Prescribing patterns of ADHD medication in children under the age of eighteen years in the Western Cape

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BPharm

Dissertation submitted in fulfillment of the requirements for the degree Master of Pharmacy in Pharmacy Practice at the Potchefstroom Campus of the North-West University

Supervisor: Prof JR Burger
Co-supervisor: Prof I Truter

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This dissertation is presented in article format. The format abides by the guidelines and standards provided by the North-West University (NWU). The dissertation is formatted into four chapters:

- Chapter 1: Introduction and study layout
- Chapter 2: Literature review
- Chapter 3: Results and discussion
- Chapter 4: Conclusion, recommendations and limitations

Chapter one contains the overview of the study, the aims and objectives of the study and the research methodology. Chapter two contains the literature review regarding attention-deficit hyperactivity-disorder (ADHD) as a psychiatric disease in children and adolescents, the prevalence of methylphenidate and atomoxetine usage and the comorbidities associated with ADHD. Chapter three contains the results of the empirical investigation in the form of two manuscripts. Manuscript one and two were submitted for possible publication to Health SA Gesondheid and South African Family Practice respectively. Each manuscript was written according to the author guidelines for the individual journal. Additional results not presented in either manuscript was also presented.

The co-authors’ contributions to the manuscripts are outlined under ‘author contributions’. All co-authors gave their consent that these manuscripts may form part of the final dissertation.
AUTHORS’ CONTRIBUTIONS (MANUSCRIPT ONE)

The contribution of each author for manuscript one entitled “The prescribing patterns of ADHD medication in children under the age of eighteen years in the Western Cape Province from 2005-2013” is provided below:

<table>
<thead>
<tr>
<th>Author</th>
<th>Contribution</th>
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<tbody>
<tr>
<td>Ms L Joubert</td>
<td>First author, responsible for conducting the literature review for the background and introduction of the paper, developing the data analysis plan and drafting the manuscript.</td>
</tr>
<tr>
<td>Prof JR Burger</td>
<td>Project leader, responsible for study design and review of the data analysis plan, providing conceptual contribution, reviewing the interpretation of the results, and reviewing the manuscript.</td>
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<tr>
<td>Prof I Truter</td>
<td>Co-supervisor of the project, responsible for assisting in the planning of the study design, providing conceptual contribution, reviewing the interpretation of the results, and reviewing the manuscript.</td>
</tr>
<tr>
<td>Prof MS Lubbe</td>
<td>Responsible for the data analysis, and review of the manuscript for critical information.</td>
</tr>
<tr>
<td>Mrs M Cockeran</td>
<td>Responsible for the data analysis, and review of the manuscript for critical information.</td>
</tr>
</tbody>
</table>

The following statement provided by the co-authors confirms their roles in the study and their permission that the manuscript may form part of this dissertation.

I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the MPharm study of L Joubert.

Prof JR Burger       Prof I Truter

Prof MS Lubbe       Mrs M Cockeran
AUTHORS’ CONTRIBUTIONS (MANUSCRIPT TWO)

The contribution of each author for manuscript two entitled “Medicine and chronic disease list conditions in Western Cape children and adolescents with ADHD” is provided below:

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</table>

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I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the MPharm study of L Joubert.

Prof JR Burger       Prof I Truter

Prof MS Lubbe
ACKNOWLEDGEMENTS

“We are so often caught up in our destination that we forget to appreciate the journey, especially the goodness of the people we meet on the way. Appreciation is a wonderful feeling, don’t overlook it.” – Unknown.

I would like to take this opportunity to, firstly, thank my parents, Hannes and Lorraine Joubert, for their unconditional love and support throughout this journey, for always believing in me and the constant reminder of my capabilities whenever I doubted their existence. The completion of this study would not have been possible without their support.

The following people also deserve a BIG thank you – Tannie Filon, Oom Dawie, Dawid, Ansu and Fericka. All the late-night support was of cardinal importance during the course of this study.

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- Ms M Ferreira for the language editing of the literature review, manuscripts and reference list.
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Lastly, to my supervisor, Prof JR Burger, thank you so very much for your undying support throughout this process. I would not have been able to finish if not for your ability to restore my passion for the academia.

I CAN DO ALL THINGS THROUGH CHRIST WHO STRENGTHENS ME

Philippians 4:13
ABSTRACT

Prescribing patterns of ADHD medication in children under the age of eighteen years in the Western Cape

The study consisted of a quantitative, retrospective drug utilisation review analysing medicine claims data from 1 January 2005 to 31 December 2013 provided by a nationally representative Pharmaceutical Benefit Management (PBM) company. The specific objectives of the empirical investigation was to: (1) determine the prevalence of ADHD in children and adolescents under the age of 18 years who received treatment with methylphenidate and/or atomoxetine in the private health sector of the Western Cape province from 2005 to 2013; (2) to identify the prescribing patterns of methylphenidate and atomoxetine in these patients; and (3) to determine the prevalence of conditions co-occurring in them.

The study population consisted of a total of 2516 patients (male:female ratio 3.5:1). To determine the prevalence of ADHD in children and adolescents from 2005 to 2013, a repeated cross-sectional study design was followed, making use of the active ingredient of the medication and the prescribed daily dose (PDD), treatment date, the gender of the patient, the patients’ age, geographical area of the prescriber, total number of patients, and total and average number of prescriptions prescribed per patient per year as medication utilisation metrics. To determine the prevalence of conditions co-occurring in children and adolescents, a cross-sectional study design was followed. For this analysis, prevalence of drugs (pharmacological classes) prescribed and chronic disease list (CDL) conditions occurring in the study population, were determined.

Analysis of prescribing patterns showed that the total number of patients receiving ADHD treatment over the study period increased by 0.29% from 2005 to 2013. Children ≤ 6 years increased by 6.00% from 2005 to 2013. The City of Cape Town Metropolitan municipality had the largest number of patients (≥75%). Prescriptions for ADHD treatment increased by 0.46% overall from 2005 to 2013 (p<0.001), with that for methylphenidate and atomoxetine increasing by 0.36% and 3.15%, respectively. The average number of methylphenidate prescriptions per patient per year increased from 3.96 ± 2.92 (95% CI, 3.69-4.23) in 2005 to 4.38 ± 2.85 (95% CI, 4.14-4.61) in 2013 (Cohen’s d=0.14), and that for atomoxetine increased from 2.58 ± 1.86 (95% CI, 1.80-3.37) in 2005 to 4.85 ± 3.66 (95% CI, 3.84-5.86) in 2013 (Cohen’s d=0.62). Although methylphenidate is not usually prescribed to children under the age of six years, it was found prescribed to children aged ≤ 6 years in PDDs ranging from 10 mg to 40.39 mg ± 11.45 mg (95% CI, 33.47-47.30) in girls, and 10 mg to 35.00 mg ± 28.87 (95% CI, -10.94-80.94) in boys which corresponds with dosages calculated for children between the 5th and 95th percentile of the Centres for Disease Control (CDC) weight-for-age and stature-for-age charts (CDC, 2014a; CDC, 2014b). A maximum PDD of 64 mg was found in children aged ≤ 6 years which compares with
the maximum recommended daily dosage (RDD) (72 mg/day) in children aged 13 to <18 years. The PDD and maximum daily doses for children in age group 2 (>6, ≤12 years) was similar to the RDD for methylphenidate. The PDD for children in age group 3 (>12, <18 years) corresponded to the RDD, although the maximum daily dose exceeded the RDD for boys in 2005. The most frequently prescribed daily dose for methylphenidate was for 20 mg daily (25.20%, N=19 254). There were no prescriptions for atomoxetine for children in age group 1 (≤6 years). The PDD for both boys and girls in age groups 2 (>6, ≤12 years) and 3 (>12, <18 years) were in line with the RDD for atomoxetine. The maximum daily dose exceeded the RDD for girls in age group 2 (>6, ≤12 years) as calculated for children between the 5th and 95th percentile of the CDC weight-for-age and stature-for-age charts (CDC, 2014a; CDC, 2014b) throughout the study period. The most frequently prescribed daily dose for atomoxetine was for 40 mg daily (39.09%, N=2469).

A total of 93 (3.70%) patients with chronic disease list (CDL) conditions were identified with ADHD. Asthma was the most prevalent CDL condition and occurred in 74.19% (N=69) of the participants, followed by epilepsy, prevalent in 17.20% (N=16) of the participants. The combination of asthma and epilepsy occurred in three patients (3.31%) and diabetes mellitus type 1 occurred in one patient (1.08%). Patients from the study population mostly received antimicrobials (54.0%), respiratory agents (9.94%), dermatologicals (6.64%), central nervous system agents (6.11%), ear, nose and throat medication (4.94%), autacoids (3.47%), analgesics (2.70%) and endocrine system agents (2.53%).

In conclusion: the prescribing of ADHD medication in the Western Cape have increased significantly from 2005 to 2013. It was also found that the majority of medication co-prescribed in the study population is indicated for acute conditions, rather than other neurodevelopmental and chronic conditions as found in previous studies. This preliminary study can lead to future studies on the influence of geographical area on the prescribing patterns of methylphenidate and atomoxetine.

Keywords: Western Cape, South Africa, children, adolescents, atomoxetine, methylphenidate, prescribing patterns, comorbid conditions
**OPSOMMING**

**Voorskryfpatrone van Aandagsgebrek-Hiperaktiwiteitstoornis (AGHS) medikasie in kinders onder die ouderdom van 18 jaar in die Wes-Kaap Provinsie**

Die ondersoek het uit 'n kwantitatiewe, retrospektiewe, medisyneverbruiksevalueringstudie bestaan, waar medisyne-eisedata vanaf 1 Januarie 2005 tot 31 Desember 2013 ontleed is. Hierdie data is deur 'n Farmaseutiese Voordele Bestuursmaatskappy verskaf. Die spesifieke doelwitte van die empiriese ondersoek was: (1) om die voorkoms van AGHS in kinders en adolessente jonger as 18 jaar in die private gesondheidsorgsektor van die Wes-Kaap Provinsie wat behandeling met metielfenidaat en/of atomoksetien vanaf 2005 tot 2013 ontvang het, te bepaal; (2) om die voorskryfpatrone van metielfenidaat en atomoksetien in hierdie kinders te bepaal; en (3) om die voorkoms van toestande wat saam met AGHS voorkom in hulle, te bepaal.

Die studiepopulasie het uit 2516 pasiënte (verhouding van mans vrouens 3.5:1) bestaan. Om die voorkoms van AGHS in kinders en adolessente jonger as 18 jaar vanaf 2005 tot 2013 in die Wes-Kaap te bepaal, is 'n herhaalde-deursnit-studieontwerp gebruik. Hierdie ontleiding het gebruik gemaak van die aktiewe bestandeel van die geneesmiddels en die voorgeskrewe daaglikse dosis, die datum van behandeling, die pasiënte se ouderdom en geslag, die geografiese ligging van die voorskywer, die totale aantal pasiënte en die totale aantal voorskrifte per pasiënt per jaar as medisyneverbruiksmetings. 'n Deursneestudie-ontwerp is gevolg om die voorkoms van ander siektetoestande in kinders en adolessente met AGHS jonger as 18 jaar te bepaal. Vir hierdie ontleiding is die voorkoms van geneesmiddels (medisyneklasse) wat voorgeskryf is, en die chroniese siekte-lys (CDL) toestande wat in die studiepopulasie voorkom, bereken.

Ontleding van voorskryfpatrone het getoon dat die aantal pasiente wat behandeling vir AGHS ontvang het, met 0.29% toegeneem het vanaf 2005 tot 2013. Kinders ≤6 jaar het vanaf 2005 tot 2013 met 6% toegeneem. Die meeste pasiënte (≥75%) was vanuit die Kaapstadse Metropool afkomstig. Voorskrifte vir die AGHS-behandeling het vanaf 2005 tot 2013 met 0.46% toegeneem ($p<0.001$), waarvan voorskrifte vir metielfenidaat en atomoksetien onderskeidelik met 0.36% en 3.15% toegeneem het. Die gemiddelde aantal metielfenidaatvoorskrifte per pasiënt per jaar het vanaf 3.96 ± 2.92 (95% CI, 3.69-4.23) in 2005 tot 4.38 ± 2.85 (95% CI, 4.14-4.61) in 2013 toegeneem (Cohen's $d=0.14$), terwyl dié van atomoksetien, van 2.58 ± 1.86 (95% CI, 1.80-3.37) in 2005 tot 4.85 ± 3.66 (95% CI, 3.84-5.86) in 2013 (Cohen's $d=0.62$) toegeneem het. Metielfenidaat word nie normaalweg aan kinders jonger as ses voorgeskryf nie, maar ten spyte van hierdie aanwyseing is daar wel voorskrifte vir kinders ≤6 jaar gevind, met 'n voorgeskrewe daaglikse dosis (VDD) van 10 mg tot 40.39 mg ± 11.45 mg (95% CI, 33.47-47.30) vir dogters en 10 mg tot 35.00 mg ± 28.87 (95% CI, -10.94-80.94) vir seuns. Hierdie dosisse stem ooreen met die doerings bereken op die 5de en 95ste persentiele van die massa-vir-ouderdom en grootte-vir-
ouderdom kaarte van die CDC (CDC, 2014a; CDC, 2014b). 'n Maksimum VDD van 64 mg is by kinders in ouderdomsgroep 1 (≤ 6 jaar) gevind, wat ooreenstem met 'n dosering vir kinders in ouderdomsgroep 3 (>12, <18 jaar). Die voorgeskrewe daaglikse dosis en die maksimum daaglikse VDDs was binne die raamwerk van die voorgestelde daaglikse doserings vir beide seuns en dogters in ouderdomsgroep 2 (>6, ≤12 jaar). Die voorgeskrewe daaglikse dosis in ouderdomsgroep 3 (>12, <18 jaar) het ooreengestem met die voorgestelde daaglikse dosering, maar het die maksimum dosering vir seuns oorskry in 2005. Die voorgeskrewe daaglikse dosis wat die meeste vir metielfenidaat voorgekom was vir 20 mg daagliks (25.20%, N=19 254). Daar was geen voorskrifte vir atomoksetien vir kinders in ouderdomsgroep 1 (≤6 jaar) nie. Die voorgeskrewe daaglikse dosis vir beide seuns en dogters in ouderdomsgroep 2 (>6, ≤12 jaar) en 3 (>12, <18 jaar) was binne die raamwerk van die voorgestelde daaglikse dosering vir atomoksetien. Die maksimum dosis vir dogters in ouderdomsgroep 2 (>6, ≤12 jaar) het die voorgestelde daaglikse dosering wel deurlopend oorskry. Die voorgeskrewe daaglikse dosis vir atomoksetien wat die meeste voorgekom het, was 40 mg daagliks (39.90%, N=2469).

'n Totaal van 93 (3.70%) pasiënte met chroniese siekte-lys toestande is geïdentifiseer. Van die siektetoestande wat op die chroniese siekte-lys verskyn, het asma in 74.19% (N=69) van pasiënte voorgekom, gevolg deur epilepsie in 17.20% (N=16) van pasiënte. Die kombinasie van asma en epilepsie het in drie pasiënte (3.31%) voorgekom en tipe 1 diabetes mellitus in een pasiënt (1.08%). Die medisyneklasse wat die meeste voorgeskryf is, was antimikrobiese middels (54.0%), respiratoriese middels (9.94%), dermatologiese middels (6.64%), sentrale senuweestelsel middels (6.11%), medikasie vir oor, neus en keel (4.94%), outakoïede (3.47%), analgetika (2.70%) en endokrienemiddels (2.53%).

Ter samevatting: Die voorskryf van AGHS-medikasie in die Wes-Kaap Provinsie het betekenisvol toegeneem van 2005 tot 2013. Daar is ook bevind dat die medisyneklasse wat die meeste voorgeskryf is vir die studiepopulasie, aangedui is vir akute toestande en nie vir neuro-ontwikkelings- of chroniese toestande, soos in die literatuur aangetoon word nie. Hierdie voorlopige studie kan lei na toekomstige studies oor die invloed van geografiese ligging op die voorskryfpatrone van metielfenidaat en atomoksetien.

Sleutelwoorde: Wes-Kaap, Suid-Afrika, kinders, atomoksetien, metielfenidaat, voorskryfpatrone, chroniese siekte-lys toestande
**LIST OF ACRONYMS AND ABBREVIATIONS**

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<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ADD</td>
<td>Attention Deficit Disorder</td>
</tr>
<tr>
<td>ADHASA</td>
<td>Attention Deficit and Hyperactivity Support Group of South Africa</td>
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<td>ADHD</td>
<td>Attention Deficit Hyperactivity Disorder</td>
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<td>ALA</td>
<td>Alpha Linolenic Acid</td>
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<td>AMCP</td>
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<td>ANOVA</td>
<td>Analysis of Variance</td>
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<td>American Psychiatric Association</td>
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<td>ATO</td>
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<td>BMD</td>
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<td>CAT</td>
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<td>CI</td>
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<td>COMT</td>
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<td>EEG</td>
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<td>Electrocardiogram</td>
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<td>EPD</td>
<td>Enzyme-potentiated Desensitization</td>
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<td>GHI</td>
<td>Global Health Insurance</td>
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<td>GP</td>
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<td>HREC</td>
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<td>ICD-10</td>
<td>International Classification of Diseases and related Health Problems (10\textsuperscript{th} Revision)</td>
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<td>MIMS</td>
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<td>Mpumalanga</td>
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<td>Medicine Usage in South Africa</td>
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<td>Full Form</td>
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<td>NAPPI</td>
<td>National Pharmaceutical Product Interface</td>
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<td>Northern Cape</td>
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<td>NET</td>
<td>Norepinephrine Transporter</td>
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<td>National Health Service</td>
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<td>National Centre for Complementary and Alternative Medicine</td>
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<td>NO</td>
<td>Nitric Oxide</td>
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<td>OCD</td>
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<td>Prescribed Daily Dose</td>
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<td>Pharmaceutical Benefit Management Company</td>
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<td>Transmission/Disequilibrium Test</td>
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<td>USB</td>
<td>Universal Serial Bus</td>
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<td>WC</td>
<td>Western Cape</td>
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<td>WHO</td>
<td>World Health Organization</td>
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CHAPTER 1: INTRODUCTION AND STUDY LAYOUT

1.1 Introduction

“People with ADD [ADHD] often have a special ‘feel’ for life, a way of seeing right into the heart of matters, while others have to reason their way methodically.” – Edward M. Hallowell.

Attention Deficit Hyperactivity Disorder (ADHD) in children is the core of this study. In this chapter, the layout of the study will be discussed. It contains the background of the literature, the problem statement, aims and objectives, the research methodology, the data analysis as well as limitations and ethical considerations pertaining to the study.

1.2 Background and problem statement

According to the National Institute of Mental Health (NIMH, 2012:1), ADHD is one of the most prevalent mental illnesses of modern times; it is most commonly found in children, but may also continue into adolescence and adulthood.

The National Health Service (NHS) of the United Kingdom (UK) estimates that between 2% and 5% of school-aged children and adolescents suffer from ADHD (NHS, 2014). During 2003, 7.8% of children in the United States of America (USA) were diagnosed with ADHD. This percentage increased to 9.5% in 2007. Vestal (2014) stated that one in every seven children in the USA suffers from ADHD and since 2003 to 2011 the number of diagnoses increased by 40%. There is, however, a noticeable difference in the diagnoses and treatment in different American states. As of 2011 it was determined that 11.0% of children (64 million children) between the ages of four and 17 years were diagnosed with ADHD in the USA (Center for Disease Control (CDC), 2014a). Children covered by Medicaid (the American Federal State Healthcare Program for the less fortunate) have at least a 50% higher chance of being diagnosed with ADHD (Vestal, 2014). It is thus evident that ADHD is becoming more prevalent in the USA.

In Africa, between 5.4% and 8.7% of school children were diagnosed with ADHD (Bakare, 2012:359). In the Democratic Republic of Congo there was a prevalence of 6%, in Nigeria 8.7% and in Ethiopia 1.5% (Bakare, 2012:359). There is a paucity of information available on ADHD in South Africa, but the best estimates indicate that approximately 5% to 8% of all South African children suffer from the condition, whereas another 10% suffer from ADHD-related symptoms (ADHASA, 2015; Bakare, 2012:359; Stead et al., 2006:7).

The prevalence of ADHD differs by gender groups. In the UK, boys are more likely to be diagnosed with ADHD than girls. However, ADHD might be under-diagnosed in girls as the majority of girls suffer from problems with attention, or lack thereof rather than hyperactivity (NHS,
The majority of diagnoses in the UK are made in children between the ages of six and 12 years. In the USA, the average age at diagnosis is seven years and the disorder is found to be three to nine times more common in boys, with girls showing an increase in diagnosis of the inattentive type (APA, 2013:63; CDC, 2014a). In accordance with international trends, South African boys are more likely to be diagnosed with ADHD than girls with male:female ratios from 2:1–9:1 (Schellack & Meyer, 2012:12; Venter, 2004:444). According to Schellack and Meyer (2012:12) the type of ADHD must always be taken into account when drawing the gender based statistics. Van der Westhuizen (2010:10) showed that the gender ratios for male:female to be 4:1 for predominantly hyperactive type ADHD diagnosis, and the gender ratio for the primarily inattentive type of ADHD is 2:1. It is thus clear that gender ratios vary. According to Polanczyk et al. (2007:945) the reasons for these variances include the geographical area, the diagnostic criteria used by the clinician to make the diagnosis and the accessibility to information on ADHD to the parents, teachers and clinicians.

Children suffering from ADHD have a difficult time adapting to the school environment as they struggle immensely to develop relationships and often have a low self-esteem. The most prevalent characteristic of ADHD shown in research is an ongoing pattern of inattention possibly combined with hyperactivity and impulsivity that interferes with normal development and functioning (APA, 2013:60; Martin, 2010:448).

There are various speculations and theories on what causes ADHD in children, but the CDC (2014b) states that some of the possible causes of ADHD could be genetic difficulties (which is the most important cause of ADHD). There is no biologic marker identified for the diagnosis of ADHD as of yet, but there is a recognised genetic influence in some extreme and uncommon cases. They are known as Fragile X-syndrome and 22q11 deletion syndrome (APA, 2013:62). According to ADHASA (2015) a shortage or an imbalance in Prostaglandins PE1 and PE3 may be a biochemical cause of ADHD. These genetic influences are not acknowledged as finite causal factors. Possible drug abuse during pregnancy, premature birth and/or low birth weight, neurotransmitter malfunction, environmental exposure to poison (e.g. lead, alcohol) and drugs may be possible causes of ADHD in children. In addition, other conditions such as brain damage, visual and auditory damage, poor diet, mood and sleep disorders, epilepsy and trauma may lead to symptoms similar to that associated with ADHD (APA, 2013:62; Bothma, 2011:6). Flisher and Hawkridge (2013:137) states that other medical disorders may account for the presentation of ADHD-like symptoms. These include: hyperthyroidism, lead poisoning, brain injuries, encephalopathies and foetal alcohol syndrome. Bakare (2012:358) is of the opinion that ADHD is nothing but a cultural phenomenon, but the CDC (2014b) does not accredit a diet high in sugar, watching violent television programmes, bad parenting and an overall cultural/household environment as contributors to the worsening of symptoms of ADHD. Venter (2004:444) agreed.
with the statement made by the APA by stating that, although the home environment, parenting, trauma, uncontrolled allergies and dietary inconsistencies play a role in the management of ADHD, it is not a direct cause of ADHD. The APA (2013:62) has found that the diagnosis for ADHD is far lower in the African American and Latino populations than in the Caucasian population of the USA as there are vast differences in the cultural upbringing and attitudes toward children’s behaviour and how to react to it, whether the reaction is disciplinary or a medical intervention.

Guidelines for the diagnosis of ADHD are specific to every country. For instance, according to the APA (2013:59), six or more of symptoms (refer to section 2.7), need to be present for a period of at least six months before the age of 12 years to such an extent that it has a negative impact on the patient’s daily activities for a diagnosis to be made, whereas a minimum of five symptoms should be present in older patients, aged 17 years and older. The manifestations must take place in more than one location (e.g. school and home). These symptoms are the main indicators of ADHD, but there are other associating features for the diagnosis of ADHD. These additional features may include a low frustration tolerance, high levels of irritability, and mood fluctuations. Delays in any development such as speech, social and motor skills are not a specific indicator for the diagnosis of ADHD but it often exists in parallel to the ADHD (APA, 2013:61).

In South Africa, the process of diagnosis and identification of clinical characteristics of ADHD is divided into three steps (Flisher & Hawkridge, 2013:136). During the first step, the clinician must screen for ADHD. During this step a detailed psychiatric assessment is done where questions are stated to the patient (child) about the central symptoms of ADHD that they experience. The diagnosis made according to these findings can only be used if the conclusion is made under ‘normal’ circumstances (i.e. the patient does not suffer from any predisposed mental disorder, is not under the influence of any substance, or if the symptoms occur in conjunction with other general medical condition (e.g. any allergic conditions). During this first step, two instruments are available to identify and diagnose ADHD and they are the clinical diagnostic interviews and the rating scales. The Diagnostic and Interview Schedule for Children (DISC-IV) and the Connor’s Parent Rating Scale Revised and Connor Teacher Rating Scale Revised are used in South Africa (Fisher & Hawkridge, 2013:136).
Flisher and Hawkridge (2013:136) explains in step two that these clinical interviews must also be done with the people involved in the child or adolescents’ day-to-day activities, whether it is a parent, teacher or caregiver. The information obtained from these sources will shed light on the child or adolescents’ family history, development, school functioning, social behaviour and possibly identify comorbid psychiatric conditions. These clinical evaluations should be done more than once if there are discrepancies between evaluations done at school and at home, and preferably in different locations (e.g. at home, at school and day care). Ideally separate facilitators who are not known do the separate evaluations to the child or adolescent. Firstly, the evaluator must establish whether the child or adolescent fulfils any of the diagnostic criteria. These include the symptoms of which the child or adolescent must present, with a minimum of six symptoms on a chronic basis. The symptoms are associated with functional disability and the onset of the symptoms had to be before the age of seven years. Flisher and Hawkridge (2013:136) states that this is of great importance, as it is a crucial point in possible misdiagnosis of ADHD. The emotional state of the child or adolescents’ must be taken into account at all times. The last step is to view the holistic picture, the clinical presentation of the child or adolescent. Thorough mental and physical examinations must take place, where the possible presentation of a mental disorder must be taken into account (Fisher & Hawkridge, 2013:136).

It is not uncommon to find comorbid psychiatric conditions with a diagnosis of ADHD in children. A study done in a Swedish population showed that 87% of cases were diagnosed along one or other co-existing disorder and 67% with two or more co-existing disorders (Soppitt, 2012:217). Possible differential diagnosis of ADHD could be oppositional defiant disorder, which occurs in approximately 50% of children diagnosed with combined ADHD and about 25% of inattentive type diagnosed children and about 40% in the overall diagnosis of ADHD, intermittent explosive disorder, specific learning disorder, intellectual disability, autism spectrum disorder, reactive attachment disorder, anxiety disorder, bipolar disorder, disruptive mood dysregulation disorder, substance use disorder which shows a 25% to 33% correspondence with children diagnosed with ADHD, personality disorder, psychotic disorder, medication-induced symptoms of ADHD and neurocognitive disorders. Conduct disorder presents in approximately 25% of children diagnosed with combined ADHD. This diagnosis mostly depends on the age of the child as well as the location in which the child moves on a daily basis (APA, 2013:65; Chinn, 2012:184; El Masry et al., 2012:197). It is often difficult to distinguish between adolescent onset mania from conduct disorder, depression and ADHD as there are many overlapping features (El Masry et al., 2012:196).
The method by which the prevalence of ADHD is assessed, the diagnostic criteria, different definitions of the condition and the literature available to the diagnosing clinician have a definite influence on the diagnosis of ADHD in the regions where the diagnosis takes place (Bakare, 2012:358). The standard by which ADHD is diagnosed in South Africa may therefore differ based on the amount of information available to the diagnosing clinician, as well as the involvement and support from the parents and teachers involved in the patient’s life. The remarkable cultural and economic difference between the districts of the Western Cape Province is enormous, stretching from prosperity to poverty. This may play a role in the quality of care received, as well as the prescription used to treat the condition.

According to Flisher and Hawkridge (2013:137) the main aim concerning the treatment of ADHD is to optimise the child or adolescents’ cognitive, emotional and social functions in order to prevent any secondary emotional or psychiatric disorders. The physical symptoms of ADHD (inattention, hyperactivity and inattention/hyperactivity) (refer to section 2.7) must be managed and under control, but the child or adolescents’ behaviour in different surroundings must also be addressed and adjusted where needed. This put in place that the child would reach a full development on all levels.

Along with the aims and objectives of the treatment of ADHD, a treatment plan must be set in place in order to achieve these aims. This treatment plan should include acute treatment of ADHD as well as psycho-education about the disease, adjustment difficulties and developmental challenges that should be expected and treatment possibilities to all parties involved in the child or adolescents’ treatment (Flisher & Hawkridge, 2013:137).

Although ADHD cannot be cured, an improvement in symptoms has been found through the combination of complementary and alternative medicine (CAM) with the pharmacologic treatment of the condition (Snyman & Truter, 2010:161). ADHD can be kept under control by making use of a more holistic approach such as dietary adjustment, psychological as well as behavioural therapy and alternative remedies (Van der Westhuizen, 2010:11). The National Centre for Complementary and Alternative Medicine (NCCAM) defines complementary medicine as making use of a different approach to treatment of a certain condition alongside the conventional treatment (NCCAM, 2014). NCCAM (2014) also defines alternative medicine as using a different approach the treatment of a certain condition instead of the conventional treatment. Flisher and Hawkridge (2013:137) stated that the acceptable first line of treatment for ADHD is behavioural therapy. This treatment will be given if the diagnosis is a milder case of ADHD, or an uncertain diagnosis, when there is no urgency and when the parents of the patient are opposed to pharmacologic intervention. Should the patient prove unresponsive to behavioural therapy treatment, pharmacotherapy must be initiated.
There are, however, only two active ingredients registered in South Africa for the treatment of ADHD i.e. methylphenidate and atomoxetine. Several studies on methylphenidate and/or atomoxetine prescribing patterns and the prevalence of ADHD in adults and children have been conducted across the world (refer to Table 2.1). All but one study (Prosser & Reid, 2009) found an increase in the number of prescriptions of methylphenidate and/or atomoxetine over the study periods. These studies differ in population size due to the fact that the studies were done in different years, different time periods and the data pool for each study differed.

Approximately 64% of South African children live in poverty and make use of the public healthcare system (UNICEF, 2010:21). According to Statistics South Africa (StatsSA, 2012:17), 17.9% of the South African population belonged to a medical aid scheme in 2004, increasing from 14.5% in 2005. The Western Cape and Gauteng provinces have the highest percentage of people who belong to medical aid schemes with percentages of 25.2% and 29.0%, respectively (StatsSA, 2012:18). This study will be based on medical aid claims data from the Western Cape Province from 2005 to 2013. The Western Cape is divided into five districts which are sub-divided into 24 local municipalities and one metropolitan municipality, which is the largest municipality in the Western Cape and consists of 64.20% of the entire population of the Western Cape (Main, 2015).

ADHD is one of the most common mental disorders of modern times and is mostly prevalent in school-aged children, but the symptoms could possibly be carried over into adolescence and adulthood (NIMH, 2012:1). Based on the foregoing discussion, the following cardinal research questions arose:

- Are the international statistics of children with ADHD also applicable to South Africa, and more importantly, in specific areas of South Africa (such as the districts in the Western Cape Province)?

- What are the prescribing patterns for methylphenidate and atomoxetine in these districts based on the rising statistics of ADHD worldwide?

Other research questions that were formulated:

- What does ADHD as an illness involve and what does the diagnosis entail?

- What is the prevalence of ADHD nationally as well as internationally?

- What treatment options are available for ADHD in South Africa?

- What does the diagnosis of ADHD entail?
• What is the usage of methylphenidate and atomoxetine containing products in the private healthcare sector of South Africa?

• Is there a difference in the prescribing patterns of methylphenidate and atomoxetine?

• Are there any differences in the prescribed daily dose (PDD) between those prescribed by general practitioners and specialists?

• What are the other central nervous system drugs co-prescribed with methylphenidate and atomoxetine containing products?

1.3 Aim and objectives

1.3.1 General aim

The general aim of this study was to investigate the prescribing of the ADHD medication, methylphenidate and atomoxetine, in children younger than 18 years in the five districts of the Western Cape Province. Data, obtained from a privately owned South African Pharmaceutical Benefit Management Company (PMB), was retrospectively analysed from 1 January 2005 to 31 December 2013.

1.3.2 Specific objectives

The study consisted of two phases – a literature review followed by an empirical investigation.

The specific objectives of the literature review were:

• Conceptualising ADHD as a psychiatric disease.

• Investigating the clinical management and pharmacologic treatment available for the treatment of ADHD in children and adolescents under the age of 18 years worldwide and nationally.

• Identifying alternative methods of managing/treating ADHD internationally and in South Africa.

• Determining comorbid and co-existing conditions diagnosed with ADHD in children and adolescents.

• Reviewing the pharmacologic class and mechanism of action of methylphenidate and atomoxetine.

• Reviewing possible side effects of methylphenidate and atomoxetine.
• Reviewing previous studies conducted on the prescribing patterns of methylphenidate and atomoxetine internationally and in South Africa.

The specific objectives of the empirical phase of the study included:

• Determining prevalence of ADHD in children and adolescents under the age of 18 years who received treatment with methylphenidate and/or atomoxetine in the private health sector of the Western Cape Province from 2005 to 2013, using a medicines claims database stratified by age, gender and geographic distribution.

• Identifying the prescribing patterns of methylphenidate and atomoxetine in children and adolescents under the age of 18 years in each district in the Western Cape.

• Determining the prevalence of comorbid conditions in children with ADHD.

1.4 Research methodology

“Research is a process in which you engage in a small set of logical steps” (Creswell, 2012:2). Research methodology is defined by Sahu (2013:3) as the science of studying how to do research properly. Sahu (2013:3) also states that the method chosen by the researcher to solve a research problem must consist of chronologic and logical steps that should assist the researcher in identifying problems, conceiving problem statements, sourcing relevant information in applying statistical tools, and to draw conclusions from these findings. The research methodology is the spine of the project that guides and inspires the researcher to do the research with confidence in order to uncover the unknown questions that society is faced with (Sahu, 2013:3).

The research phases, study design, setting and data source, target population and data analysis will be discussed in the next section.

1.4.1 Research phases

This study consisted of two phases: a literature review phase and an empirical phase.

1.4.1.1 Literature review phase

The literature review was conducted to establish previous reports in this field of study, i.e. the prescription patterns of methylphenidate and atomoxetine. This phase of the study included a description of the prevalence of ADHD in South Africa and internationally, including a brief background of the disease, aetiology, diagnosis and treatment and comorbid conditions. The two main pharmaceutical treatments available in South Africa indicated for ADHD, namely methylphenidate and atomoxetine, were discussed with regard to mechanism of action, dosage,
drug-drug interactions and possible side-effects of these drugs. The prescribing patterns of methylphenidate and atomoxetine were reviewed nationally and internationally. Clinical and alternative methods for the management of ADHD in children were also reviewed in South Africa as well as internationally.

The literature review searches were conducted on various database search engines for publications between 2000 and 2016.

1.4.1.2 Empirical investigation

The empirical investigation consisted of a retrospective drug utilisation review (RDUR) of medicine claims data.

According to the Academy of Managed Care Pharmacy (2009), a drug utilisation review (DUR) is a continuous evaluation of prescribing, dispensing and utilisation of medication based on set criteria. When the criteria are or are not met, it leads to a change or changes in the prescription, dispensing and utilisation of medication. A DUR is put in place as a feature guarantee measure that provides the direction to take action to correct mistakes made in the past as well as to get the appropriate feedback from the prescriber (AMCP, 2009). In 1977, The World Health Organization (WHO, 2003:8) defined DUR research as the “marketing, distribution, prescription and the use of drugs in a society, with special emphasis on the resulting medial, social and economic consequences”.

Hartzema et al. (2008:160) define drug utilisation research as a diverse compilation of descriptive as well as analytical methods for the quantification, insight and review of the steps (prescribing, dispensing and use) taken during treatment and for the division of interventions to increase the quality of this process. A more recent definition of DUR provided by Wettermark et al. (2016:7) state that DUR is concentrated on all aspects of drug use (i.e. economic, social and medical). All of these aspects have particular consequences. The consequences for the social aspects include wrongful use of medication while the economic consequences will include the cost of medicines in a particular social setting. The risks and benefits of medication therapy will then be the consequences of the various medical aspects of DUR. Wettermark et al. (2016:7) also state that DUR studies make use of a variety of information sources such as wholesale and prescriptions data (or for the purpose of this study medical aid claims data).

A DUR can be placed in one of three categories, namely retrospective, concurrent and prospective. In this study, a retrospective DUR was performed. A retrospective DUR is a structured study that interprets sequences of drug utilisation relative to set criteria that consist of the revision of therapeutic treatment and intervention after the treatment has taken place. This type of review takes place after the patients have received the necessary drug treatment and may
be used to prevent a previous mistake in the prescribing of a drug(s) in the future (AMCP, 2009:1; Hartzema et al., 2008:161; Hennessy et al., 2003:1494).

There are a few issues that can be identified with a retrospective DUR. These include the suitable and inappropriate use of generic drugs, the clinical abuse of some of the drugs prescribed, contraindications and drug interactions, it can be used to identify an improper period of treatment (whether it is too long or too short), wrongful dosages prescribed, correct use of the drugs prescribed and the therapeutic exactness of the treatment (AMCP, 2009:4).

The research design, data source and setting, target and study population and data analysis will be described in the subsequent paragraphs.

1.4.1.2.1 Study design

A research design is defined by Sreejesh et al. (2014:27) as a framework or blueprint for piloting a research study as proficiently as possible. It states the steps that need to be taken in order to collect, measure and analyse information that will assist the researcher to structurally solve a particular research problem.

This study followed a quantitative descriptive approach as the main focus of the study consisted of objective, numerical data. Quantitative research is based on logic instead of theories. Chronologic steps need to be taken in order to answer research questions stated by the researcher (Brink et al., 2012:97). Descriptive statistics are numerical measures and graphical approaches used to arrange, present and describe the characteristics of a variable in a sample (Fisher & Marshall, 2009:95).

To determine the prevalence of ADHD in children and adolescents under the age of 18 years in the Western Cape Province from 2005 to 2013, a repeated cross-sectional study design was followed, making use of the active ingredient of the drug and the prescribed daily dose, treatment date, the gender of the patient, the patients’ age, geographical area of the prescriber, total number of patients, and total and average number of prescriptions prescribed per patient per year as drug utilisation metrics. To determine the prevalence of conditions co-occurring in children and adolescents under the age of 18 years with ADHD, a cross-sectional study design was followed. For this analysis, prevalence of medicine (pharmacological classes) prescribed and chronic disease list (CDL) conditions occurring in the study population, were determined. A repeated cross-sectional study makes use of the same data and/or information in various samples at regulated intervals, meaning the data and/or information remains the same but the sample of study participants vary over time (Almond & Sinharay, 2012:1; UK data service, 2015:4,9). A cross-sectional study examines all the information from the study sample, consisting of various
groups within the sample i.e. age or gender, at a particular point in time (Salkind, 2010; Brink et al., 2012:101).

1.4.1.2.2 Setting and data source

In this study, medicine claims data for the period of 1 January 2005 to 31 December 2013 for children and adolescents in the Western Cape were obtained from a South African Pharmaceutical benefit management (PBM) company. Pharmaceutical benefit management companies are expert entities that manage prescription drug benefits for their customers (Mullins & Wang, 2002:10). According to the PBM Company supplying the data for the study, it renders benefit management services to 22 medical aid schemes in South Africa, or approximately 1.6 million members. They process claims from pharmacies and dispensing doctors based on the product claimed.

Based on the 2013 mid-year population statistics (Statistics South Africa (StatsSA, 2013:3), South Africa was populated by 52 982 000 people in 2013, of whom 11.4% (6 016 900 people) resided in the Western Cape Province. The PBM company therefore provided benefits to ~3.06% of the South African population in the Western Cape Province (StatsSA, 2013:3). The data fields that were extracted from the database included:

- the date the prescription was filled;
- a prescription number;
- an encrypted patient member- and dependant-numbers;
- the patient’s gender;
- the patient’s date of birth;
- the trade name of the prescripted drug;
- the National Pharmaceutical Product Interface (NAPPI)-code;
- the active ingredient;
- the quantity of the medicine items dispensed;
- the number of days supplied;
- the diagnosis (International Statistical Classification of Diseases and Related Health Problems (ICD) code; and the
• the address of the prescriber’s practice

Data were depersonalised by the Pharmaceutical Benefit Management company (PBM). Each member/dependant was allocated a unique member code from the PBM. This made it possible to trace a specific patient over the period of nine years, as this number did not change remained the same for a patient over the nine years and the same number was not allocated to more than one patient.

The PMB has the following processes put in place to ensure the reliability and legitimacy of the data such as:

• Data reliability corroboration: The PMB confirmed the claim field format, the provider of the healthcare service was confirmed, the validity of the membership and the dependant code was validated, the waiting period was confirmed (where applicable) and a duplicate check was done by the PMB to insure integrity of the data.

• Eligibility management.

• Medicine usage and clinical management: During this part of the validation process, the majority of limits were identified; these were the limit on repeat prescriptions refills, quantities, drug to age and gender, products that require pre-authorisation and particular scheme exclusions, pre-existing conditions, validity of prescriber speciality, broad category and specific product exclusions and waiting periods. All these aspects formed part of the medicine usage agreement. The clinical management included the prevention of active ingredient duplications, verifying the maximum daily dosages, checking for drug allergies, and appropriateness of medicine for the specific age, and disease and gender interactions.

• Pricing management: This part of the process took care of the price file management as the generic reference pricing.

• Fully incorporated pre-authorisation services.

• Exception management.

• Chronic disease list management (a list that specifies treatment for the 25 conditions covered by the PMB benefits).

• Prescribed Minimum Benefit (PMB) management and other conditions (PMB is a set of specific benefits that ensures that all member of any medical aid has access to certain minimum health benefits regardless of medical scheme benefits).
• Medicine management in capitation environments.

• Online reporting on medical expenditure.

• Supplementary services: Network management, development and implementation of reference price lists, formulary management (management of the chronic and non-chronic disease list, and PMB conditions and real-time benefits corroboration) price and product file management.

1.4.1.2.3 Target population

A statistical population is defined as a group with special characteristics that has to be studied to determine certain facts. A study population as a population defined by the number of participants selected, method of participant selection, occupation, age, gender, geographic location, religion, ethnic group, marital status or any characteristic needed to assist in the variables of a particular study. It is a total assembly of people or items that the researcher finds interesting and that meet the set criteria of the researcher. The researcher must ‘describe’ the research participant in as much detail and information as possible (Banerjee & Chaudhury, 2010:61; Brink et al., 2012:131; Nieuwenhuis, 2012:103). In this study, only data from the database applicable to the Western Cape Province for the medicine items methylphenidate and atomoxetine prescribed to children younger than 18 years was included.

Children (male and female) under the age of 18 years were the focus of this study. The target population therefore consisted of all male and female children and adolescents under the age of 18 years in the private healthcare sector who belonged to a medical aid scheme and have received methylphenidate and/or atomoxetine treatment during the study period. The date of birth was provided by the database. The date 1 January was used as the reference date to calculate the age per year group per year per gender. The number of patients receiving methylphenidate and/or atomoxetine per district in each year was analysed. Age grouping was recalculated annually as the subjects got older.

The study population consisted of data only from the database applicable to the Western Cape Province for the medicine items methylphenidate and atomoxetine prescribed to children under the age of 18 years.
Table 1.1: The age classification is based on the dosage regime for methylphenidate and atomoxetine

<table>
<thead>
<tr>
<th>Age</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0, ≤6 years</td>
<td>Paediatric patients including all patients from birth up to the age of 6 years, including the age of 6 years.</td>
</tr>
<tr>
<td>&gt;6, ≤12 years</td>
<td>Children including all patients above the age of 6 years which does not include 6 years, up to the age of 12 years, including the age of 12 years.</td>
</tr>
<tr>
<td>&gt;12, &lt;18 years</td>
<td>Adolescents including all patients above the age of 12 years which does not include 12 years, under the age of 18 years, excluding the age of 18 years.</td>
</tr>
</tbody>
</table>

Table 1.1 displays the age group categories which was allocated based on the recommended dosage regime for a particular age for both methylphenidate and atomoxetine. As neither methylphenidate nor atomoxetine is indicated for children under the age of six years (Snyman, 2014:2), the age groups in which the researcher divided the participants during the course of the study stayed the same for methylphenidate and atomoxetine.

The researcher made use of all data for patients who comply with the inclusion criteria. Table 1.2 indicate the inclusion and exclusion criteria for this study.

Table 1.2: Inclusion and exclusion criteria for the study

<table>
<thead>
<tr>
<th>Data fields</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>The National Pharmaceutical product Interface (NAPPI) code</td>
<td>NAPPI codes specified for methylphenidate and atomoxetine</td>
<td>-</td>
</tr>
<tr>
<td>Drug trade name</td>
<td>Included in order to determine the specific (brand name) methylphenidate/atomoxetine containing products.</td>
<td>-</td>
</tr>
<tr>
<td>Patient's gender</td>
<td>Both male and female patients was included in this study</td>
<td>Patient was not included if data was incomplete.</td>
</tr>
<tr>
<td>Patient's age</td>
<td>Patients were only included if age data was complete. Only patients aged ≤18 years were eligible for this study.</td>
<td>Patient was not included if this data was not complete as age was an important variable</td>
</tr>
<tr>
<td>Practitioner's practice postal code</td>
<td>Included in order to determine the residential area of the patient as all participants in the study must have resided in the Western Cape during the time of the study.</td>
<td>-</td>
</tr>
</tbody>
</table>
1.5 Data analysis

The data for this study were analysed by using the Statistical Analysis System® SAS 9.4® programme (SAS Institute Inc., 2002-2010) and SPSS for Windows SPSS (IBM Corp., 2013) in consultation with the Statistical Consultation Services of the North-West University. Microsoft® Office Excel 2010 was used for general computations. The variables and statistical analysis employed in the study is described in subsequent paragraphs.

1.5.1 Study variables

Table 1.3 indicates the variables that were used in the study.

Table 1.3: Study variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient of drug</td>
<td>The pharmacological classification was done by using the MIMS® (Monthly Index of Medical Specialties), where medication are listed according to pharmacological active ingredients and registered trade names (Snyman, 2011). Individual products on the data were also identified using NAPPI (National Approved Product Pricing Index) codes (Snyman, 2011).</td>
</tr>
<tr>
<td>Treatment date</td>
<td>The treatment date (i.e. the date the prescription was filled) was used to indicate the study period.</td>
</tr>
<tr>
<td>Patient's gender</td>
<td>Patients were placed in two categories i.e. male and female.</td>
</tr>
<tr>
<td>Patient's age</td>
<td>The age of a patient was determined on the treatment date (calculated from the date of birth of the patient and the date of treatment). A total of three age groups were defined which was allocated based on the recommended dosage regime for a particular age for both methylphenidate and atomoxetine (refer to Table 1.1).</td>
</tr>
<tr>
<td>Geographical area</td>
<td>Prescriber practice addresses were grouped according to province, district council, municipality and main place level, to allow investigation of differences in the prescribing patterns of methylphenidate and atomoxetine in the Western Cape.</td>
</tr>
<tr>
<td>Chronic disease list condition (CDL)</td>
<td>Medication treatment for each chronic condition is derived from the appropriate treatment algorithms and classification is done according to the individual chronic condition. These conditions as well as the medication used in the treatment of these conditions are identified and used as included in the South African Chronic Disease List. To identify the CDL conditions, ICD-10 coding was used. The following classification system were used to classify the CDL conditions: Cardiovascular disease - which includes hypertension, hyperlipidaemia, coronary artery disease, cardiac failure, cardiomyopathy disease and dysrhythmia. Respiratory disease – which includes asthma, chronic obstructive pulmonary disease and bronchiectasis; Diabetes mellitus – which includes type 1- and type 2 diabetes mellitus; Diabetes insipidus; Hypothyroidism; Psychiatric disease – includes bipolar mood disorder and schizophrenia; Rheumatoid arthritis; Systemic lupus erythematosus; Gastro-intestinal disease – which includes Crohn’s disease and ulcerative colitis; Central nervous system disease, – which includes epilepsy, Parkinson’s disease and multiple sclerosis;</td>
</tr>
<tr>
<td>Variable</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Chronic renal disease; Haematological disease – which includes haemophilia A and B. Glaucoma.</td>
<td></td>
</tr>
<tr>
<td>Prescribed daily dosage (PDD)</td>
<td>According to the WHO (2003:39) the PDD is defined as “the average dose prescribed according to a representative sample of prescriptions.” The average daily amount of a drug prescribed can be determined through the PDD. The PDDs will be calculated by multiplying the quantity of tablets dispensed by the tablet strength, divided by the days’ supply (treatment period).</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>The total number of patients on the database receiving treatment with methylphenidate and/or atomoxetine over the study period.</td>
</tr>
<tr>
<td>Total number of prescriptions</td>
<td>The total number of prescriptions for methylphenidate and/or atomoxetine given to the total number of patients over the study period.</td>
</tr>
</tbody>
</table>

### 1.5.1.1 Descriptive statistics

Statistics form part of a mathematical study that is used to analyse, interpret and summarise numerical observations (Carlson & Winquist, 2014:2).

The gender, age groups, number of patients receiving methylphenidate and/or atomoxetine, number of CDL co-existing conditions, number of co-prescribed active ingredients (with methylphenidate and atomoxetine), prescribed daily dose and number of medication items claimed during the course of the study period were explained by means of descriptive statistics that included: means, standard deviations, 95% confidence intervals, medians and frequencies. A brief description of each statistical measure follows.

#### 1.5.1.1.1 The arithmetic mean

According to Pietersen and Maree (2012a:188), the most frequently used measure in statistics is the arithmetic mean, which calculates the average of data values. This is done by adding all of the observations (e.g. number of prescriptions) and dividing them by the number of measurements (e.g. total number of patients) in order to measure the core inclination (Pagano & Gauvreau, 2000:38). The following formula (Pagano & Gauvreau, 2000:39) can be used for the calculation of the arithmetic mean:

\[
\bar{X} = \frac{1}{n} \sum_{i=1}^{n} X_i,
\]
Where:

\[
\sum = \text{The additive value of } (x_i - \bar{x})
\]

\[
\bar{x} = \text{The mean value of the data set.}
\]

\[
x_i = \text{The values of the variable.}
\]

1.5.1.1.2 The median

When the dataset is ranked from the lowest value to the highest, the median is the value at exactly 50% of the rank (in the middle); this means that half the set falls above this value and the other half below (Pagano & Gauvreau, 2000:41). Should the rank be an even number, the middle two numbers will be added to one another and divided by two numbers (Pagano & Gauvreau, 2000:41). Pietersen and Maree (2012a:188) states that the median indicates the central value of the data distribution, and therefore it divides the data into halves. The median is also a measure of central tendency, but it is not quite as sensitive to each specific measurement as the mean (Pagano & Gauvreau, 2000:41).

1.5.1.1.3 Standard deviation

In order to define the term 'standard deviation', Pagano and Gauvreau (2000:46) define the term variance as “the amount of variability, or spread, around the mean of the measurements.” Variance is not used as often as standard deviation as it does not have the same units of measurement as the mean of the measurements. The standard deviation is defined as “the positive square root of variance” (Pagano & Gauvreau, 2000:47). According to Helmenstine (2014), the calculation of the standard deviation starts by calculating the mean. The mean is then deducted from each number and square in that finding. All of these findings are then added together and divided by one less than the quantity of data points. By doing this, one has calculated the variance. The square root of the variance is the standard deviation (Helmenstine, 2014). The standard deviation can be calculated as follows (Pagano & Gauvreau, 2000:46):

\[
s^2 = \frac{1}{n} \sum_{i=1}^{n} (x_i - \bar{x})^2
\]

Variance is

\[
N = \text{The numerical value of the sample size.}
\]
The additive value of \( \sum (X_i - \bar{X}) \) is the sum of the deviations from the mean.

\( X_i \) = The values of the variable.

Therefore standard deviation is \( s = \sqrt{s^2} \) (Pagano & Gauvreau, 2000:47)

1.5.1.1.4 The 95% confidence interval

Should 100 random samples be drawn and 100 different confidence intervals be calculated, 95 of these intervals will include the true population of the study. This is the 95% confidence interval (Pagano & Gauvreau, 2000:215). It is a measure that is utilised when estimating population parameters by using an interval (Pietersen & Maree, 2012b:201). The confidence interval is designed by using the point estimate of the parameter the researcher is interested in calculating, the degree of variation at that point estimate as well as the measure of confidence required. This particular point estimate can be found in the middle interval where the girth is dependent on the confidence level as well as the degree of variation. The girth of the confidence interval is wider when the confidence level is high and it is narrower when the confidence interval is low(er).

1.5.1.1.5 The relative frequency

A relative frequency is a useful tool for the comparisons of sets of data with an uneven number of observations. The relative frequency of an interval is the proportion of the total number of observations that appear in a specific interval (Pagano & Gauvreau, 2000:13). Should this proportion be multiplied by 100%, the percentage of values in that interval will be made clear (Pagano & Gauvreau, 2000:13).

1.5.1.2 Inferential statistics

Carlson and Winquist (2014:2) state that inferential statistics interpret the significance of the descriptive statistics. The inferential statistics employed in this study included the tests of association and the Poisson regression model. The Bonferroni correction was used when multiple comparisons were made. Cohen’s \( d \)-value was used as effect size, and is a measure of magnitude of the difference between the average number of prescriptions per patient by age group and gender with \( d \geq 0.8 \) established as a large effect size with practical significance. Cramér’s \( V \) statistic was used to test the practical significance of this association (with Cramér’s \( V \geq 0.5 \) defined as practically significant) in the case of chi-square or Fisher’s exact tests.
1.5.1.2.1 Tests of association

The chi-square test identifies the differences between totals of categorical data and also states whether it is due to more than only one chance (Pagano & Gauvreau, 2000:345). It is a test known to be a non-parametric test where two nominal variables are being examined. It states whether the association between the variables is statistically significant. The Fisher’s exact test is similar to the chi-square test — the only difference is that it performs a precise calculation of the \( p \)-value when there are fewer than five observations (Pietersen & Maree, 2012c:250). The following formula is used to calculate the chi-square and Fisher’s exact tests (Pagano & Gauvreau, 2000:345):

\[
\chi^2 = \sum_{i=1}^{rc} \frac{(O_i - E_i)^2}{E_i}
\]

\( O_i \) = The noted frequencies in each class of the contingency table.

\( E_i \) = The expected frequencies when the null hypothesis is known to be true.

\( rc \) = Degrees of freedom

1.5.1.2.2 The Poisson regression model

The Poisson regression model is used to model certain events that do not occur frequently. Poisson is used when the data set has an extremely large \( N \)-value and a very small \( p \)-value (Pagano & Gauvreau, 2000:172).

1.6 Ethical considerations

The study was approved by the Health Research Ethics Committee (HREC) of the Faculty of Health Sciences (NWU-00179-14-S1), as well as the Board of Directors of the PMB. Informed consent was not needed in this study as there was no individual patient, prescriber, provider or medical scheme that could be identified. There was no direct contact with any of the parties and no participants were directly involved in the study.

1.7 Chapter summary

Chapter one discussed the ‘why’, ‘where’ and ‘how’ of this study by providing a short background for ADHD, followed by a problem statement and the aims and objectives of the study. The chapter also provided the different phases of the study, with a detailed explanation of each one. The ethical consideration was also briefly discussed in this chapter.
CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

In this chapter, Attention Deficit Hyperactivity Disorder (ADHD) as a psychiatric disorder is conceptualised, and the co-existing conditions and misdiagnoses associated with ADHD are discussed. A description of the different methods for treating and managing ADHD internationally and nationally, the clinical management of ADHD namely the pharmacologic treatments and non-pharmacological methods available in South Africa, the pharmacologic mechanism of action and class of methylphenidate and atomoxetine as well as possible side-effects of methylphenidate and atomoxetine will also be given. The chapter concludes with a review of previous studies conducted on the prescribing patterns of methylphenidate and atomoxetine in South Africa, particularly in the Western Cape.

2.2 Conceptualisation of ADHD as a disease

2.2.1 Definition and classification of ADHD

A mental disorder is “a syndrome characterized by clinically significant disturbance in an individual’s cognition, emotion regulation or behaviour that reflects a dysfunction in the psychological, biological or developmental processes underlying mental functioning. Mental disorders are usually associated with significant distress or disability in social, occupational or other important activities. An expectable or culturally approved response to a common stressor or loss, such as death of a loved one, is not a mental disorder. Socially deviant behaviour (e.g. political, religious or sexual) and conflicts that are primarily between the individual and society are not mental disorders unless the deviance or conflicts results from a dysfunction in the individual, as described above.” (American Psychiatric Association (APA), 2013:20). In accordance with the definition of the APA (2013:20), ADHD is a mental disorder identified by an ongoing pattern of inattention, more specifically the preservation of selective attention, possibly combined with hyperactivity and impulsivity to such an extent that a maladapted, inconsistent development and functioning of a child is created. Various risk factors may initiate the symptoms of the different sub-types of ADHD. ADHD is also known as a neurodevelopmental disorder (Soppitt, 2012:217; Widmaier et al., 2006:239).
According to Bothma (2011:3), ADHD can be classified into three main types, namely the ‘primarily hyperactive-impulsive’, ‘primarily inattentive’ and a combination of both. Venter (2004:446) indicates an additional fourth type of ADHD known as ‘partial remission’, mostly identified in older children who do not present with all of the symptoms.

An overeager motor ability is usually noticed but hardly acknowledged before the age of four years in children with ADHD, as the child will be merely perceived as ‘busy’ or ‘naughty’. According to the APA (2013:61), hyperactivity refers to an overactivity in motor skills, often at inappropriate times; e.g. the child will run up and down or fidget, talk or tap on an object. During adolescence, the physical symptoms of the condition tend to stabilise, even though fidgeting and tapping will appear at times and anti-social behaviour, feelings of restlessness, and impatience may set in (APA, 2013:62).

Impulsivity is defined as a hasty action, not clearly thought through, sometimes with permanent damage as a result e.g. the child will run across the road without looking out for oncoming vehicles (APA, 2013:61). The reason for this is possibly due to a yearning for instant satisfaction, a known trait of children suffering from ADHD. Children who are primarily hyperactive-impulsive tend to be restless and are overly talkative, normally impulsive, tend to interrupt others (like their peers, parents or teachers) by speaking out of turn and they are often perceived as an annoyance to the people around them (CDC, 2014b). These children find it hard to sit still upon receiving instructions, taking in the instructions communicated to them by parents and teachers, do homework or eating. These children are also more prone to injuries (CDC, 2014b).

Inattention is characterised as wandering off the subject matter, not focussing on the task at hand, and lack of determination (APA, 2013:61). Primarily inattentive children are disorganised, but it is not done maliciously or out of disobedience (APA, 2013:61), and they do not finish tasks, even with minimal complexity, and they tend to forget details that ‘fill in the bigger picture’ of the content of their day-to-day lives, nor follow instructions. The majority of the inattentive symptoms manifest in primary school years (APA, 2013:62).

Children with ADHD do not have to fall into any particular one of the impulsive/hyperactive/inattentive types of ADHD, but a combination in equal parts of the symptoms in one case is also a possibility (CDC, 2014b). There is controversy about the complete inability to concentrate. According to Venter (2004:445) these children can concentrate for extended periods of time if they show a particular interest in something. It is not uncommon for these children to be able to watch an interesting, stimulating television programme for long periods of time.
Children suffering from ADHD have a difficult time adapting to the school environment as they struggle immensely to develop relationships and often lack self-esteem (Cruz, 2010:448; El Masry et al., 2012:192). According to Chinn (2012:183) it is not so much the child who complains of the onslaughts of the disorder, but rather one of the many adults present in the child’s day-to-day activities. The majority of official sources, as stated by Venter (2004:446), rarely separate ADHD from Attention Deficit Disorder (ADD). ADHD is the universal term used for both of these conditions. The ADD group of people is attention deficit and distracted. It is mostly prevalent overweight girls and it is associated with a poor self-esteem (Venter, 2004:446).

2.2.2 History/aetiology of ADHD

In previous years ADHD was known as Hyperkinesis Disorder of Childhood, Attention Deficit Disorder (ADD) and Minimal Brain Dysfunction (Wilens, 2006:143). When addressing the aetiology of any mental disorder, Thompson (2012:37) suggests the four P’s, namely the ‘predisposing factors’, the ‘precipitating factors’, the ‘perpetuating factors’ and the ‘protective factors’, and the influence of the psychological, biological and social factors on these four factors. The interaction between a child, the child’s environment and the family situation plays a large role in the development of the child and the possibility of a mental disorder such as ADHD (Thompson, 2012:37).

The possible sources of the origin of ADHD are incessant. ADHD can be redefined as adaptive responses to environmental contexts. This means that this psychiatric disorder could be due to evolutionary perspectives leading to the symptoms of ADHD in some children i.e. the symptoms of ADHD occur in some children due to a selection force leading these symptoms to be advantageous in some instances (Jensen et al., 2006:96). It is hypothesised that the increased motor ability, inattention and impulsivity are all because of these selection forces and are seen as adaptive traits based on the ancestral, as well as current environments, causing the child to be ‘response ready’ rather than able to solve problems (Jensen et al., 2006:97).

The biochemical origin of ADHD is still novel. Ceylan et al. (2010:1492) conducted a study on 35 children with ADHD and 35 children without ADHD, homogenously divided according to age, weight and gender to determine the levels of oxidants and antioxidants present in both children with and without ADHD. The most common sub-type of ADHD found among the subjects was the combined type ADHD (57%), followed by inattentive ADHD (40%) and hyperactive/impulsive ADHD (3%) (Ceylan et al., 2010:1492). Remarkably high levels of malondialdehyde (MDA) and nitric oxide (NO) were found in the participants suffering from ADHD. These participants also had elevated levels of catalase antioxidant enzyme (CAT), but this observation was not found to be statistically significant. Glutathione peroxidase levels were significantly higher in the control subjects, but subjects who had no family history of ADHD showed much higher levels of
glutathione peroxidise than those who do have a family history of AHDH. Superoxidase dismutase level activity did not present a statistical significance. There were no particular differences in levels of these biochemical substances between the sub-types of ADHD. Ceylan et al. (2010:1493) found an imbalance in these biochemical substances in children and adolescents with ADHD, contributing to another potential source of the origin of this disorder.

2.3 Prevalence and epidemiology of ADHD

ADHD is escalating across the world. The percentage of children found to have ADHD in the United States of America (USA) during 2003 was 7.8%, with an increase to 9.5% in 2007 (CDC, 2014a). From 2003 to 2011, the number of diagnoses increased by 40% (Vestal, 2014), and as of 2011 it was determined that 11.0% of children (64 million children) between the ages of 4–17 years were diagnosed with ADHD in the USA (CDC, 2014a). Children covered by Medicaid (the American Federal State Healthcare Program for the less fortunate) have a 50% higher chance of being diagnosed with ADHD as they are most likely to grow up in impoverished conditions and do not have access to the necessary resources (Vestal, 2014). The National Health Service (NHS) of the United Kingdom (UK) estimates that between 2% and 5% of school-aged children and adolescents in the UK suffer from ADHD (NHS, 2014). The prevalence of ADHD among school children in Africa range between 5.4% and 8.7% (Bakare, 2012:359). In the Democratic Republic of Congo, there was a 6% prevalence, 8.7% in Nigeria and 1.5% in Ethiopia (Bakare, 2012:359). There is paucity of information available in South Africa on ADHD but best estimates indicate that 8-10% of children in South Africa suffer from this illness (Attention Deficit Hyperactivity Support Group of South Africa (ADHASA), 2015; Bakare, 2012:359; Stead et al., 2006:7).

The prevalence of ADHD differs by gender. For example, boys in the UK are more likely to be diagnosed with ADHD than girls; however, ADHD might be under-diagnosed in girls as the majority of girls suffer from problems with attention, or lack thereof rather than hyperactivity (NHS, 2014). The majority of diagnosis in the UK is made in children between the ages of 6 and 12 years. In the USA, the average age of diagnosis is 7 years and the disorder is found to be three to nine times more common in boys (CDC, 2014a). In the USA boys are being diagnosed with ADHD more frequently than girls (boy-to-girl ratio 2:1), but girls are showing an increase in diagnosis of the inattentive type (APA, 2013:63).

In accordance with international trends, South African boys are more likely to be diagnosed with ADHD than girls with male to female ratios from two to nine male diagnoses for every female diagnosis (Schellack & Meyer, 2012:12; Venter, 2004:444). The type of ADHD must always be taken into account when drawing gender-based statistics (Schellack & Meyer, 2012:12). Van der Westhuizen (2010:10) showed that the gender ratios throughout male to female to be four male diagnoses for every female diagnosis for predominantly hyperactive type ADHD diagnosis, and
the gender ratio for the primarily inattentive type of ADHD is two male diagnoses for every female diagnosis. The reasons for these variances may include the geographical area, the diagnostic criteria used by the clinician to make the diagnosis and the accessibility to information on ADHD to the parents, teachers and clinicians (Polanczyk et al., 2007:945). The geographical area (rural vs. urban) may play a role in the prescribing of medication. A study conducted in Australia found that the medical practitioners in rural areas perceive their location to affect their prescribing along with the distance to the patients’ residence to and from the practice, lack of diagnostic facilities in the vicinity, the patients’ expectation of receiving a prescription and the level of monitoring a patient may need during therapy (Cutts & Tett, 2003:129). It was also found that doctors in these remote areas prefer to prescribe the most recent drug available on the market as they may have less side-effects, requiring minimal monitoring of the patient, but this finding declined as the practise became more rural, possibly explained by lack of pharmaceutical representation and information in these areas. It is, however, still possible to find information via the internet (Cutts & Tett, 2003:129).

Perrold et al. (2010:460) conducted a study on the perceptions and knowledge of ADHD in primary school teachers in the Cape Town Metropolitan and found a substantial shortage in knowledge of ADHD among teachers in the Metropolitan and its borders (Perrold et al., 2010:464). Most of the teachers in the study could, however, identify the major symptoms indicating the possibility of ADHD, i.e. the fidgeting, lack of concentration and organisation. The teachers also knew that a multi-modal treatment method (parent- and teacher training along with medication) will benefit the child’s disorder (Perrold et al., 2010:467). The teachers indicated a major lack of knowledge on the epidemiology of ADHD as a disorder (Perrold et al., 2010:468), but also stated that they have received little to no guidance on the disorder and that many of their ‘facts’ came from the media’s portrayal of ADHD (Perrold et al., 2010:470).

2.4 Possible causes of ADHD

There are various speculations and theories on the exact cause of ADHD in children, but the CDC (2014b) states that some of the possible causes of ADHD could be genetically related difficulties. As of yet, no biological marker has been identified for the diagnosis of ADHD, but there is a recognised genetic influence in some extreme and uncommon cases. These cases are known as ‘Fragile X-syndrome’ and ‘22q11 deletion syndrome’ (APA, 2013:62). El Masry et al. (2012:193) states that the two main neurotransmitters being investigated are dopamine and serotonin. According to ADHASA (2015) a shortage or an imbalance in prostaglandin’s PE1 and PE3 may be a biochemical cause of ADHD. These influences are not acknowledged as finite causal factors. Twin studies have, however, shown a 75% of the heritability of these symptoms across the population, but no single gene has been identified as the single cause of ADHD as a mental disorder (Chinn, 2012:183). Possible drug abuse during pregnancy, premature birth and/or low
birth weight, neurotransmitter malfunction, environmental exposure to poison e.g. lead, alcohol and drugs may be possible causes of ADHD in children as it possibly alters the genetic makeup of the child (APA, 2013:62). Chinn (2012:186) agrees with the aforementioned statement, but also mentions zinc deficiency as a possible cause. In addition, other conditions such as brain damage, visual and audio damage, poor diet (artificial colourants and additives in individual cases), mood and sleep disorders, epilepsy and trauma may lead to symptoms similar to that associated with ADHD (APA, 2013:62; Bothma, 2011:6; El Masry et al., 2012:193).

Other medical disorders may account for the presentation of symptoms similar to those of ADHD. These include: hyperthyroidism, brain injuries, encephalopathy and foetal alcohol syndrome (Fisher & Hawkridge, 2013:137). There is also controversy about the role of dietary habits, parenting, and overall cultural environments such as the school and household as contributors to the worsening of symptoms of ADHD. For instance, according to Bakare (2012:358), ADHD is nothing but a cultural formation, whereas the CDC (2014b) is of the opinion that a diet high in sugar, exposure to violent television programmes, bad parenting and an overall cultural/household environment play no role in the symptoms of ADHD. The APA (2013:62), on the other hand, regard the home environment, parenting, trauma and dietary inconsistencies as role-players in the management of ADHD. Venter (2004:444) agrees with the statement made by the APA by saying that factors such as the environment at home, trauma, and diet are important in the management of ADHD but that it does not cause ADHD.

2.5 Pathophysiology of ADHD

“The brains of these children are different” (El Masry et al., 2012:192). Numerous studies have been conducted in children with ADHD compared to a controlled group where it has been found that the children suffering from ADHD have anatomical differences in brain size. Children with ADHD show a different brain function pattern than children without ADHD (El Masry et al., 2012:192).

There are various pathways to explain why children with ADHD present certain symptoms. These include the dopaminergic, nonadrenergic and serotonergic pathways of which the dopaminergic is the most prominent (Waldman & Gizer, 2006:400). The executive function difficulties are thought to be due to a defective dorsolateral-striatal pathway, whereas the symptom of instant gratification is possibly due to the frontal-ventral striatal pathway (El Masry et al., 2012:193). Skokauskas et al. (2011:295), however, found that few studies have been done on these anatomical differences and the sample sizes used in these studies are relatively small, thus the generalisability and validity may not be adequate and it leaves room to conduct further studies on the subject.
2.6 The function of neurotransmitters in ADHD

2.6.1 Dopamine

Dopamine is defined as ‘a naturally occurring sympathetic nervous system neurotransmitter that is the precursor of norepinephrine. It is produced in the substantia nigra and transmitted in the putamen and caudate nucleus’ (Mosby’s Dictionary of Medicine, Nursing and Health Professions, 2009:576).

Dopamine is a catecholamine formed when tyrosine, an amino acid, is taken up by axon terminals and converted by tyrosine hydroxylase to L-dihydroxy-phenylalanine (L-Dopa). This is the rate-limiting step in the process, as tyrosine hydroxylase is the rate-limiting enzyme. Dopadecarboxylase then converts the L-Dopa into dopamine (Widmaier et al., 2006:168). Catechol-O-methyl-transferase, (COMT) is an enzyme that takes part in the initial steps of the metabolism of catecholamine and dopamine is a substrate for COMT (Westfall & Westfall, 2006:164). The dopamine transporter (DAT) main function is to re-uptake excess dopamine and terminates its actions and is included in the physiology of cognition, behaviour, reward and mood and is affected by drugs such as amphetamines (Giomani & Sugiyama, 2006:66).

Tripp and Wickens (2008:692) conducted a review on the neural mechanisms fundamental to positive reinforcement and how this altered sensitivity to positive reinforcement account for many of the symptoms associated with ADHD. Tripp and Wickens (2008:691) came to the conclusion that children with ADHD differ from children without ADHD with regard to response and processing to reinforcement. It was suggested that there is a difference in the degree and timing of anticipatory dopamine cell firing called the dopamine transfer deficit (DTD) theory. It is a result of what happens in the brain on a cellular level and it is accepted throughout that the phasic activity in dopamine cells is related to positive reinforcers. The DTD theory is based on certain postulates: The dopamine cell response to positive reinforcement transfers earlier in normal children, on cues that predict reinforcement. This provides instant reinforcement on cellular level when reinforcement is postponed. In children without ADHD, the DTD theory suggests that they have a normal cell response when those cells are stimulated by the possibility of dopamine transmission i.e. those cells receive a stimulus that predict a positive cell reinforcement when behavioural reinforcement is not instant. On the other hand, the DTD theory suggests that children with ADHD do not react to the stimulus that predicts the reinforcement. That cell reinforcement does not develop normally as it would in a child without ADHD. This leads to a weak or no predictive dopamine cell transmission which in turn has the unwanted behavioural normal children

1 A positive reinforcer is defined as a stimulus that increases or maintains the probability that a behaviour that it follows will transpire again (Tripp & Wickens, 2008:692).
will maintain response even after reinforcement is continued due to continuous anticipatory dopamine fire whereas children with ADHD do not have anticipatory dopamine cell fire, causing the behavioural response to stop much faster (Tripp & Wickens, 2008:694; Tripp & Wickens, 2009:584). In addition, children with ADHD may take part in ‘off task’ behaviour that will result in immediate reinforcement. This finding may corroborate a statement made by Venter (2004:445) saying that children with ADHD can concentrate for prolonged periods of time if the stimulus is interesting enough for the child.

Hawi et al. (2005:958) conducted a study on mono-aminergic candidate genes in order to identify the association between genetics and ADHD. The candidate genes for neurotransmitter systems involved in ADHD include precursor genes (e.g. thyrosine hydroxylase for dopamine), receptor genes (DRD1, D2, D3, D4 and D5), transporter genes (e.g. DAT1), metabolite genes (e.g. the gene involved for COMT) and conversion genes (e.g. dopamine decarboxilase) (Waldman & Gizer, 2006:401). A total of 179 ADHD-affected nuclear families of Irish descent were included in this study and one or both parents of the ADHD child were interviewed. It was found that 25% of mothers and 35% of fathers taking part in this study has been affected by ADHD. A total of 17 genes were examined, of which six dopaminergic and three serotoninergic markers passed the threshold to be considered as connected to ADHD. These markers were: DRD4, DRD5, DAT1 (contributed the most of all the markers), SERT, TPH2, TH, DDC, SNAP-25 and 5HT1B. These findings indicate that ADHD may be due to paternal transmission of the risk allele (highest ration of transmitted:nontransmitted) of the gene at nine independent sites. When investigating the gene transmission, there was a strong connection between transmission from fathers to daughters and a weak connection between mothers and sons, which is one of the possibilities why more boys are diagnosed with ADHD than girls.

Althaus et al. (2010:20) conducted a study to determine the effects of variants of the DAT1 polymorphism on the performance of cortical-evoked potentials that is associated with ADHD. The findings of both the DAT1 polymorphism and ADHD-related problems are associated with awareness-related processing of conscious error and the anticipation of negative feedback. This suggests that DAT1 may manipulate a system that is susceptible to aloof stimuli and their conscious processing. DAT1 affects reinforcement-controlled learning in ADHD indicating that the 10/10R carriers are less capable of increasingly becoming more conscious of making mistakes and less of learning to predict negative consequences that it entails (Althaus et al., 2010:30).

Park et al. (2014:610) conducted a study in children between the ages of six to 15 years in order to differentiate between possible perinatal risk factors involved in ADHD subtypes. The behaviour of the children was evaluated by the Children’s Behaviour Checklist (CBCL), the Disruptive Behavioural Disorder Rating (DBDS) which was completed by the parents. Among the 147 participants with ADHD included in this study, 41.9% (n=65) suffered from inattentive ADHD
(ADHD-I) and the remaining 52.9% (n=82) suffered from combined type ADHD (ADHD-C) (Park et al., 2014:611). The participants suffering from ADHD-C were more likely to suffer from comorbid conditions, and were more aggressive. Their score on the CBCL tests were also far more externalising than the rest of the participants who were tested. Among the 147 children who participated in the study, 97.96% (n=144) were genotyped for the DAT1 gene and five alleles were found, adding more evidence that the DAT1 gene plays a role in the aetiology of ADHD. The presence of postpartum depression, maternal stress during the gestational period and any changes in the primary caretaker in the child’s first three years also played a cardinal role in both types of ADHD (I and C). ADHD-I was more commonly associated with an ‘older’ mother, a prolonged time to speaking a sentence and less frequent vital prenatal exams whereas ADHD-C was more commonly associated with younger paternal age, a variation in primary caretaker (a carer other than the mother) within the first three years of the child’s life. Children with ADHD-C were also less likely to suffer from any post-partum health issues when compared to ADHD-I.

All of the studies reviewed have one persistent aetiological factor and that is the presence of genetic markers especially DAT1, in ADHD, followed by parental involvement of the children with the disorder.

2.6.2 Norepinephrine

Similar to dopamine, norepinephrine is also a catecholamine and is synthesised on a similar basis as dopamine. As with dopamine, tyrosine is converted to L-Dopa by tyrosine hydroxylase. Dopa-decarboxylase then converts the L-Dopa to dopamine. The dopamine is then converted to the neurotransmitter norepinephrine (Widmaier et al., 2006:168). Norepinephrine then acts as a neuromodulator that enhances the signals carried over by the sensory inputs, leading to the neurons in the locus ceruleus (LC) in the brain pons to improve information processing (Widmaier et al., 2006:239).

Norepinephrine plays an essential role in several processes, inter alia, contributing to the storage and recovery of memory, as well as when the effort to remain intellectually alert is required to complete a task or to distinguish between executive function or reasoning (Hunt, 2006).

A study was conducted on 382 children (subjects) and their families (N=1298) of Chinese Han-descent (Shang et al., 2015:90), to assess the relationship between the norepinephrine transporter gene associated with visual memory and ADHD. For every female diagnosed with ADHD a subsequent 6.21 males were diagnosed with ADHD. The majority of these subjects were diagnosed with combined type ADHD (67.3%), 5.7% with hyperactive/impulsive ADHD and 27% with inattentive ADHD. The single nucleotide polymorphism (SNP) rs36011 was found to show an association with ADHD, but after multiple tests, the statistical significance did not stay the
same. The rs30611 T allele, however, was nominally significant when solely considered. A mutation on the TG halotype (rs36011 (T)/rs1566652 (G)) demonstrated a positive association with ADHD (Shang et al., 2015:90). A study concluded that there are new associations of a halotype rs36011 T-allele and rs1566652 G allele of the norepinephrine transporter gene (SLA6A2) with the diagnosis of ADHD on Pattern Recognition Memory- and Spatial Recognition Memory tasks after numerous comparisons have been corrected (Shang et al., 2015:92).

According to (Hohmann et al., 2015:429), the carriers of homozygotes genetic coding of the norepinephrine transporter (NET) variants (SLC6A2), the minor rs3785157 T-alleles, are far more likely to be associated with a diagnosis of ADHD and these children with the homozygotic carriers of the T-allele, score much higher on the CBCL externalising behaviour problems and the Youth Self-Report attention trouble. The high scores on these particular checklists are mostly associated with the ages between eight and 15 years. There was also a noteworthy association between the homosygous carriers of the major 28386840 A alleles and an ADHD lifetime diagnosis (Hohmann et al., 2015:429).

2.7 Symptoms of ADHD

The symptoms of ADHD differ slightly in children of different developmental phases. The preschool child is observed as busy, always running into obstacles, not watching where he or she is going, shows a lack of attention and concentration, mostly observed during story time, does not want to share and also shows inability to wait for his or her turn, as well as a need for instant gratification (El Masry et al., 2012:194). The primary school child is mostly perceived as ‘different’ by his or her peers and teachers, often experiencing social rejection and academic failure. In the adolescent, the hyperactivity subdues, but inattention and inner agitation is still persistent (El Masry et al., 2012:196).

In order for a diagnosis of ADHD to be made, six or more symptoms need to be present for a period of at least six months before the age of 12 years. The symptoms have to be to such an extent that it has a negative impact on the patient’s daily activities. A minimum of five symptoms should be present in patients 17 years and older (APA, 2013:59). The manifestations of symptoms must take place in more than one location e.g. school and home. The following symptoms are an indication of the primarily inattentive type of ADHD:

- Patients do not pay close attention to details or makes unnecessary mistakes in their day-to-day activities e.g. school- or homework.

- Patients struggle to sustain their attention span (e.g. the patient finds it difficult to stay focussed during situations such as conversations or lectures).
- Patients struggle to complete their tasks at home, school or work.

- Patients struggle to prioritise their tasks, and have poor time management and organisational skills.

- Patients are sometimes reluctant to engage or accept a challenge requiring an extended period of focus.

- Patients tend to lose their possessions or any objects or materials.

- Patients are easily distracted and tend to forget simple daily tasks (e.g. due dates of assignments, or to feed a pet).

It has been noticed that symptoms tend to be more controlled and less prominent in a disciplined surrounding where the child is rewarded for good behaviour, is constantly stimulated and in forced one-on-one conversations (APA, 2013:61).

The following symptoms are indicators of the primarily hyperactive/impulsive type of ADHD:

- Patients constantly fidget.

- Patients struggle to remain seated when required to stay in their seats.

- Patients struggle to sit still and will climb on inappropriate objects and surfaces (e.g. tables, windowsills and cupboards). This feeling of restlessness can continue in older patients.

- Patients struggle to be silent when playing or doing work.

- Patients are always moving and busy as if they are being driven by an external power source. They also tend to talk excessively.

- Patients fail to wait until a question is completed – instead, they tend to shout out the answers in class.

- Patients find it difficult to wait their turn and will frequently interrupt during conversation.

The symptoms mentioned above are the main indicators of ADHD, but there are other associating features for a final diagnosis. These features may include a low frustration tolerance, high levels of irritability and mood fluctuations. Delays in any development such as speech, social and motor skills are not specific indicators for the diagnosis of ADHD but these are often present in conjunction with ADHD (APA, 2013:61).
2.8 Comorbidities associated with ADHD

Mosby’s Dictionary of Medicine, Nursing and Other Health Professions (2009:422) defines comorbidity as “Two or more co-existing medical conditions or disease processes that are additional to an initial diagnosis”. Comorbidity (or co-existing disorders) include a cluster of single conditions (any co-existing condition) in a patient, with an index disease as centre of interest in the single comorbid interactions, only an assumed interaction with the index disease (Radner et al., 2014:253).

As seen in the definition by Mosby’s, the terms ‘comorbidity’ and ‘co-existing’ are used interchangeably, whereas a review conducted by Meghani et al. (2013:2) found that the interchangeable use of these terms to be an error. Meghani et al. (2013:2) identified two separate meanings for these terms: Comorbid conditions are indicated when conditions occur along with an indicator condition at a much higher rate and can’t be seen as mere coincidence. Co-existing conditions, however, also known as multiple health conditions, indicate the simultaneous occurrence of health conditions where no single condition can be identified as the main indicator condition (Meghani et al., 2013:2). Patel et al. (2012:27) stated that comorbidity defines a patient who has been diagnosed with a particular disease, but also meet the diagnostic criteria for one or more disorder in addition to the original diagnosis.

It is not uncommon to find co-existing psychiatric conditions when ADHD is diagnosed in children. A study done in a Swedish population showed that 87% of the cases were diagnosed along one other co-existing disorder and 67% were diagnosed with two or more co-existing disorders (Soppitt, 2012:218). Patel et al. (2012:25) reviewed that approximately 67% of children with ADHD presented one or more additional mental or neurodevelopmental disorder of disease in comparison to the 11% without ADHD. A study by Patel et al. (2012:43) found that 33% of children with ADHD had one co-existing condition, 16% presented two co-existing conditions and 18% of children with ADHD had three or more co-existing conditions. A possible differential diagnosis of ADHD could be oppositional defiant disorder. This condition occurs in approximately 50% of children diagnosed with combined ADHD, in about 25% of inattentive type diagnosed children and in about 40% in the overall diagnosis of ADHD. Intermittent explosive disorder, specific learning disorders, intellectual disability, autism spectrum disorder, reactive attachment disorder, anxiety disorders, bipolar disorder, disruptive mood dysregulation disorder and substance-abuse which shows a correspondence of 25 to 33% with children diagnosed with ADHD. Personality disorder, psychotic disorder, medication-induced symptoms of ADHD and neurocognitive disorders and conduct disorder presents in approximately 25% of children diagnosed with combined ADHD. This diagnosis is mostly determined by the child’s age and daily location (APA, 2013:65; El Masry et al., 2012:197; Soppitt, 2012:218). It is often difficult to distinguish onset
mania in adolescents from conduct disorder, depression and ADHD, as there are many overlapping features (El Masry et al., 2012:196).

2.8.1 Oppositional defiant disorder (ODD) and conduct disorder (CD)

Oppositional defiant disorder (ODD) and conduct disorder (CD) are often viewed as synonyms, but they differ by the predominance of behavioural issues in the phenotype (Tolan & Leventhal, 2013:2). Conduct disorder and ODD are both known as disruptive behaviour disorders and externalising disorders. (Cornforth et al., 2012:171; Gatzke-Kopp, 2013:448). An externalising disorder is defined as problematic developmental behaviour carried out by a person — this behaviour usually has a direct impact on the people in their immediate surroundings (Gatzke-kopp et al., 2013:448). Externalising disorders are frequently identified in children with ADHD, with rates up to 90% (Patel, et al., 2012:28). Various studies have found the prevalence of ODD and/or CD in children with ADHD to vary between 13.5% and 26.8% (CD alone) (Cuffe et al., 2015:5; Jensen et al., 2015:29), 19.00% and 59.3% (ODD alone) (Mitchison & Njardvik, 2015:3; Cuffe et al., 2015:5), 45.5% and 60.5% (ODD and CD) (Cuffe et al., 2015:5). Takeda et al. (2012:421) found the presence of co-morbid externalising disorders in 18.0% of children with ADHD. Children suffering from ODD have trouble being compliant to the demands of others and have difficulties with schoolwork. Children with ODD are observed as uncooperative, hostile, negative, insolent, irritable and argumentative to such an extent that it affects the child's social and academic performance. These symptoms can also disrupt parents, teachers and peers and can be present for as long as six months. This disorder differs from ADHD as it does not apply to children who do not like school, find it hard to concentrate for an extended period of time, forget instructions and who are impulsive. It is however difficult to distinguish as many children with ADHD may develop some of the symptoms associated with CD and ODD. It has been found that approximately 50% of children with ODD and CD also meet the criteria for ADHD. These symptoms should, however, not be confused with children who are tired, hungry or upset as these symptoms may also occur, but not as frequent as children with ODD (APA, 2013:63; Glicken, 2009:358; Cornforth et al., 2013:171; Tolan & Leventhal, 2013:3). The severity of ODD as a behavioural disorder is to a lesser extent and it is diagnosed much earlier in life (as early as preschool years) whereas and is often identified as a precursor to CD, which is diagnosed a little later, more toward school-going ages (Tolan & Leventhal, 2013:3; Gatzke-kopp, 2013:448).

The symptoms of ODD include temper tantrums, defying and disobeying rules and regulations set out by parents and teachers, therefore frequently causing arguments (Glicken, 2009:358).

The symptoms of CD include dishonesty and these children are known to commit theft easier than children without CD. Patients with CD also show high levels of aggression towards other people and animals, they tend to destruct the belongings and property of others and struggle to
show regards for rules and authority. It is all over delinquent behaviour (Tolan & Leventhal, 2013:3).

CD is twice as common in boys as in girls (Tolan & Leventhal, 2013:3). Children with ODD often developed CD (or symptoms that are similar to those of CD) later in life (Cornforth et al., 2012:171).

2.8.2 Autism Spectrum Disorder (ASD)

ASD is classified as a pervasive developmental disorder. ADHD and ASD both present symptoms of inattention and an under development in social behaviour. These children also find it challenging to cope with normal day-to-day activities. A child with ASD often finds it difficult to comprehend the world in their direct surroundings. There is a vast difference between the social rejection by peers of children with ASD and the identification of the facial and tonal communication cues leading to segregation and disconnection of children with ASD from the rest of the world. A child with ADHD will have a tantrum due to lack of impulse control whereas a child with ASD will have a fit of temper because of an intolerance to changes in his or her daily routine (APA, 2013:64; Glicken, 2009:229; Harris & Brown, 2012:214).

The speech and language skills of children with ASD may start to develop normally, followed by a sudden loss or a ‘slowing down’ in the development of the skills they acquired during development. It is therefore advised that early intervention and treatment take place to prevent a complete lack of speech. A patient’s voice can present a strange pitch and a sentence may be uttered with a certain rhythm. Children with ASD prefer communicating via physical gestures as it may be difficult to present verbal communication. Children with ASD also suffer from echolalia (also known as echologia or echophrasia), a condition where the child may repeat a phrase. Non-verbal communication e.g. waving good bye or a specific facial expression that indicates a reaction or an emotion is not always understood and these children struggle to express these gestures themselves (Soppitt, 2012:229).

Other symptoms of ASD include shortcomings in social-emotional reciprocity, attempts at nonverbal communication during social interactions, inappropriate use of interpersonal social cues (i.e. facial expressions, smiling and gazing), challenges to develop, maintain and comprehend various kinds of relationships, repetitive patterns of behaviour (children with ASD tend to follow a set-out strict routine), restricted activities and limited interests (APA, 2013:50; Harris & Brown, 2012:214). These symptoms must be recognisable early in life (before 30 months of age) but may only become present when the limited capacity of the child exceeds the social requirements. The three main areas of interest are: repetitive behaviour, shortcoming in social relations and slow language development. Should shortcomings be noticed in all three of these
areas, the disorder is classified as classic autism. When normal development of speech and communication is present, it is classified as Asperger’s syndrome (APA, 2013:50; Scahill et al., 2014:7; Tager-Flusberg, 2014:652).

A study found a higher incidence of ADHD and autism spectrum disorder (ASD) in children that were diagnosed with an atopic allergy before the age of three years (Chen et al., 2014:317). A similar study also found a higher incidence of ADHD and ASD in children diagnosed with an atopic allergy before the age of two years compared to their healthy counterparts (Liao, 2016:171). Other studies conducted on children with atopic conditions associated with ADHD, allergic rhinitis and asthma in particular, found that these children have had a higher incidence of developing ADHD and vice versa (Bener et al., 2014:24; Brawley et al., 2004:664; Chen et al., 2014:317).

2.8.3 Intermittent Explosive Disorder (IED)

The diagnostic criteria for IED include a total failure to control aggression, which leads to a verbal or physical outburst. When these outbursts lead to damage to property or physical injury more than three times in a 12-month cycle, the child can be acknowledged for further testing to diagnose IED. The reaction or outburst is normally hyperbolised as the child tends to overreact to a normal provocation. IED is normally diagnosed around the age of six (APA, 2013:466).

2.8.4 Bipolar Mood Disorder

A person with bipolar mood disorder (BMD) has manic and depressive phases. The times between these phases vary from patient to patient, based on their current personal circumstances (Fearley, 2012:258). The disorder consists of periodic shifts in frame of mind ranging from the manic to major depression to hypomania to a combination of emotional states (Eisendrath et al., 2013:1063). Patients with BMD may also show increased motor activity, a lack of concentration and frequent impulsive reactions which can be associated with an elevated mood. A child with BMD can experience a certain phase (e.g. manic) for up to four days, whereas a child with ADHD will have several changes in mood throughout the day (APA, 2013:64).

According to Hassan et al. (2011:196), 0.5% of children with ADHD presented with symptoms of bipolar disorder or hypomania.

2.8.5 Tic disorders (TDs)

According to the APA (2013:81) a tic is defined as “a sudden, rapid, recurrent, non-rhythmic motor movement or vocalization.” TDs (e.g. Tourette syndrome) are chronic neuropsychiatric disorders and not mental health conditions, identified by tics. Tics are rather common among children. One in every five children may experience a random tic that lasts a few weeks.
TDs can be identified as vocal tics or chronic motor tics. Tourette’s syndrome is identified by multiple motor as well as vocal tics present for a period of time, but not necessarily concurrently for a minimum period of 12 months since the first tic was observed. The initial clinical findings in approximately 80% of cases are the manifestations of motor tics and the remaining 20% present with vocal tics, but eventually all patients present with a combination of both. The start of the symptoms should be before the age of 18 years (generally between the ages of two and 15 years) and the cause may not be due to a substance (e.g. stimulants) or other disease (e.g. Huntington’s disease) (Aminoff & Kerchner, 2013:1004; APA, 2013:81; Ravenscroft, 2012:240; Thompson & Thompson, 2012:209).

TDs are usually associated with other conditions such as ADHD, high functioning ASD and OCD. The most common disorders associated with TDs, however, are sensory modulation difficulties, learning difficulties, central auditory processing disorder, mood disorders (e.g. depression), OCD, CD, self-harming behaviour and ASD (Ravenscroft, 2012:241).

2.8.6 Obsessive Compulsive Disorder (OCD)

A patient with OCD has the urge to repeat certain movements or actions based on an obsession or a set of ‘rules’ set out by the patient him-/herself (APA, 2013:80). When an obsessive-compulsive reaction takes place, the impulse or irrational idea of the patient intrudes his or her direct awareness. The only way to bring relief to anxiety is by reacting on an impulse (Eisendrath and Lichtmacher, 2013:1041). The obsessions are thoughts and impulses and the compulsions are attempts to displace the obsessive thoughts (Glicken, 2009:143).

Patients will present impulses and obsessions or a combination of both. These obsessions and compulsions are time consuming and it places a significant amount of stress on normal day-to-day functioning (i.e. social and work environment). When a patient with OCD can’t act upon impulses and obsessions, it causes anxiety. The obsessions and compulsions are not as a result of a substance of any kind nor due to another medical condition (APA, 2013:237; Glicken, 2009:143). Patients with OCD are often seen as unadventurous, methodical, neat, tidy, conscientious, and highly intelligent.

2.8.7 Depression and anxiety

Depression and anxiety are known as internalising disorders (Magdalena, 2012:239). According to Patel et al. (2012:28) an internalising disorder can be described as a disorder on an emotional level of development (i.e. depression and anxiety), whereas an externalising disorder refers to a physical manifestation of the disorder.
2.8.7.1 Depression

Depression is defined as ‘a mood disturbance characterized by feelings of sadness, despair and discouragement, resulting from and normally proportionate to some personal loss or tragedy’ (Mosby’s Dictionary of Medicine, Nursing and Health Professions, 2009:531). According to the APA (2013:160) five or more symptoms need to be present during two consecutive weeks of which the two main symptoms (patients presents with one or the other or both) is a depressed mood and loss of interest or pleasure of any kind. These symptoms include:

- The depressed mood has to be present for the majority of the day, every day to such an extent it is noticed by others.
- Diminished curiosity or interest in pleasure of hobbies and/or usual daily activities. Others usually note this.
- Considerable weight loss or weight gain or a daily increase or decrease of appetite.
- Daily insomnia or hyposomnia.
- Psychomotor agitation and retardation (patient feels slowed down and restless).
- Fatigue.
- Delusions of guilt and feelings of worthlessness.
- Inability to make decisions and a lack of concentration.
- Constant thoughts about death, suicide, plans to commit suicide and an actual suicide attempt.

The following symptoms are symptoms of major depression in children (Glicken, 2009:128):

- Vague complaints about physical ailments such as stomach-aches or headaches.
- Frequent absenteeism from school and poor academic performance.
- Thoughts and/or attempts to run away from home.
- Inexplicable emotional outbursts accompanied by shouting, crying and complaining.
- Boredom.
- Absent interest in seeing or meeting friends.
- Substance abuse.
- Isolation from a social environment and lack of effective communication.
- Fear of death.
- Amplified sensitivity to negative criticism or failure.
- Increased hostility, irritability and anger.
- Recklessness.
- Difficulty to build and maintain relationships.

Up to 7% of adolescents with major depression commit suicide (Glicken, 2009:128). This has been found particularly among boys, especially when substance abuse accompanies depression (Glicken, 2009:127). Mitchison and Njardvik (2015:3) found that 21.43% of children with ADHD presents with comorbid depression.

The various type of anxiety, OCD, panic disorder and agoraphobia, phobias, post-traumatic stress disorder (PTSD), developmental coordination disorder and learning disorder will be discussed in the paragraphs that follow.

2.8.7.2 Anxiety

Mosby's Dictionary of Medicine, Nursing and Health Professions (2009:123) defines anxiety as: “anticipation of impending danger and dread accompanied by restlessness, tension, tachycardia, and breathing difficulty not necessarily associated with an apparent stimulus.” Different types of anxiety can be distinguished i.e. separation anxiety, generalized anxiety and social anxiety. Each of these anxieties will be discussed separately.

2.8.7.2.1 Separation anxiety

Separation anxiety is found quite frequently among infants and toddlers. Anxious behaviour can be observed among children when leaving the parents, as well as difficulty falling asleep due to a fear of abandonment and nightmares (Glicken, 2009:142; Magdalena, 2012:239). This is generally found in children whose parents were in accidents or the parent(s) is too ill to take care of them. These children also have a hard time going to school or to go to a friend’s house for a play-date (Glicken, 2009:142). According to the APA (2013:190), the symptoms of separation anxiety include an inapt anxiety and fear experienced by the child, mostly centred on his or her closest family member(s). This fear needs to last for at least four consecutive weeks in order to make a positive diagnosis (APA, 2013:191).
2.8.7.2.2 Generalised Anxiety Disorder (GAD)

GAD is one of the most common anxiety disorders identified in children. These children always worry and obsess about every minor detail of their lives especially schoolwork and timeliness. These children present with physical symptoms of their anxiety including tremors, sweating (palms), and exhaustion. Children with GAD usually have a very low self-esteem, are constantly seeking reassurance and also show signs of being perfectionists (Glicken, 2009:143; Papadakis & McPhee, 2013:1041). The symptoms of GAD include (APA, 2013:222):

- Chronic apprehension and worry for the majority of the day (consecutive days) for a minimum of six months for no particular reason or for insignificant events.

- The patient finds it hard to control any form of worry.

- An interruption of day-to-day life to a significant extent.

- Symptoms are not present due to substance abuse or any medical condition that may lead to anxiety.

The only difference between a person with ADHD and a person with an anxiety disorder is that the person with ADHD becomes inattentive due to an attraction to a different stimulus and preoccupation with something that they enjoy doing, whereas the person with an anxiety disorder becomes inattentive due to persisting feelings of worry and stress (APA, 2013:64).

2.8.7.2.3 Social anxiety

The diagnostic criteria for social anxiety disorders include a fear of one or several social interactions where the person may be exposed to personal ridicule; they fear that the symptoms of their anxiety may come to light at a social interactive event, which may leave them embarrassed. Social events always initiate the anxiety and is therefore, always avoided. The social ‘threat’ posed to the patient is proportionally smaller than the fear or anxiety experienced by the patient. These symptoms need to be present for six months or more to be eligible for diagnosis. Social anxiety cannot be diagnosed if similar symptoms associated with this particular type of anxiety are induced by substance abuse. The main symptom of social anxiety disorder is a persistent fear of being embarrassed and judged in a social situation, which may lead to public ridicule. These children also present with physical symptoms such as heart palpitations, tremors, profuse perspiration, diarrhoea, panic attacks, blushing, and muscle tension (Glicken, 2009:143).

Takeda et al. (2012:421) found internalising disorders to be present in 22.9% and internalising-and externalising disorders present in 18.0% of children with ADHD. Similar studies found internalising disorders to be present in 8-50% of children with or without ADHD (Armstrong et al.,
2.8.7.2.4 Panic disorder and agoraphobia

A panic disorder is diagnosed by using the following criteria (APA, 2013:208):

- Recurring panic attacks that occur without warning.
- A minimum of one panic attack per month, either due to an ongoing concern or worry about having these attacks or a particular change in behaviour due to these attacks.
- The symptoms are not caused by substance abuse or another medical disorder.

Agoraphobia is defined as a constant fear of being in a trapped situation with no escape and no help. This can often be observed in children who already suffer from illnesses like asthma, OCD and separation anxiety (Glicken, 2009:144; Papadakis & McPhee, 2013:1040). A diagnosis of agoraphobia will include three or more of the following symptoms (APA, 2013:217):

- Fear of public transportation.
- Moving in open spaces.
- Being trapped in enclosed spaces.
- Standing in a queue or being part of a large throng of people.
- Being outside of the house alone.
- Avoidance of any of the above-mentioned situations due to the fear of not being able to escape, or the possibility of a panic attack.
- Fear and anxiety, often bigger than the actual threat at hand.
- An occurrence of the symptoms for a minimum of six months.
- An interruption of normal daily activities.
- The fear is much stronger in the presence of another medical condition (e.g. Parkinson’s disease).

Phobias are unrealistic, excessive and hyperbolised fears of particular situations or objects. Experiencing these phobias may interfere with children’s social, academic and personal lives to
a large extent (Glicken, 2009:145). It is considered as a form of ‘displacement’ where the true feelings are substituted with something that can be avoided (Eisendrath and Lichtmacher, 2013:1041).

2.8.8 Post-traumatic Stress Disorder (PTSD)

Post-traumatic Stress Disorder (PTSD) is found in people who have previously experienced a traumatic or life-threatening occurrence that causes disturbing thoughts, related to the original trauma. It is extremely difficult to get rid of these thoughts once it has settled into the conscious awareness of the child. The child will experience the physical and emotional stress brought on by the occurrence of these thoughts and they end up highly agitated and wound up (Glicken, 2009:145).

2.8.9 Developmental Coordination Disorder (DCD)

A child with Developmental Coordination Disorder (DCD) has a hard time to develop and master finely coordinated motor skills — usually to such an extent that motor skills are far below what is expected at a certain age. Children with DCD come across as gauche as they are permanently bumping into objects and are inaccurate when performing any activity that requires motor skills. These deficits significantly interfere with the daily activities appropriate for the age of the child, it impacts the academic productivity and performance of the child, prevocational and vocational performance and how the children suffering from DCD play. These symptoms start showing in the earliest developmental stages and it is not attributable to a visual impairment, an intellectual disability and/or a neurological disorder (APA, 2013:74).

2.8.10 Learning Disorder (LD)

The definition of a learning disorder (LD), according to Breuggemann Taylor (2014:2), consists of three parts, including a heterogeneous group of individuals who are unable to perform certain academic tasks regardless of an average intelligence, those who has not been exposed to particular and appropriate academic opportunities, and those who are considered talented in certain areas, but with average performance in other areas. The diagnostic criteria for LD include:

- Patients find it challenging to learn and to utilise any form of academic skill(s) which is identifiable by at least one of these symptoms being present for a minimum of six months:
  - Patients struggle to read and read at a much lower speed than someone without LD.
  - Difficulty in comprehension.
  - Patients find spelling difficult.
• Patients find writing extremely challenging, and writing is accompanied with multiple spelling and grammatical errors, and poor understanding and organisation of paragraphs and cohesion.

• Mathematics is difficult to comprehend and apply.

• Patients’ academic skills are below the skills of their age group. This affects their academic and professional presentation and wellbeing.

• The patient can be diagnosed during school years, but symptoms can only present when the patient is forced to make use of the skills he or she lacks.

2.9 Co-existing conditions associated with ADHD

2.9.1 Asthma and other atopic diseases

Asthma is the chronic inflammation of the lungs and airways. Symptoms include shortness of breath, wheezing, tightness in the chest and coughing (Schwinghammer, 2006:906). Atopic allergies occur when a person, with a genetic predisposition to hypersensitivity for particular allergens, is exposed to a stimulus, triggering a reaction such as asthma, eczema, allergic rhinitis and food allergies (Mosby’s Dictionary of Medicine, Nursing and Health Professions, 2009:162).

Fasmer et al. (2011:567) found that there was an increase in the prescription for anti-asthma medication in children and adolescents with ADHD and vice versa. Chen, M et al. (2013:1210) found that children with asthma have a 7% higher chance of developing ADHD compared to their healthier counterparts. They are also more prone to develop allergic rhinitis (67.9%) and atopic dermatitis (19.6%). There was, however, a higher probability of ADHD among children with allergic rhinitis compared to those with atopic dermatitis (Chen, M et al., 2013:1210). Bener et al. (2014:23) also found a strong association between allergic conditions and children with comorbid asthma and ADHD. Bener et al. (2014:22) also established that children with comorbid ADHD and asthma suffer from a severe vitamin D deficiency and the majority of these patients were also overweight or obese. The vitamin D deficiency served as a predictor in asthmatic children with ADHD (Bener et al., 2014:25).

Brawley et al. (2004:664) have found that 43% of children with ADHD have tested positive for allergic rhinitis after a skin-prick test. Children who have been diagnosed with atopic dermatitis before the age of two years are also more likely to develop ADHD (3.7%) and ASD (0.5%) (Liao et al., 2016:250).
2.9.2 Epilepsy

Studies have shown that there are definite associations between epilepsy and ADHD in children. Widmaier et al. (2006:233) defines epilepsy as a neurological disorder that is associated with unsynchronised cerebral neuron discharges.

Kauffman et al. (2009:728) conducted a review and came to the conclusion that there are a few studies that have found possible explanations for the co-existence of epilepsy and ADHD. These include the fact that both ADHD and epilepsy are quite common in children, that both these conditions may have similar underlying causes and that epilepsy can cause and/or aggravate ADHD.

A study conducted by Kwong et al. (2016:57) found that children with epilepsy are more prone to be associated with ADHD than children with asthma. Inattentive type ADHD was the most prevalent in children with epilepsy. A review conducted by Reilly (2011:885) also found that children with epilepsy are more often associated with inattentive ADHD than hyperactive and/or impulsive ADHD. No concise explanation was found for this phenomenon (Reilly, 2011:890).

2.10 Management of ADHD in children

ADHD cannot be cured, but there are various ways of controlling symptoms. This section will provide a brief overview of alternative methods for the treatment and management of ADHD (i.e. diet and neurofeedback), followed by a discussion of the main pharmacologic treatments available in South Africa.

2.10.1 Diet

According to Millichap and Yee (2012), low levels of omega-3 and -6 long chain fatty acids (LC-PUFA) have been found in the red blood cells of children with ADHD. Average doses of 300-600 mg/day of omega-3 and 30-60 mg/day of omega-6 on a continuous basis have been tested optimal in reports of effectiveness and safety, but the long-term beneficial effects must still be investigated further.

The additive and salicylate-free diet, also known as the Feingold diet, states that grapes, apples, cold meats, hot dogs, sausage and cold drinks containing any form of artificial colorant and flavouring should be avoided. Any red and orange dyes should also be completely eliminated from the diet, as well as the preservatives butylated hydroxyanisole and butylated hydroxytoluene (Millichap & Yee, 2012).

The oligo-antigenic (hypoallergenic) diet eliminates the majority of sensitising food antigens or allergens including foods such as cow’s milk, wheat, chocolate, cheese, citrus fruits and nuts.
Food allergies were investigated as a trigger for ADHD symptoms through a trial of enzyme-potentiated desensitization (EPD) in children with ADHD. The EPD permitted these children to reintroduce the food that previously presented sensitivity (Millichap & Yee, 2012).

Foods containing sugar and aspartame have been reported to increase the symptoms of ADHD, especially hyperactivity. Inattention has been noted after sugar intake but not after aspartame. Another possibility regarding sugar and cognitive impairment in ADHD is a hypoglycaemic response after a large sugar intake. In comparison to sugar, aspartame had no effect on cognition or on the behaviour of children with ADHD. A deficiency in glucose will have an effect on the cognitive function and an EEG will show slow wave rhythms of the brain (Millichap & Yee, 2012).

A high-fat-low-carbohydrate diet, known as the ketogenic diet, was initially used in the treatment of epilepsy. Due to the fact that many children with epilepsy present with symptoms of ADHD and vice versa, the ketogenic diet has been introduced as part of treatment, but the mechanism is still unclear (Millichap & Yee, 2012). Studies have also shown that children with ADHD often have extremely low ferritin levels and require iron supplementation to decrease the ADHD scale ratings. Low levels of zinc have been found in children with ADHD. Studies have been done with zinc as monotherapy and zinc replacing methylphenidate — these methods have resulted in benefits (Millichap & Yee, 2012).

Alpha linolenic acid (ALA), also known as flaxseed oil, has also investigated in the holistic treatment of ADHD, as shown in a study by Joshi et al. (2006:18). The study treatment group received 200 mg of flaxseed oil (in the form of ALA) combined with 25 mg of vitamin C twice a day for a period of 12 weeks. The same children were monitored pre- and post-treatment to determine a possible change in the psychopathology along with the changes in the red blood cell (RBC) membrane plasma peroxides and essential fatty acids (EFA). Before the onset on treatment, the children with ADHD had significantly lower RBC membrane liposome levels compared to non-ADHD patients. There was also a remarkable increase in EPA and docosahexaenoic acid (DHA) levels and a noticeable decrease in arachidonic acid. Individuals scored much better for inattention, restlessness, self-control and impulsivity post-treatment (Joshi et al., 2006:19). This study proved that flaxseed oil can benefit children with ADHD and have a beneficial impact on treatment (Joshi et al., 2006:20).

2.10.2 Neurofeedback

According to Skokauskas et al. (2011), neurofeedback has the most promising evidence of reducing symptoms of ADHD.

A randomised control study was conducted by Meisel et al. (2013:13) to explore the effects of neurofeedback versus standard pharmacologic treatment, assessed reading, writing, reading
comprehension, mathematics and oral expression. According to feedback given by the mothers of the participants, neurofeedback showed significant improvement in the overall symptoms of ADHD, but even more for the symptoms associated with inattention. Oppositional defiant behaviour, however, did not improve significantly in the neurofeedback group. Teachers reported that neurofeedback had a significant effect on reading, reading comprehension and writing (Meisel et al., 2013:15). The group that received pharmacological treatment also reported significant improvements in the symptoms associated with ADHD especially those symptoms associated with hyperactivity and impulsivity and oppositional defiant behaviour (Meisel et al., 2013:13). The baseline readings for both groups showed that patients in the pharmacological group experienced an improvement in attention levels and substantially higher scores in mathematics and reading (Meisel et al., 2013:16). Post-assessment showed that the pharmacological group had longer attention spans and higher mathematical scores. By the six-month follow-up assessment, however, there was no difference between the two groups, except that the pharmacological group showed higher mathematical scores. This study did prove that children receiving neurofeedback treatment can maintain their progress and even improve on that progress up to two months after the treatment has ended and one in three children will maintain their progress up to six months after the treatment has ended, which lends itself to the belief that the brain can be trained (Meisel et al., 2013:20). This study has found that neurofeedback can be used as long-term alternative treatment for ADHD, but also as complementary treatment in conjunction with pharmacologic treatment.

2.10.3 Pharmacologic treatments available in South Africa

In this section, three of the main pharmacological treatments available in South Africa will be discussed, as well as previously conducted studies to prove the effectiveness and safety of these three treatments.

2.10.3.1 Clonidine

2.10.3.1.1 Mechanism of action of clonidine

Clonidine is a selective alpha2-agonist that is situated in the presynaps and is mainly indicated for the treatment of migraine (prophylaxis) and hypertension (Rossiter, 2014:450). Sallee (2008) reviewed the role of alpha2-agonists in the treatment of the symptoms of ADHD and found that clonidine, among other alpha2-agonists increases noradrenergic entrance from the locus ceruleus and stimulates the post-synaptic alpha2A receptors. This stimulation of the receptors leads to the modulation of nonadrenergic levels in the prefrontal cortex, which then leads to the reduction of symptoms regarding behaviour and attention (Sallee, 2008).
Previous studies have been conducted on the efficiency of clonidine in the treatment of ADHD. A randomised, double-blind placebo controlled clinical trial, conducted by Palumbo et al. (2008:181), was implemented to study the effects of clonidine, methylphenidate, clonidine and methylphenidate, as well as a placebo on the symptoms of primary ADHD. This study has found that participants receiving clonidine, with or without methylphenidate, performed better than those not receiving treatment with clonidine. Unfortunately, this finding proved to hold no statistical significance (Palumbo et al., 2008:185). Palumbo et al. (2008:186) also found that clonidine was not as effective for the treatment of ADHD when compared to methylphenidate, but there was a definite added benefit when clonidine was used in conjunction with methylphenidate. However, a more recent study conducted by Kollins et al. (2011:1407, 1411) between March 2008 and February 2009, found that the combination of extended-release clonidine and methylphenidate showed great improvement in symptoms by the fifth week of the study. Jain et al. (2011:176) also reported similar results.

2.10.3.1.2 Possible side-effects, contra-indications and drug interactions of clonidine

Possible side-effects of clonidine include anorexia nervosa, dizziness and headaches, Raynaud’s disease, gastro-intestinal disturbances, painful salivary glands and dryness of the mouth, skin reactions, urinary incontinence, fluid retention, fatigue and increased blood glucose levels (Snyman, 2016:59).

Several drug interactions with clonidine include methylphenidate, hypertension medication (α- and β-blockers), neuroleptic drugs and central nervous system depressants All of these, except for methylphenidate, may potentiate the effects of clonidine or make use of the same receptors needed by clonidine to take effect. Methylphenidate may even lead to death when administered along with clonidine (Snyman, 2016:59).

According to Snyman (2016:59) the use clonidine has not yet been proven safe in children and adolescents in South Africa.

2.10.3.2 Methylphenidate

2.10.3.2.1 Mechanism of action of methylphenidate

Methylphenidate is defined as a central nervous system stimulant that is prescribed for the treatment of ADHD in children (Mosby’s Dictionary of Medicine, Nursing and Health Professions, 2009:1184). The pharmacologic mechanism of action is similar to that of cocaine due to the fact that this causes an increase in synaptic dopamine levels (Morton & Stockton, 2000:160). Methylphenidate stimulates the brain’s cortex as well as its stimulation systems (Marcia, 2002). Cocaine and methylphenidate bind to the same part of the cortex (Morton & Stockton, 2000:160).
When looking at the structure of this drug, methylphenidate will act as a dopamine and a noradrenaline re-uptake inhibitor, which will lead to longer-lasting receptor effects of dopamine (Marcia, 2002). The suggested mechanism of action is the release and increase in dopamine levels in the central nervous system. The effect upon the release of dopamine takes place after the transport of dopamine. This leads to a higher level of postsynaptic dopamine, which activates the motor inhibitory system, consequently leading to the inhibition of impulsiveness, one of the many prominent symptoms of ADHD. This therefore assists the patients in focusing and to broaden the attention span (Morton & Stockton, 2000:160).

A study conducted by Chou et al. (2015:2307) found a decrease in impulsivity in patients with methylphenidate; this was possibly due to an increased activity in the left inferior frontal gyrus.

2.10.3.2.2 Administration, dosages and efficacy of methylphenidate

According to Yang et al. (2012:280, 282), methylphenidate-responsive adolescents perceive their quality-of-life to be lower than those of adolescents without chronic illness, even though symptoms may have improved with treatment. Cheon et al. (2009:565) conducted a study to examine the relationship between the α-2a-adrenergic receptor (ADRA2A-1291) C and G polymorphisms and the effect of treatment with methylphenidate on symptoms of ADHD in adolescents. G/G genotype was associated with a superior reaction to treatment with methylphenidate which was also associated with an improvement in behavioural scores (Cheon et al., 2009:566).

Salatino-Oliveira et al. (2011:217) investigated the association between the COMT Val158Met gene and the improvement in oppositional behaviour in ADHD symptoms when receiving treatment with methylphenidate. The study suggests that, having at least one Met-allele could make a significant difference in oppositional behaviour when receiving methylphenidate compared to those who are homozygotic for Val-alleles (Salatino-Oliveira et al., 2011:219). Salatino-Oliveira and colleagues furthermore showed an association between the presence of the COMT Val158Met polymorphism and the reduction of oppositional behaviour while receiving methylphenidate (Salatino-Oliveira et al., 2011:220). In another study, conducted by Chou et al. (2015:2304), it was found that post-treatment with methylphenidate also showed an increase in activation in the left inferior frontal gyrus compared to the pre-treatment images.

The dose for children under the age of six years have not been established, but children over six years may receive an initial dose of 5 mg twice a day (breakfast and 11:00 AM) increased weekly, if needed, up to 20–30 mg per day with a maximum of 60 mg/day. A dosage of more than 2 mg/kg/day may be administered under the careful supervision of a specialist (Rossiter, 2014:508).
Slow releasing methylphenidate products may be prescribed to children over the age of six years. The initial dose is 18 mg in the morning and increased with 18 mg at a time with a maximum dose of 54 mg daily for children from six to 12 years and from 13 to 18 years the maximum dose is 72 mg/day (Rossiter, 2014:508). This is the preferred formulation of methylphenidate as it eliminates the mid-morning dose. In some cases, however, an additional dose may be required (Flisher & Hawkridge, 2013:139).

2.10.3.2.3 Possible side effects and drug interactions of methylphenidate

Possible side effects of methylphenidate include insomnia, anorexia, gastric discomfort, and headaches, worsening of depression and anxiety symptoms. An increase in tic disorders may also be experienced during this treatment.

According to Mick et al. (2011:467), methylphenidate may cause a minimal elevation in systolic and diastolic blood pressures, but not enough to be statistically significant. Hammerness et al. (2009:88) also showed that there were no statistically significant changes in electrocardiogram (ECG) readings in response to treatment with methylphenidate. However, any cardiovascular pathology or family history thereof should always be taken into account when prescribing methylphenidate. Any form of methylphenidate should be avoided in patients with substance abuse problem (Flisher & Hawkridge, 2013:139). Monoamine oxidase inhibitors (MAOI) should not be taken with these drugs or within 14 days after treatment has stopped. Patients with bipolar disorder should also not consider this treatment as extreme manic episodes may be triggered (Novartis® Pharmaceuticals Corporation, 2013:1).

2.10.3.3 Atomoxetine

2.10.3.3.1 Mechanism of action of atomoxetine

Atomoxetine is classified as a non-stimulant psychotherapeutic agent used in the treatment of ADHD (Mosby’s Dictionary of Medicine, Nursing and Health Professions, 2009:160).

The mechanism by which atomoxetine improves inhibition is still unknown (Chamberlain et al., 2009:550), however, it has been shown that atomoxetine acts selectively, inhibiting the presynaptic noradrenalin transporter which leads to the inhibition of noradrenalin reuptake leading to the increased concentration of noradrenalin (Baldessarini, 2006:431; Christman et al., 2004:1022) along with dopamine in the prefrontal cortex (Barton, 2005:i26). Barton (2005:i26) also states that because the levels of dopamine and noradrenalin are being elevated in the prefrontal cortex only, it seems highly unlikely that atomoxetine does not have any abusive properties nor will it cause motor tics.
Chou et al. (2015:2305) found an improvement in attention in patients receiving atomoxetine. This may possibly be due to decreased activity in the inferior prefrontal cortex and an increased activity in the dorsal anterior cingulated cortex and the dorsolateral prefrontal cortex (Chou et al., 2015:2307). Atomoxetine also decreases cingulo-frontal activation, which may lead to the increase in focus and attention (Chou et al., 2015:2308). Biederman et al. (2006:1108) furthermore showed that atomoxetine improved hyperactivity and impulsivity.

2.10.3.3.2 Administration, dosage and efficacy of atomoxetine

Compared to placebo, atomoxetine will improve ADHD and ODD symptoms simultaneously in children and adolescents whom have previously failed to improve with parental intervention as found by Dell’Agnello et al. (2009:829).

The initial dose for adult/children weighing 70 kg or more is 40 mg per day for exactly one week (7 days) where after it should be titrated up to maximum 80 mg/day (Rossiter, 2014:507). For patients less than 70 kg the dosage is 0.5 mg/kg/day for 7 days where after the dosage is titrated up to a maximum dosage of 1.2 mg/kg/day (Rossiter, 2014:508).

2.10.3.3.3 Drug interactions and side-effects associated with atomoxetine

Atomoxetine interacts with a number of medicines of which the most important is interactions with paroxetine, quinidine or fluoxetine as these drugs will inhibit the liver enzyme Cytochrome P450 2D6 (CYP 2D6) that metabolises atomoxetine. Atomoxetine should not be taken within 14 days after treatment with MOAI) has been stopped (Baldessarini, 2006:445; Eli Lilly and Company®, 2014:3, Ogbru, 2014). Atomoxetine should furthermore be avoided in children and/or teenagers with suicidal thinking patterns.

Atomoxetine is generally well tolerated (Wilens et al., 2006:116). However, a statistically significant increase in cardiac activity has been reported, including an increase in pulse rate, systolic- and diastolic blood pressure. Atomoxetine may also lead to hepatic damage (Eli Lilly and Company®, 2014:4).

2.11 Prescribing patterns of psychotropic medication (methylphenidate and atomoxetine)

Table 2.1 provides a summary of studies conducted on methylphenidate and/or atomoxetine prescribing patterns and the prevalence of ADHD in adults and children.

Based on Table 2.1, it can be deducted that all but one study found an increase in the prescriptions of methylphenidate and/or atomoxetine over the study period. Methylphenidate is still the most desired treatment with regard to first line treatment for ADHD. Boys still receive the
majority of prescriptions for ADHD medication, but a few studies indicated that the male:female ratios are declining. The average age group that received treatment for ADHD was between the ages of six and 12 years. Co-prescribed medication, for the treatment of other psychiatric disorders, included anti-anxiety/tranquilizers, bipolar disorder, antidepressants, psychotropic medication and anticonvulsants. Co-prescribed medication for the treatment of co-existing illnesses included analgesics, antipyretics, antihistamines, penicillin, cephalosporins and decongestants. Co-existing conditions included were as follow: oppositional defiant disorder/conduct disorder, depression, and autism spectrum disorder.
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<th>Study design</th>
<th>Country / Population / Age / Location / Inception year</th>
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Total observations = 3 366 862.  
Inception period: 2000-2003 | The children diagnosed with bipolar disorder received 0.24% of the prescriptions, depression or anxiety received 0.59% of the prescriptions and ADHD received 0.61% of the prescriptions for psychotropic medication. Methylphenidate was the most prominent drugs prescribed (0.55%), antidepressants were prescribed in 0.26% of cases and tranquilizers and anti-psychotic drugs were prescribed in 0.24% of cases. A total 1.19% of children under the age of four years on the Medicaid program received a prescription for the treatment of depression, ADHD, anxiety of other psychological illnesses such as bipolar mood disorder. Children younger than the age of one (0.17%) received psychotropic medication and 0.34% of children between the ages of one and two also received prescriptions for these illnesses. By the age of four years, ADHD was the most common illness to be treated (0.2%), after which came psychosis (0.1%), depression (0.2%) and lastly came bipolar disorder (0.005%). Children suffering from depression and anxiety was most commonly found in children between the ages of one and two and bipolar mood disorder and ADHD was most commonly found in children aged three to four. The most of the study population consisted of boys (52%). |
| Lui et al. (2014) | Treatment of ADHD and anxiety and possible reasons for differences in treatments | Retrospective cross-sectional | USA (26 states)  
Sample 1: N = 20 461  
Sample 2: N = 62 064  
Patients 4-18 years  
Inception period: 1999–2006 | There was a total of two pool samples. Both samples included children already diagnosed with ADHD and anxiety. The first excluded autism, bipolar disorder, depression, schizophrenia and psychosis and tics/Tourette syndrome. The second sample also excluded these same psychiatric co-existing conditions as the first, but included oppositional defiant disorder/conduct disorder and depression as these conditions are the most frequent co-existing conditions in children with ADHD. Sample 1 received monotherapeutic treatment (48.0%) the most of the time where sample 2 received monotherapeutic treatment (44.5%) mostly as well. Combination therapy was found in sample 1 (11.0%) and for sample 2 (13.2%). Multi-drug treatment options was found quite common in sample 2. |
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| Dalsgaard et al. (2013) | ADHD medication prescription patterns for children and adolescents with ADHD and Autism Spectrum Disorder | Cohort | Denmark  
N = 852 711  
Patients 6-17 years  
Inception period: 1990-2000 | Stimulant medication used as monotherapy was used the most in both samples, with 33.8% and 27.5% respectively. The second most popular monotherapeutic treatment in both samples was for antidepressants, 5.4% and 7.6% respectively, followed by atomoxetine which was only found in sample 1 (3.7%) and antipsychotic monotherapy in sample 2 (3.6%).  
Combination therapy, consisting of antidepressants and stimulants was found in sample 1 (4.1%) and sample 2 (5.0%). Stimulants and alpha-agonists as combination therapy was found in sample 1 (2.3%). Stimulant and antipsychotic combination therapy was observed in sample 2 (2.4%).  
The most common drugs prescribed, either as mono- or combination therapy, was methylphenidate, amphetamine, atomoxetine, clonidine, risperidone and sertraline. |
| Boland et al. (2015) | Prescribing of psychotropic drugs in children | Cohort | Ireland  
N = 188 833 - 311 579  
Patients aged ≥4-15 years  
Inception period: 2002-2011 | ADHD medication use was most prevalent in children and adolescents suffering from ADHD and autism spectrum disorder in children between the ages of 10 to 13 years.  
ADHD was diagnosed in 11 553 of the participants of which 61% received treatment with ADHD medication.  
A further 9 698 participants were diagnosed with autism spectrum disorder of which 16% were treated with ADHD medication.  
Treatment with ADHD medication increased 5.8-fold for children between the ages of six and 13 years.  
Use of ADHD medication in young children suffering from ADHD, autism spectrum disorder and other psychiatric conditions increased overall in the over a period of a decade of which the highest increase was in children suffering from ADHD. |
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<td>Akici et al. (2013)</td>
<td>Methylphenidate prescriptions compared between children, adolescents and adults</td>
<td>-</td>
<td>Istanbul, N = 5,681 Patients aged one - 55 years *This study made use of child, adolescent and adult data, but for the purpose of this study, only the data on children and adolescents was used.</td>
<td>(95% CI: 3.44 - 3.92) and increased to 7.51/1000 GMS population (95% CI: 7.24 – 7.78) in 2011. Atomoxetine was made available from 2007 and became the second most popular drug prescribed, after methylphenidate. The prevalence rate of atomoxetine prescriptions from 2007 (1.00/1000 GMS population; 95% CI: 0.88 – 1.12) increased to 1.57/1000 (95% CI: 1.45-1.70) in 2011. Overall, boys received 63% of the prescriptions for psychostimulants, whereas, girls received 54% of the prescriptions. During the course of the study period, it was observed that 61% of all the participating children (boys and girls) received prescriptions for a minimum of three successive months.</td>
</tr>
<tr>
<td>Prosser and Reid (2009)</td>
<td>Variation in prescriptions for psychostimulants</td>
<td>Retrospective analysis</td>
<td>South Australia, N = 7,849 Patients aged ≥ 18 years Inception period: 1990-2000 and 2001-2006</td>
<td>A total of N = 5,681 prescriptions for methylphenidate were analysed of which only N = 805 (14.1%) of prescriptions included age and gender information. Of these N = 805 prescriptions 78.6% (N = 618.24) were given to people under the age of 18 years, of which 74.1% (N = 458.12). The most prevalent age group in this study was the age group six to 12 (51.9%) years, thus children are more prevalent in ADHD diagnosis and are treated with methylphenidate prescriptions. This study did not indicate a prescribing pattern of any kind, but a quantity of people/children receiving methylphenidate in Istanbul could be identified. Increase in prescriptions from 1990-1995 followed by a prominent decline. From 2000-2004 another increased was noticed followed by a large decrease in 2005 and 2006. Children between the ages of five and nine years received the majority of new prescriptions, followed closely by children aged ten to 14 years of age. A noticeable decline in the male:female ratio from 1990 (5.4:1) – 2006 (4.3:1) with many variances in each time period. The average start age for the period 1990-2000, for psychostimulant prescriptions was 9.35 years (SD = 3.25). For boys, the average start age was 9.41 years (SD = 3.21) and for girls, the average start age was 9.02 years (SD = 3.39). The...</td>
</tr>
<tr>
<td>Author and year</td>
<td>Measurement</td>
<td>Study design</td>
<td>Country / Population / Age / Location / Inception year</td>
<td>Key findings</td>
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<tr>
<td>-----------------</td>
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<td>--------------------------------------------------------</td>
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</tr>
<tr>
<td>Prosser, Reid and Lambert (2014)</td>
<td>The increase in psychostimulant prescriptions in New South Wales and South Australia</td>
<td>-</td>
<td>South Australia and New South Wales N = 7 489; N = 69944 Patients aged ≥ 18 years Inception period: 2000-2010</td>
<td>difference in average ages for boys and girls where psychostimulant prescriptions were introduced was found to be statistically significant ($p = 0.001$). Psychostimulant use was stopped by 1688 children between 1990-2000 (56% from period 1995-2000 and 44% from period 1995-2000). Children in areas (defined by postal codes) with a lower socioeconomic standard were more likely to receive psychostimulants in both study periods. Prescribing patterns for psychostimulants in New South Wales was monitored from 2000-2011 and compared to the prescribing patterns of South Australia from 2000-2006 as New South Wales is a larger study population. Overall increase from 10.91 new cases/1000 youths in 2000 to approximately 11.0 new cases/1000 youths in 2010 that received new prescriptions for psychostimulants across all ages. In South Australia it was observed that there was a prominent increase in new prescriptions from 2000-2004 followed by a subsequent prominent decrease from 2005-2006. In New South Wales a small decline was observed in 2002, followed by a steady incline from 2002 to 2004, a steady decline from 2004-2006 and a steady incline from 2006-2010 Male:Female ratios declined in both South Australia and New South Wales. The number of girls using psychostimulant medication increased 6.5 times in New South Wales from 1990-2000. The approximated average duration of treatment in both New South Wales and South Australia was 2 years. More than 25% of psychostimulants prescribed stopped for one year. About 46% of children in New South Wales had a minimum of one pause in treatment, possibly due to drug holidays.</td>
</tr>
<tr>
<td>Truter and Kotze (2005)</td>
<td>Prescribing patterns of methylphenidate in South Africa to a population belonging to a</td>
<td>Exposure, cohort, drug utilisation</td>
<td>South Africa N = 115 (medical aid claims data)/Patients aged &lt;10-≥40 years Inception period:</td>
<td>A total of 160 out of 455 (35.2%) prescriptions for methylphenidate where issued on the chronic benefit of the medical aid and the diagnosis for use was only listed with chronic prescriptions. Only 152 out of 455 prescriptions for methylphenidate included a diagnosis of which “ADD of Childhood” and “Hyperkinetic Syndrome of Childhood”.</td>
</tr>
<tr>
<td>Author and year</td>
<td>Measurement</td>
<td>Study design</td>
<td>Country / Population / Age / Location / Inception year</td>
<td>Key findings</td>
</tr>
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<td>----------------</td>
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</tr>
<tr>
<td>Truter (2005)</td>
<td>medical aid in 2002</td>
<td>Retrospective exposure cohort drug utilisation study</td>
<td>South Africa N = 106/Patients aged ≥ 25 (medical aid claims data)/Inception period: 1 January 2002 – 31 December 2002</td>
<td>A total of 73.0% of the study population were male and 79.1% of these patients were under the age of 18 years. Female population received from a much younger age with a percentage of 44% of the female population under the age of 10 years.</td>
</tr>
<tr>
<td>Truter (2009)</td>
<td>Prescribing patterns of methylphenidate to children in South Africa</td>
<td>Retrospective exposure drug utilisation study</td>
<td>South Africa N = 34 733/ ≥ 18 years (medical aid claims data) / Inception year: 2004</td>
<td>The average age of patients younger than 25 years was 10.5 years (SD = 3.9) for males and 9.8 years (SD = 4.6) for females. The majority of patients included in this study were males (75.6%). A total of 48% of all prescriptions were dispensed between August and November 2002. A total of 506 products were prescribed to females and 1793 to males, including methylphenidate. Other drug classes frequently prescribed included antihistamines, decongestants, penicillins and cephalosporins, analgesics, anticonvulsants and antipyretics.</td>
</tr>
</tbody>
</table>
2.12 Chapter summary

The conceptualisation of ADHD as a psychiatric disease was conducted in this chapter. The aetiology, prevalence and epidemiology of ADHD were discussed, followed by possible causes of ADHD and the pathophysiology of ADHD. The functions of neurotransmitters (dopamine and norepinephrine) was also investigated and discussed. The clinical symptoms were discussed followed by the clinical management (complementary and pharmacological) of ADHD. The pharmacological treatments were further discussed along with the various mechanisms of action, side-effects and contra-indications of clonidine, methylphenidate and atomoxetine. Furthermore, the most prevalent co-existing conditions often found in children with ADHD was also elaborated and the national and international prescribing patterns of psychostimulants and atomoxetine were discussed in this chapter. Consequently, the aims of the literature objectives are met.

The following chapter will contain the results of the empirical investigation in manuscript format.
CHAPTER 3: RESULTS AND DISCUSSION

3.1 Introduction

The results of the empirical investigation for this study will be reported and discussed in this chapter. The specific objectives of the empirical investigation were addressed in paragraph 1.3.2 of this dissertation. The results of the empirical investigation were presented in two manuscripts and a section designated ‘Additional results’ as indicated in Table 3.1.

Table 3.1: Empirical investigation objectives attainment

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Cross-reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>The determination of the prevalence of ADHD in children and adolescents</td>
<td>Manuscript one (Paragraph 3.2)</td>
</tr>
<tr>
<td>under the age of 18 years who received treatment with methylphenidate and</td>
<td></td>
</tr>
<tr>
<td>atomoxetine in the private health sector of the Western Cape Province</td>
<td></td>
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<tr>
<td>from 2005 to 2013, using a medicines claims database stratified by age,</td>
<td></td>
</tr>
<tr>
<td>gender and geographic distribution.</td>
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<tr>
<td>Identifying the prescribing patterns of methylphenidate and atomoxetine</td>
<td>Manuscript one (Paragraph 3.2)</td>
</tr>
<tr>
<td>in children and adolescents under the age of 18 years in each district in</td>
<td>Paragraph 3.3</td>
</tr>
<tr>
<td>the Western Cape.</td>
<td></td>
</tr>
<tr>
<td>Determination of the prevalence of comorbid conditions of ADHD.</td>
<td>Manuscript two (Paragraph 3.4)</td>
</tr>
</tbody>
</table>

Manuscript one is titled ‘Methylphenidate and atomoxetine prescribing trends in children in the Western Cape Province of South Africa, 2005-2013’. The paper was written according to the specific guidelines of the Health SA Gesondheid journal, as was given at http://www.elsevier.com/journals/health-sa-gesondheid/1025-9848/guide-for-authors#92000 on the November 25, 2016 (refer to Appendix B.1). It conformed to the guidelines for authors per requirements of the specific journal (refer to Appendix B.2). Manuscript two is entitled ‘Medicine and chronic disease list conditions in Western Cape children and adolescents with ADHD’. The paper was written according to the specific guidelines of the South African Family Practice, as was given at http://www.sajp.org.za/index.php/sajp/pages/view/submission-guidelines on November 28, 2016 (refer to Appendix D.1 and D.2). The references cited in each of the manuscripts appear of each respective article, as well as in the complete reference list at the end of the dissertation.
3.2 Manuscript one

Methylphenidate and atomoxetine prescribing trends in children in the Western Cape Province of South Africa, 2005-2013

Liezl Jouberta, Johanita R Burgera, Ilse Truterb, Martie S Lubbea & Marike Cockeranb

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Ethical considerations

The study was conducted according to the Declaration of Helsinki. Ethical approval was obtained from an authorised, licensed Research Ethics Committee before the study commenced (Ethics number: 00179-14-S1). Confidentiality was maintained at all times and data was analysed anonymously.

Conflicts of interest

There were no conflicts of interest during the course of this study.

Acknowledgements

The authors would like to thank the PBM company for providing the data in order to conduct the study. We would also like to thank Me Anne-Marie Bekker for assisting with the data analyses, Me Helena Hoffman for checking the references and Me Marelize Ferreira for proof reading the article.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.
Abstract
Background: There is a marked paucity of data in the geographical ADHD treatment patterns in children in South Africa. The aim of this study was to determine and describe the prescribing trends of methylphenidate and atomoxetine in children under the age of 18 years residing in the Western Cape Province.

Method: Retrospective claims data from 1 January 2005 to 31 December 2013 were analysed. In this analyses, the total number of patients, and total and average number of yearly prescriptions per patient was used as the drug utilisation metrics.

Results: A total of 2516 patients (male:female ratio 3.5:1) received ADHD treatment over the study period, with a 0.29% increase from 2005 to 2013. Children ≤6 years increased by 6% from 2005 to 2013. The City of Cape Town Metropolitan municipality had the largest number of patients (≥75%). Prescriptions for ADHD treatment increased by 0.46% overall from 2005 to 2013 (p<0.001), with that for methylphenidate and atomoxetine increasing by 0.36% and 3.15%, respectively. The average number of yearly methylphenidate prescriptions per patient increased from 3.96 ± 2.92 (95% CI, 3.69-4.23) in 2005 to 4.38 ± 2.85 (95% CI, 4.14-4.61) in 2013 (Cohen’s d=0.14), and that for atomoxetine from 2.58 ± 1.86 (95% CI, 1.80-3.37) in 2005 to 4.85 ± 3.66 (95% CI, 3.84-5.86) in 2013 (Cohen’s d=0.62).

Conclusion: Prescribing patterns for ADHD medication in the Western Cape have increased significantly from 2005 to 2013. This preliminary study can lead to future studies on the influence of geographical area on the prescribing patterns of methylphenidate and atomoxetine.

Keywords: Western Cape; South Africa; children; adolescents; atomoxetine; methylphenidate; prescribing patterns

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most prevalent mental illnesses of modern times (National Institute of Mental Health, 2012), affecting between 2% and 5% of school-aged children and adolescents in the United Kingdom (UK) (National Health Service [NHS], 2014), compared to 11.0% in the USA (Centers for Disease Control, 2014), and approximately 8% to 10% in South Africa (Attention Deficit and Hyperactivity Support Group of South Africa, 2015).

Prevalence of ADHD differ by gender, the diagnostic criteria used by the clinician to make the diagnosis, and the accessibility to information on ADHD for parents, teachers and clinicians, as well as the geographical area (Fayyad et al., 2007; Madsen, Ersbøll, Olsen, Parner & Obel,
2015; Polanczyk, De Lima, Horta, Biederman & Rohde, 2007; Polanczyk, Wilcutt, Salum, Kieling & Rohde, 2014; Weinstein et al., 2014; Willcutt, 2012). The geographical area may therefore potentially influence the subsequent prescribing of medication. For instance, Cutts and Tet (2003) found that Australian medical practitioners in rural areas perceive their location to affect their prescribing in conjunction with the distance of the patient’s residence to and from the practice, a lack of diagnostic facilities in the vicinity, the patients’ expectation of receiving a prescription and the level of monitoring that a patient may need during therapy. It was also found that doctors in these remote areas prefer to prescribe the latest drug available on the market as they may have fewer side effects and would possibly minimise monitoring of the patient. However, this observation seemed to diminish as the practise became more rural, possibly explained by lack of pharmaceutical representation and information in these areas, although it was still possible to obtain information from the internet (Cutts & Tet, 2003). The effect of the geographic area on the use of ADHD medication in South Africa is limited. By using medical aid administrator data for 355 998 patients for a one-month period in 2004, Truter (2009) showed that the Western Cape Province had, compared to the other provinces in South Africa, the highest percentage of claims for ADHD medication for children aged under 18 years. The reasons for the differences in these prescribing patterns were not clear.

The population of the Western Cape Province represents approximately 11.2% of the total population of South Africa (Statistics South Africa, 2014). The Western Cape Province covers 129 462 km² (10.6% of the county's surface area) and is the fourth largest province in the country according to surface area and population measurements (Main, 2015). The Western Cape is divided into five districts which are sub-divided into 24 local municipalities as well as one metropolitan municipality (Main, 2015). Approximately 15% of the population who are beneficiaries of medical aid schemes resides in the Western Cape Province along with 17.34% of the country’s general practitioners (15 general practitioners per 10 000 people in the private sector) (Council for Medical Schemes, 2015).

Methylphenidate and atomoxetine are the two active substances registered in South Africa for the treatment of ADHD. However, there is a significant paucity of data in South Africa on the prescription patterns of these substances, in particularly the Western Cape. Studies focussing on prescription patterns of medication assist in the explanation of trends, quantities and appropriateness of medication use, as well as treatment compliance (Jain, Khan, Upadhyaya & Abhijeet, 2013). The aim of this study was thus to investigate the prescribing patterns of methylphenidate and atomoxetine in children and adolescents under the age of 18 years in the Western Cape Province by analysing medical claims data over a period of nine consecutive years.
2 Method and materials

2.1 Study design

This study followed a longitudinal design. A retrospective, descriptive, drug utilisation review was conducted by analysing medicine claims data over a nine-year period. These claims were provided by a database of one of the largest pharmaceutical benefit management (PBM) companies for medical aid schemes in South Africa. Between 1 January 2005 and 31 December 2013, this database comprised of 56442797 prescription claims in total for the Western Cape.

The data fields available for this study included the following: The National Pharmaceutical Product Interface codes (NAPPI-codes), a treatment date, a patient dependant code, an encrypted clinician, the pharmacy and medical scheme numbers, active substances dispensed (trade and generic name), the quantity of each substance supplied, the strength, treatment period, gender, date of birth, ICD-10 code and the municipal district within which each item was claimed.

2.2 Study population

The study population comprised of all children under the age of 18 years on the database: These children had to receive at least one prescription for methylphenidate and/or atomoxetine during the study period, and reside in the Western Cape Province, South Africa. All participants were categorised by gender and divided into three age groups; age group 1 (≤ 6 years); age group 2 (>6, ≤12 years) and age group 3 (>12, <18 years). The patients’ ages were calculated according to the age on the date of the claim in line with his/her date of birth taking the first of January of the following year as index date.

Drug utilisation metrics used in the study included the number of patients stratified by age, gender and district, the total and average number of yearly prescriptions per patient, stratified by age and gender.

2.3 Statistical analysis

Changes in the annual number of methylphenidate and atomoxetine prescriptions per patient per year were modelled over time by fitting a repeated measures Poisson regression model using the generalised estimating equations procedure in SPSS (IBM Corp., 2013). Pairwise comparisons were adjusted for multiple comparisons using the Bonferroni correction.
The results would have been considered to be statistically significantly if \( p \leq 0.05 \). Cohen’s-\( d \) value was used to determine the effect size of the difference between the average number of prescriptions per patient by age group and gender with \( d \geq 0.8 \) defined as a large effect with practical significance.

3. Results and findings

Table 1 shows the demographic characteristics of the study population over the nine-year study period. The total number of children and adolescents under the age of 18 years receiving ADHD medication ranged from 1.45% in 2005 to 1.12% in 2013. The majority were boys (male:female ratio 3.5:1). Analysis by age group showed a 6.00% increase in the number of patients aged ≤6 years (age group 1) receiving treatment for ADHD from 2005 to 2013, in comparison to a 0.10% increase in those children aged >12, <18 years and 0.50% increase in age group 2 (≥6, ≤12 years) (Table 1).

Table 2 depicts the age and gender distribution of the patients receiving methylphenidate and atomoxetine over the study period by district and local municipality. Overall, the majority of patients resided in The City of Cape Town Metropolitan Municipality (≥ 75%). Prevalence of patients receiving ADHD treatment in this municipality, however, decreased by 0.20% during the study period. In the Stellenbosch and Witzenberg local municipalities (Cape Winelands district), the number of patients receiving ADHD treatment decreased by 0.12% and 1.00% from 2005 to 2013, respectively, compared to a 0.92% increase in patients residing in the Drakenstein local municipality, and a 2.00% increase in patients residing in the Breede Valley. The number of patients receiving ADHD treatment residing in the Eden district increased by 0.58% overall from 2005 to 2013. In particular, there were increases of 2.25%, 0.27% and 1.50%, respectively, for Mossel Bay, George and Knysna local municipalities, whereas the number of patients from Bitou and Oudtshoorn local municipalities decreased by 5.25% and 6.66% respectively. The number of patients in the Overberg and West Coast districts increased by 1.29% and 3.17%, respectively during the study period. The number of patients in local municipalities in particular, increased for Overstrand (4.00%), Swartland (2.00%) and Saldanha (2.50%).

Table 3 depicts the general prescribing patterns of ADHD treatment overall and that of methylphenidate and atomoxetine, respectively, from 2005 to 2013. Treating year as a fixed effect, it is shown that a significant change in the total number of prescriptions per patient per year occurred over time (\( \chi^2(8)=123.457, p<0.001 \)).
The estimated marginal means are reported in Table 4. From 2005 to 2013 prescriptions for methylphenidate increased by 0.36%, whereas that for atomoxetine increased by 3.15% (Table 3). The male:female ratio stayed relatively constant over the study period for methylphenidate prescriptions. Overall, prescribing of methylphenidate increased by 0.31% from 2005 to 2013 for boys vs. 0.55% for girls. For prescriptions containing atomoxetine, the male:female ratio fluctuated over the study period, with an overall increase of 4.16% in the percentage of boys from 2005 to 2013, vs. 1.64% for girls. Analysis by age group shows that prescriptions for methylphenidate increased by 13.00% for children aged 0, ≤6 years (age group 1) compared to a 0.15% increase in children aged >6, ≤ 12 years and 0.64% for those in age group 3 (>12, <18 years). There were no prescriptions for atomoxetine for patients aged ≤ 6 years. Prescriptions for patients in age group 2 (>6, ≤12 years) increased by 1.32% over the study period whereas prescriptions for children aged >12, <18 years increased by 6.04% (Table 3).

The mean number of methylphenidate prescriptions per patient per year increased marginally from 3.96 ± 2.92 (95% CI, 3.69-4.23) in 2005 to 4.38 ± 2.85 (95% CI, 4.14-4.61) in 2013 (Table 3). This difference in means was not practically significant (Cohen’s d=0.14). The mean number of atomoxetine prescriptions per patient per year increased from 2.58 ± 1.86 (95% CI, 1.80-3.37) in 2005 to 4.85 ± 3.66 (95% CI, 3.84-5.86) in 2013. This difference was moderate (Cohen’s d=0.62).

4. Discussion

In light of the paucity of data on the geographical ADHD treatment patterns in children in South Africa, this longitudinal study aimed to describe the prescribing patterns of methylphenidate and atomoxetine in children under the age of 18 years in the Western Cape in particular, using medicine claims data obtained from a large PBM company. We identified a number of key findings.

We determined that approximately 2–3% of the total number of children and adolescents in the Western Cape on the database received either methylphenidate and/or atomoxetine over the nine-year study period. The majority of patients in our study population were boys, with a ratio of three to four male diagnoses for every female diagnosis. These findings were similar to other South African studies (Schellack & Meyer, 2012; Venter, 2004) as well as to international studies (American Psychiatric Association, 2013; NHS, 2014). According to Schellack and Meyer (2012), the type of ADHD may influence gender-based statistics. This was shown by Van der Westhuizen (2010) determining the ratio of male to female to be four male diagnoses for every female diagnosis for predominantly hyperactive type ADHD diagnosis, and the gender
ratio for the primarily inattentive type of ADHD was two male diagnoses for every female diagnosis. In our study however, we were not able to differentiate between the different types of ADHD.

Analysis by age group showed the progressive prescribing of methylphenidate for children aged six years and younger. Methylphenidate is usually not administered to children below the age of six years, as safety and efficacy in this age group has not been established (Rossiter, 2014; Snyman, 2014). Similar to our findings, there have been several reports of the use of psychotropic medication in preschool populations worldwide. For example, a study conducted in the USA on this particular matter indicated that 1.19% of children under the age of four years received prescriptions for psychotropic medication of which 0.61% of these prescriptions was for ADHD, 0.34% were given to children between the ages of one and two years and 0.17% of children were still infants (Garfield et al., 2015). The findings in our study could be due to an increase in diagnoses of ADHD in age group 1 or the prescribing of methylphenidate for off-label use. Off-label prescriptions for methylphenidate have been issued to children suffering from narcolepsy, autism, behavioural disorders and intellectual disabilities (Dalsgaard, Nielsen & Simonsen, 2013; Trenque, Herlem, Taam & Drame, 2014).

Based on geographical area, the Cape Town Metropolitan Municipality had the highest number of ADHD patients in the entire Western Cape. This may be ascribed to this municipality consisting of 64.20% (as per our calculation based on the figures obtained from the Local Government Handbook for South Africa) (Main, 2015) of the total population in the Western Cape. Areas where the number of patients receiving ADHD treatment increased over the study period included the Overberg and West Coast districts and the Breede Valley, Drakenstein, Mossel Bay, George, Knysna, Overstrand, Swartland, and Saldanha Bay local municipalities, whereas that in the Cape Town metropolitan Municipality, Witzenberg, Stellenbosch, Bitou, Oudtshoorn, and Theewaterskloof local municipalities decreased.

There was a significant increase in the number of ADHD treatment prescriptions claimed overall, as well as the average number of prescriptions per patient per year. These trends are in line with international studies. For example, Olfson, Crystal, Huang and Gerhard (2010) conducted a study on the trends in antipsychotic medication use in young children and have found that the rate at which these drugs were used approximately doubled from 1999 to 2001 and 2007. These prescriptions were inclusive of children receiving treatment for ADHD where it was found that there was a corresponding increase in the use of psychotropic medication for these children over the study period. Possible reasons for these findings include the treatment of other psychiatric conditions diagnosed along with ADHD (e.g. bipolar mood disorder)
(Hassan, Agha & Thapar, 2011). Most prescriptions in our study were for methylphenidate; however, prescriptions for atomoxetine increased proportionally more than that of methylphenidate over the nine-year study period. This trend was also shown by previous studies conducted in South Africa (Truter, 2005; Truter, 2014) as well as international studies (Boland et al., 2015; Shyu et al., 2016). Atomoxetine was registered with the South African Medicines Control Council in June 2005, which may explain the rather large increase (~4%) in use from 2005 to 2006 (Fivas, 2006).

5. Conclusion and limitations

The findings of this longitudinal study indicate that the prescribing patterns of methylphenidate and atomoxetine in the Western Cape Province are in agreement with other South African and international studies showing a general increasing trend. We furthermore confirmed that methylphenidate is still the main method of treatment for ADHD in the Western Cape, and that particularly boys had the highest prescribing prevalence. Based on frequency, prescribing prevalence increased in a number of municipalities in the Western Cape. We also found prescriptions for methylphenidate to children under the age of 6 years. Guidelines for the prescribing of methylphenidate in children require careful assessment and monitoring of patients (Vaughan & Kratochvil, 2006). Therefore more research is warranted to determine the influence of geographical area on the availability of specialised care for children receiving this substance.

The limitations of this study included that data were obtained from only one of the PMBs in South Africa — generalisability and external validation of the data is therefore limited. Data for the study also only included claims that were actually reimbursed by the patient’s medical aid scheme. The results of this study may therefore be an underreporting of prevalence in the Western Cape Province.

References


<table>
<thead>
<tr>
<th>Gender, n (%)</th>
<th>Boys</th>
<th>Girls</th>
</tr>
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<tbody>
<tr>
<td>Boys</td>
<td>349</td>
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<tr>
<td>(77.90)</td>
<td>(21.13)</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>392</td>
<td>105 (22.31)</td>
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<td>(78.87)</td>
<td>(21.85)</td>
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<tr>
<td></td>
<td>282</td>
<td>81 (22.03)</td>
</tr>
<tr>
<td>(77.69)</td>
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<tr>
<td></td>
<td>269</td>
<td>76 (22.03)</td>
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<td>(77.97)</td>
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<tr>
<td></td>
<td>440</td>
<td>123 (22.03)</td>
</tr>
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<td>421</td>
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<td>(72.59)</td>
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<td>Age (years), n (%)</td>
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<td></td>
<td>1 (0.22)</td>
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</tr>
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<td>2 (0.40)</td>
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</tbody>
</table>

*Percentages calculated using the total number of patients < 18 years in the Western Cape Province, on the database (N) for each respective year, as denominator.

**Percentages calculated using the total number of patients < 18 years in the Western Cape Province claiming ADHD medication on the database (n) for each respective year, as denominator.
<table>
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<tr>
<th>District/Local municipality</th>
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<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
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</table>
Table 3. Prescriptions for methylphenidate and atomoxetine from 2005 to 2013, stratified by gender and age

<table>
<thead>
<tr>
<th>Year</th>
<th>Girls (n (%))</th>
<th>Boys (n (%))</th>
<th>Total number of prescriptions for methylphenidate, n (%)</th>
<th>Number of ADHD prescriptions in total population (database), N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>386 (21.94)</td>
<td>1373 (78.06)</td>
<td>1759 (96.60)</td>
<td>1821</td>
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<tr>
<td>2006</td>
<td>300 (17.78)</td>
<td>1387 (82.22)</td>
<td>1687 (85.12)</td>
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<tr>
<td>2007</td>
<td>401 (20.71)</td>
<td>1335 (76.90)</td>
<td>1736 (86.11)</td>
<td>2016</td>
</tr>
<tr>
<td>2008</td>
<td>392 (20.71)</td>
<td>1330 (77.24)</td>
<td>1722 (86.97)</td>
<td>1980</td>
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<tr>
<td>2009</td>
<td>569 (21.42)</td>
<td>2088 (78.58)</td>
<td>2657 (87.27)</td>
<td>3044</td>
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<tr>
<td>2010</td>
<td>631 (24.07)</td>
<td>1990 (75.93)</td>
<td>2621 (88.16)</td>
<td>2973</td>
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<td>2011</td>
<td>559 (24.80)</td>
<td>1695 (75.20)</td>
<td>2254 (78.58)</td>
<td>2543</td>
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<td>2012</td>
<td>529 (24.07)</td>
<td>1896 (78.19)</td>
<td>2425 (87.05)</td>
<td>2714</td>
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<tr>
<td>2013</td>
<td>597 (24.95)</td>
<td>1796 (75.05)</td>
<td>2393 (90.30)</td>
<td>2650</td>
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</tbody>
</table>

Average number of methylphenidate prescriptions per patient, mean ± SD (95% CI):
- 2005: 3.96 ± 2.92 (3.69-4.23)
- 2006: 3.80 ± 3.11 (3.51-4.10)
- 2007: 5.21 ± 3.14 (4.88-5.55)
- 2008: 5.45 ± 3.30 (5.08-5.82)
- 2009: 5.08 ± 3.10 (4.81-5.35)
- 2010: 5.06 ± 3.23 (4.88-5.34)
- 2011: 4.89 ± 3.08 (4.61-5.17)
- 2012: 4.83 ± 3.08 (4.56-5.10)
- 2013: 4.38 ± 2.85 (4.14-4.61)

Total number of prescriptions for atomoxetine, n (%): 62 (3.53), 295 (17.49), 280 (16.13), 258 (15.00), 387 (14.57), 352 (13.43), 289 (12.82), 289 (11.92), 257 (10.73)
<table>
<thead>
<tr>
<th>Gender, n (%)****</th>
<th>Boys</th>
<th>37</th>
<th>224</th>
<th>238</th>
<th>195</th>
<th>291</th>
<th>229</th>
<th>213</th>
<th>172</th>
<th>191</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>(59.68)</td>
<td>(75.93)</td>
<td>(85.00)</td>
<td>(75.58)</td>
<td>(75.19)</td>
<td>(65.06)</td>
<td>(73.70)</td>
<td>(59.52)</td>
<td>(74.32)</td>
</tr>
<tr>
<td>Girls</td>
<td>25</td>
<td>71</td>
<td>42</td>
<td>63</td>
<td>96</td>
<td>123</td>
<td>76</td>
<td>117</td>
<td>66</td>
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</tr>
<tr>
<td></td>
<td>(40.32)</td>
<td>(24.07)</td>
<td>(15.00)</td>
<td>(24.42)</td>
<td>(24.81)</td>
<td>(34.94)</td>
<td>(26.30)</td>
<td>(40.48)</td>
<td>(25.68)</td>
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<td>Age (years), n (%)****</td>
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<td>-</td>
<td>-</td>
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<tr>
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<td>&gt;6, ≤ 12</td>
<td>38</td>
<td>192</td>
<td>123</td>
<td>182</td>
<td>215</td>
<td>178</td>
<td>148</td>
<td>105</td>
<td>88</td>
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<td></td>
<td>(61.29)</td>
<td>(65.09)</td>
<td>(43.93)</td>
<td>(70.54)</td>
<td>(55.56)</td>
<td>(50.57)</td>
<td>(51.21)</td>
<td>(36.33)</td>
<td>(34.24)</td>
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<td>&gt;12, &lt; 18</td>
<td>24</td>
<td>103</td>
<td>157</td>
<td>76</td>
<td>172</td>
<td>174</td>
<td>141</td>
<td>184</td>
<td>169</td>
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<tr>
<td></td>
<td>(38.71)</td>
<td>(34.92)</td>
<td>(56.07)</td>
<td>(29.46)</td>
<td>(44.44)</td>
<td>(49.43)</td>
<td>(48.79)</td>
<td>(63.67)</td>
<td>(65.76)</td>
<td></td>
</tr>
<tr>
<td>Average number of atomoxetine prescriptions per patient, mean ± SD (95% CI)</td>
<td>2.58 ± 1.86</td>
<td>3.78 ± 4.15</td>
<td>5.96 ± 4.53</td>
<td>6.45 ± 3.81</td>
<td>6.14 ± 4.07</td>
<td>6.77 ± 3.74</td>
<td>5.35 ± 4.37</td>
<td>5.67 ± 3.85</td>
<td>4.85 ± 3.66</td>
<td></td>
</tr>
</tbody>
</table>

*Percentages calculated using the total number of patients on the database (N) for each respective year, as denominator

**Percentages calculated using the total number of patients claiming ADHD medication on the database (n) for each respective year, as denominator

***Percentages calculated using the total number of patients claiming methylphenidate (n) on the database for each respective year, as the denominator

****Percentage calculated using the total number of patients claiming atomoxetine (n) on the database for each respective year, as the denominator
Figure 1. Change in the mean number of prescriptions per patient per year from 2005 to 2013
Table 4: Estimated marginal means — change in the mean number of prescriptions per patient per year from 2005 to 2013

<table>
<thead>
<tr>
<th>Year</th>
<th>Mean</th>
<th>Lower</th>
<th>Upper</th>
<th>p-value*</th>
<th>Effect size</th>
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<td>4.065</td>
<td>3.789</td>
<td>4.361</td>
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<td>2006</td>
<td>3.988</td>
<td>3.706</td>
<td>4.291</td>
<td>1.000</td>
<td>0.008</td>
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<td>2007</td>
<td>5.554</td>
<td>5.214</td>
<td>5.916</td>
<td>&lt;0.001</td>
<td>0.126</td>
</tr>
<tr>
<td>2008</td>
<td>5.739</td>
<td>5.360</td>
<td>6.145</td>
<td>&lt;0.001</td>
<td>0.127</td>
</tr>
<tr>
<td>2009</td>
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<td>5.135</td>
<td>5.693</td>
<td>&lt;0.001</td>
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<td>5.415</td>
<td>5.129</td>
<td>5.718</td>
<td>&lt;0.001</td>
<td>0.136</td>
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<td>2011</td>
<td>5.179</td>
<td>4.901</td>
<td>5.474</td>
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<td>2012</td>
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<td>4.868</td>
<td>5.428</td>
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<td>2013</td>
<td>4.569</td>
<td>4.331</td>
<td>4.820</td>
<td>.293</td>
<td>0.052</td>
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</tbody>
</table>

* Bonferroni correction for multiple comparisons; ** Reference category
3.3 Prescribed daily doses

The study population comprised of 2516 children under the age of 18 years on the database receiving prescriptions (N=21,723) for methylphenidate and/or atomoxetine during the study period, residing in the Western Cape Province. All participants were categorised by gender and divided into three age groups; age group 1 (≤6 years); age group 2 (>6, ≤12 years) and age group 3 (>12, <18 years).

Drug usage was determined by means of the prescribed daily dose (PDD), in order to determine whether methylphenidate and atomoxetine were prescribed according to the recommended daily dosages (RDDs) (Table 3.2). Based on the 2011-South African National Health and Nutrition Examination Survey (SANHANES-1) (Shisana et al., 2013:204), the majority of children aged 0-14 years in the Western Cape province had a normal to healthy BMI (78% of boys and 74% of girls, respectively). Normal or healthy weight is defined as a BMI at the 5th percentile to less than the 85th percentile for children and teenagers of the same age and sex (CDC, 2015).

Table 3.2 shows the dosages calculated according to the weight on the 5th and 95th percentile of the CDC stature-for-age and weight-for-age charts (CDC, 2015) (refer to Appendix C.1 and C.2) and maximum dosages according to the South African Medicines Formulary (Rossiter, 2014:507-508) and Monthly Index of Medical Specialties (Snyman, 2016:2). Table 3.3 shows the PDDs for methylphenidate and atomoxetine claimed over the 9-year study period, stratified by age and gender.
Table 3.2: Recommended daily dosages (RDDs) for methylphenidate and atomoxetine in children under the age of 18 years calculated, based on product strengths available

<table>
<thead>
<tr>
<th>Gender</th>
<th>Drug / Recommended dosage</th>
<th>Recommended daily dosage (RDD) per age group (Average weight)</th>
<th>Maximum daily dosage (mg)</th>
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<td><strong>Boys</strong></td>
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<td></td>
<td>Methylphenidate 2 mg/kg/day</td>
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</tr>
<tr>
<td></td>
<td>Age groups (weight)*</td>
<td>Age group 1 (17 ≤ 27 kg)</td>
<td>Age group 2 (&gt; 27 ≤ 30 kg)*</td>
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<td></td>
<td>35 ≤ 54 mg (only indicated for 6 years and older)</td>
<td>&gt;54 ≤ 60 mg</td>
<td>≤72 mg/day</td>
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<td>Atomoxetine</td>
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<td></td>
<td>&lt;70 kg: 0.5 mg/kg/day</td>
<td>not indicated</td>
<td>&gt;10 &lt; 18 mg</td>
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<td>&gt;70 kg: 1.2 mg/kg/day</td>
<td>not indicated</td>
<td>≤ 40 mg</td>
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<tr>
<td></td>
<td>Methylphenidate 2 mg/kg/day</td>
<td></td>
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<tr>
<td></td>
<td>Age groups (weight)**</td>
<td>Age group 1 (16 ≤ 27 kg)</td>
<td>Age group 2 (&gt; 27 ≤ 31 kg)</td>
</tr>
<tr>
<td></td>
<td>35 ≤ 54 mg (only indicated for 6 years and older)</td>
<td>≤ 60 mg/day</td>
<td>≤ 72 mg/day</td>
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<tr>
<td></td>
<td>Atomoxetine</td>
<td></td>
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<tr>
<td></td>
<td>&lt; 70 kg: 0.5 mg/kg/day</td>
<td>not indicated</td>
<td>&gt; 10 &lt; 18 mg</td>
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<tr>
<td></td>
<td>&gt; 70 kg: 1.2 mg/kg/day</td>
<td>not indicated</td>
<td>&gt; 25 ≤ 40 mg</td>
</tr>
</tbody>
</table>

* Dosages were calculated between the 5th and 95th percentile of the CDC weight-for-age and stature-for-age charts. As there are two percentile intervals on the CDC charts, there are two values for each interval in each age group.
# Table 3.3: Prescribed daily doses (PDDs) for methylphenidate and atomoxetine stratified by age and gender

<table>
<thead>
<tr>
<th>Age groups</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
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<tbody>
<tr>
<td><strong>Methylphenidate</strong></td>
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<tr>
<td>0 ≤ 6 years</td>
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<tr>
<td>Girls (mean ± SD) (95% CI)</td>
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</tr>
<tr>
<td>10.00</td>
<td>35.00±28.87 (-10.94-80.94)</td>
<td>11.43±3.78 (7.93-14.92)</td>
<td>36.00</td>
<td>-</td>
<td>10.00</td>
<td>15.00±7.07 (-48.53-78.53)</td>
<td>18.67±15.01 (-18.62-55.96)*</td>
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<td></td>
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<tr>
<td>Boys (mean ± SD) (95% CI)</td>
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<tr>
<td>&gt; 6, ≤ 12 years</td>
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<td>Girls (mean ± SD) (95% CI)</td>
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<td>Boys (mean ± SD) (95% CI)</td>
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<tr>
<td>30.58±55.28 (26.09-35.06)**</td>
<td>27.71±15.87 (26.40-29.01)</td>
<td>30.58±12.71 (29.52-31.64)</td>
<td>31.69±14.35 (30.52-32.86)</td>
<td>30.86±13.68 (30.01-31.71)</td>
<td>33.33±16.20 (32.29-35.80)</td>
<td>34.43±18.77 (33.05-35.21)</td>
<td>34.24±15.55 (33.27-36.74)</td>
<td>35.70±15.93 (34.66-36.74)</td>
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</tr>
<tr>
<td>Age groups</td>
<td>2005</td>
<td>2006</td>
<td>2007</td>
<td>2008</td>
<td>2009</td>
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<tr>
<td><strong>Atomoxetine</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>0 ≤ 6 years</td>
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<tr>
<td>&gt; 6, ≤ 12 years</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Girls (mean ± SD)</td>
<td>31.18±10.97</td>
<td>39.78±47.49</td>
<td>37.39±7.37</td>
<td>36.82±15.33</td>
<td>34.83±7.13</td>
<td>38.22±11.54</td>
<td>47.77±20.38</td>
<td>39.41±17.80</td>
<td>41.59±11.66</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(23.81-38.55)</td>
<td>(25.83-53.72)</td>
<td>(34.21-40.58)</td>
<td>(31.63-42.00)</td>
<td>(33.07-36.58)</td>
<td>(35.68-40.75)</td>
<td>(40.54-55.00)</td>
<td>(34.30-44.52)</td>
<td>(35.79-47.39)</td>
</tr>
<tr>
<td>Boys (mean ± SD)</td>
<td>31.59±11.41</td>
<td>32.35±12.83</td>
<td>37.02±12.60</td>
<td>37.67±10.98</td>
<td>33.17±11.32</td>
<td>37.25±11.38</td>
<td>39.03±14.36</td>
<td>32.98±9.75</td>
<td>34.06±9.58</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(27.07-36.10)</td>
<td>(30.24-34.46)</td>
<td>(34.52-39.52)</td>
<td>(35.87-39.46)</td>
<td>(31.34-35.00)</td>
<td>(34.94-39.55)</td>
<td>(30.37-35.59)</td>
<td>(31.78-36.35)</td>
<td></td>
</tr>
<tr>
<td>&gt; 12, &lt; 18 years</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Girls (mean ± SD)</td>
<td>42.71±16.84</td>
<td>111.09±146.96</td>
<td>49.26±15.88</td>
<td>36.40±16.00</td>
<td>51.30±12.76</td>
<td>52.86±9.18</td>
<td>38.84±22.12</td>
<td>50.11±17.19</td>
<td>54.72±15.61</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(32.99-52.44)</td>
<td>(45.93-176.25)**</td>
<td>(41.61-56.92)</td>
<td>(30.07-42.73)</td>
<td>(46.54-56.06)</td>
<td>(49.96-55.76)</td>
<td>(32.03-45.64)</td>
<td>(45.95-52.27)</td>
<td>(50.18-59.25)</td>
</tr>
<tr>
<td>Boys (mean ± SD)</td>
<td>31.36±12.62</td>
<td>48.25±37.96</td>
<td>48.69±16.86</td>
<td>59.91±10.99</td>
<td>52.64±15.06</td>
<td>49.56±21.95</td>
<td>57.47±14.85</td>
<td>59.42±25.84</td>
<td>58.80±16.92</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(22.33-40.39)</td>
<td>(39.75-56.75)</td>
<td>(45.86-51.53)</td>
<td>(56.76-63.07)</td>
<td>(50.14-55.14)</td>
<td>(45.80-60.47)</td>
<td>(54.48-60.47)</td>
<td>(54.67-64.18)</td>
<td>(55.76-61.85)</td>
</tr>
</tbody>
</table>

*Median = 10 mg; ** Median = 20; *** Median = 60 mg
Table 3.4: Dosages and trade names available for methylphenidate and atomoxetine

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Trade name</th>
<th>Dosages available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>Methylphenidate HCL-Douglas®</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>Ritalin®</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>Ritalin LA®</td>
<td>10/ 20/ 30/ 40 mg</td>
</tr>
<tr>
<td></td>
<td>Concerta®</td>
<td>18/ 27/ 36/ 54 mg</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Strattera®</td>
<td>10/ 18/ 25/ 40/ 60/ 80 mg</td>
</tr>
</tbody>
</table>

Methylphenidate is usually not given to children below the age of six years, as safety and efficacy in this age group has not been established (Rossiter, 2014; Snyman, 2014). Based on the findings from this study (refer to paragraph 3.2; manuscript one, Table 1), methylphenidate was prescribed to a few patients aged ≤ 6 years, at PDDs ranging from 10 mg to 40.39 ± 11.45 mg (95% CI, 33.47-47.30) in girls, and 10 mg to 35.00 ± 28.87 (95% CI, -10.94-80.94) in boys, which correspond with the dosages calculated for children between the 5th and 95th percentile of the CDC weight-for-age and stature-for-age charts. However, maximum dosages of 64 mg were prescribed (Table 3.2), which compares to the maximum daily dosage of 72 mg/day in children aged 13-<18 years or a younger child with a weight of approximately 30 kg. The PDD for age group 2 (>6, ≤ 12 years) and 3 (>12,< 18 years) was below the RDD for both boys and girls and would be appropriate for children weighing less than 17 kg according to the CDC stature-for-age weight for-age charts (Appendix C). The maximum dosages for both boys and girls, however, were in line with the RDD from 2006 to 2013, but the maximum RDD was exceeded in 2005 for boys in age group 2 (>6, ≤ 12 years) with a dosage of 85.78 mg. It has been found that approximately 19.1% of girls and 18.2% of boys in the Western Cape are overweight according to their BMI (Shisana et al., 2013:205). The percentage of overweight children in the study population could not be determined as there was no data available on the patients’ weight, thus the high dosages could not be verified.

The PDD most frequently prescribed for methylphenidate was 20 mg daily (25.20%) out of a total of 19 254 prescriptions for methylphenidate (refer to Table 3 in manuscript one). Although the maximum dose for methylphenidate should not exceed 72 mg/day, this RDD was calculated according to the maximum dosage under specialist supervision (Rossiter, 2014:508). These results indicate that the majority of the participants in this study received methylphenidate in dosages within the general recommended dosage range that does not have to be monitored intensively.
In accordance with the age restriction of atomoxetine prescriptions (Rossiter, 2014:507), there were no prescriptions for children under the age of six years in the study population. For both boys and girls, the PDDs for atomoxetine were within the range for the RDD according to the weight-for-age percentiles (refer to Appendix C) for boys and girls weighing between 21 kg to 68 kg (>6, < 18 years) and 20 kg to 56 kg (>6, < 18 years), respectively. The maximum daily dosage for atomoxetine for girls in age group 2 (>6, ≤ 12 years) exceeded the RDD for children with a weight-for-age between the 5th and 95th percentile throughout the study period. The PDD only exceeded the RDD for girls in age group 2 (>6, ≤ 12 years) in 2011 (47.77 mg) and 2013 (41.59 mg) marginally for girls with a weight-for-age between the 5th and 95th percentile. The PDD for children in age group 3 (>12, < 18 years) remained in line with the RDD, but the maximum daily dosage exceeded the RDD in 2006 (86.21 mg) and 2011 (85.08 mg).

The PDD most frequently prescribed for atomoxetine was 40 mg daily (39.90%) out of a total of 2,469 prescriptions for atomoxetine. A dosage of 40 mg would be included in age group 2 (>6, ≤ 12 years) for boys (> 21 ≤ 41 kg) and girls (> 41 kg ≤ 68 kg). Based on dose calculations according to weight > 70 kg (Table 3.2), the maximum dose is not supposed to exceed 81.6 mg/day for boys aged < 18 years, or 67.2 mg/day for girls aged < 18 years, according to the RDD.
3.4 Manuscript two

Medicine and chronic disease list conditions among children and adolescents with ADHD in the Western Cape

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We declare that we have no financial or personal relationships, which may have inappropriately influenced the writing of this paper.

Keywords:
children; adolescents; Attention-Deficit/Hyperactivity Disorder (ADHD); Western Cape; chronic disease list (CDL) conditions; medicine prescribing patterns

Abstract

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) co-occurs with a variety of comorbid and coexisting conditions. There is, however, little information available about the prevalence of these in children with ADHD. This study determined the prevalence of medicine (pharmacological classes) prescribed and chronic disease list (CDL) conditions occurring in children and adolescents with ADHD in the Western Cape.

Methods: A retrospective, cross-sectional study was conducted on medicine claims data from 1 January 2005 to 31 December 2013 for a total of 2516 children <18 years of age with ADHD residing in the Western Cape. CDL conditions were identified by using ICD-10 codes on claims reimbursed from prescribed minimum benefits. The pharmacological class of medicine received at least once during the study period were identified using the MIMS classification system. Data were analysed descriptively.

Results: A total of 93 (3.70%) patients had CDL conditions. Of these, 70.2% (n=90) of the children presented with one CDL condition. Asthma was most prevalent, occurring in 74.19% (n=69) of patients, followed by epilepsy with 17.20% (n=16). A combination of asthma and epilepsy was found in three patients (3.13%). Other CDL conditions included diabetes mellitus type 1 (1.08%, n=1), hypothyroidism (1.08%, n=1), and multiple sclerosis (3.23%, n=3). A total of 1691 patients (67.21%) received other drugs at least once during the study period. The most prevalent pharmacological classes were antimicrobials (54.82%, n=927), respiratory system agents (10.00%, n=169), dermatologicals (6.68%, n=113), central nervous system agents (6.15%, n=104), ear,
Conclusion: This study provided valuable information about the CDL conditions and medicine used in children and adolescents with ADHD in the Western Cape. Future studies should consider increasing the sample pool in order to increase the generalisability of findings.

Introduction
Attention-Deficit/Hyperactivity Disorder (ADHD) has been noted to co-occur with a variety of comorbid (i.e. situations in which one or more diseases coexist with an index disease under study) and coexisting conditions (i.e. the simultaneous occurrence of health conditions where no single condition can be identified as the main indicator condition). Several population- and clinical-based studies report that more than half of ADHD cases have at least one psychiatric comorbidity.1-5 For example, Jensen et al. showed that 87% of children and adolescents with ADHD in Switzerland presented with one comorbid condition and that 67% presented with more than one comorbid condition. 1 Another study conducted in Denmark found that 52% of children with ADHD presented with one comorbid condition and 26.2% presented with two comorbidities.6 In Iran it was found that at least one psychiatric comorbid condition is present in 73% of children and adolescent cases of ADHD7 whereas a study in Turkey determined that 96.3% of children and adolescents between the ages of six and 18 had at least one psychiatric comorbid diagnosis.8 In the United States of America (Minnesota) it was found that 62% of children with ADHD presented with at least one comorbid condition,9 whereas Cuffe et al. determined that 54.7% of children with ADHD in South Carolina and 64.8% in Oklahoma respectively had at least one comorbid disorder.5

Comorbid conditions frequently occurring in children with ADHD can be classified as internalising disorders (e.g. where a person feels internal distress and emotional discomfort) or externalising disorders (e.g. problematic developmental external behaviour and has a direct impact on the people in their direct surroundings.9,10 Externalising disorders (e.g. oppositional defiant disorder (ODD) and conduct disorder (CD) is found in approximately 40% to 90% of children with ADHD.5,11 The prevalence of ODD and/or CD in children with ADHD vary between 13.5%-26.8% (CD alone),12 19.00% - 59.3% (ODD alone),5,12 and 45.5%-60.5% (ODD and CD),3 whereas internalising disorders (e.g. depression such as bipolar disorder and disruptive mood dysregulation disorder; and anxiety) is present in approximately 8-50% of children with ADHD.10,13,15 According to Takeda et al.15 comorbid internalising disorders are found in 22.9% and externalising disorders in 18.0% of ADHD patients, and both internalising and externalising are found disorders in 26.7% of ADHD patients. A similar study by Armstrong et al.11 has found that 17% of children with ADHD met the criteria for internalising disorders, 21% for externalising disorders and 36% for both internalising and externalising disorders.

Children diagnosed with ADHD may also experience problems with addiction, and other psychiatric and neurocognitive disorders.16 A total of 21.43% of children with ADHD was also found to suffer from clinical depression.17 Other coexisting conditions that may occur frequently include intermittent explosive disorder, specific learning disorders and intellectual disability, and autism spectrum disorder (ASD).18,19

Presence of comorbidities and/or coexisting conditions in children and adolescents with ADHD mostly depend on the child’s age, as well as his or her general daily surroundings and environment.16,18,20 For example, ODD and CD are more commonly found in younger children whereas symptoms of depression, anxiety and tic disorders are identified at a later stage in life.6,20 Autism spectrum disorder (ASD) and intellectual disabilities are also mostly identified in early childhood,6 whereas ODD may be present through all ages.15 The various subtypes of ADHD may also influence the prevalence of comorbid conditions as it has been found that anxiety disorders and epilepsy are found more often in children with the inattentive subtype of ADHD in comparison to children with the combined or hyperactive subtypes.5,6,22,23 Children, boys in particular, with ADHD and coexisting ASD symptoms are found to express more internalising- and externalising behavioural symptoms compared to children with uncomplicated ADHD (i.e. without coexisting disorders).24-26

Children with ADHD and anxiety, ODD/CD and depression in general, receive more treatment with psychotrophic drugs (mono- and polypharmacy) than children with only ADHD and anxiety.27 It has also been found that concomitant treatment with psychostimulants and antipsychotics are increasing in children with ADHD and comorbidities.14,27,28

Children with ADHD experience a lower quality of life regarding their own experiences, interaction with their peers and their families – the quality of life can be even lower when coexisting conditions are
Attention-Deficit/Hyperactivity Disorder (ADHD) affects between 5.4% and 8.7% of school-aged children in South Africa. There is a paucity of information available on the prevalence of comorbidities and/or coexisting in children with ADHD in South Africa – therefore the aim of this study was to determine the prevalence of medicine (main pharmacological classes) prescribed and chronic disease list (CDL) conditions occurring in children and adolescents with ADHD younger than 18 years in the Western Cape.

Methods

Study design
This study followed a cross-sectional design. A retrospective, descriptive drug utilisation review was conducted by analysing medicine claims data for children under the age of 18 years with ADHD from in the Western Cape Province between 1 January 2005 and 31 December 2013, provided by one of the largest pharmaceutical benefit management (PBM) companies for medical aid schemes in South Africa. The PBM currently manages the medicine benefits of 1.7 million beneficiaries on behalf of 40 medical schemes. All of South Africa’s pharmacies and 98% of all dispensing doctors are on this service provider database. Data for 1 509 621 patients for 2005 were obtained, compared with 1 558 090 patients for 2006, 1 178 596 patients for 2007, 974 497 patients for 2008, 1 033 057 for 2009, 968 158 for 2010, 864 977 for 2011, 815 810 for 2012, and 809 857 for 2013. In 2005, these patients represented 22.1% of all beneficiaries covered by medical aid schemes registered in terms of the Medical Schemes Act (Act 131/1998) in South Africa, compared with 21.9% in 2006, 15.8% in 2007, 9.6% in 2008, 13% in 2009, 11.7% in 2010, 10.3% in 2011, 9.5% in 2012, and 9.3% in 2013.

The data fields available included the National Pharmaceutical Product Interface codes (NAPPI-codes), treatment dates, the active substances dispensed (trade and generic name, pharmacological class), gender, date of births and International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) code under which each medicine item was claimed.

Study population
Prescribing of methylphenidate and/or atomoxetine was used as a proxy for the diagnosis of ADHD. The study population therefore comprised of a total of 2 516 children with ADHD younger than 18 years on the database residing in the Western Cape during the study period (2005–2013).

Variables
The patients’ ages were calculated according to the age on the date of the claim in line with his/her date of birth taking the 1st of January of the following year as index date. Patients were categorised by gender and divided into three age groups; age group 1 (≤ 6 years); age group 2 (>6, ≤12 years) and age group 3 (>12, <18 years).

The types and numbers of CDL conditions per patient were counted for all ADHD patients receiving at least one medicine claim per year containing an ICD-10 code for any of the 27 CDL conditions. These were: Addison’s disease (E27.1), asthma (J45), bipolar mood disorder (F30-F39), bronchiectasis (J47, Q33.4, A14-A15), cardiac failure (I11, I27.9, I50), cardiomyopathy (I42), chronic obstructive pulmonary disease (J44), coronary artery disease (I20.0, I25.0), Crohn’s disease (K50.0, K50.1, K50.8, K50.9), diabetes insipidus (E23.2), diabetes mellitus type 2 (E11, E12, I13.115 O24.1), diabetes mellitus type 1 (E10, E12, O24.0), dyslipidemia (E78), dysrhythmias (I47.2, I48, I49), epilepsy (G40, G41), glaucoma (H40-H42, Q15.0), haemophilia A and B (D66, D67, D68), hypertension (I10, I12, I13, I15), hypothyroidism (E02, E03), lupus erythematosus (M32, L93, L93.2), multiple sclerosis (G35), Parkinson’s disease (G20, G21, G22), rheumatoid arthritis (M05, M06, M08), schizophrenia (F20), ulcerative colitis (K51), Human Immunodeficiency Virus (HIV) (B20-B24) and chronic renal disease (N18.9).

Medicine claims not associated with an ICD-10 code for any of the CDL conditions were examined to determine the main pharmacological classes of medicine prescribed at least once per patient during the study period. Pharmacological classes were identified by using the MIMS classification system.

Statistical analysis
Statistical analyses were performed by using the SAS® version 9.4. Variables were characterised by using descriptive statistics.

Results
A total of 93 (3.70%) patients in the study population had CDL conditions (Table I). Out of these patients, 70.2% (n=90) presented with one CDL condition. A further three patients presented with two conditions (Table I). Asthma was the most prevalent condition, occurring in 96.77% (n=69) of patients, followed by epilepsy with 17.20% (n=16). A combination of asthma and epilepsy was found in three patients (3.13%). Other CDL
conditions included diabetes mellitus type 1 (1.08%, n=1), hypothyroidism (1.08%, n=1), and multiple sclerosis (3.23%, n=3).
## Table I: Prevalence of Chronic Disease List (CDL) conditions

<table>
<thead>
<tr>
<th>CDL conditions</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with one CDL condition</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12 (13.33)</td>
<td>12 (13.33)</td>
<td>17 (18.89)</td>
<td>13 (14.44)</td>
<td>20 (22.22)</td>
<td>13 (14.44)</td>
<td>90 (96.77)</td>
</tr>
<tr>
<td>Patients with two CDL conditions</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (33.33)</td>
<td>1 (33.33)</td>
<td>0</td>
<td>0</td>
<td>1 (33.33)</td>
<td>0</td>
<td>3 (3.22)</td>
</tr>
<tr>
<td><strong>CDL Conditions</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10 (14.48)</td>
<td>8 (11.59)</td>
<td>11 (15.94)</td>
<td>10 (14.48)</td>
<td>16 (23.19)</td>
<td>14 (20.29)</td>
<td>69 (74.19)</td>
</tr>
<tr>
<td>Asthma/Epilepsy</td>
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<td>-</td>
<td>-</td>
<td>1 (33.33)</td>
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<td>0</td>
<td>0</td>
<td>1 (33.33)</td>
<td>0</td>
<td>3 (3.13)</td>
</tr>
<tr>
<td>Diabetes Mellitus Type 1</td>
<td>-</td>
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<td>-</td>
<td>0</td>
<td>0</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.08)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (12.50)</td>
<td>3 (18.75)</td>
<td>3 (18.75)</td>
<td>2 (12.50)</td>
<td>4 (25.00)</td>
<td>2 (12.50)</td>
<td>16 (17.20)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
<td>1 (1.08)</td>
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<tr>
<td>Multiple sclerosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>1 (33.33)</td>
<td>2 (66.66)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (3.22)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13 (13.98)</td>
<td>13 (13.98)</td>
<td>17 (18.28)</td>
<td>13 (13.98)</td>
<td>21 (22.58)</td>
<td>16 (17.20)</td>
<td>93 (100)</td>
</tr>
</tbody>
</table>
The pharmacological drugs prescribed at least once per ADHD patient during the study period is shown in Table II.

Table II: Prevalence of pharmacological classes prescribed per ADHD patient, according to the Monthly Index of Medical Specialties

<table>
<thead>
<tr>
<th>Pharmacological classification</th>
<th>Sub classification</th>
<th>Prevalence, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Sedative hypnotics</td>
<td>1 (0.06)</td>
</tr>
<tr>
<td></td>
<td>Anxiolytics</td>
<td>15 (0.88)</td>
</tr>
<tr>
<td></td>
<td>Antidepressants</td>
<td>34 (2.00)</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics</td>
<td>28 (1.65)</td>
</tr>
<tr>
<td></td>
<td>Anti-epileptics</td>
<td>7 (0.41)</td>
</tr>
<tr>
<td></td>
<td>Antivertigo/ Anti-emetics</td>
<td>18 (1.06)</td>
</tr>
<tr>
<td></td>
<td>Antimigraine</td>
<td>1 (0.06)</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>Coughs and colds</td>
<td>73 (4.29)</td>
</tr>
<tr>
<td></td>
<td>Bronchodilators</td>
<td>43 (2.53)</td>
</tr>
<tr>
<td></td>
<td>Mucolytics</td>
<td>18 (1.06)</td>
</tr>
<tr>
<td></td>
<td>Anti-asthmatics</td>
<td>35 (2.06)</td>
</tr>
<tr>
<td>Ear, nose and throat</td>
<td>Topical nasal</td>
<td>43 (2.53)</td>
</tr>
<tr>
<td></td>
<td>Ear drops and ointments</td>
<td>10 (0.59)</td>
</tr>
<tr>
<td></td>
<td>Mouth and throat preparations</td>
<td>31 (1.82)</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>Antispasmodic</td>
<td>11 (0.65)</td>
</tr>
<tr>
<td></td>
<td>Acid reducers</td>
<td>12 (0.71)</td>
</tr>
<tr>
<td></td>
<td>Laxatives</td>
<td>3 (0.18)</td>
</tr>
<tr>
<td></td>
<td>Antidiarrhoal</td>
<td>3 (0.18)</td>
</tr>
<tr>
<td>Anthelmintics</td>
<td>Anthelmintics</td>
<td>34 (2.00)</td>
</tr>
<tr>
<td>Dermatologicals</td>
<td>Antibacterial, antiseptic agents</td>
<td>3 (0.18)</td>
</tr>
<tr>
<td></td>
<td>Antiparasitics</td>
<td>3 (0.18)</td>
</tr>
<tr>
<td></td>
<td>Fungicides</td>
<td>5 (0.29)</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
<td>34 (0.34)</td>
</tr>
<tr>
<td></td>
<td>Acne</td>
<td>65 (3.82)</td>
</tr>
<tr>
<td></td>
<td>Emollients and protectives</td>
<td>3 (0.18)</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Anti-infective</td>
<td>5 (0.29)</td>
</tr>
<tr>
<td></td>
<td>Combination products (anti-</td>
<td>3 (0.18)</td>
</tr>
<tr>
<td></td>
<td>infective and corticosteroids)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decongestants</td>
<td>6 (0.35)</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>2 (0.12)</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>Betalactams</td>
<td>770 (45.27)</td>
</tr>
<tr>
<td></td>
<td>Antifungals</td>
<td>1 (0.06)</td>
</tr>
<tr>
<td></td>
<td>Antiprotozoal</td>
<td>8 (0.47)</td>
</tr>
<tr>
<td></td>
<td>Antiviral agents</td>
<td>39 (2.29)</td>
</tr>
<tr>
<td></td>
<td>Erythromycin and other macrolides</td>
<td>85 (5.00)</td>
</tr>
<tr>
<td></td>
<td>Tetracycline</td>
<td>8 (0.47)</td>
</tr>
<tr>
<td></td>
<td>Quinolones</td>
<td>7 (0.41)</td>
</tr>
<tr>
<td>Endocrine system</td>
<td>Antidiabetic agents</td>
<td>1 (0.06)</td>
</tr>
<tr>
<td></td>
<td>Antihypoglycaemic agents</td>
<td>1 (0.06)</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
<td>41 (2.41)</td>
</tr>
<tr>
<td>Anaesthetics</td>
<td>General anaesthetics</td>
<td>3 (0.81)</td>
</tr>
<tr>
<td></td>
<td>Local anaesthetics</td>
<td>5 (0.29)</td>
</tr>
</tbody>
</table>
A total of 1691 patients (67.21%) received other drugs at least once during the study period. Drugs could be classified in 20 different pharmacological classes. The most prevalent pharmacological classes were antimicrobials (54.82%, n=927), respiratory system agents (10.00%, n=169), dermatologicals (6.68%, n=113), central nervous system agents (6.15%, n=104), ear, nose and throat medicine (4.97%, n=84), autacoids (3.49%, n=59), analgesics (2.72%, n=46), as well as endocrine system agents (2.54%, n=43).

Within the pharmacological class of antimicrobials (N = 918), patients mostly received betalactam antimicrobial medication (n = 770, 83.88%) followed by erythromycin and other macrolides (n = 84, 9.26%), and anti viral medication (n = 39, 4.25%).

In the class of respiratory agents (N=169), patients mostly received, medication for the treatment of coughs and colds (n = 73) (43.20%), followed by bronchodilators (25.44%), anti-asthmatic medication (20.71%) and mucolytic medication n = 18 (10.65%). Treatment indicated for ear, nose and throat diseases (N=84) consisted of topical nasal preparations (51.20%), ear drops and ointments (11.91%), as well as mouth and throat preparations (36.91%). A total of 3.47% of the patients received prescriptions for antihistamines. For patients receiving analgesics (N=46), combination analgesic preparations were prescribed most (49.57%). Amongst the central nervous system medication (N=104), antidepressants had the highest percentage of prescriptions (32.69%), followed by antipsychotics (26.92%) and antivertigo/ anti-emetics (17.31%). Anxiolytic medication was prescribed to 14.42% of patients followed by anti-epileptic medication (6.73%). In the dermatological class (N=113), acne preparations were the most frequently prescribed (57.52%), followed by corticosteroids (30.09%) and fungicides (4.43%). Amongst the endocrine agents (N=42), the corticosteroids were most frequently prescribed (95.46 %). One prescription for antidiabetic and antihypoglycaemic agents were identified (Table II) and this is similar to the finding of one patient with diabetes mellitus type 1 in 2010 (Table I).

**Discussion**

As there is paucity of information available on the prevalence of comorbidities and/or coexisting conditions in children with ADHD in South Africa, this cross-sectional study aimed to describe the prevalence of chronic disease list (CDL) conditions, and the most frequently prescribed medicine in children with ADHD younger than 18 years in the private health sector of the Western Cape.
Over the study period, a total of 93 children presented with CDL conditions, of which asthma and epilepsy was most prevalent. Similar findings have been reported by several other studies, showing asthma to affect 7–15% of children and being a leading cause of childhood chronic medical illness. Conversely, children with asthma are also more likely to develop ADHD as many of the symptoms of asthma are linked with the symptoms of ADHD (i.e. the shortness of breath and hyperactivity and inattention of ADHD). Children with asthma have been reported to have greater difficulty in school performance compared with their peers as their often-described hyperactive and impulsive behaviours have been thought to be secondary to this chronic illness or to its treatments. It has also been found that many asthmatic children with ADHD have a severe vitamin D deficiency and suffer from obesity. A meta-analysis found a 40% increase in obesity in children with ADHD. The co-occurrence of asthma as CDL conditions in our patient population is supported by the relatively high use of respiratory system drugs, autacoids, and antimicrobials. Medication for coughs may also be linked to the treatment of asthma, whereas cold medication may be linked to the antimicrobial prescription prevalence.

Previous epidemiological studies found associations between epilepsy and asthma in adults. Silverberg et al. also established recently discovered that the prevalence of epilepsy was associated with allergic diseases in children, in particular severe forms of eczema, asthma, hay fever and food allergies. These allergic diseases are known as atopic allergies and are formed when a person, with a genetic predisposition to hypersensitivity to particular allergens, is exposed to a stimulus, triggering a reaction such as asthma, eczema, allergic rhinitis and food allergies. We determined that the possibility of coexisting atopic conditions presented itself in our findings as patients who received autacoids and topical-and systemic corticosteroids frequently over the course of the study period. These drug classes are typical treatment options for atopic allergies. Other studies conducted on atopic conditions associated with ADHD, allergic rhinitis and asthma in particular, found that children with asthma and allergic rhinitis had a higher incidence of developing ADHD and vice versa. In addition, a higher incidence of ADHD and autism spectrum disorder (ASD) was found in children that were diagnosed with an atopic allergy before the age of two to three years.

A relatively high percentage of patients in our study had only epilepsy as a CDL condition. This finding was in line with previous studies showing approximately 12%–31.5% of children with epilepsy indicated clinical signs of ADHD. According to Reilly, the reasons for these observations include that both conditions are frequently diagnosed in children, that seizures may worsen or even cause symptoms of ADHD and that both conditions may have the same root causes. Reilly also showed that children with epilepsy are at an increased risk of developing symptoms of inattention. The origin of this phenomenon, however, is still to be established. The co-occurrence of epilepsy as a CDL condition in our patient population is supported by the relatively high use of anti-epileptic drugs. Many anti-epileptic drugs may also mimic symptoms associated with ADHD. The effect of anti-epileptic medication on children with or without ADHD, however, was outside the scope of this study as there was no clinical data available to properly establish the effects of these drugs. Children with epilepsy are also more likely to be associated with ADHD rather than children with asthma. Our observations are contradictory to this statement, although, it should be noted that our study sample was too limited to make finite conclusions and the data were expressed by descriptive statistics only.

Children with diabetes significantly suffer more frequently from ADHD than children without diabetes, particularly children with diabetes mellitus type 1. However, according to Kapellen et al., it is possible that children with diabetes mellitus type 1 are more frequently seen by medical care providers and are thus more likely to be evaluated and receive an appropriate diagnosis. On the other hand, it has been found that there was no significant prevalence of diabetes mellitus type 1 in children with ADHD, but the prevalence of diabetes mellitus type 2 has proven to be significant. We identified only one child with ADHD that had diabetes mellitus type 1 as a coexisting condition. It should be noted again that our study population was rather limited.

We found the prevalence of antimicrobial prescribing in the Western Cape to be similar to that of other international studies. Younger children (i.e. pre-school aged) are generally more exposed to the prescribing of antimicrobials as this is, presumably, the age group where children are introduced to day care centres. These communal exposures to various illnesses may lead to the increase in microbial infections. In this study, we showed that the prevalence of prescriptions for betalactam antibiotics was the highest amongst antimicrobials prescribed. This was also shown by previous studies.

Acne occurs in 70–87% of adolescents. Children with ADHD are twice as likely to develop or be associated with acne. As expected, treatment for acne was found under our top five most co-prescribed medications, since our study consisted largely of adolescents.

The prescriptions for several patients in our study population included medication for the central nervous system,
especially antidepressants, antipsychotics, anxiolytics and antivertigo/anti-emetics. According to Stein,\textsuperscript{62} most of these drugs are used for the treatment of anxiety disorders. Anxiety in children decrease significantly during treatment with antidepressants, in particular the selective serotonin reuptake inhibitors and the serotonin and noradrenaline reuptake inhibitors).\textsuperscript{63} The study by Strawn et al. \textsuperscript{63} was similar to our study as it also showed that the majority of patients received antidepressant and antipsychotic medication. We furthermore found prescriptions for antispasmodics and acid reducers to be similar to those of anxiolytics which is in agreement with findings by Dufton et al.\textsuperscript{64} showing that children experiencing frequent abdominal pain and discomfort have met the criteria to be diagnosed with an anxiety disorder.

In summary, it was observed that the majority of patients received acute medication, which could possibly be indicated for the treatment of bacterial upper respiratory tract infections, general colds and seasonal allergies, as well as fever.

**Conclusion and study limitations**
The preliminary research project provided insight into the prevalence of medicine (pharmacological classes) prescribed and chronic disease list (CDL) conditions occurring in children and adolescents younger than 18 years with ADHD in the Western Cape. We found that asthma and epilepsy were the most prevalent CDL conditions in our study population, and contrary to other literature, asthma was the most prevalent coexisting disorder. We also found that the following drugs were most frequently administered to ADHD patients: betalactam antibiotics, erythromycin and other macrolides, medication for the treatment of coughs and colds, acne and allergic rhinitis. In contrast to what is already known, our study found that the majority of children with ADHD in the Western Cape Province received treatment for acute disorders, rather than chronic neurodevelopmental disorders.

As our sample size was only from the private health sector within the Western Cape Province and thus limited, our findings cannot necessarily be generalised to the overall population. Future studies may want to make use of a larger data pool in order to increase generalisability.

**Ethical considerations**
This study was approved by the Health Research Ethics Committee of the North-West University (NWU-00179-14-A1). Permission for the use of the data was granted through the contract between Medicine Usage in South Africa (MUSA) and the South African Pharmaceutical Benefit Management Company (PBM). The data were analysed anonymously. Privacy and confidentiality of the data were maintained at all times; therefore no patient or medical scheme can be traced.


44. Mosby’s Dictionary of Medicine, Nursing & Health Professions. 8th ed. St. Louis, M.O. Elsevier; 2009. Atopic allergies; p. 162.

3.5 Chapter summary

This chapter contained the results of the empirical investigation presented in the form of two manuscripts and an additional section, thereby fulfilling the empirical objectives of the study. Chapter 4 concludes the content of the dissertation with the final conclusions based on the study objectives, study limitations and strengths, and recommendations for future research.
CHAPTER 4: CONCLUSION, RECOMMENDATIONS AND LIMITATIONS

4.1 Introduction

This dissertation consisted of four chapters in total. Chapter 1 contained the overall motivation for the study by means of the aims, objectives, problem statement, methodology, and study design. Chapter 2 consisted of the literature review whereas chapter 3 contains the results of the empirical investigation. This final chapter will entail the key findings of this study overall, set recommendations for future studies and detail the study limitations.

4.2 Conclusions derived from the literature review

The specific objectives of the literature review were to:

- Conceptualise ADHD as a psychiatric disease.
- Investigate the clinical management and pharmacologic treatment available for the treatment of ADHD in children and adolescents under the age of 18 years worldwide and nationally.
- Identify alternative methods of managing/treating ADHD internationally and in South Africa.
- Determine comorbid and co-existing conditions diagnosed with ADHD in children and adolescents.
- Review pharmacologic class and mechanism of action of methylphenidate and atomoxetine.
- Review possible side effects of methylphenidate and atomoxetine, and
- Review previous studies conducted on the prescribing patterns of methylphenidate and atomoxetine internationally and in South Africa.

The conclusion from the literature study is addressed in paragraph 4.2.1–4.2.4.
4.2.1 Conceptualisation of ADHD as a disease

ADHD was conceptualised as a psychiatric disease in chapter 2, (section 2.2) based on the objectives of the literature review.

As previously stated, ADHD is defined as a psychological and neurodevelopmental disorder identified by an ongoing pattern of inattention and possibly combined with hyperactivity and impulsivity (section 2.2.1). As such, there are three types of ADHD, namely, inattentive, hyperactive-impulsive and a combination of the two, and a fourth, namely partial remission (section 2.2.1).

The combined type ADHD was found to be most prevalent subtype found among patients (57%), followed by the inattentive type (40%) and then the hyperactive/impulsive subtype (3%) (section 2.3). The prevalence of ADHD in children and adolescents vary between 2% and 11% internationally, whereas the prevalence of ADHD in Africa ranges approximately between 5.4% and 8.7% (section 2.3) (Bakare, 2012:359; CDC, 2014a). On an international scale, the prevalence of ADHD is still higher in boys compared to girls (APA, 2013:63; CDC, 2014a; NHS, 2014). The prevalence of ADHD in South Africa was found to be similar to international trends (Schellack & Meyer, 2012:12; Venter, 2004:444), but it was observed that the prevalence of ADHD in girls is also increasing as the male:female ratios are starting to decline nationally and internationally (section 2.11, Table 2.1). Possible reasons for this decline in ratios is an increase in diagnosis of ADHD in girls, and therefore an increase in the use of psychotropic medication among girls (section 2.11, Table 2.1).

The finding and studying of the aetiology and origin of ADHD is incessant (section 2.2.2). The predisposing-, precipitating-, perpetuating- and protective factors (Thompson et al., 2012:37) (section 2.2.2) all have an influence on the aetiology of ADHD. The possibility of adaptation to the environment (section 2.2.2) is another theory attempting to find the exact (Jensen et al., 2006:96), but elusive origin of ADHD. It was also noticed that ADHD possibly has a biochemical origin. Studies have shown that children with ADHD have increased levels of malondialdehyde, nitric oxide, catalase antioxidant enzyme, and glutathione peroxidise (Ceylan et al., 2010:1492) (section 2.2.2). ADHD may also be caused by genetically related issues (even though no particular biomarker has been identified) and malfunctioning neurotransmitters (CDC, 2014b) (section 2.4). A possibility of a prostaglandin imbalance is also regarded as a possible cause of ADHD (ADHASA; 2015). Drug abuse during pregnancy, environmental risk factors, vitamin and mineral deficiencies, exposure to poison, physical damage to the brain, eyes and ears were also discussed as a possible cause of ADHD, followed by the mention of the possible relevance of diet and conditions that may present with similar symptoms as ADHD (i.e. hyperthyroidism, foetal
alcohol syndrome and encephalopathy) (APA, 2013:62; El Masry et al., 2012:19; Flisher & Hawkridge, 2013:137; Bothma, 2011:60; Soppitt, 2012:186). The cultural beliefs concerning the possible causes of ADHD (section 2.4) are controversial. For example, Bakare (2012:358) is of the opinion that ADHD is merely a cultural formation, whereas the CDC (2014b) states that diet, parenting, violent television programs and the overall household/cultural environment play no role.

“The brains of these children are different” (Thompson et al., 2012:192). Several studies have been conducted on the anatomical differences in brain size in children with ADHD compared to healthy children (section 2.5). There is thought to be difficulties in the dorsolateral and fronto-ventral striatal pathways. The dopaminergic-, serotonergic- and non-adrenergic pathways and markers are thought to explain the presence of ADHD in children, of which the dopaminergic pathways are the most prominent (section 2.5). In chapter 2, section 2.6.1, the dopamine transfer deficit (DTD) theory is discussed (Tripp & Wickens, 2008:694; Tripp & Wickens, 2009:584). This theory is based on the assumption that the dopamine cell response after positive reinforcement is much more rapid in healthy children when reinforcement is predicted. This provides instant reinforcement when on cellular level if reinforcement is postponed, leading to normal, controlled behaviour. Children with ADHD do not respond at cellular level when it is indicated that reinforcement will take place, which leads to transfer deficits of dopamine, which then leads to the certain behaviour patterns found in ADHD patients. The DAT gene and alleles associated with DAT was discussed next in this study. Norepinephrine is said to play a cardinal role in the storage and recovery of memory (section 2.6.2). The SLA6A2 gene and associated alleles are also possibly associated with the prevalence of ADHD (Shang et al., 2015:92).

Chapter 2, section 2.7 provides a brief summary of the general observations among pre-school-, primary school children and adolescents with ADHD. Pre-school children fail to pay attention when required, have the tendency to run into objects, find it difficult to share toys and objects and cannot wait their turn (El Masry et al., 2012: 194). Peers and teachers of primary school children perceive these children as slightly different when showing signs of inattention and/or hyperactivity. Hyperactivity seems to subdue in adolescence, while inattention still persists (El Masry et al., 2012:196).

The primary symptoms according to the DSM-IV are listed in section 2.7. A minimum of six of these symptoms must be present for a period of at least six months before the age of 12 and a minimum of five symptoms must be present in children/adolescents younger than 17 years.
4.2.2 Clinical management and pharmacologic treatment for ADHD

The alternative and pharmacological management of ADHD is discussed in section 2.10.1-2.10.3.3.3.

4.2.2.1 Alternative methods of managing/treating ADHD

The alternative management of ADHD was discussed in accordance with the literature review objectives in section 2.10. The efficacy of diet (section 2.10.1) (including supplementation with vitamins, minerals and omegas), on the management of ADHD was discussed and it was found that children with ADHD show beneficial progress in the management of ADHD symptoms. The Feingold Diet (additive and salicylate free) eliminates grapes, apples, processed meat, beverages containing artificial colorants and preservatives. The oligo-antigenic (hypoallergenic diet) eliminates food antigens and allergens which may trigger ADHD symptoms such as cow’s milk, wheat, chocolate, cheese, fruits and nuts. The effect of sugar and aspartame has also been linked to hyperactivity and inattention has been noticed after sugar intake. Aspartame has no effect on cognitive performance, whereas a hypoglycaemic response after sugar intake will have an effect on cognitive functions. The ketogenic diet is based on a low carbohydrate and high fat content and was first developed for the treatment of epilepsy but the mechanism is still unclear (Millichap & Yee, 2012). Decreased ferritin and zinc levels have been associated with ADHD and these patients are in need iron and zinc supplementation to improve symptoms of ADHD (Millichap & Yee, 2012). The effect of flaxseed oil and vitamin C on the symptoms of ADHD (section 2.10.1) showed a remarkable increase in DHA and EPA levels in children with ADHD and there was a decrease in attention, restlessness and impulsivity in children with ADHD (Joshi et al., 2006:18).

It was found that children who received neurofeedback (section 2.10.2) showed improvement with inattention with regard to their behaviour, but also in reading, reading comprehension and writing. There was, however, no improvement in mathematical skills, but all other improvements were still maintained after two months of the treatment (Meisel et al., 2013:20) (section 2.10.2).

4.2.2.2 Pharmacologic treatment for ADHD

The clinical management of ADHD in children was discussed in chapter 2, section 2.10. Three active substances have been identified namely clonidine (section 2.10.3.1), methylphenidate (section 2.10.3.2) and atomoxetine (section 2.10.3.3).

4.2.2.2.1 Clonidine

Clonidine, an alpha_2_-agonist (section 2.10.3.1) was found to be beneficial in the treatment of symptoms of ADHD as it leads to the modulation of noradrenergic levels in the prefrontal cortex,
which then leads to the improvement in symptoms. Studies conducted on the efficacy of clonidine in the treatment of ADHD showed that treatment with clonidine was better than receiving no treatment; however, methylphenidate was still the most effective drug in the treatment of ADHD. It was also proven that clonidine can be used in conjunction with methylphenidate (Plaumbo et al., 2008:185-186). Side effects of clonidine such as dizziness, headaches and Raynaud’s disease were discussed in section 2.10.3.1.2, followed by potentially fatal drug interactions such as an interaction between clonidine and methylphenidate (section 2.10.3.2.1).

Methylphenidate and atomoxetine, the two main active ingredients used in the treatment of ADHD, was discussed in chapter 2 section 2.10

4.2.2.2.2 Methylphenidate

Methylphenidate acts as a dopamine and noradrenalin re-uptake inhibitor. This leads to the effects of the dopamine receptors lasting longer (section 2.10.3.2.1). The increase in post-synaptic dopamine that binds to the cortex and increases the activity in the left inferior frontal gyrus is responsible for the reduction in ADHD symptoms, especially the impulsivity (section 2.10.3.2.1).

The presence of the G/G genotype of the alpha2Aa adrenergic receptor showed a superior reaction to treatment with methylphenidate with regard to behavioural improvement (Chen et al., 2009:565) (section 2.10.3.2.2). Studies conducted on the efficacy of methylphenidate have found that oppositional behaviour in patients with ADHD react better to treatment with methylphenidate when the patient has the COMT Val158Met polymorphism (Salatino-Oliveira et al., 2011:217;220) (section 2.10.3.2.2). Therefore, children with behavioural problems react better to treatment with methylphenidate in terms of behavioural disorders, possibly due to the presence of the G/G genotype or the COMT Val158Met polymorphism.

In accordance with the literature objectives, the recommended daily dosages and possible side effects of methylphenidate and atomoxetine were discussed in section 2.10.3.2.3. The safety of methylphenidate has not yet been established in children younger than six years, but a maximum dose of 2 mg/kg/day can be administered under close supervision from a healthcare provider. The recommended daily dosage, however, stipulates that 60 mg/day should not be exceeded. Methylphenidate is also available in a slow release formulation to be administered to children over the age of six years. The maximum dose of the slow release formulation is 72 mg/day (section 2.10.3.2.2) (Rossiter, 2014:508).

Side effects associated with methylphenidate include insomnia, anorexia, gastric discomfort and aggravation of bipolar, depression and anxiety symptoms. It has been proven that
methylphenidate does not have a significant effect on cardiovascular pathology (Mick et al., 2011:467; Hammerness et al., 2009:88), but should be taken into account when prescribing methylphenidate. Treatment with methylphenidate should absolutely be avoided within 14 days after cessation of treatment with MAOI's (section 2.10.3.2.3) (Novartis® Pharmaceuticals Corporation, 2013:1).

4.2.2.2.3 Atomoxetine

Atomoxetine is a non-stimulant drug indicated for the treatment of ADHD (Mosby’s Dictionary of Medicine, Nursing and Health Professions, 2009:160). The exact mechanism of action of atomoxetine is still unknown, but it has been found that atomoxetine inhibits the presynaptic noradrenalin transporter which leads to increased concentration of noradrenalin in the body as the re-uptake of noradrenalin is inhibited (Chamberlain et al., 2009:550; Baldessarini, 2006:431; Christman et al., 2004:1022). Atomoxetine increases dopamine and noradrenalin in the prefrontal cortex (Barton, 2005:i26) (section 2.10.3.3.1) and improves attention by decreasing activity in the inferior prefrontal cortex and increasing activity in the dorsal anterior cingulated cortex and dorsolateral prefrontal cortex and deactivation of the cigulofrontal activity (Chou et al., 2015:2305) (section 2.10.3.3.1).

The initial dose of atomoxetine for children and adults weighing more than 70 kg is 40 mg daily for exactly seven days; after this period, it should be gradually titrated up to a maximum dose of 80 mg per day (Rossiter, 2014:507) (section 2.10.3.3.2). The maximum dosage for atomoxetine in children/adults weighing less than 70 kg is 80 mg/day and 1.2 mg/kg/day for children/adults weighing less than 70 kg (Rossiter, 2014:507) (section 2.10.3.3.2). The most pertinent drug interactions with atomoxetine is paroxetine, fluoxetine and quinidine as these drugs may inhibit the liver enzymes needed to metabolise atomoxetine which may lead to increased, possibly dangerous, levels of atomoxetine in the system (section 2.10.3.3.3). Atomoxetine should also be avoided within 14 days of treatment with MAOIs (Baldessarini, 2006:445; Eli Lilly and Company®, 2014:3; Ogbru, 2014) (section 2.10.3.3.3). Atomoxetine also has a ‘black box’ warning stating that, children or adolescents with suicidal tendencies should avoid treatment at all costs (section 2.10.3.3.3). Atomoxetine has been associated with an increase in cardiac activity and may also lead to liver damage (Eli Lilly and Company®, 2014:4), but is otherwise well tolerated (section 2.10.3.3.3).
4.2.3 Comorbid and coexisting conditions associated with ADHD

The difference between comorbid conditions and co-existing conditions are discussed in section 2.9. There are various definitions for comorbidity. Comorbidity is defined as a cluster of single medical conditions that is alongside a medical condition diagnosed prior to the identification of the subsequent conditions in a single patient (Mosby’s Dictionary of Medicine, Nursing and Other Health Professions; 2009:422; Radner et al., 2014:253). The difference between comorbid and co-existing conditions are as follow; comorbid condition are indicated when conditions occur with an indicator disease, whereas co-existing conditions indicates the simultaneous occurrence of health conditions where no single conditions can be identified as the indicator condition (Meghani et al., 2013:2).

It is not uncommon to find other co-occurring conditions in children with ADHD (section 2.9). For example, Soppitt (2012:184) and Patel et al. (2012:25) showed that one ‘co-existing’ condition was present in 33% to 87% of patients with ADHD and two or more was present in 16% to 67% of patients with ADHD (section 2.9).

The main comorbid and co-existing conditions associated with ADHD as described in the DSM-IV, was included in chapter 2 (section 2.8.1-2.9.2). These conditions include:

- Oppositional defiant disorder (ODD)/conduct disorder (CD)
- Autism spectrum disorder (ASD)
- Intermittent explosive disorder (IED)
- Bipolar mood disorder (BMD)
- Tic disorders (TDs)
- Obsessive compulsive disorder (OCD)
- Depression and anxiety
- Panic disorders and agoraphobia
- Post-traumatic stress disorder (PTSD)
- Developmental co-coordination disorder (DCD);
- Learning disorder (LD);
• Asthma and atopic allergies, and

• Epilepsy.

The symptoms of ADHD are often similar to the symptoms of other psychiatric or neurodevelopmental disorders which can be found in patients with ADHD (section 2.9). It was also established that ADHD is not always accompanied by a psychiatric or a neurodevelopmental disorder, but also other chronic and acute conditions such as asthma and epilepsy (sections 2.9.1 and 2.9.2, respectively).

4.2.3.1 Oppositional defiant disorder (ODD)

ODD and CD are both known as externalising disorders (problematic developmental behaviour that affects the people in their immediate surroundings (section 2.8.1) (Gatzke-kopp et al., 2013:448). Approximately 50% of children with ODD and CD also meet the criteria for ADHD, making ODD and CD of the most prevalent comorbid conditions associated with ADHD (section 2.8.1).

4.2.3.2 Autism spectrum disorder (ASD)

Both ADHD and ASD present with symptoms of inattention and underdeveloped social behaviour (section 2.8.2). Children with ADHD are bound to have temper-tantrums due to lack of impulse control whereas a change in daily routine will cause a temper-tantrum in children with ASD (APA, 2013:64; Glicken, 2009:229; Harris & Brown, 2012:214) (section 2.8.2).

A positive association between ASD and ADHD and atopic allergies before the ages two to three years has been made (Chen et al., 2014:317; Liao, 2016:171) (section 2.8.2).

4.2.3.3 Intermittent explosive disorder (IED)

The diagnostic criteria for IED include failure to control aggression leading to a verbal and/or physical eruption. When these eruptions lead to damage to property or physical injury more than three times in a cycle of 12 months, a child can be acknowledged for further testing for a possible diagnosis of IED (APA, 2013:466) (section 2.8.3).

4.2.3.4 Bipolar mood disorder (BMD)

Bipolar mood disorder (BMD) consists of manic and depressive phases. The elapsed time between these two between these two phases vary from patient to patient (Fearley, 2012:258) (section 2.8.4). The difference between BMD and ADHD is, when a patient with BMD experiences a mood phase, it can last up to several days, whereas, a child with ADHD may experience several
changes in their mood in a day. Symptoms of BMD have been associated with 0.5% of children with ADHD (section 2.8.4).

4.2.3.5 Tic disorders (TDs)

Tic disorders (TDs) are chronic neuropsychiatric disorders, and are not classified as mental health conditions. The symptoms associated with TDs are chronic motor tics (80%) or vocal tics (20%), but eventually patients will present with symptoms of both types of tics (APA, 2013:81) (section 2.8.5). Associations with TDs include ADHD, ASD and OCD (Ravenscroft, 2012:241) (section 2.8.5).

4.2.3.6 Obsessive compulsive disorders (OCD)

A patient with OCD has the urge to repeat certain movements/actions based on an obsession or self-imposed rules (APA, 2013:80) (section 2.8.6). The majority of children with OCD present with obsessions and compulsions, but it is possible to present with obsessions without any routines and rituals (Barker, 2012:243) (section 2.8.6).

4.2.3.7 Depression and anxiety

Depression and anxiety are known as internalising disorders (Magdalena, 2012:239) (section 2.8.7.1 and 2.8.7.2 respectively).

Internalising disorders have been found in 8% to 50% of children with or without ADHD. (Armstrong et al., 2015:740; Halldorsdottir & Ollendick, 2013:311; Patel et al., 2012:28; Schatz & Rostain, 2006:141; Takeda, 2012:421; Wilkinson, 2009:376)

The difference between a child with an anxiety disorder and a child with ADHD is that a child with an anxiety disorder lacks attentiveness due to stress and worry, whereas a child with ADHD becomes inattentive because of something more interesting than the task at hand (APA, 2013:64) (section 2.8.7).

4.2.3.8 Panic disorders and agoraphobia

Phobias are unrealistic fears of particular situations or objects (section 2.8.11). These fears interfere with all aspects of the child’s life (Glicken, 2009:145) (section 2.8.11). Agoraphobia is defined as a constant fear of being trapped with no escape and no help. This particular phobia is often observed in children who suffer from illnesses like asthma, OCD, and separation anxiety (Eisendrath & Lichtmacher, 2013:1040; Glicken, 2009:144) (section 2.8.11).
4.2.3.9 Post-traumatic stress disorders (PTSD)

Post-traumatic stress disorder is found in people who have experienced life-threatening situations (section 2.8.8). This traumatic experience then causes recurring thoughts related to the experience. The physical manifestations are observed as these children are perceived as agitated and stressed (Glicken, 2009:145) (section 2.8.8).

4.2.3.10 Developmental co-ordination disorder

Children with DCD struggle to develop fine motor skills (section 2.8.9). These children are observed as clumsy, and they tend to underachieve in any activity that requires fine motor skills, which could negatively impact academic performance (APA, 2013:74) (section 2.8.9).

4.2.3.11 Learning disorders (LD)

Learning disorder (LD) is found in people who are unable to perform a certain academic task, despite their level of intelligence. They might not have been exposed to appropriate academic opportunities, but can be talented in other areas yet, may never excel in these areas (section 2.8.10). The LD may be recognised during the school-aged years but it may only come into effect when the patients have to use the skills they lack (Breuggemann Taylor, 2014:2) (section 2.8.10).

4.2.3.12 Asthma and atopic allergies

It has been found that anti-asthmatic medication is prescribed more often to children with ADHD and vice versa (section 2.9.1). These children are also more likely to suffer from an atopic allergy (Fasmer et al., 2016:567) (section 2.9.1). There is a strong association between co-existing asthma and atopic allergies in children with ADHD and/or ASD (Chen et al., 2013:1210; Liao et al., 2016:250) (section 2.9.1).

4.2.3.13 Epilepsy

Associations between epilepsy and ADHD have been found in the literature (section 2.9.12). There is a larger association between epilepsy and ADHD than between asthma and epilepsy (Kauffman et al., 2009:728; Kwong et al., 2016:57) (section 2.9.2).

Epilepsy is associated with inattentive type ADHD, but there is no concise explanation for this phenomenon (Kwong et al., 2016:57; Reilly; 2011:885; 890) (section 2.9.2).
4.2.4 Studies conducted on the prescribing patterns of methylphenidate and atomoxetine internationally and in South Africa

An overall increase in national and international studies was found the prescription of methylphenidate and atomoxetine of which methylphenidate is still the first line treatment of choice for ADHD. Treatment for ADHD is still mostly prescribed to boys, but many studies have shown a decrease in the male:female ratio as more girls are being diagnosed with ADHD. The age group of six to 12 years still receive the majority of prescriptions throughout the literature (Refer to section 2.11, Table 2.1). Co-prescribed medication, for the treatment of other psychiatric disorders, included anti-anxiety/tranquilizers, bipolar disorder, anti-depressants, psychotropic medication and anti-convulsants. Co-prescribed medication for the treatment of co-existing illnesses included analgesics, antipyretics, antihistamines, penicillin, cephalosporins and decongestants. Co-existing conditions included was oppositional defiant disorder/conduct disorder, depression and autism spectrum disorder (Refer to section 2.11, Table 2.1).

4.3 Overall findings of the empirical study

The specific objectives of the empirical phase of the study included:

- Determining the prevalence of ADHD in children and adolescents under the age of 18 years who received treatment with methylphenidate and atomoxetine in the private health sector of the Western Cape Province from 2005 to 2013, using a medicines claims database stratified by age, gender and geographic distribution.

- Identifying the prescribing patterns of methylphenidate and atomoxetine in children and adolescents under the age of 18 years in each district in the Western Cape.

- Determining the prevalence of co-morbid conditions in children with ADHD.

The findings according to the objectives of the empirical study were achieved in Chapter 3.

4.3.1 Prevalence of ADHD treatment in children and adolescents in the Western Cape

This objective was achieved in manuscript one (refer to section 3.2).

Approximately 2–3% of the total number of children and adolescents in the Western Cape on the database received either methylphenidate and/or atomoxetine over the study period of nine years. The majority of patients in our study population were boys, with a ratio of three to four male diagnoses for every female diagnosis. These findings were similar to other South African studies.
Analysis by age group showed the progressive prescribing of methylphenidate for children aged six years and younger. Methylphenidate is usually not administered to children younger than six years, as safety and efficacy in this age group has not been established (Rossiter, 2014; Snyman, 2014) (refer to section 2.10.3.2.2). There have been several reports of the use of psychotropic medication in preschool populations worldwide; these are similar to the findings of the present study. For example, a study conducted in the USA on this particular matter indicated that 1.19% of children under the age of four years received prescriptions for psychotropic medication of which 0.61% of these prescriptions was for ADHD, 0.34% were given to children between the ages of one and two years and 0.17% of children were still infants (Garfield et al., 2015) (section 2.11). The findings in this study could be due to an increase in diagnoses of ADHD in children aged ≤6 years or the prescribing of methylphenidate for off-label use. Off-label prescriptions for methylphenidate have been issued to children suffering from narcolepsy, autism, behavioural disorders and intellectual disabilities (refer to section 2.11, Table 2.1).

4.3.2 Prescribing patterns of methylphenidate and atomoxetine

This objective was achieved in manuscript 1 (refer to section 3.2), as well as the section containing additional results (refer to section 3.3).

In accordance with the empirical objectives, the total number of children (boys being the majority) receiving treatment for ADHD increased from 1.45% in 2005 to 2.47% in 2013 (refer to section 3.2, Table 1). The highest increase in prescriptions for ADHD medication was found in age group 1 (6.00%) (refer to section 3.2, Table 1).

Based on geographical area, the Cape Town Metropolitan Municipality had the highest number of ADHD patients in the entire Western Cape Province (Refer to chapter 3 section 3.2, Table 2). This number may be due to the fact that the Cape Town Metropolitan Municipality consists of 64.20% of the total population in the Western Cape (as per calculations based on the figures obtained from the Local Government Handbook for South Africa) (Main, 2015) (refer to section 1.2). Over the duration of the study, the number of patients receiving ADHD treatment increased in the following areas: Overberg and West Coast districts and the Breede Valley, Drakenstein, Mossel Bay, George, Knysna, Overstrand, Swartland, and Saldanha Bay local municipalities. The following areas showed a decrease during the study period: Cape Town Metropolitan Municipality, Witzenberg, Stellenbosch, Bitou, Oudtshoorn, and Theewaterskloof local municipalities (refer to section 3.2, Table 2). The male:female ratio for methylphenidate remained relatively stable over
the study period, but atomoxetine prescriptions for boys increased by 4.16% and 1.64% for girls (refer to section 3.2, Table 2).

There was a significant increase in the number of prescriptions per patient during the study period (refer to section 3.2, Table 3). Overall, there was a higher increase in prescriptions for atomoxetine (3.15%) than for methylphenidate (0.13%). A small increase in prescriptions for methylphenidate were found in boys (0.31%) and girls (0.55%) (refer to section 3.2, Table 3). The biggest increase was for the prescription of methylphenidate (13.00%) for children in age group 1 (0, ≤6 years). There were no prescriptions for atomoxetine for children in age group 1 (0, ≤6 years), but the biggest increase for prescriptions for atomoxetine was found in children in age group 3 (>12, <18 years) (6.04%) (refer to section 3.2, Table 3). The mean number of prescriptions per patient per year didn’t show a significant increase (Cohen’s $d=0.14$) and a fair increase was found in atomoxetine prescriptions per patient per year (Cohen’s $d=0.62$) (refer to section 3.2).

These trends are in line with international studies (refer to section 2.11, Table 2.1). Most prescriptions in the study were for methylphenidate; however, prescriptions for atomoxetine increased significantly more than that of methylphenidate over a study period of nine years. This trend was also present in studies previously conducted in South Africa (Truter, 2005; Truter, 2014) as well as international studies (Boland et al., 2015; Shyu et al., 2016) (refer to section 2.11, Table 2.1).

The recommended daily dose (RDD) for methylphenidate and atomoxetine was calculated according to the 5th and 95th percentile of the CDC stature-for-age and weight-for-age charts and the product strengths available (refer to section 3.3, Table 3.2).

The prescribed daily dose (PDD) for methylphenidate for children aged ≤6 years ranged between 10 mg to 40.39 ± 11.45 mg (95% CI, 33.47-47.30) in girls, and 10 mg to 35.00 ± 28.87 (95% CI, -10.94-80.94) in boys (refer to section 3.3 Table 3.3). These doses are in line with the RDD for children in age group 3 (>12, <18 years) or a young child weighing approximately 30 kg. The PDD for children in age group 2 (>6, ≤12 years) and 3 (>12, <18 years) was below the RDD, but the maximum doses were in line with appropriate the RDD for these age groups from 2006–2013. In 2005, the maximum daily dose was exceeded for boys in age group 2 (>6, ≤12 years) and 3 (>12, <18 years) with a dose of 85.78 mg (refer to section 3.3, Table 3.3). The most frequent PDD for methylphenidate was for 20 mg daily (section 3.3). In general, the majority of prescriptions for methylphenidate were within the boundaries of the RDD (refer to section 3.3). The PDD for atomoxetine for both boys and girls in age groups 2 (>6, ≤12 years) and 3 (>12, <18 years) were mostly within the range of the calculated RDD (refer to section 3.3, Table 3.2). The maximum daily dose for girls in age group 2 (>6, ≤12 years), however, exceeded the RDD throughout the study period, but the PDD for girls
in age group 2 (>6, ≤12 years) was only marginally exceeded in 2011 and 2013 (refer to section 3.3). For children in age group 3 (>12, <18 years) the PDD remained in accordance with the RDD, but the maximum daily dose was exceeded in 2006 and 2011 (refer to section 3.3). The most frequent PDD for atomoxetine was 40 mg daily (refer to section 3.3).

4.3.3 Prevalence of conditions comorbid in children and adolescents under the age of 18 years with ADHD

The objective was achieved in manuscript 2 (refer to section 3.4).

There are various definitions for comorbid and co-existing conditions (Meghani et al., 2013:2; Mosby's Dictionary of Medicine, Nursing and Other Health Professions, 2009:422; Patel et al., 2012:27; Radner et al., 2014:253). These two terms are often used interchangeably, even though they have two separate meanings (refer to section 2.9). As this was a cross-sectional study, it could not be determined whether these conditions were comorbid or co-existing conditions; therefore, these will be referred to as ‘other co-occurring conditions’. These conditions were determined by the chronic disease list (CDL) conditions and the main pharmacological classes of other medicine received at least once by patients during the study period.

A total of 93 (3.70%) of children in with ADHD in the Western Cape Province presented with co-occurring chronic disease list conditions (CDL) of which 70.2% (n=90) presented with one CDL conditions and 3.2% (n=3) presented with two CDL conditions (refer to section 3.4, Table I). Asthma was the most prevalent co-occurring CDL condition (96.77%), followed by epilepsy (17.20%). Both asthma and epilepsy was prevalent in three patients (refer to section 3.4, Table I). The other CDL conditions included type 1 diabetes mellitus, hypothyroidism and multiple sclerosis (MSS) (refer to section 3.4, Table 2). A unique relation between hypothyroidism and multiple sclerosis co-occurring with ADHD was found, but all of these instances comprised of no more than two people in a particular year (refer to section 3.4, Table I).

The top five pharmacological classes received by patients are as follow: antimicrobials (54.82%), respiratory system agents (10.00%), dermatologicals (6.68%), central nervous system agents (6.15%), ear, nose and throat medicine (4.97%), autacoids (3.49%), analgesics (2.72%) and endocrine system agents (2.54%) (refer to section 3.4, Table II).

From the antimicrobial class, patients mostly received beta-lactam antibiotics. Treatment for respiratory conditions was mostly listed as medication for coughs and colds and the treatment for ear, nose and throat diseases, the treatment was mostly received for eardrops and ointments. Treatment for pain and fever consisted mostly form combination analgesic preparations (refer to section 3.4, Table II).
Antidepressants were the most prevalent medication group used in the central nervous system class, acne preparations were the most prevalent medication group used in the dermatological class and corticosteroids were the most prevalent medication group used in the endocrine agent class (refer to section 3.4, Table II).

The study found asthma to be more prevalent among children with ADHD than epilepsy. This is contradictory to the literature stating that ADHD is associated with epilepsy more often than to asthma (Kwong et al., 2016) (refer to section 2.9.2). The possibility of co-existing atopic conditions was also determined in this study, as there were prescriptions for autacoids and topical- and systemic corticosteroids. The literature stated associations between asthma, atopic allergies and ADHD and ASD (Chen et al., 2013; Fasmer et al., 2016; Liao et al., 2016) (refer to section 2.9.1).

The prevalence of co-existing epilepsy in this study is in line with the literature and states that epilepsy and ADHD may have similar root causes, and therefore, the high prevalence of epilepsy in patients with ADHD and vice versa (Kauffman et al., 2009) (refer to section 2.9.2).

It was found that antimicrobial agents were used mostly in young children. This is in agreement with the literature, as communal exposures to microbes from day care centres may increase microbial infections (Rossignoli et al., 2007) (refer to section 3.4).

Positive associations between ADHD and acne have been found in children with ADHD (Dreno et al., 2003; Gupta et al., 2014). As the study population mostly consisted of children and adolescents, the presence of acne treatment was imminent (refer to section 3.4).

Patients possibly received medication for the central nervous system for the treatment of anxiety disorders; these drug classes are indicated for the treatment of anxiety disorders in children (Stein, 2013; Strawn et al., 2015; Dufton et al., 2009) (refer to section 3.4).

In conclusion, the overall findings of this study indicated that the majority of prescriptions were given for the treatment of conditions that could be considered acute diseases.

4.4 Study strengths and limitations

The findings of this study must be measured, considering its limitations. This study was mainly limited by the pool size. Data were derived from only one province in South Africa; therefore, external validity was limited. The study population only included children listed as active members on a medical aid in the private healthcare sector. Although the PMB that was used is considered one of the largest in South Africa, only 17.9% of the South African population belong to private
medical aid schemes, according to StatsSA (2012:17). This means that the majority of the population was not included in this study.

Another limitation was that the data did not allow the researchers to distinguish between the various types of ADHD, and whether methylphenidate and/or atomoxetine were used for off-label purposes such as treatment for narcolepsy, ASD, ODD/CD or intellectual disability.

There are, however, quite a few benefits regarding the use of administrative data (Crystal et al., 2007:12). It covers a broad range of people who are covered under the scheme with all-inclusive advantages, as well as information on care in the majority of settings. This leads to ample statistical supremacy. It also provides a detailed analysis of rare conditions, comorbidities, subgroups as well as individuals with severe and complicated diagnoses of several illnesses. Large research studies can access this information at a minimal cost. Most populations can be accessed, including minority groups. Access to this information also broadens the horizons on healthcare knowledge about people with disabilities, other genetic makeup, and mental illnesses. Administrative data sources obtain diagnostic and treatment information from healthcare providers instead of consumers themselves; therefore, the data is unobstructed and derived from the entire population covered. This avoids any bias and may assist any beneficiary with the inability to do a self-report. Medicine claims data contain a very long, detailed history over years on healthcare events per covered beneficiary. These include dates of diagnoses, treatments and follow-ups. This information be updated quite frequently at minimal costs. It indicates the initiation date of medical treatment and patient compliance. The administrative claims data are also programmed to contain information on the geographic region where the medial diagnosis and treatment took place as well as the healthcare providers involved in the healthcare of the beneficiary, which is very helpful when investigating possible prescribing and treatment patterns as well as effect patterns (Crystal et al., 2007:12).

4.5 Recommendations

This study has found increases in prescriptions for methylphenidate and especially atomoxetine from 2005–2013, and has also identified the possibility of ‘off-label’ usage of methylphenidate. The prevalence of co-existing disorders in children with ADHD was also deemed important as there was, and still is, paucity of available information on co-existing conditions of ADHD in South Africa, particularly in the Western Cape Province.

Recommendations for future studies include furthering the impact of geographical location on the prescribing patterns of ADHD medications in children, but also prescribing patterns of medication in general which may be influenced by geographical location. Future studies on the prescribing patterns of atomoxetine are also recommended from the results of this study to establish if
prescriptions for atomoxetine continue to increase over time. Studies could be done on the influence of gender on the prescribing of ADHD medication use to establish whether the ratio is continuously changing over time or not.

Concerning the findings of comorbid and co-existing conditions, future studies could include chronic and acute treatments involved when treating such conditions. The effect of children’s gender on the prevalence of comorbid ADHD can also be studied in the future to determine whether there are any differences and whether this ratio also changes over time.

Economic factors involved in the treatment of ADHD and co-existing conditions and the changes thereof over time is also recommended for future studies

4.6 Chapter summary

This chapter entailed a short but detailed summary on the findings of this study along with the limitations and recommendations for future studies based on the prevalence of ADHD in children and adolescents, the geographical influence on prescriptions and co-existing conditions associated with ADHD. Hereby the final chapter of this dissertation is concluded.
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APPENDIX A

A.1 Ethics certificate

Ms MJ Eksteen
Pharmacy Practice

Dear Ms Eksteen

APPROVAL: ETHICS APPLICATION: NWU-00179-14-A1 (MJ EKSTEEN-L JOUBERT) "MEDICINE PRESCRIBING PATTERNS IN A SECTION OF THE PRIVATE HEALTH SECTOR UTILISING DATA FROM A PHARMACEUTICAL BENEFIT MANAGEMENT COMPANY IN SOUTH AFRICA"

Thank you for amending your sub-study “Prescribing patterns of ADHD medication in children under the age of eighteen years in the Western Cape Province from 2005-2013” application. All ethical concerns have now been addressed and ethical approval is granted until 31/12/2017.

Please note that any changes to the approved application must be submitted to the Health Research Ethics Committee for approval before implementation.

Yours sincerely

Prof Minrie Greeff HREC Chairperson

8 September 2015
File reference: 9.1.5.3
APPENDIX B

B.1: SA Health Gesondheid Author Guidelines


Open Access

Health SA Gesondheid is an open access journal: all articles will be immediately and permanently free for everyone to read and download. University of Johannesburg charges a publication fee of R 1150 (South African Rand) per published page (PDF format) inclusive of taxes (also known as an article publishing charge APC) which needs to be paid by the authors or on their behalf e.g. by their research funder or institution. If accepted for publication in the journal following peer-review, authors will be notified of this decision and requested to pay the article processing charge in due time. Following payment of this charge, the article will be published by University of Johannesburg in Health SA Gesondheid which is made freely available at no further charge through ScienceDirect (Open Access). No article will be published until page fees are paid in full and proof of payment has been received by the Editorial Office.

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Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:

- E-mail address
- Full postal address
All necessary files have been uploaded:

*Manuscript:*

- Include keywords
- All figures (include relevant captions)
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APPENDIX C

C.1: Stature-for-age and weight-for-age percentiles (girls) (CDC, 2015)
C.2: Stature-for-age and weight-for-age percentiles (boys)(CDC, 2015)
APPENDIX D

D.1: South African Family Practice Author Guidelines


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