CR TAB	17	1258.65 ± 1410.91	21397.02
REQUIP® 1.0MG	SINEMET 25/250 TAB	SINEMET® CR TAB	17	1392.56 ± 1563.13	23673.54
CARBILEV® 25/100 TAB	PEXOLA® 1MG TAB	SINEMET® CR TAB	16	1541.32 ± 1987.89	24661.04
PEXOLA® 1MG TAB	SINEMET® 25/100 TAB	SINEMET® CR TAB	16	1813.09 ± 2571.07	29009.48
AKINETON® 2MG TAB	PEXOLA® 0.25MG TAB	SINEMET® 25/100 TAB	15	1156.18 ± 1462.60	17342.72
2008					
REQUIP® 1.0MG	SINEMET® 25/100 TAB	SINEMET® CR TAB	38	945.15 ± 65.77	35915.75
CARBILEV® 25/100 TAB	REQUIP® 1.0MG	REQUIP® 2.0MG	35	1352.93 ± 261.05	47352.60
CARBILEV® 25/100 TAB	PEXOLA® 0.25MG TAB	SINEMET® CR TAB	31	1646.43 ± 571.65	51039.35
CARBILEV® 25/100 TAB	PARKILYNE® 5MG TAB	SINEMET® CR TAB	26	1134.07 ± 75.97	29485.82
REQUIP® 0.5MG	REQUIP® 1.0MG	SINEMET® 25/100 TAB	22	941.57 ± 98.28	20714.49
CARBILEV® 25/100 TAB	ELDEPRYL® 5MG TAB	SINEMET® CR TAB	21	1451.68 ± 171.66	30485.36
CARBILEV® 25/100 TAB	REQUIP® 1.0MG	SINEMET® CR TAB	19	964.91 ± 171.68	18333.30
CARBILEV® 25/100 TAB	REQUIP® 2.0MG	SINEMET® CR TAB	18	1239.34 ± 54.17	22308.06
CARBILEV® 25/250 TAB	COMTAN® 200MG TAB	PEXOLA® 1MG TAB	16	1954.85 ± 564.75	31277.58
PEXOLA® 0.25MG TAB	SINEMET® 25/100 TAB	SINEMET® CR TAB	15	1302.62 ± 379.28	19539.26

As previously mentioned, Table 4.43 consists of the combinations that had been the trendiest from 2005 to 2008 according to the highest frequency of occurrence:

Table 4.43: Trade names of three medicine items most frequently found together on Parkinson's disease prescriptions

Trade names of medicine items			Number of different categories present
Carbilev® / Sinemet®	Carbilev® / Sinemet®	Eldepryl®	2
		Pexola®	2
		Requip®	2
		Comtan®	2
		Artane®	2
	Pexola®	Pexola®	2
		Eldepryl®	3
		Akineton®	3
	Eldepryl®	Akineton®	3
		Permax®	3
	Requip®	Requip®	2
	Comtan®	Artane®	3
Madopar®	Eldepryl®	Comtan®	3
Category division of medicine items, in accordance with the MIMS classification system			
RED - Levodopa combinations YELLOW - Dopamine agonists BLUE - Anticholinergics GREEN - MOAI PINK - COMT			

In this section combinations of medicine items per prescription in three different categories were only discussed if not previously mentioned in section 4.3.8.2.

As indicated in Table 4.43 the medicine item that were present in all combinations had the same primary active ingredient namely levodopa (Carbilev® / Sinemet® and Madopar®). In section 2.7.4 it is stated that the dose of levodopa should gradually be increased (Aminoff, 2009a:471; Beers, 2006a:1883; Snyman, 2010:42), with the response of the patient and state of the disease kept in mind. This would offer an explanation of two levodopa containing medicine items on one prescription.

Furthermore, according to literature (see section 2.7.4 and 2.9), a dopamine agonist (Permax® and Requip®) or a COMT inhibitor (Comtan®) formed a preferred choice of treating the "on-off" period that might be experienced with levodopa treatment (Aminoff, 2009a:471; Schwinghammer, 2003:556). Comtan® also increases the dopamine levels in the brain (Clarke, 2002:26), adding to the achievement of treatment outcomes. In advanced Parkinson's disease a COMT inhibitor, an MOAI and levodopa are seen as a combination rather advanced to that of levodopa treatment alone (Talati *et al*., 2009:505).

The selection of an MOAI (Eldepryl®) in combination with a levodopa or dopamine agonists, purely improves the dopamine levels in the brain (see section 2.7.6.11). In effect the levodopa dose might be decreased because of the mechanism of action of selegiline products (Ives *et al*., 2004:596; Rascol *et al*., 2005:952; Schwinghammer, 2003:558),

depending on the severity of the disease. The treatment algorithm of the Council of Medical Schemes, however, indicates selegiline (Eldepryl®) to be the medicine item of choice if a patient's cognition is intact (Council for Medical Schemes, 2009). If patients become functionally disabled and were younger than 60 years, an anticholinergic medicine item (Akineton®) was added to the regimen (Schwinghammer, 2003:553).

The next section of this thesis contains the discussion of four Parkinson's disease medicine items that are prescribed in combination on one prescription as from 2005 to 2008.

4.3.7.4 Prescriptions with four Parkinson's disease medicine items

In this section the discussion entails the analysis of four Parkinson's disease medicine items prescribed together. This was done from 2005 to 2008, according to the top ten prescriptions with the highest frequency of occurrence in each year. Table 4.44 contains the summarised information of the top ten prescription combinations and was compiled from Table A.33 in appendix A.

Although the average number of medicine items per prescription increased, the frequency of these combinations, however, decreased rather drastically from previously mentioned combinations. The highest frequency of a prescription with four medicine items in combination rendered only 16 prescriptions in 2005 and 2008 (Refer to Table 4.44). The smallest frequency was 4 prescriptions with the same combination of medicine items in 2008. This indicates that four medicine items being prescribed in combination Parkinson's disease had not been a common trend from 2005 to 2008.

With focus on each medicine item in a certain category, a pattern started to show in each period. In addition to this a simplified summary of all the preferred combinations that occurred from 2005 to 2008, can be seen in Table 4.45.

Table 4.44: Prescriptions with four Parkinson's disease medicine items according frequency and average cost

Trade Name				Frequency (n)	Average cost per prescription (R)	Total cost (R)
2005						
AKINETON® 2MG TAB	PEXOLA® 1MG TAB	SINEMET® 25/250 TAB	SINEMET® CR TAB	16	2065.97 ± 0.01	33055.48
ARTANE® 2MG TAB	COMTAN® 200MG TAB	ELDEPRYL® 5MG TAB	SINEMET® CR TAB	12	1965.66 ± 351.74	23587.94
CARBILEV® 25/100 TAB	REQUIP® 1.0MG	REQUIP® 2.0MG	SINEMET® CR TAB	10	2011.69 ± 7.48	20116.93
ELDEPRYL® 5MG TAB	PEXOLA® 0.125MG TAB	SINEMET® 25/250 TAB	SINEMET® CR TAB	10	1490.68 ± 136.38	14906.79
AKINETON® 2MG TAB	ELDEPRYL® 5MG TAB	PERMAX® 0.05MG TAB	SINEMET® 25/100 TAB	9	1203.16 ± 0.00	10828.44
COMTAN® 200MG TAB	PEXOLA® 0.25MG TAB	SINEMET® 25/100 TAB	SINEMET® CR TAB	8	2732.48 ± 140.20	21859.82
CARBILEV® 25/100 TAB	CARBILEV® 25/250 TAB	PEXOLA® 1MG TAB	SINEMET® CR TAB	7	1724.50 ± 58.38	12071.48
ELDEPRYL® 5MG TAB	MADOPAR® TAB	PEXOLA® 0.25MG TAB	SINEMET® CR TAB	7	2213.63 ± 17.07	15495.40
REQUIP® 1.0MG	REQUIP® 5.0MG	SINEMET® 25/100 TAB	SINEMET® CR TAB	7	2081.27 ± 0.00	14568.89
ARTANE® 2MG TAB	ELDEPRYL® 5MG TAB	MADOPAR® HBS CAP	MADOPAR® TAB	6	907.25 ± 19.68	5443.48
2006						
CARBILEV® 25/100 TAB	REQUIP® 0.5MG	REQUIP® 1.0MG	REQUIP® 2.0MG	12	729.50 ± 15.03	8754.02
MADOPAR® HBS CAP	MADOPAR® TAB	REQUIP® 2.0MG	REQUIP® 5.0MG	12	1766.10 ± 4.00	21193.24
CARBILEV® 25/100 TAB	REQUIP® 5.0MG	REQUIP® 1.0MG	SINEMET® CR TAB	11	1667.92 ± 5.36	18347.09
ARTANE® 2MG TAB	ELDEPRYL® 5MG TAB	MADOPAR® HBS CAP	MADOPAR® TAB	9	860.91 ±17.87	7748.17
COMTAN® 200MG TAB	MADOPAR® HBS CAP	MADOPAR® TAB	PEXOLA® 1MG TAB	9	3138.32 ± 62.08	28244.89
ARTANE® 2MG TAB	COMTAN® 200MG TAB	ELDEPRYL® 5MG TAB	SINEMET® CR TAB	8	1906.79 ± 91.14	15254.29
CARBILEV® 25/100 TAB	PEXOLA® 0.125MG TAB	PEXOLA® 0.25MG TAB	SINEMET® CR TAB	8	1214.58 ± 0.00	9716.64
REQUIP® 5.0MG	REQUIP® 1.0MG	SINEMET® 25/100 TAB	SINEMET® CR TAB	8	1173.70 ±0.56	9389.56
AKINETON® 2MG TAB	ELDEPRYL® 5MG TAB	SINEMET® 25/100 TAB	SINEMET® CR TAB	7	1577.27 ± 60.95	11040.90
ELDEPRYL® 5MG TAB	PEXOLA® 0.125MG TAB	SINEMET® 25/250 TAB	SINEMET® CR TAB	7	1374.44 ± 302.63	9621.08
2007						
CARBILEV® 25/100 TAB	REQUIP® 0.5MG	REQUIP® 1.0MG	SINEMET® CR TAB	12	1782.82 ± 24.27	21393.87
CARBILEV® 25/100 TAB	REQUIP® 0.5MG	REQUIP® 1.0MG	REQUIP® 2.0MG	11	796.05 ± 0.02	8756.54
MADOPAR® HBS CAP	MADOPAR® TAB	REQUIP® 0.25MG	REQUIP® 0.5MG	11	1079.73 ± 96.45	11877.08
MADOPAR® HBS CAP	MADOPAR® TAB	REQUIP® 2.0MG	REQUIP® 5.0MG	11	1679.11 ± 121.02	18470.24
AKINETON® 2MG TAB	CARBILEV® 25/100 TAB	COMTAN® 200MG TAB	SINEMET® CR TAB	8	1643.15 ± 200.25	13145.17
REQUIP® 0.5MG	REQUIP® 1.0MG	SINEMET® 25/100 TAB	SINEMET® CR TAB	8	1164.88 ± 33.30	9319.07
AKINETON® 2MG TAB	COMTAN® 200MG TAB	ELDEPRYL® 5MG TAB	SINEMET® CR TAB	7	1998.74 ± 255.30	13991.20
CARBILEV® 25/100 TAB	PEXOLA® 0.125MG TAB	PEXOLA® 0.25MG TAB	SINEMET® CR TAB	7	1242.12 ± 0.00	8694.84
MADOPAR® TAB	REQUIP® 0.25MG	REQUIP® 0.5MG	SINEMET® CR TAB	7	1063.08 ± 58.00	7441.56
AKINETON® 2MG TAB	CARBILEV® 25/100 TAB	REQUIP® 1.0MG	REQUIP® 2.0MG	6	1253.42 ± 2.01	7520.52
2008						
REQUIP® 0.25MG	REQUIP® 0.5MG	STALEVO® 100/25MGTAB	STALEVO® 50/12.5 TAB	16	1092.88 ± 11.99	17486.05
CARBILEV® 25/100 TAB	REQUIP® 0.5MG	REQUIP® 1.0MG	SINEMET® CR TAB	13	1767.55 ± 15.46	22978.11
CARBILEV® 25/100 TAB	DISIPAL® 50MG TAB	PEXOLA® 0.25MG TAB	PEXOLA® 1MG TAB	12	2436.01 ± 70.53	29232.12
COMTAN® 200MG TAB	REQUIP® 2.0MG	SINEMET® 25/100 TAB	SINEMET® CR TAB	9	2577.37 ± 190.65	23196.33
REQUIP® 1.0MG	REQUIP® 2.0MG	SINEMET® 25/100 TAB	SINEMET® CR TAB	7	1870.53 ± 52.48	13093.74
AKINETON® 2MG TAB	CARBILEV® 25/100 TAB	COMTAN® 200MG TAB	SINEMET® CR TAB	6	1726.04 ± 19.86	10356.21
AKINETON® 2MG TAB	ELDEPRYL® 5MG TAB	MADOPAR® HBS CAP	MADOPAR® TAB	6	1285.11 ± 98.55	7710.64
CARBILEV® 25/100 TAB	PEXOLA® 0.25MG TAB	SINEMET® CR TAB	STALEVO® 150/37.5 TAB	6	3335.35 ± 527.18	20012.11
CARBILEV® 25/100 TAB	REQUIP® 1.0MG	REQUIP® 2.0MG	REQUIP® 5.0MG	4	1511.61 ± 0.00	6046.44
MADOPAR® TAB	REQUIP® 0.25MG	REQUIP® 0.5MG	SINEMET® CR TAB	4	1011.85 ± 12.44	4047.40

Table 4.45: Trade names of four medicine items most frequently found in combination on Parkinson's disease prescriptions

Trade names per medicine item				Number of different categories present
Carbilev® / Sinemet®	Carbilev® / Sinemet®	Carbilev® / Sinemet®	Pexola®	2
		Requip®	Requip®	2
		Pexola®	Pexola®	2
			Akineton®	3
			Eldepryl®	3
			Comtan®	3
			Stalevo®	2
		Comtan®	Akineton®	3
			Requip®	3
		Akineton®	Eldepryl®	3
	Requip®	Requip®	Requip®	2
			Akineton®	3
			Madopar®	2
	Pexola®	Pexola®	Disipal®	3
		Madopar®	Eldepryl®	3
	Eldepryl®	Comtan®	Artane®	4
			Akineton®	4
		Permax®	Akineton®	4
Madopar®	Madopar®	Requip®	Requip®	2
		Eldepryl®	Artane®	3
			Akineton®	3
		Comtan®	Pexola®	3
Stalevo®	Stalevo®	Requip®	Requip®	2

Category division of medicine items, in accordance with the MIMS classification system

RED	-	Levodopa combinations
YELLOW	-	Dopamine agonists
BLUE	-	Anticholinergics
GREEN	-	MOAI
PINK	-	COMT

Table 4.45 gives an indication of the various categories to which the medicine items were divided. These categories are very closely to the MIMS classification system used in this study, only broadened. By analysing these combinations it became clear that in effect there were only 3 combinations of medicine items per prescription that contained four different medicine items. In sections 4.3.8.1 to 4.3.8.3 the logic concerning the combinations of one to three medicine items in different categories was discussed.

The focus now was only on the medicine item combinations present in four different categories. Eldepryl® (Selegiline) and Comtan® (entacapone) in combination with levodopa containing medicine items act on increasing the dopamine levels in the brain. Eldepryl® mainly works on inhibition of the enzyme, MAO (Aminoff, 2009a:476) whereas Comtan® inhibits the enzyme COMT (Clarke, 2002:26) from metabolising dopamine. This gives an added effect of increasing dopamine levels, even more so when used in combination. Anitcholinergic medicine items were added in combination to this, namely Artane® and Akineton®. These medicine items were accompanied by indications that the patients that

received them were younger than 60 years being functionally disabled although their cognition was still intact (Council for medical schemes, 2009). Another medicine item of choice was Permax® (dopamine agonist). Dopamine agonists are added to increase the effect of levodopa or decreasing the occurrence of "on-off" periods often experienced by chronic patients (Schwinghammer, 2003:556).

All of these medicine items were used in combination in order to increase the effect of dopamine. This could indicate the severity of the disease, also giving an indication of the difficulty experienced in finding the most appropriate treatment.

Prescriptions that had five combinations of medicine items are discussed in the subsequent section.

4.3.7.5 Prescriptions with five Parkinson's disease medicine items

Table A.34 in Appendix A contains all the information on prescriptions with combinations of five Parkinson's disease medicine items. According to the occurrence of combinations with five medicine items, there were not more than seven different prescription combinations in each study period. Therefore there was a need for compiling a top ten list according to frequencies.

Table 4.46 contains the combinations of medicine items encountered on the data from 2005 to 2008. Although there were five medicine items on these prescriptions, there was not any combination that contained medicine items from more than four categories, as indicated in Table 4.46. This implies that all of the combinations encountered had already been discussed in one of the previous sections (see section 4.3.8.2 – 4.3.8.4).

Apart from the fact mentioned above, this stresses the intensified dosage required by several patients, seeing that in various cases medicine items or categories were repeated. It is important to find the right combination that effectively treats a certain patient, because of patient variations being a key component.

Table 4.46: Trade names of five medicine items most frequently found together on Parkinson's disease prescriptions

Trade names of medicine items					Number of different categories present
Carbilev® / Sinemet®	Carbilev® / Sinemet®	Requip®	Requip®	Requip®	2
				Akineton®	3
				Eldepryl® / Parkilyne®	3
			Permax®	Eldepryl® / Parkilyne®	3
		Comtan®	Comtan®	Eldepryl®	3
				Akineton®	3
			Pexola®	Pexola®	3
				Artane®	4
			Eldepryl®	Akineton®	4
				Artane®	4
				Requip®	4
	Requip®	Requip®	Stalevo®	Akineton®	3
			Requip®	Requip®	2
	Eldepryl®	Akineton®	Permax®	Permax®	4
		Artane®	Pexola®	Madopar®	4
Category division of medicine items, in accordance with the MIMS classification system					
RED - Levodopa combinations YELLOW - Dopamine agonists BLUE - Anticholinergics GREEN - MOAI PINK - COMT					

The subsequent section contains an overview on the prescriptions containing a combination of 6 medicine items.

4.3.7.6 Prescriptions with six Parkinson's disease medicine items

In Table A.36 there were two combinations containing six medicine items. Table 4.47 gives an indication hereof:

Table 4.47: Trade names of six medicine items most frequently found together on Parkinson's disease prescriptions

Trade names of medicine items						Number of different categories present
Carbilev® / Sinemet®	Sinemet®	Sinemet®	Pexola®	Pexola®	Comtan®	3
		Requip®	Requip®	Requip®	Eldepryl®	3
Category division of medicine items, in accordance with the MIMS classification system						
RED - Levodopa combinations YELLOW - Dopamine agonists GREEN - MOAI PINK - COMT						

According to this it clearly shows that there were no new or different combinations. The occurrence of these combinations also was not significant. In 2005 the one combination only

occurred once, whereas in 2008 the other combination occurred on five different prescriptions. An explanation on the combination of medicine items used was discussed in sections 4.3.8.2 to 4.3.8.4.

The section that follows briefly entails some interactions that might occur when some of these medicine items are being used in combination.

4.3.7.7 Parkinson's disease medicine item interactions

In chapter two of this study, the interactions that might occur between other medicine items and Parkinson's disease medicine items were discussed. The following section briefly enlightened the medicine item interactions among the Parkinson's disease medicine items themselves.

The majority of interactions among these medicine items only occur in conjunction with the use of levodopa. Some interactions also have desired outcomes, whereas others could be tolerated with some adjustments. The following are interactions that might occur, and possible interventions that could make the interaction bearable (see section 2.7):

Table 4.48: Interactions among Parkinson's disease medicine items

Trade names between which interactions might take place		Interaction	Comment / intervention
Levodopa products: Carbilev®/ Sinemet® Madopar® Stalevo®	MOAI's[1]	Hypertensive crisis	* Effect might occur – therapy should be evaluated, or levodopa dose can be ↓
	Pexola® (pramipexole) or Requip® (ropinirole)[2]	Increased C_{max} values of levodopa	Desired effect
	Artane® (trihexyphenidyl)[3]	↓ absorption and ↓ effectiveness of trihexyphenidyl	↑ dose of Artane® required (see section PDD)
	Disipal® (orphenadrine)[4]	Amplified effect of levodopa	Desired effect
	Eldepryl®/ Parkilyne® (selegiline)[5]	Intensifies dyskinesias	Selegiline ↓ the need of levodopa, thus levodopa dose can be ↓ slowly[6]

(Turner, 2006:450[3],452[1],454[5]; Rossiter, 2010: 455[3,4], 456[1], 458[2]; Lennon medicines, 2004[1]; GlasoSmithKline, 2007[2]; Rascol *et al*., 2005:952[6]; Schwinghammer, 2003:558[6])

* Both MOAIs and levodopa individually have the probability of causing blood pressure to decrease by inducing orthostatic hypotension (Bhattacharya *et al*., 2003:223). A research study done by this team confirmed that neither the regularity nor brutality of the orthostatic hypotension increased when these items were used together (Bhattacharya *et al*., 2003:223). All of these medicine items have the tendency of interactions with other medication as well; these interactions are listed in various Tables in chapter 2 section 2.7. of this thesis.

A short summary on the combinations of Parkinson's disease medicine items per prescription follows in the subsequent section.

4.3.7.8 A summary of Parkinson's disease medicine items together on prescriptions

The frequencies of medicine items prescribed in combination decreased rather drastically with an increase of medicine items per prescription throughout the study period. Figure 4.6 below, illustrates the highest number of repeated prescriptions according to the number of medicine items per prescription during the study period. Refer to Tables A.30 to A.36 in appendix A for detailed figures.

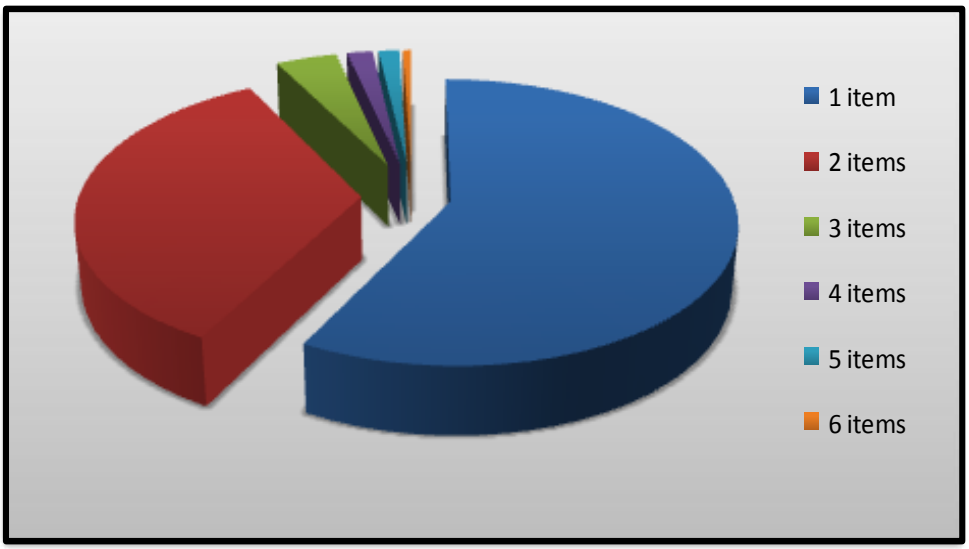

Figure 4.6: Frequencies of repeated prescriptions according to medicine item combinations per prescription

The number of medicine items per prescription increased, although in most cases the repetition of the same medicine item, only various strengths, was noticeable. This was done to ensure the right dose as per active ingredient to successfully treat the disease symptoms (see section 2.7).

In section 2.1 of this study, Parkinson's disease was defined as a neurodegenerative disease (Fahn & Sulzer, 2004:139). Because of this Sigh *et al.* (2007:29) also confirmed in section 2.7, that there are no guarantees that treatment would alter the degenerative course of the disease. Furthermore they stipulated that treatment should strive to make the patients' life as normal as possible. In this attempt, medicine items were added to treatment regimens as the disease progressed, increasing prescription expenditures. This observation was also confirmed in a study by Schenkman (2001:44-45) and his researchers in section 2.11.

The section that follows contains all the combinations of Parkinson's disease medicine items, in conjunction with other CNS medicine items.

4.3.8 Parkinson's disease medicine items together with CNS medicine items on a prescription

The following section includes a discussion that evaluated prescribing patterns of prescriptions that contained Parkinson's disease medicine items together with CNS medicine items on a prescription.

Tables A.38 to A.43 in appendix A, represent the top thirty prescriptions according to frequency with Parkinson's disease medicine items together with CNS medicine items on a prescription. The top thirty combinations were chosen according to the highest frequencies as there were CNS medicine items found in quite a variety of different combinations. Thus, with reference to interactions with antiparkinson medicine items together with CNS medicine items on a prescription, only the interactions that occurred within the top thirty list were mentioned, although other interactions also might have occurred.

Table 4.49 illustrates the different active ingredients of CNS medicine items encountered on the top thirty list according to frequencies together with Parkinson's disease medicine items. The MIMS classification system was used throughout this study (see section 2.7.2), and was therefore also used in a generalised division of active ingredients of CNS medicine items (Snyman, 2010:1-50):

Table 4.49: MIMS classification of CNS medicine items together with Parkinson's disease medicine items on top thirty lists of frequencies

1.1 CNS stimulants	1.2 Sedative hypnotics	1.3 Anxiolytics	1.4 Antidepressants
• Piracetam • Modafanil	• Diazepam • Nitrazepam • Triazolam • Temazepam • Zolpidem • Zopiclone	• Alprazolam • Lorazepam • Diazepam • Bromazepam • Oxazepam • Ketazolam • Clobazam • Hydroxyzine	• Amitryptilyne • Imipramine • Dothiepin • Mianserien • Fluoxetine • Paroxetine • Citalopram • Sertriline • Escitalopram • Fluvoxamine • Duloxetine • Venlafaxine • Mirtrazapine • Sulpiride
1.5 Antipsychotics	**1.6 Anti-epileptics**	**1.8 Antivertigo & anti-emetic agents**	**1.9 Antimigraine**
• Fluphenazine • Trifluoperaxine • Haloperidol • Risperidone • Clozapine • Zuclopentixol • Quetiapine • Olanzapine	• Valproate • Carbamazepine • Gabapentin • Clonazepam	• Cinnarizine	• Sumatriptan
1.10 Alzheimer's disease • Donepezil • Galantamine • Memantine	RED – BENZODIAZEPINES BLUE – TCA GREEN – SSRI ORANGE - SNRI		

* Table A.38 to Table A.43 portrays the frequencies associated with the combination of antiparkinson medicine items together with CNS medicine items

According to Table 4.49, categories 1.2 (Sedative hypnotics, 1.3: Anxiolytics) to 1.4 (Antidepressants) of the MIMS classification system were primarily represented among the frequencies of CNS medicine items together with Parkinson's disease medicine items. The section that follows entails a brief discussion on the possible reasons for combinations, as well as possible interactions encountered with Parkinson's disease medicine items in general together with CNS medicine items.

This section was discussed under the main categories of the CNS medicine items in the MIMS. Where possible the category as a whole, with a few medicine items as exceptions (benzodiazepines present in more than one category), were discussed.

4.3.8.1 CNS stimulants together with Parkinson's disease medicine items

In this category of the MIMS classification system, there were two medicine items that were prescribed with Parkinson's disease medicine items and other CNS medicine items. The two medicine items were: piracetam (n = 28) (see Tables A.39 and A.41) and modafini (n = 1) (see Table A.42).

Modafinil's main indications are to improve alertness in patients with unwarranted daytime sleepiness also closely related to narcolepsy (Snyman, 2010:1; Teitleman, 2001:134). In the United States the use of modafinil was debated, as for some patients modafinil replaces other stimulants, like amphetamines (Cahill, 2005:1), seeing that side-effects are less annoying and non-existent in some patients (O'Connor, 2004). A European medicines agency, however recommended that the use of modafinil should be restricted to narcolepsy, and not other sleep disturbances like sleep apnoea or excessive sleepiness (Hollis, 2010). Reasons for this were the benefits of the medicine item only outweigh the risk of side-effects in the case of narcolepsy. As mentioned in section 2.5.1 Parkinson's disease patients struggle with numerous different sleep disorders. Thus for this study's purpose the assumption were made that this medicine item was used together with Parkinson's disease medicine items because of its use in sleep disorders. Furthermore, Teitleman (2001:1341) pointed out that excessive sleepiness could possibly be the result of depression or psychosis. Modafinil together with Parkinson's disease medicine items occurred only once and also together with antidepressants and an anxiolytic medicine item (see Table A.42). Modafinil treatment results in normal sleep at night, as it assists in daytime sleepiness (Teitleman, 2001:1341). This was probably another reason for the use thereof together with Parkinson's disease medicine items.

According to the MIMS (Snyman, 2010:1), piracetam is indicated for unintentional syndromes that commonly occur with the process of ageing. In a study conducted by Ince Gunal *et al*. (2008:175-178) the use of piracetam was established in neurodegenerative disorders, for example ataxia. Relief was found in the posture and way of walking of the patients in the assembled study. Ataxia and the use of piracetam therefore, was labelled as a neurodegenerative disorder (Malykh, 2010:297) associated with movement impairment. As discussed in section 2.5 there are numerous other movement disorders. Fragile X-associated tremor/ataxia syndrome (see section 2.5.6) and Friedreich's ataxia (see section 2.5.4) are both ataxia associated movement disorders. Conclusively this all adds up to a rather self-explanatory reason for this medicine item to be used together with Parkinson's disease medicine items and other CNS medicine items.

There seem to be no serious potential drug-drug interactions (Refer to Tables 2.7 to Table 2.15), encountered with these two medicine items and Parkinson's disease medicine items (see section 2.7).

4.3.8.2 Sedative hypnotics together with Parkinson's disease medicine items

Sleep disturbances are rather commonly found among Parkinson's disease patients (Lökk, 2010:96; Jahan *et al*., 2009:538; Dhawan *et al*., 2006:227), and were discussed more in-depth in section 2.6.1 of this study.

Parkinson's disease is accompanied by chemical changes in the brain, and is frequently encountered in patients of a more matured age (Pal *et al*., 1999:1). As the severity of Parkinson's disease increases, it also has an amplifying effect on the incidence of depression and anxiety of the patients (Pal *et al*., 2004:166-167). Another study pointed out the fact that a reason for Parkinson's disease patients' poor sleeping patterns was the occurrence of depression among them (Korczyn, 2006:164-165). Although no definite reasons for sleep disorder in Parkinson's disease patients were established, the majority of Parkinson's disease patients suffer sleep disorders whether it being the inability to sleep at night, or to fall asleep during the day (Oerlemans & De Weerd, 2002:148). These statements imply reasons for Parkinson's disease medicine items and CNS hypnotics encountered together on prescriptions.

The following potential drug-drug interactions were identified:

- Diazepam (benzodiazepines) together with levodopa containing products (Table A.39). The effect would be a decrease in the antiparkinson's effect of levodopa (Turner, 2006:468). The frequency of this combination, however, was only 22 prescriptions from 2005 to 2008. According to Tatro (2004:819), the interaction of levodopa with benzodiazepines could possibly occur with minor severity if any.

- Zopiclone together with carbamazepine (Tables A.41 and A.42). The frequency of this combination was only four times from 2005 to 2008. However, the sedative effect of zopiclone could be compromised (Turner, 2006:472).

Both the identified interactions were possibly tolerated by patients, because of the minor severity of the occurrence, and possible benefits outweighing the side-effects.

4.3.8.3 Anxiolytic medicine items together with Parkinson's disease medicine items

Anxiety is another important disorder that accompanies Parkinson's disease, and that needs to be recognised (Pandya *et al*., 2008:857). An additional study (Allot *et al*., 2005:182-183) indicated that the pathophysiology of Parkinson's disease contributes to patients' developing anxiety and depression. Furthermore with Parkinson's disease's progression rate, the occurrence of anxiety and depression, seems rather unavoidable (Manor *et al*., 2009:455). Disorders affecting the frame of mind of a patient overall impair the quality of life of Parkinson's disease patients (Carod-Artal *et al*., 2008:107).

The above-mentioned studies and statements, conclude reasonable belief of Parkinson's disease medicine items used in conjunction with anxiolytic medicine items. Throughout the study period the occurrence of these medicine items in combination was evident (Refer to Tables A.38 to A.42). The overlapping of anxiolytic and sedative medicine items (e.g. benzodiazepines) made it difficult in solely labelling the condition as anxiety or sleep disturbance (Rossiter, 2010:474). Benzodiazepines have a multitude of indications, anxiety disorders and the use as a hypnotic, furthermore assisting in the treatment of spasms, for example dystonia (Jankovic, 2006:870) (see section 2.5.5). Levodopa's adverse effects (see section 2.7.4.1.3) of the initiation of anxiety in some patients (Aminoff, 2009a:473; Baron, 2005:41; Lennon medicines, 2004), was another probable reason for the concomitant use of these medicine items.

The only evident potential drug-drug interactions that could have taken place were:

- Levodopa together with benzodiazepines as mentioned in the previous section (section 4.2.4).

4.3.8.4 Antidepressants together with Parkinson's disease medicine items

Depression is a rather common disorder frequently encountered in combination with Parkinson's disease (Chen & Cheng, 2008:179; Suzuki *et al*., 2009:15). According to data the majority of CNS medicine items that were used in conjunction with Parkinson's disease medicine items, were antidepressants (Refer to Table A.38 to A.43). Also mentioned in section 4.4.2, the severity of depression in Parkinson's disease patients increase as the degenerative course of Parkinson's disease progresses (Pal *et al*., 2004:166-167). The arguments about the occurrence hereof together with Parkinson's disease were discussed more comprehensively in section 2.6.2 of this study. Two separate studies (Stella *et al*.,

2008:160-162; Suzuki *et al*., 2009:17-18) conducted on depression in Parkinson's disease clearly indicated that the occurrence in these patients was relatively inevitable, reassuring the appropriate use of antidepressants in conjunction with Parkinson's disease medicine items.

Possible interactions that could have occurred with Parkinson's disease medicine items were:

- Levodopa with tricyclic antidepressants (Tables A.38 to A.43). The frequencies of these medicine items used in conjunction were widely represented among data from 2005 to 2008. Theoretically the tricyclic antidepressants were to delay levodopa being absorbed by the patient (Tatro, 2004:832), but the severity of the interaction actually occurring, showed moderate to negligible practical significance. Postural hypotension also have a tendency of occurring (Turner, 2006:452), although it does not prohibit the concomitant use.

- Selegiline together with serotonin reuptake inhibitors (SSRIs) was seen in Tables A.39 to A.42. Major severity of interaction is encountered with the simultaneous use hereof (Tatro, 2004:1196). Also mentioned in section 2.7.6.1, is the use of a SSRI or TCA that must be discontinued two weeks prior to treatment with selegiline (Aspen pharmaceuticals, 2007; Turner 2006:454). This was a retrospective study, thus questions are raised to whether the correct advice was given to patients, seeing that data indicated the occurrence of simultaneous use taking place on a few accounts.

- Anticholinergic (biperidine and trihexyphenidyl) together with TCA (Tables A.39 to A.42) indicates an amplified anticholinergic effect, and should be monitored (Rossiter, 2010:455; Snyman, 2007:491; Turner, 2006:450, 452).

- Tricyclic antidepressants could have potential drug-drug interactions with the following CNS medicine items:

    - Clonazepam (benzodiazepine) (Tatro, 2004:1419): The prevalence of this combination was very low over the study period (n = 12) (Table A. 40).

    - Fluoxetine (Tatro, 2004:1426) and fluvoxamine (Tatro, 2004:1427) can increase the toxicity of TCA items: In Table A.40 (fluoxetine) and Table A.41 and A.42 (fluvoxamine) the prevalence of the combinations were noticed. Fluoxetine only represented a minority of twelve prescriptions and fluvoxamine together with a TCA in total represented five repeated prescriptions of the specific combination over the study period. Even though the severity of the

potential drug-drug interactions taking place was seen as moderate and feasible to take place, the benefits of the treatment probably outweighed the risks.

- Valproate sodium (Tatro, 2004:1448) could amplify the side-effects and plasma concentration of TCA items. As mentioned above the benefits of the treatment probably outweighed the risk, because of documentation stating that the interaction would take place although only in moderate severity. The prevalence (n = 16) hereof was seen in Table A.41.

- Paroxetine (SSRI) in combination with carbamazepine (Table A.40) did not occur frequently (n = 10), but the carbamazepine levels might increase with paroxetine (Turner, 2006:480). Therapy must be monitored and dose adjustments can take place in future.

4.3.8.5 Antipsychotics together with Parkinson's disease medicine items

Evidently the use of antipsychotic medicine item usage together with Parkinson's disease medicine items appeared not to be improbable (Refer to Tables A.38 to A.40, A.42 and A.43). Psychosis, hallucinations, delusions and nightmares are commonly found side-effects of dopaminergic (Clarke, 2002:24), levodopa (Aminoff, 2009a:473; Baron, 2005:41; Lennon medicines, 2004), selegiline in combination with levodopa (Aspen pharmaceuticals, 2007; Schwinghammer, 2003:558) and COMT inhibitors (Aminoff, 2009a:476; Novartis, 2000; Standaert & Young, 2009) (see section 2.7).

The occurrence of psychosis in Parkinson's disease is not only present because of medication effects, but is also frequently encountered because of the process of Parkinson's disease (Aarsland *et al*., 1999:496; Holroyd *et al*., 2001:738). Furthermore antipsychotic medicine items' simultaneous use with Parkinson's disease medicine items might have been for the treatment of other movement disorders (see section 2.5). Among other medicine items antipsychotics were indicated for symptomatic relief of tic disorders (see section 2.5.11) (Eidelberg & Pourfar, 2007). More specifically, risperidone, fluphenazine and haloperidol (Eidelberg & Pourfar, 2007), were used in the treatment of chorea, also a type of movement disorder (see section 2.5.2).

The following are probable drug-drug interactions that could have occurred:

- Fluphenazine together with biperidine (Refer to Table A.39). The potential drug-drug interaction would have had moderate severity, with suspected effectiveness of fluphenazine that decreased (Tatro, 2004:1054). Furthermore fluphenazine with carbidopa (Refer to Table A.39) possibly would have had moderate interaction, inhibiting levodopa/carbidopa effects (Tatro, 2004:829).

- Haloperidol together with biperidine and orphenadrine (Refer to Table A.38). Moderate severity with variable effects might have been encountered. Suspected tardive dyskinesia might occur (Tatro, 2004:672).

- Risperidone together with paroxetine (Refer to Table A.40). Metabolism of risperidone could be inhibited, increasing side-effects (Tatro, 2004:1168). Risperidone together with carbamazepine (Refer to Table A.40). In contrast to paroxetine, carbamazepine increases the metabolism of risperidone.

- Trifluoperazine together with biperidine (Refer to Table A.38). This interaction would have had moderate severity, where the effect of tripluoperazine could be suspected to decrease (Tatro, 2004:1054).

No other medicine item interactions were encountered in Tables A.38 to A.43 among anti-psychotic medicine items.

4.3.8.6 Anti-epileptic medicine items together with Parkinson's disease medicine items

In Table 4.49 the anti-epileptic medicine items that were used together with Parkinson's disease medicine items were given. In Appendix A, Tables A.38 to A.42 illustrates data, where these medicine items were used simultaneously. These combinations represented rather high frequencies.

In section 2.5.9 of this study, Myoclonus was discussed as a movement disorder. This disorder also originates in the CNS affecting the intentional movements of patients (Lees, 2002:20; Vercueil, 2006:327; Schlaggar & Mink, 2003:40,48), and could be the result of other neurodegenerative disorders (Caviness & Brown, 2004:598). No definite connotation could be made as yet, whether myoclonus has an epileptic origin. Nonetheless clonazepam, carbamazepine and volproate assist in the relief of symptoms (Schlaggar & Mink, 2003:48; Beers, 2006). Myoclonus being a movement disorder with a possible epileptic component, clarifies one reason for the concomitant use of the medicine items. Tremor is another movement disorder (see section 2.5.11) in which gabapentin and other anti-epileptic

medicine items assist in relieving the symptoms thereof (Baron, 2005:48; Chen & Swope, 2007:467; Lees *et al*., 2010:251). Clonazepam is also a possible medicine item that is used in severe tic disorders (see section 2.5.11) (Eidelberg & Pourfar, 2007). Carbamazipine's effectiveness in the treatment of another movement disorder, chorea (see section 2.5.2), was also established (Yilmaz, 2006:29).

The following were potential drug-drug interactions that could have taken place:

- Interaction of levodopa in combination with clonazepam (benzodiazepines) as mentioned in section 4.4.2 (Tatro, 2004:819).
- Clonazepam together with TCA (Tatro, 2004:1419), discussed in section 4.4.4.
- Valproate sodium together with TCA (Tatro, 2004:1448). This interaction was also briefly explained in section 4.4.4.

The following section briefly entails the antivertigo and anti-emetic medicine items together with Parkinson's disease medicine items.

4.3.8.7 Antivertigo and anti-emetic medicine items together with Parkinson's disease medicine items

The only simultaneous use of medicine items in this category of CNS medicine items that were used together with Parkinson's disease medicine items was cinnarazine (see Table A.38). The incidence of this combination of medicine items was relatively high (n = 480), compared to others.

Contradictory to cinnarazine assisting in the treatment of possible Parkinson's disease symptoms, it is believed that cinnarazine has the tendency in inducing Parkinsonism like symptoms (Teive, 2004:245). The incidence of Parkinson's disease medicine items together with cinnarazine was rather questionable. Sedation and drowsiness (Janssen pharmaceutica, 2004), varying in intensity, are known side-effects of cinnarazine that could have the slightest indication in assisting in sleep disorders in Parkinson's disease.

The only potential drug-drug interaction that might have been encountered, was an antihistamine (cinnarazine) together with an anticholinergic Parkinson's disease medicine item (see section 2.7.5.5), increasing the anticholinergic effects.

4.3.8.8 Antimigraine medicine items together with Parkinson's disease medicine items

The extrapyramidal system is associated with the pathology of Parkinson's disease. The question was raised whether the extrapyramidal system is also associated with migraine, however the sole exclusion could not be made (Barbanti & Fabrini, 2002:9). Speculations of associations between essential tremor and migraine were dismissed with results that confirmed the co-existence of essential tremor (Barbanti *et al*., 2010:686) as well as Tourette's syndrome and migraine (Barbanti & Fabrini, 2002:8). Literature hypothesised the prevalence in co-occurrence of these diseases was relatively high (Barbanti & Fabrini, 2002:8), contradictory to data over this research period (Sumatriptan, n = 22) (Refer to Table A.40).

This argument states that migraine simply co-exists with movement disorders like essential tremor and Tourette's syndrome, providing an acceptable reason for the antimigraine medicine item used together with Parkinson's disease medicine items (see sections 2.5.11 and 2.5.12).

There were no known potential drug-drug interactions among the medicine items that were used in this specific combination with the antimigraine medicine items (Tatro, 2004:1608) (Refer to Table A.40).

4.3.8.9 Alzheimer's disease medicine items together with Parkinson's disease medicine items

Parkinson's disease's neurodegenerative origin furthermore results in other forms of neurological disorders accompanying it, for instance dementia (Colosimo *et al*., 2003:852-853; Ravina *et al*., 2005:938). An Alzheimer's disease medicine item, donepezil was well accepted in treating Parkinson's disease dementia, furthermore improving the cognitive state of the patient, not aggravating Parkinson's disease itself (Aarsland *et al*., 2002:711; Ravina *et al*., 2005:938). Another Alzheimer's disease medicine item, galantamine, also proved to improve the cognition and motor response in Parkinson's disease patients with dementia (Aarsland *et al*., 2003:940; Hohnadel *et al*., 2007:550). Memantine, the last Alzheimer's disease medicine item used together with Parkinson's disease medicine items, presented some relief in mice inflicted with Huntington disease (Friedman, 2010:37), another movement disorder (see section 2.5.6). Progressive supranuclear palsy (see section 2.5.10), a disorder accompanied by Parkinson's and Alzheimer's disease like symptoms (Warren *et al*.,

2005:239) , could also have been treated with Alzheimer's disease medicine items together with Parkinson's disease medicine items (Karceski, 2008:72).

Alzheimer's disease medicine items together with Parkinson's disease medicine items weren't found frequently on prescriptions throughout the study period (donepizil, n = 4; galantamine, n = 22; memantine, n = 6) (Refer to Tables A.40, A.42 and A.43). Nevertheless, the above-mentioned statements, provide adequate explanations for these medicine items' simultaneous use.

No severe potential drug-drug interactions could have taken place between Parkinson's disease medicine items and Alzheimer's disease medicine items (Tatro, 2004:1547).

The section that follow entails a brief evaluation of the prescribing patterns of medicine items prescribed in Parkinson's disease regarding the prescribed dosage of the specific medicine item.

4.3.9 Prescribed daily dosage (PDD)

The subsequent section contains the discussion on the PDD on medicine items used in Parkinson's disease. The PDD (as defined in section 3.4.2.1.5) of each of the medicine items was evaluated against the acceptable theoretical registered dosages as indicated through the Martindale® and MIMS®. The following Table contains a summary of the acceptable dosages according to the above-mentioned sources in addition to the recommended use of antiparkinson's agents as previously mentioned (see section 2.7):

In Table A.37 in appendix A, the PDD of each Parkinson's disease medicine item was given for the entire study period. The registered acceptable dosages (Refer to Table 4.50) were evaluated against the PDD (Refer to Tables 4.51 to 4.53). Principally the discussions were done according to the active ingredient/s. In some cases the formulation of the medicine items varied in strength only and the applicable use thereof was only evident as the treatment regimen progressed according to severity of the disease.

Table 4.50: Summary of acceptable dosages of Parkinson's disease medicine items

Medicine item	Active ingredients	Acceptable theoretical dosage
Carbilev® 25/100 TAB / Sinemet® 25/100 TAB	Carbidopa / Levodopa	*Initial dose*: 25 mg carbidopa/100 mg levodopa tds (one tablet) *Increase gradually* *Maintenance dose range*: carbidopa = 75 mg – 200 mg levodopa = 750 mg – 2 g
Carbilev® 25/250 TAB / Sinemet® 25/250 TAB		
Sinemet® CR TAB	Carbidopa / Levodopa	*Initial dose*: 50 mg carbidopa/ 200 mg levodopa bd (one tablet) *Increased gradually* *Initial dose not exceeding:* 600 mg levodopa *Patient on immediate release levodopa tablets*: *Initial dose*: same amount of levodopa , increased with intervals of 4 to 12 hours. *Depending on clinical response of patient* *Maintenance dose*: 100 mg carbidopa / 400 mg levodopa to 400 mg carbidopa/ 1.6 g levodopa
Madopar® TAB	Benserazide HCL (50 mg) / Levodopa (200 mg)	*According to levodopa*: *Initial dose*: 50 mg tds / qid (half a tablet) *Advanced stages initial dose: 100 mg tds* *Maintenance dose*: between 400 to 800 mg Usually 600 mg (3 tablets) *Rarely needed*: 1 g (Maximum 5 tablets dialy)
Madopar® HBS CAP	Benserazide HCL (25 mg) / Levodopa (100 mg)	*According to levodopa*: *Initial dose*: 100 mg tds (one capsule) Not exceeding 600 mg Adjusted every 2 to 3 days depending on response
Stalevo® 100/25 mg TAB / Stalevo® 150/37.5 mg TAB / Stalevo® 50/12.5 mg TAB	Levodopa / Carbidopa / Entacapone	*Patients on levodopa/ carbidopa and separate entacapone should switch to combination tablet* *Patients not receiving entacapone:* Similar/ less levodopa Previous dose of levodopa higher than 800 mg daily, first start entacapone treatment separately Titrate optimum dose using a strength available - not exceeding 10 tablets per day
Eldepryl® 5 mg TAB / Parkilyne® 5 mg TAB	Selegiline	Initial dose: 5 mg in the morning, increase to 10 mg daily (single dose / divided)
Pexola® 0.125 mg TAB / Pexola® 0.25 mg TAB / Pexola® 1 mg TAB	Pramipexole	Initial dose: 0.125 mg tds (one tablet 0.125 mg pramipexole) *Second week increase* to: 0.25 mg tds (one tablet 0.25 mg pramipexole) *Third week increase to*: 0.50 mg tds (two tablets 0.25 mg pramipexole) *Maximum dose*: 4.5 mg daily
Requip® 0.25 mg TAB/ Requip® 0.5 mg TAB/ Requip® 1 mg TAB/ Requip® 2 mg TAB/ Requip® 5 mg TAB	Ropinirole	*Initial dose*: 0.25 mg tds (one tablet 0.25 mg ropinirole) *Increase weekly intervals, for 4 weeks* *After week 4*: increase increaments with 1.5 mg / 3 mg not exceeding 9 mg *Maximum dose*: 24 mg daily (± four 5 mg ropinirole tablets)
Requip® XL 2 MG SRT / Requip® XL 4 MG SRT / Requip® XL 8 MG SRT	Ropinirole	Dose to be given only once daily Week 1: 2mg Week 2: 4 mg Week 3: 6 mg Week 4: 8 mg Not exceeding 24 mg daily
Disipal® 50 mg TAB	Orphenadirne	*Initial dose*: 150 mg daily (divided doses) *Increased by 50mg every 2-3 days* *Maintenance dose*: 150 – 300 mg daily (3-6 tablets) *Maximum dose*: 400 mg daily (8 tablets)
Artane® 2 mg TAB/ Artane® 5 mg TAB	Trihexyphenidyl	*Initial dose*: 1 mg daily *Increase: increments of* 2 mg → 6 mg → 10 mg dialy every 3 to 5 days *Advanced cases*: 12 to 15 mg daily *Maximum*: 20 mg daily
Comtan® 200 mg TAB	Entacapone	*Initial dose*: 200 mg together with levodopa dose *Maximum dose*: 200 mg ten times daily (20 tablets)
Tasmar® 100 mg TAB	Tolcapone	*Initial dose:* 100 mg tds *Maximum dose*: 200 mg tds
Akineton® 2 mg TAB	Biperiden	*Initial dose*: 2 mg tds / qid *Maximum dose*: 16 mg daily
Akineton® 5mg/ml INJ		2mg IM/IV repeated every 30minutes *Maximum dose*: 4 doses in 24 hours
Aspen-Bromocriptine 2.5 mg TAB	Bromocriptine	*Week 1*: 1 – 1.25 mg at night *Week 2*: 2 – 2.5 mg at night *Week 3*: 2.5 mg bd *Week 4*: 2.5 mg tds *Maximum dose*: 30 mg daily (some cases even 40 mg)
Permax® 0.05 mg TAB/ Permax® 0.25 mg TAB/ Permax® 1 mg TAB	Pergolide	*First administration*: 0.05 mg *Then*: 0.05 mg bd for 2- 4 days *Increase with* 0.1mg / 0.25 mg tds for 3 – 4 days *Increase to daily dose of*: 1.5 mg daily *Maintenance dose*: 2.1 -2.5 mg daily *Maximum dose*: 3 mg daily

(Snyman, 2010:41-43; Sweetman, 2010)

4.3.9.1 PPD of medicine items with one active ingredient

Firstly the medicine items containing one active ingredient were evaluated. Table 4.51 consists of the medicine items with one active ingredient, compiled from Table A.37 in appendix A.

Table 4.51 PDD of medicine items with one active ingredient

Trade name	Active ingredient	Number of medicine items (n)	Mean ± Std Dev (mg)
AKINETON® 2MG TAB	BIPERIDEN	14751	4.80 ± 5.48
AKINETON® 5MG/ML INJ		210	3.05 ± 2.74
ARTANE® 2MG TAB	TRIHEXYPHENIDYL	2480	8.62 ± 20.94
ARTANE® 5MG TAB		19	6.58 ± 2.79
ASPEN BROMOCRIPTINE® 2.5MG	BROMOCRIPTINE	1252	4.80 ± 3.91
COMTAN® 200MG TAB	ENTACAPONE	1607	704.48 ± 938.69
DISIPAL® 50MG TAB	ORPEHNADRINE	3725	156.61 ± 197.77
ELDEPRYL® 5MG TAB	SELEGILINE	6479	8.53 ± 14.75
PARKILYNE® 5MG TAB		990	7.45 ± 2.79
PERMAX® 0.05MG TAB	PERGOLIDE	310	0.13 ± 0.15
PERMAX® 0.25MG TAB		339	0.72 ± 0.49
PERMAX® 1MG TAB		456	3.26 ± 4.77
PEXOLA® 0.125MG TAB	PRAMIPEXOLE	3886	0.39 ± 1.06
PEXOLA 0®.25MG TAB		5700	0.95 ± 1.84
PEXOLA® 1MG TAB		3937	2.89 ± 3.64
REQUIP® 0.25MG	ROPINIROLE	1254	0.86 ± 1.04
REQUIP® 0.5MG		1173	1.46 ± 0.85
REQUIP® 1.0MG		2319	3.24 ± 3.02
REQUIP® 2.0MG		1599	7.84 ± 8.04
REQUIP® 5.0MG		484	14.56 ± 2.48
REQUIP® XL 2MG SRT		3	2.93 ± 1.01
REQUIP® XL 4MG SRT		5	4.00 ± 0.00
REQUIP® XL 8MG SRT		2	12.00 ± 5.66
TASMAR® 100MG TAB	TOLCAPONE	76	225.48 ± 115.11

4.3.9.1.1 PDD of biperiden containing medicine items

Parkinson's disease medicine items that contain biperiden were:

- Akineton® 2 mg tablets and
- Akineton® 5 mg/ml injections

According to Table 4.51 a Parkinson's disease patient received approximately 2 tablets (4.80 mg ± 5.48 mg) of Akineton® 2 mg tablets daily. This dose was seen as below the recommended dose of 1 tablet (2 mg) three to four times daily (3 – 4 tablets) (Refer to Table 4.50). The susceptibility to a lower dose in the case of some patients could, however, not be excluded.

The maximum dose indicated in Table 4.50 for Akineton® 5 mg/ml injections was 4 doses (8 mg) in 24 hours. The mean (3.05 mg ± 2.74) dosage of this medicine item did not exceed this registered dose, and was within the prescribed range (Refer to Table 4.50).

4.3.9.1.2 PDD of thrihexyphenidyl containing medicine items

Artane® 2 mg and Artane® 5 mg tablets were the only medicine items containing thrihexyphenidyl on the database from 2005 to 2008 (Refer to Table 4.51).

As indicated in Table 4.50 the treatment regimen with this medicine item is not altogether uncomplicated. The data stipulated only the average PDD and not the precise increments with which the regimen was followed. It is, however, clear that on average, neither Artane® 2 mg tablets (8.62 mg ± 20.94 mg) nor Artane® 5 mg tablets (6.58 mg ± 2.79) exceeded the maximum daily dose that could be used for this individual medicine item.

4.3.9.1.3 PDD of bromocriptine containing medicine items

There was only one medicine item that contained bromocriptine namely, Aspen-Bromocriptine® 2.5 mg tablets.

The treatment regimen of this medicine item is accompanied by rather complex steps, solely depending on the response of the individual patient. A more or less final dose of 7.5 mg daily over an period of four weeks should be reached, with increases in different increments over that period (Refer to Table 4.50). Thus the prescribing of Aspen-Bromocriptine® 2.5 mg tablets did not propose any major irregularities, as the PDD was more or less 4.80 mg ± 3.91 mg per day (Refer to Table 4.51).

4.3.9.1.4 PDD of entacapone containing medicine items

Comtan® 200 mg tablets were the only medicine item that contained solely entacapone. Entacapone in combination with levodopa and carbidopa was discussed in section 4.5.3.

There was no specific dose indicated for this medicine item, only emphasising the simultaneous use with levodopa (Refer to Table 4.50). Table 4.51 indicated that on average

patients received 3 – 4 tablets (704.48 mg ± 938.69 mg) well within the maximum range of 20 tablets (2 g) daily (Refer to Table 4.50).

4.3.9.1.5 PDD of orphenadrine containing medicine items

The only medicine item evaluated with this active ingredient was Disipal® 50 mg tablets. Table 4.50 clearly indicated that after increasing the therapy with increments of 50 mg, the maintenance dose was to vary between 150 – 300 mg daily. Indisputable to the results (156.64 mg ± 197.77 mg) found upon the database for the study period of this study (Refer to Table 4.51).

4.3.9.1.6 PDD of selegiline containing medicine items

Eldepryl® 5 mg tablets and their generic equivalent medicine item Parkilyne® 5 mg tablets were the only medicine items on the database that contained selegiline.

Results obtained corresponded with literature results, as the PDD of both Eldepryl® 5 mg tablets (8.53 mg ± 14.73 mg) and Parkilyne® 5 mg tablets (7.45 mg ± 2.79 mg) did not exceed 10 mg daily (Refer to Table 4.50 and Table 4.51).

4.3.9.1.7 PDD of pergolide containing medicine items

Pergolide as active ingredient was present in three different strength formulations:

- Permax® 0.05 mg tablets
- Permax® 0.25 mg tablets
- Permax® 1 mg tablets

Permax® 0.05 mg tablets (0, 13 mg ± 0.15 mg) and Permax® 0.25 mg tablets (0.72 mg ± 0.49 mg) were mainly part of the initiation of therapy with pergolide, also representing values in agreement upon registered dosages (Refer to Table 4.50 and Table 4.51). Contradictory to the set apart maximum dose of 3 mg daily, Permax® 1 mg tablets indicated that 50% of patients (median= 3 mg) received more than 3 mg daily (Refer to Table A.37), with an average PDD 3.26 mg ± 4.77 mg daily (Refer to Table 4.51).

4.3.9.1.8 PDD of pramipexole containing medicine items

On the database, there was one medicine item in various strengths that contained pramipexole as active ingredient, namely:

- Pexola® 0.125 mg tablets
- Pexola® 0.25 mg tablets
- Pexola® 1 mg tablets

Upon evaluation of this active ingredient, no irregularities were encountered with the dosages that were prescribed for the specific medicine items. Pexola® 0.125 mg tablets (0.39 mg ± 1.06 mg) were indicated as a dose of 0.375 mg daily in the first week of pramipexole treatment (Refer to Table 4.50). The difference of 0.02 mg was seen as practically insignificant by the researcher of this study. Pexola® 0.25 mg tablets had a dosage range of between 0.75 and 1.50 mg daily depending on the second or third week of therapy, with results (0.95 mg ± 1.84 mg) representing an acceptable average PDD (Refer to Table 4.51). Furthermore the treatment regimen indicated the PDD should increase with small increments. The average daily dose of Pexola® 1 mg tablets (2.89 mg ± 3.64 mg) did not exceed the specified maximum dose of 4.5 mg daily.

4.3.9.1.9 PDD of ropinirole containing medicine items

Parkinson's disease medicine items that contain ropinirole in various strengths as well as in its extended release form included the following:

- Requip® 0.25 mg tablets
- Requip® 0.5 mg tablets
- Requip® 1 mg tablets
- Requip® 2 mg tablets
- Requip® 5 mg tablets
- Requip® XL 2 MG SRT
- Requip® XL 4 MG SRT
- Requip® XL 8 MG SRT

extended release tablets

Ropinirole tablets in a range of different strengths were probably formulated for their specific use in the therapeutic treatment of Parkinson's disease. The initial dose, as indicated in Table 4.51 supposedly starts at 0.75 mg daily with dose variations and increased increments

that take place, not exceeding a dose of 24 mg daily (Refer to Table 4.51). In this research study no distinction was made with regard to individual patients following their specific treatment regimen. An overall evaluation of all the different strengths of Requip® tablets, however, did not indicate irregularities exceeding the maximum PDD of 24 mg (Refer to Table 4.50 and Table 4.51).

At the time of this study the extended release tablets had been newly introduced to the market. Nevertheless no irregularities were found in the prescribing thereof, with not one of the four strengths exceeding the maximum PDD of 24 mg (Refer to Table 4.51).

4.3.9.1.10 PDD of tolcapone containing medicine items

From 2005 to 2008, there was one medicine item with the active ingredient of tolcapone, namely Tasmar® 100 mg tablets.

The average PDD of this medicine item represented 225.48 mg ± 115.11 mg which was higher than the maximum dose of 200 mg daily as indicated through literature (Refer to Table 4.50). Table A.37 also indicated that 50% of *patients* received more than 200 mg per day.

4.3.9.2 PDD of medicine items with two active ingredients

The subsequent section contains the brief evaluation of the PDD of medicine items that contain two active ingredients. Table 4.52 is a summarised Table compiled from Table A.37 in appendix A, and indicates the PDD of these medicine items with respect to individual active ingredient.

Table 4.52 PDD of medicine items with two active ingredients

Trade name	Active ingredient	Number of medicine items (n)	Mean ± Std Dev (mg)
According to active ingredient one			
CARBILEV® 25/100 TAB	CARBIDOPA	25618	94.49 ± 137.52
CARBILEV® 25/250 TAB		8816	85.92 ± 131.86
MADOPAR® HBS CAP	BENSERAZIDE HCL	1098	216.81 ± 354.68
MADOPAR® TAB		5624	149.98 ± 234.14
SINEMET® 25/100 TAB	CARBIDOPA	15425	92.35 ± 128.77
SINEMET® 25/250 TAB		4557	99.52 ± 164.42
SINEMET® CR TAB		11297	133.10 ± 160.41
According to active ingredient two			
CARBILEV® 25/100 TAB	LEVODOPA	25618	377.97 ± 550.07
CARBILEV® 25/250 TAB		8816	859.24 ± 1318.58
MADOPAR® HBS CAP		1098	433.62 ± 709.36
MADOPAR® TAB		5624	299.96 ± 468.28
SINEMET® 25/100 TAB		15425	369.40 ± 515.06
SINEMET® 25/250 TAB		4557	995.25 ± 1644.19
SINEMET® CR TAB		11297	532.41 ± 641.64

4.3.9.2.1 PDD of levodopa/carbidopa containing medicine items

The following were all the medicine items that contained levodopa and carbidopa in one formulation:

- Carbilev® 25/100 tablets
- Sinemet® 25/100 tablets
- Carbilev® 25/250 tablets
- Sinemet® 25/250 tablets

Carbilev® and Sinemet® tablets are generic equivalent medicine items. In Table 4.50 the initial and maintenance dose of both levodopa and carbidopa were indicated. The data, however, limit this research in specifically indicating the specific stage of Parkinson's disease treatment of patients (Refer to Table 4.52). Neither of the medicine items exceeded the maximum daily dose as indicated in Table 4.50.

Another formulation that contained levodopa and carbidopa was the controlled release tablet:

- Sinemet® CR tablets

Carbidopa concentration that was prescribed in this formulation was on average 133.10 mg ± 160.41 mg daily, and the levodopa concentration represented 532.41 mg ± 641.64 mg daily. Both active ingredients were within the range of the preferred maintenance dose (Refer to Table 4.50).

4.3.9.2.2 PDD of levodopa/benserazide containing medicine items

Madopar® tablets and Madopar® HBS capsules (modified release) were the only medicine items that contained this combination of active ingredients.

- Madopar® tablets were prescribed with an average PDD of 299.96 mg ± 468.28 mg levodopa and 149.98 mg ± 234.14 mg benserazide. According to Table 4.50, the maintenance dose of levodopa should be between 400 and 800 mg, with a ratio of 1:4 in favour of levodopa indicating the dose of benserazide not to be more than 100 and 400 mg. Thus this medicine items was prescribed within the specified range, with no irregularities encountered.

- Madopar® HBS capsules. The formulation of these capsules only indicated to be taken once daily, however also did not indicate any irregularities as the average PDD of both active ingredients did not exceed the desired dose recommendations (Refer to Table 4.50 and Table 4.52).

4.3.9.3 PDD of medicine items with three active ingredients

The discussion of this section briefly entails the medicine items with three active ingredients. Table 4.53 indicated the PDD of the specific medicine item according to each of the individual active ingredients. Table 4.53 was compiled from Table A.37 in appendix A.

Table 4.53 PDD of medicine items with three active ingredients

Trade name	Active ingredient	Number of medicine items (n)	Mean ± Std Dev (mg)
According to active ingredient one			
STALEVO® 100/25MGTAB	CARBIDOPA	341	89.09 ± 33.97
STALEVO® 150/37.5 TAB		289	160.96 ± 59.17
STALEVO ®50/12.5 TAB		71	39.54 ± 31.29
According to active ingredient two			
STALEVO® 100/25MGTAB	ENTACPONE	341	712.69 ± 271.72
STALEVO® 150/37.5 TAB		289	858.45 ± 315.59
STALEVO ®50/12.5 TAB		71	632.70 ± 500.68
According to active ingredient three			
STALEVO® 100/25MGTAB	LEVODOPA	341	356.34 ± 135.86
STALEVO® 150/37.5 TAB		289	643.84 ± 236.69
STALEVO ®50/12.5 TAB		71	158.18 ± 125.17

4.3.9.3.1 PDD of levodopa/carbidopa/entacapone containing medicine items

Medicine items formulated with these active ingredients were encountered in different strength variations:

- Stalevo® 100/25 mg tablets
- Stalevo® 150/37.5 mg tablets
- Stalevo® 50/12.5 mg tablets

The recommended use of these formulations was relatively vague, because of the initiation of these specific medicine items depending on previous treatment regimens, even so a clear indication was made that a dosage of 10 tablets should not be exceeded (Refer to Table 4.50). Stalevo® 100/25 mg tablets had an average PDD of 3.5 tablets, Stalevo® 150/37.5 mg tablets on average represented 4 tablets daily and Stalevo® 50/12.5 mg tablets represented an average PDD of 3 tablets (Refer to Table 4.53). These medicine items, however, did not reveal any irregularities regarding the PDD.

4.3.9.4 Summary on the PDD

After the evaluation of the prescribing patterns of medicine items used in Parkinson's disease against the specific measuring instrument of the PDD the following conclusions were made. Of all the medicine items used there were only two medicine items that clearly indicated average PDD, above the maximum daily dosage, although the prescribed daily dose higher than the maximum dose, did not indicate to be much more. These two medicine items were: Permax® 1mg and Tasmar®100mg. Both the medicine items indicated that 50% of the medicine items consumed by patients were more than maximum average PDD.

In retrospect the prescribing patterns of the medicine items prescribed were evaluated against the PDD, and no major irregularities were found.

The subsequent section entails the discussion on the refill adherence of Parkinson's disease medicine items.

4.3.10 Refill-adherence rate (AR)

The refill-adherence rates were calculated according to the precise method as stipulated for refill-adherence rates in section 3.4.2.1.6. In this section the refill-adherence rates according to the trade names of medicine items were evaluated, as well as the cost implications thereof.

In the first section the overall refill-adherence rates were discussed, thereafter a discussion followed on the refill-adherence rates according to gender and age groups.

4.3.10.1 Refill adherence rates according to all applicable medicine items

Table 4.54 consists of the individual number of medicine items on which AR were calculated, divided into their specific AR categories:

Table 4.54: Refill AR on all applicable medicine items (per individual Trade name)

AR category		Number of medicine items	AR (%)
1	AR ≤ 90%	4 691	53.50
2	90% < AR ≤ 110%	3 225	36.78
3	AR > 110%	852	9.72
Total number of medicine items		8 768	

Table 4.54 indicated that the majority of antiparkinson medicine items (53.50%, n = 4691) had unacceptable refill-adherence rates below 90%. Only 36.78% (n = 3 225) of antiparkinson medicine items were within the acceptable range of between 90% and 110%. Refill-adherence rates above the acceptable rates represented 9.72% (n = 852). An average refill-adherence rate represented 92.29% ± 180.70% (n = 8 768) from 2005 to 2008. A research study (Grosset *et al*., 2005:250) on the adherence in Parkinson's disease patients indicated that a 97% adherence rate was obtained through manual tablet counts, and a 96% adherence rate on electronic tablet counts. The study furthermore reported 57% of patients to have missed doses, and 23% of patients to have taken extra doses. The technique used in this study was different to the research done by Grosset *et al*. (2005:250), thus no comparative conclusion could be made, however the refill-adherence rate of this study proved to be unacceptably low.

A study conducted by researchers (Buetow *et al*., 2009:24) in New Zealand indicated possible reasons to Parkinson's disease medication that were taken late, extra or not taken at all, to be the following:

- → Sudden withdrawal of medication
- → Instructions were wrong, unclear or misinterpreted
- → Lack of knowledge
- → Forgetfulness

Furthermore researchers were of meaning that co-morbid conditions, higher health services used and aggravation of symptoms could be related to the non-adherence to Parkinson's disease medication (Kulkarni *et al*., 2006:119).

The subsequent section entails the overview on the refill-adherence rates according to the male and female gender groups.

4.3.10.2 Refill-adherence rates according to gender

In this section only the medicine items associated to the male and female gender were discussed, with the exclusion of medicine items associated to the gender identification as unidentified (see section 4.1).

The information regarding each individual gender group is summarised in Table 4.56 below:

Table 4.55: Refill AR according to gender groups

AR category		MALE		FEMALE	
		Number of medicine items	AR (%)	Number of medicine items	AR (%)
1	AR ≤ 90%	2 112	52.33	2 578	54.50
2	90% < AR ≤ 110%	1 519	37.64	1 705	36.06
3	AR > 110%	405	10.03	447	9.45
Mean ± Std Dev (%)		90.83 ± 175.21		93.99 ± 186.99	

In both gender groups the highest adherence rates represented were in category 1, indicating that more than 50% of the antiparkinson medicine items dispensed for male (52.33%, n = 2 112) and female (54.50%, n = 2 578) patients between 2005 and 2008 were subject to unacceptably low refill-adherence rates (≤ 90%). The average refill-adherence rates of male (90.83 ± 175.21) and female (93.99 ± 186.99) patients did not indicate any practical significant difference (d = 0.02). A more generalised study (Anderson *et al*., 2005:622) on the refill-adherence rates to repeat prescriptions were done with regard to patients and prescribers. Results obtained from Anderson *et al*. (2005:622) indicated no practical significance between gender groups, although the male patients had a higher rate of oversupply than females and a lower rate of undersupplies. This study's results were furthermore comparable also indicating that males had a higher rate of oversupply than females (10.03%, n = 405). Another study conducted (Kulkarni, *et al*., 2006:103) indicated no significant difference between gender groups and their adherence rates to Parkinson's disease medication.

The next section includes the discussion on the refill AR between the six different age groups.

4.3.10.3 Refill-adherence rates according to age

The six different age groups were evaluated in this section according to their refill-adherence rates to their antiparkinson medicine items. The following Table 4.56 indicates the refill-adherence rates according to the different age groups:

Table 4.56: Refill AR according to age

Age group	Variables	AR category		
		1	2	3
		AR ≤ 90%	90% < AR ≤ 110%	AR > 110%
1	Number of medicine items	255	65	53
	AR (%)	68.36	17.43	14.21
	Mean ± Std Dev (%)	89.89 ± 213.19		
2	Number of medicine items	300	126	61
	AR (%)	61.60	25.87	12.53
	Mean ± Std Dev (%)	94.49 ± 215.87		
3	Number of medicine items	529	282	100
	AR (%)	58.07	30.95	10.98
	Mean ± Std Dev (%)	85.81 ± 172.43		
4	Number of medicine items	1 021	736	200
	AR (%)	52.17	37.61	10.22
	Mean ± Std Dev (%)	92.87 ± 166.68		
5	Number of medicine items	1 394	1 136	265
	AR (%)	49.87	40.64	9.48
	Mean ± Std Dev (%)	97.57 ± 202.17		
6	Number of medicine items	1 192	880	173
	AR (%)	53.10	39.20	7.71
	Mean ± Std Dev (%)	87.75 ± 150.70		

Compared to the other age groups, age group one had the highest unacceptable refill-adherence rate (≤ 90%) of 68.36% (n = 255). A possible reason for this could be that the incidence of Parkinson's disease among this groups' individuals is rather rare. However, there is the possibility that the medicine items classified as antiparkinsons medicine items, might have been used for another movement disorder (see section 2.5 and section 4.4), more commonly found among individuals of this age.

The percentage unacceptable refill-adherence rates (≤ 90%) decreased from age group one (68.36%, n = 255) to age group five (49.87%, n = 1 394), thereafter increasing again to age group six (53.10%, n = 1 192). Age group five indicated an unacceptable refill adherence rate of 49.87%, although it represented the best figures in the specific AR category. The percentage acceptable refill-adherence rate (90% < AR ≤ 110%) increased from 17.43% in age group one (n = 65) to 39.20% in age group six (n = 880). Possible reasons indicated for

the better refill-adherence rate (compared to other age groups) might have been that the caregivers looking after these patients were more alert and aware of medicine item schedules.

Even though the refill adherence rates vary between the different age groups they indicated no practical significance.

The refill-adherence rates will now be evaluated according to the trade names of the individual medicine items.

4.3.10.4 Refill-adherence rates according to trade names

In this section all the antiparkinson medicine items' refill-adherence rates, according to their trade names were evaluated. Table 4.57 indicated all the antiparkinson trade names, active ingredients and specific refill-adherence rates.

Table 4.57: Refill AR according to trade names and active ingredients

Trade name	Total number of medicine items	AR categories						Mean ± Std Dev (%)
		1		2		3		
		Number of medicine items	AR (%)	Number of medicine items	AR (%)	Number of medicine items	AR (%)	
BIPERIDEN								
AKINETON® 2MG TAB	1 123	675	60.11	332	29.56	116	10.33	89.43 ± 203.09
AKINETION® 5MG/ML INJ	16	15	93.75	1	6.25			26.51 ± 27.83
TRIHEXYPHENIDYL								
ARTANE® 2MG TAB	181	94	51.93	77	42.54	10	5.52	96.54 ±131.25
ARTANE® 5MG TAB	5	2	40	2	40	1	10	94.28 ± 13.49
BROMOCRIPTINE								
ASPEN BROMOCRIPTINE® 2.5MG	80	51	63.75	21	26.25	8	10.00	123.95 ± 364.42
LEVODOPA/ CARBIDOPA								
CARBILEV® 25/100 TAB	1 707	956	56.00	619	36.26	132	7.73	84.90 ± 135.69
CARBILEV® 25/250 TAB	601	307	51.08	240	39.93	54	8.99	92.98 ± 175.60
SINEMET® 25/100 TAB	1 031	575	55.77	363	35.21	93	9.02	85.56 ± 137.81
SINEMET® 25/250 TAB	309	162	52.43	121	39.16	26	8.41	89.53 ± 169.26
SINEMET® CR TAB	625	310	49.60	264	42.24	51	8.16	88.35 ± 125.58
LEVODOPA/BENSERAZIDE HCL								
MADOPAR® HBS CAP	59	24	40.68	27	45.76	8	13.56	85.77 ± 32.89
MADOPAR® TAB	271	144	53.14	101	37.27	26	9.59	82.61 ± 32.84
LEVODOPA/CARBIDOPA/ENTACAPONE								
STALEVO® 100/25MG TAB	43	13	30.23	17	39.53	13	30.23	98.63 ± 30.73
STALEVO® 150/37.5 TAB	40	12	30.00	16	40.00	12	30.00	284.33 ± 681.07
STALEVO® 50/12.5 TAB	9	2	22.22	2	22.22	5	55.56	422.22 ± 967.43
ENTACAPONE								
COMTAN® 200MG TAB	102	50	49.02	37	36.27	15	14.71	116.52 ± 290.00
ORPHENADRINE								
DISIPAL® 50MG TAB	279	158	56.63	83	29.75	38	13.62	101.61 ± 257.92
SELEGILINE								
ELDEPRYL® 5MG TAB	339	142	41.89	170	50.15	27	7.96	84.98 ± 33.71
PARKILYNE® 5MG TAB	97	24	24.74	62	63.92	11	11.34	125.03 ± 295.53
PERGOLIDE								
PERMAX® 0.05MG TAB	30	10	33.33	14	46.67	6	20.00	198.54 ± 531.32
PERMAX® 0.25MG TAB	30	11	36.67	16	53.33	3	10.00	86.26 ± 29.07
PERMAX® 1MG TAB	35	13	37.14	15	42.86	7	20.00	130.25 ± 240.82
PRAMIPEXOLE								
PEXOLA® 0.125MG TAB	454	266	58.59	137	30.18	51	11.23	107.05 ± 262.93
PEXOLA® 0.25MG TAB	496	298	60.08	155	31.25	43	8.67	80.44 ± 60.85
PEXOLA® 1MG TAB	254	125	49.21	96	37.80	33	12.99	93.14 ± 105.35
ROPINIROLE								
REQUIP® 0.25MG	136	72	52.94	46	33.82	18	13.25	107.12 ± 263.82
REQUIP® 0.5MG	109	48	44.04	50	45.87	11	10.09	80.46 ± 34.42
REQUIP® 1.0MG	166	79	47.59	71	42.77	16	9.64	82.11 ± 35.92
REQUIP® 2.0MG	100	44	44.00	48	48.00	8	8.00	84.80 ± 29.87
REQUIP® 5.0MG	32	6	18.75	19	59.38	7	21.88	188.74 ± 513.45
REQUIP® XL 2MG SRT								
REQUIP® XL 4MG SRT	2					2	100	132.02 ± 21.71
REQUIP® XL 8MG SRT								
TOLCAPONE								
TASMAR® 100MG TAB	7	3	42.86	3	42.86	1	14.29	504.13 ±1100.76

***** areas where values are missing, were possibly medicine items not repeated more than once (refer to figure 3.1)

Biperiden, levodopa/carbidopa and pramipexole containing medicine items had on average unacceptable refill-adherence rates below 90% (Refer to Table 4.57).

The highest unacceptable refill-adherence rate, however, was that of Akineton® 5mg/ml injections (biperiden) which represented 93.76% (n = 15). A possible reason for this might be the indication thereof not being indicated for chronic use, but in the treatment of Parkinson's disease related symptom crises (see section 4.3.5.1).

The other biperiden containing medicine item Akineton® 5mg tablets (60.11%, n = 675), bromocriptine containing medicine items, Aspen-bromocriptine® 2.5mg tablets (63.76%, n = 52) and pramipexole medicine items Pexola® 0.25mg tablets (60.08%) represented unacceptable refill-adherence rates (<90%). Levodopa/carbidopa containing medicine items also revealed unacceptably low refill-adherence rates between 49% and 56% (Refer to Table 4.57).

Possible reasons for the unacceptably low refill-adherence rates encountered with these medicine items might have been the adverse effects encountered with treatment. Commonly encountered adverse effects with levodopa containing medicine items might be the occurrence of mental disturbances, nausea and dose-related dyskineasias (see section 2.7.4.1.3). With the treatment of bromocriptine and pramipexole containing medicine items, almost similar adverse effects occur, with the aggravating of mental disturbances if simultaneously used with levodopa (see section 2.7.4.2.3). Pramipexole products were withdrawn from markets in 2007, on request of the FDA, as it supposedly increased reports of causing serious heart valve damage (see section 2.7.2), thus indicating other possible reasons for unacceptably low refill-adherence rates with this medicine item.

Medicine items that presented with the highest acceptable refill-adherence rates between 90% and 110% were selegiline and ropinirole containing medicine items. The specific items were Parkilyne® 5mg tablets with 63.92% (n = 62) and Requip® 5mg tablets with 59.38% (n = 19). Although the number of medicine items for both products remained relatively low, the statistics were favourable as both the medicine items are essential components in the treatment regimens of Parkinson's disease (see section 2.9).

The medicine item with an unacceptably high refill-adherence rate, was Stalevo® 50/12.5 mg tablets (55.56%, n = 5), containing a combination of levodopa, carbidopa and entacapone. As previously mentioned, the recommended use as well as administration of this medicine item is rather complex and vague, as it depends on the response and previous treatment of a patient (see section 4.5). This might be a possible reason for the unacceptably high refill-adherence rate (>110%) as the correct dosage of treatment with this medicine item might still have been in its trial and error phase.

In the section that follows, the days supplied was evaluated.

4.3.10.5 Days supplied

The days supplied for this study was defined as the number of days that passed between the first day that a medicine item was received, until the day of the next refill of the same medicine item. The criteria according to the days supplied are indicated in Table 3.4 (section 3.4.2.1.6). The following Table 4.58 indicated the number of medicine items and the percentages according to the criteria as indicated on antiparkinson medicine items (n = 8 769) on which refill-adherence was done from 2005 to 2008.

Table 4.58: Days supplied

Days supplied categories		Days supplied on antiparkinson medicine items on which refill adherence rates were calculated	
	Criteria (days)	Number of medicine items	Days supplied results (%)
1	≤ 60	1 791	**20.41**
2	> 60 ≤ 90	732	**8.35**
3	> 90 ≤ 120	560	**6.39**
4	> 120 ≤ 180	786	**8.98**
5	> 180 ≤ 360	1 534	**17.49**
6	> 360 ≤ 720	1 716	**19.57**
7	> 720 ≤ 1 080	900	**10.26**
8	> 1080	751	**8.56**

According to Table 4.58 the majority of medicine items on which the refill-adherence rates were calculated indicated a rate of 20.41% (n = 1791) for medicine items refilled within ≤ 60 days. The lowest percentage of days between refill, was in category three (> 90 ≤ 120) representing 6.39% (n = 560). From Table 4.58 a visible trend showed that apart from category one with the majority of days between refills, categories five to seven had relatively high values in contrast to other categories. Results implied that the majority of patients refilled their prescription only within one to three years (> 360 ≤ 1 080) which justifies the poor refill-adherence rates (see section 4.3.10.1 – 4.3.10.3) encountered among Parkinson's disease patients.

4.3.10.6 Cost implication of unacceptable refill-adherence rates

In this section the implication of unacceptable refill-adherence rates were evaluated against the cost implications thereof. The following Figure 4.7 illustrates the cost used in order to compile relevant evaluations (see section 3.4.2.1.9):

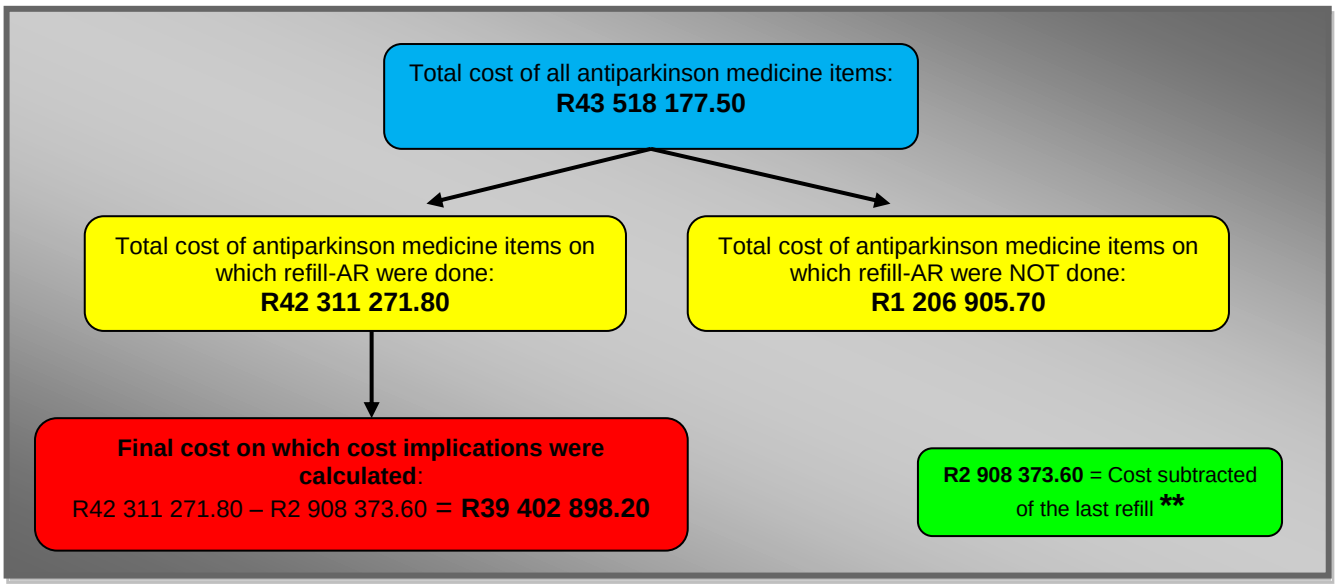

Figure 4.7: Final cost used to calculate cost implications of refill adherence

** Section 3.4.2.1.6 indicated the formula on how calculations were done

Table 4.59 indicates the expenditure for each individual category that was used in order to estimate the cost implications of unacceptable refill-adherence rates related to antiparkinson medicine items.

Table 4.59: Expenditures according to adherence rate categories

AR categories		Number of medicine items	Total cost (R)
1	AR ≤ 90%	4 691	16 398 512.00
2	90% < AR ≤ 110%	3 225	20 429 788.00
3	AR > 110%	852	2 574 597.00

As the majority of antiparkinson medicine items had unacceptably low refill-adherence rates (53.50%, n= 4 691), the cost implications associated with these low refill-adherence rates represented 41.62% (n = R16 398 512.00) of the total cost (N = R39 402 898.20) of medicine items included in this study. Furthermore the cost implications associated with medicine item refill-adherence with the acceptable range of between 90% and 110% accounted for 51.85% (n = R20 429 788.00) of the total cost (N = R39 402 898.20). Unacceptably high

refill-adherence rates were those of >110% that accounted for 6.54% (n = R2 574 597.00) of the total cost (N = R39 402 898.20).

Even thought the acceptable refill-adherence rate expenditure accounted for the majority of the total antiparkinson medicine item expenditure in this study (51.85%, n = 3 225), the expenditure linked to unacceptable refill-adherence rates of ≤ 90% and ≥ 110% would not be considered negligible (48.16%, n = 5 543), and would carry great concern for parties involved.

The subsequent section consists of the summary on refill-adherence rates of antiparkinson medicine items.

4.3.10.7 Summary on refill adherence

The overall results indicated that the majority of antiparkinson medicine items represented unacceptably low refill-adherence rates below 90%, which added to uneconomical use of medicine item expenditure. The majority of prescriptions were refilled within 60 days. Biperiden, bromocriptine, pramipexole and levodopa containing medicine items had on average unacceptably low refill-adherence rates.

The poor obedience to treatment schedules of antiparkinson medicine items in the private health care sector of South Africa, not only adds to the aggravation of Parkinson's disease symptoms and possible death, but also indicated enlarged wasteful health care expenditure.

4.4 Chapter summary

In this chapter all the results obtained from the empirical investigation for the period of 1 January 2005 to 31 December 2008 were discussed. All the aspects that concerned the total database and the Parkinson's disease data were discussed comparatively whenever possible with respect to various parameters. The combinations in which anitparkinson medicine items were prescribed, as well as antiparkinson medicine items together with CNS medicine items were discussed. Furthermore the refill-adherence rates and the cost implications thereof were discussed.

The results discussed and trends identified in this chapter, should be used as a basis for additional, more detailed studies of the rational use of medicine items and prescribing patterns. In future, the results could be used to assist in more cost analyses that would lead to better prescribing and cost-effectiveness.

CHAPTER 5:

Conclusions and recommendations

This chapter portrays the conclusions and recommendations. The conclusions and recommendations are based on the results obtained from the empirical investigation as well as the literature review, and are directed according to the specific objectives of this study. Also stated in this chapter are the factors that limited the extent and relevance of this study.

5.1 CONCLUSIONS

In the section to follow, the conclusions drawn from this study were stipulated against the literature review and the results obtained through the empirical investigation.

- **Specific objective one was to conceptualise Parkinson's disease through a literature review in order to form a better understanding of the disease and other movement disorders associated with Parkinson's disease.**

Through a literature overview, the main concepts regarding Parkinson's disease were investigated. In relation to this, the incidence, etiology, pathophysiology and clinical features regarding this disease were set apart, intensifying the insight to what the disease entails. In conclusion to this, literature indicated the cause of Parkinson's disease as unknown, with the degeneration of neurons in the midbrain as the main characteristic (see section 2.1). Apart from the unknown etiology of the disease literature indicated environmental factors and persons' genes to play an important role in the development of Parkinson's disease (see section 2.2). Literature indicated that the loss of dopaminergic neurons and the occurrence of Lewy bodies to be two distinct facts within the pathophysiology of the disease (see section 2.3). Tremor at rest, bradykinesia, rigidity and postural instability were persistent throughout literature as the fundamental clinical features of Parkinson's disease (see section 2.4).

Movement disorders indicated to be one of the most disabling neurological disorders that affect the middle-aged and elderly population. Furthermore only a few movement disorders were discussed to briefly understand the outlines of causes and treatment thereof. Research

also indicated that many movement disorders appeared to be medicine induced and could be avoided in future (see section 2.5.1).

The disabling effect of Parkinson's disease on a patient's well-being was emphasised widely throughout literature. As a result of limited time this study focused only on two CNS diseases co-occurring with Parkinson's disease, namely sleep disturbances and depression. This study's literature review, however, concluded that the occurrence of sleep disorders could be an age-related deficit, not necessarily to be attributed to Parkinson's disease. Depression on the other hand is believed to be attributed to Parkinson's disease because of the impairment of patients' quality of life (see section 2.6).

- **Specific objective two was to determine treatment protocols of Parkinson's disease, and reviewing adherence to medicine treatment through previous studies.**

Literature accentuates the main goal of Parkinson's disease treatment to only improve the quality of life and patients' ability to go about as normally as possible, as there are no guarantees that the treatment will alter the degenerative cause of the disease (see section 2.7.1). Difficulty in finding treatment algorithms that were exactly the same within the literature, led to the evaluation of treatment algorithms of different years. After evaluation of these protocols, without any concerns of major differences and irregularities over the past few years, the chosen treatment algorithm that was used throughout this study was that of the Council of Medical Schemes (2009) of South Africa. Apart from the treatment algorithms set apart, another method on evaluation of the treatment of Parkinson's disease was the recommended use of each individual antiparkinson medicine item (Refer to Table 4.51 and section 2.7).

Even though limited studies on the adherence in Parkinson's disease were available, adherence to treatment in Parkinson's disease was emphasised, as the implications of non-adherence adds to aggravation of disease symptoms, leading to death and amplified health care costs. Literature indicated numerous methods of measuring the adherence to treatment protocols, namely tablet counts, electronic medication monitors, clinical response assessment, and others. The method of choice in this study was that of refill-adherence rates. Numerous reasons for non-adherence as well as recommendations on improving adherence were encountered throughout the literature study (Refer to section 2.10 and section 4.6).

- **Specific objective three was to conceptualise from previous studies what pharmacoeconomics and its specific methods entail.**

Through a literature review the economic impact of Parkinson's disease was stipulated. In conclusion research indicated that the expenditure of these patients is not restricted to medicine treatment, but would also include hospitalisation, caregivers, inpatient care, doctors' visits and rehabilitation costs. These cost implications affects the patient, insurance parties and society. Furthermore the WHO also stressed the importance of the burden that the disease carries, and emphasised that necessary steps needed to be taken to improve health issues (refer to section 2.11).

Various methods of pharmacoeconomics were discussed according to applicable examples where possible, with the exception on CMA where examples on Parkinson's disease were rather limited (refer to section 2.11.2), because of limited generic substitutable medicine items on the market.

- **Specific objective four was to analyse the general prescribing patterns of medicine items used in Parkinson's disease and the costs associated, according to demographics such as age, gender and prescriber.**

Overall the results indicated that Parkinson's disease patients were in the minority compared to patients with other diseases from 2005 to 2008. This also meant that the total cost, number of medicine items and prescriptions claimed for Parkinson's disease patients were inferior to those of the total database (refer to section 4.3.1). Respectively to each set of data, the medical scheme and patient contributions, were rather comparable, although there was an increase from 2005 to 2008 for both sets of data, the patient contribution of the total database was higher than that of a Parkinson's disease patient (refer to Table 4.3). A CPI calculation also indicated great practical significance in the expression of Parkinson's disease medication expenditures (refer to Table 4.4).

Females represented 55% and males 44% of all patients claiming through the database from 2005 to 2008. Parkinson's disease gender distribution shared more or less the same figures from 2005 to 2008. The prescribing of antiparkinson medicine items thus indicated that the incidence of Parkinson's disease in a section of the private health care sector of South Africa to be greater among females than males (refer to section 4.3.2.1.3), contrary to suggested statistics.

Different age categories were identified on the database, *i.e*. age group one (0 ≥ 40 years), age group two (40 ≥ 50 years), age group three (50 ≥ 60 years), age group four (60 ≥ 70 years), age group five (70 ≥ 80 years) and age group six (80 > years). The results regarding the prescribing of antiparkinson medicine items portrayed that the prevalence of Parkinson's increased parallel to age. The highest frequency of medicine items and prescriptions with antiparkinson medicine items, had been prescribed to patients between the ages of 70 and 80 years, with a sharp increase from the age of 50 years (refer to section 4.3.2.2.7), as had also been confirmed by other studies.

Results obtained through the evaluation of antiparkinson medicine items prescribed throughout the study period, indicated that the majority of medicine items and prescriptions had been prescribed by general medical practitioners, followed by neurologists (refer to section 4.3.3.1).

In conclusion the results obtained from this study indicated that the prescribing patterns of antiparkinson medicine items according to demographic parameters, indicated that the prevalence of Parkinson's disease in a section of the private health care sector of South Africa, was the highest among females and patients older than 70 years. Another clear indication was that antiparkinson medicine items were mainly prescribed by general medical practitioners.

- **Specific objective five was to determine the cost of different medicine treatment protocols used in Parkinson's disease in order to evaluate prescribing patterns accordingly.**

Throughout this study, it became more evident that the treatment of the disease was rather complex and depended on numerous factors, namely the age of the patient, disease stage, side-effects, tolerability and others. In this study the treatment per patient over a period of time was not identified, which meant that the exact stage of the disease as well as entire treatment regimen was not known. Apart from this no major irregularities were found among the combinations in which the antiparkinson medicine items were used, justifying an objective evaluation of expenditures, although an addition of medicine items to a needed treatment protocol indicated added expenditures (see section 4.3.7).

The average cost per yearly treatment per patient for each specific study period represented the following, 2005: R2 619.54 ± R4 179.72, 2006: R2 559.49 ± R4 237.23, 2007: R 2740.96 ± R4 337 and 2008: R2 627 ± R4 424.53, and indicated no evident consistency trend

throughout the study period (see section 4.3.6). Contrary to this the medical schemes' contribution decreased with more or less 2.5% from 2005 (89.14%) to 2008 (86.63%) (see Table 4.37). The decrease in medical scheme contributions consequently showed an increase in patient contributions (2005:10.86%, 2006: 11.53%, 2007: 11.57%, 2008: 13.37%) per year, which added to the financial burden of this chronic disease (see section 4.3.6).

The cost per tablet indicated that all tablets had had an increase in cost at some point in time throughout the study period from 2005 to 2008. Akineton® 5mg/ml injections had the highest cost per vial, although it is only indicated in emergency situations and not for chronic use. Furthermore the medicine item that had the highest cost per tablet were Permax® 1mg and Tasmar®100mg (see section 4.3.5), and were also the two medicine items with a slight indication of being over-prescribed according to its prescribed daily dosages (see section 4.3.9). Overall results portrayed good compliance to prescribing according to the PDD of all the medicine items.

Through the analysis of Parkinson's disease medicine items prescribed in combination, the overall impression represented good compliance to treatment algorithms, with no major implications encountered with the combinations in which the medicine items were prescribed (see section 4.3.7 and 4.3.10). A common trend, however, persisted from 2005 to 2008 and indicated a decrease in frequencies with the addition of more antiparkinson medicine items per prescription. The addition of antiparkinson medicine items to a prescription was attributed to the degenerative nature of the disease, with the aggravation of symptoms with disease progression. Even though this led to amplified expenditure no mistake was detected in the prescribing patterns thereof (refer to section 4.3.7).

- **Specific objective six was to determine the comprehensiveness of prescriptions with both antiparkinson and other central nervous system (CNS) medicine items.**

The results of this study indicated that CNS medicine items together with antiparkinson medicine items per prescriptions were represented rather well. The CNS medicine items were categorised according to the MIMS classification system, with the highest frequencies encountered in combination with antiparkinson medicine items being the antidepressants, hypnotics, antipsychotics and anxiolytic medicine items. This was also discussed in the literature review. Possible reasons for the simultaneous use of CNS medicine items with antiparkinson medicine items were given where possible, indicating no irregularities of major concern (see section 4.3.8). Reasons mainly consisted of the obvious reason of another CNS disease together with Parkinson's disease, or in other cases the treatment of another

movement disorder was considered as a possibility that could not have been excluded, as neither the diagnosis or ICD 10 codes were available on the database (see section 4.3.8).

The majority of these medicine items used concomitantly indicated no severe drug-drug interactions. Although the use of selegiline together with TCAs was seen as a main concern, the retrospective aspect of this study limited the knowledge of the researcher in knowing whether the right instructions of use had been followed. Another medicine item used together with antiparkinson medicine items that was rather questionable, was that of cinnarizine (Antivertigo & anti- emetic agents), although having sedative affects, it might induce undesired adverse effects in Parkinson's disease patients (refer to section 4.4.8).

Because of the fact that ICD 10 codes were not available on the database, and no distinct irregularities were found among the concomitant use of the CNS medicine items together with antiparkinson medicine items the expenditures related to these prescription could not be labelled as uneconomical.

- **Specific objective seven was to determine whether Parkinson's disease patients are adherent in their repeating of prescriptions.**

The results of this study portrayed overall poor obedience to treatment protocols in Parkinson's disease patients in a section of the private health care sector of South Africa. This could lead to the aggravation of disease symptoms with the possibility of death, and amplified health care costs. The majority of Parkinson's disease patients were those between 70 and 80 years, also indicating the best refill adherence rates, with a possible reason indicated as the age group with the most consistent care through caregivers. No practical significant difference was indicated between the refill adherence rates of the two gender groups. Biperiden, bromocriptine and pramipexole medicine items had on average unacceptable low refill-adherence rates below 90% (see section 4.3.10).

According to the days supplied, the results indicated that the majority of Parkinson's disease patients had received medication between 360 and 1 080 days. This not only has severe consequences for patients, but also adds to uneconomical expenditure. The majority of antiparkinson medicine items had unacceptable low refill-adherence rates with the cost implication thereof representing 41.62% of the total cost of medicine items that were included in this study (see section 4.3.10).

5.2 RECOMMENDATIONS

The following are recommendations proposed for future studies:

- More in-depth research should be done on diseases simultaneous with Parkinson's disease.
- Further investigation should be conducted on possible drug-drug interactions with Parkinson's disease medicine items, other than the CNS drug-drug interactions mentioned within this study.
- Investigate whether the medicine item treatment regimens of Parkinson's disease patients are different when they have acceptable or unacceptable low refill-adherence rates.

- Limited literature concerning the status of Parkinson's disease in South Africa was available. More in-depth studies should be performed concerning Parkinson's disease in South Africa.

5.3 LIMITATIONS

Throughout the study there were various limitations that influenced the applicability.

- Only one PMB's data were used in the study and made generalisation of results difficult, thus no comparisons were made regarding the cost of the disease in the total private health care sector of South Africa.

- No direct manipulation of the data was possible. The perspective that the information was reliable and valid from the PMB's database was used throughout the study with regard to the data analysis.

- The lack of clinical detailed data (*i.e.* diagnosis, stage of the disease, or medical history) limited the study. The relevance of some usage patterns and indications for treatment could not be determined precisely.

5.4 CHAPTER SUMMARY

This chapter included the conclusions with respect to the specific research objectives of this study, as well as the recommendations made for future studies. Also noted in this chapter were the limitations encountered in this study.

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