

Prescribing patterns of central nervous system drugs among children, adolescents and their families with/without treatment for ADHD

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BPharm

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*“For I know the plans I have for you,” declares the Lord,
“plans to prosper you and not to harm you, plans to
give you hope and a future.” – Jeremiah 29:11*

LIST OF ACRONYMS

AACAP	American Academy of Child and Adolescent Psychiatry
AAP	American Academy of Pediatrics
ADHD	Attention-Deficit/Hyperactivity Disorder
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANOVA	One-way analysis of variance
APA	American Psychiatric Association
ASD	Autism spectrum disorder
BPA	Bisphenol A
CD	Conduct disorder
CDC	Centers for Disease Control and Prevention
CDL	Chronic Disease List
CNS	Central nervous system
COMT	Catechol-O-methyltransferase
CYP	Cytochrome P450
DA	Dopamine
DAT	Dopamine Transporter
DCD	Developmental co-ordination disorder
DEHP	di (2-ethylhexyl) phthalate
DRD2	Dopamine D2 receptor
DRD4	Dopamine D4 receptor
DRD5	Dopamine 5 receptor
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, version-5
DUR	Drug Utilisation Research
FDA	Food and Drug Administration
GABA	γ -aminobutyric acid
GAD	General Anxiety disorder
H	Histamine

ICD10	International Classification of Diseases, 10th Revision
LD	Learning Disabilities
MAO	Monoamine Oxidase enzyme
MAOI	Monoamine Oxidase Inhibitor
MUSA	Medicine Usage in South Africa
NE	Norepinephrine/ Noradrenalin
NET	Norepinephrine transporter
OCD	Obsessive compulsive disorder
ODD	Oppositional defiant disorder
PAH	Polycyclic aromatic hydrocarbon
PBM	Pharmaceutical Benefit Management company
PDD	Prescribed daily dose
PFC	Poly-fluoroalkyl chemical
PMB	Prescribed Minimum Benefits
PTSD	Post-traumatic stress disorder
RD	Reading disability
RDD	Recommended daily dose
SAD	Social anxiety disorder
SAMF	South African Medicines Formulary
SAS	Statistical Analysis System® program
SERT	Serotonin transporter
SES	Socio-economic status
SNAP25	Synaptosomal Associated Protein of 25Kd
SNRI	Serotonin and norepinephrine re-uptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SUD	Substance use disorder
TCA	Tricyclic antidepressant
TD	Tic disorder
USA	United States of America

WHO

World Health Organization

5-HT

5-Hydroxytryptamine

ABSTRACT AND KEYWORDS

Prescribing patterns of central nervous system drugs among children, adolescents and their families with/without treatment for ADHD

This study set out to investigate possible differences in the prescribing patterns of central nervous system (CNS) medication in children and adolescents with and without treatment for ADHD in the South African private health sector, as well as family tendencies regarding methylphenidate and atomoxetine usage. A retrospective, longitudinal study was performed analysing medicine claims data from a nationally representative Pharmaceutical Benefit Management (PBM) company for the study period 1 January 2005 to 31 December 2013.

During the study period, the prevalence of ADHD in children and adolescents increased from 2.11% in 2005 to 4.40% in 2013. When the ADHD prevalence in families of children with and without ADHD was analysed, there was an increase from 2005 (14.94%) to 2013 (29.09%). ADHD children and adolescents who also received prescriptions for other CNS medication received higher average prescribed daily doses (PDD) than ADHD children and adolescents who did not receive any CNS medication. The highest number of methylphenidate- (16.69%) and atomoxetine- (13.75%) containing items that exceeded the recommended daily dose was for children six years and younger.

Prevalence of CNS medication usage in children and adolescents aged 18 years and younger decreased from 5.12% in 2005 to 4.48% in 2013. ADHD children and adolescents who received CNS medication increased, whereas prescribing decreased in CNS-only children and adolescents. Antidepressants were the most prevalent CNS active ingredient prescribed to ADHD children, and represented 41.51% of all CNS prescriptions. Among the antidepressants, the selective serotonin reuptake inhibitors (SSRIs) were the most frequently prescribed (20.99%). The most common prescribed CNS medication prescribed to non-ADHD children and adolescents was the pharmacological class anxiolytic agents (39.12%).

Potential drug-drug interactions, including potential significant level 1, 4 and 5 drug-drug interactions, were identified in a total 1.94% (n = 4 530) of all prescriptions for methylphenidate. The highest number of potential drug-drug interactions with methylphenidate was found in prescriptions for which imipramine (51.79%) and amitriptyline (37.00%) were indicated. Of all atomoxetine prescriptions claimed during the study period, 3.89% (n = 1 038) had potential significant level 1 or 2 drug-drug interactions. Overall, escitalopram (37.67%) and citalopram (29.58%), in combination with atomoxetine, accounted for the most frequent potential drug-drug interactions.

In conclusion, this study established prevalence statistics of ADHD in South African children and adolescents, as well as the prevalence of CNS medication usage among these children and adolescents. Secondly, the prevalence of ADHD in families of children and adolescents with, and without ADHD, was determined. Methylphenidate and atomoxetine prescribing patterns in children and adolescents were determined by comparing the prescribed daily dose and the recommended daily dose in the different age groups.

This study also concluded the prevalence of CNS medication usage among ADHD and non-ADHD children and adolescents with specific reference to age- and gender groups and the most frequently prescribed CNS medications for both the ADHD children and adolescents and the non-ADHD children and adolescents. Lastly, potential drug-drug interactions were determined on prescriptions for methylphenidate and atomoxetine and other CNS medication.

KEYWORDS: Attention-Deficit/Hyperactivity Disorder, children, adolescents, family, central nervous system medication, potential drug-drug interactions

OPSOMMING EN SLEUTELWOORDE

Voorskrifpatrone van sentrale senuweestelselmedikasie tussen kinders, adolessente en hul families met/sonder behandeling vir ADHD

Hierdie studie het gepoog om die moontlike verskille in voorskrifpatrone te bepaal van sentrale senuweestelselmedikasie (SSS) in kinders en adolessente met en sonder behandeling vir ADHD in die Suid-Afrikaanse private gesondheidsektor, sowel as familiële neigings ten opsigte van metielfenidaat- en atomoksitien-verbruik. 'n Retrospektiewe, longitudinale studie is uitgevoer wat medikasie-eise-data van 'n nasionaal verteenwoordigende farmaseutiese voordelebestuursmaatskappy analiseer vir die tydperk 1 Januarie 2005 tot 31 Desember 2015.

Gedurende die studietydperk het die voorkoms van ADHD in kinders en adolessente toegeneem vanaf 2.11% in 2005 tot 4.4% in 2013. Toe die ADHD-voorkoms in families van kinders met en sonder ADHD geanaliseer is, was daar 'n toename vanaf 2005 (14.94%) tot 2013 (29.09%). ADHD-kindere en -adolessente wat ook voorskrifte ontvang vir ander SSS-medikasie, het hoër gemiddelde voorgeskrewe daaglikse dosisse (VDD) ontvang as ADHD-kindere en -adolessente wat nie enige SSS-medikasie ontvang nie. Die hoogste hoeveelheid metielfenidaat- (16.69%) en atomoksitien-bevattende (13.75%) items wat die voorgeskrewe daaglikse dosis oorskry, was vir kinders ses jaar en jonger.

Die voorkoms van SSS-medikasiegebruik in kinders en adolessente 18 jaar en jonger het afgeneem vanaf 5.12% in 2005 tot 4.48% in 2013. ADHD-kindere en -adolessente wat SSS-medikasie gebruik, het toegeneem, terwyl die voorskryf van slegs SSS-medikasie vir kinders en adolessente afgeneem het. Antidepressante was die mees algemene SSS-aktiewe bestanddeel voorgeskryf aan ADHD-kindere, en het 41.51% van alle SSS-voorskrifte uitgemaak. Tussen die antidepressante is die selektiewe serotonien-heropname-inhibeerders (SSHI) meeste voorgeskryf (20.99%). Die mees algemene voorgeskrewe SSS-medikasie voorgeskryf aan nie-ADHD-kindere was die farmakologiese klas anksiolitiese middels (39.12%).

Potensiële geneesmiddel-geneesmiddel interaksies, insluitend potensiële beduidende vlak 1, 4 en 5 geneesmiddel-geneesmiddel interaksies is geïdentifiseer in 'n totale 1.94% (n = 4 530) van alle voorskrifte vir metielfenidaat. Die hoogste aantal potensiële geneesmiddel-geneesmiddel interaksies met metielfenidaat is gevind in voorskrifte waarvoor imipramien (51.79%) en amitriptilien (37.00) aangedui is. Van al die atomoksitien voorskrifte geëis gedurende die studietydperk, het 3.89% (n = 1 0380) 'n potensiële beduidende vlak 1 of 2 geneesmiddel-geneesmiddel interaksies gehad.

Ten slotte het hierdie studie die voorkomsstatistieke van ADHD in Suid-Afrikaanse kinders en adolessente, sowel as die voorkoms van SSS-medikasiegebruik by hierdie kinders en adolessente bepaal. Tweedens is die voorkoms van ADHD in families van kinders en adolessente met en sonder ADHD bepaal. Metielfenidaat en atomoksitien voorskrifpatrone in kinders en adolessente is bepaal. Metielfenidaat- en atomoksitien voorskrifpatrone in kinders en adolessente is bepaal deur die voorgeskrewe daaglikse dosis en die aanbevole daaglikse dosis in die verskillende ouderdomsgroepe bepaal.

Hierdie studie het ook 'n gevolgtrekking gemaak oor die voorkoms van SSS-medikasiegebruik tussen ADHD- en nie-ADHD-kinders en -adolessente met spesifieke verwysing na ouderdoms- en geslagsgroepe en die mees algemene voorgeskrewe SSS-medikasie vir beide die ADHD-kinders en -adolessente en die nie-ADHD-kinders en -adolessente. Laastens is potensiële geneesmiddel-geneesmiddel interaksies bepaal op voorskrifte vir metielfenidaat en atomoksitien en ander SSS-medikasie.

SLEUTELWOORDE: Aandaggebrekhiperaktiwiteitsteuring, kinders, adolessente, familie, sentrale senuweestelselmedikasie, potensiële geneesmiddel-geneesmiddel-interaksies

PREFACE

This dissertation has been written in article format as required by the North-West University. Chapter 3 contains the results in the form of two manuscripts, which will be submitted to the following journals for possible publication: *Journal of clinical pharmacy and therapeutics*, and *Pharmacoepidemiology and drug safety*. The manuscripts were written in accordance with the author guidelines provided by each respective journal, and included in the annexures. The bibliography of the dissertation, however, was written in the Harvard style, as required by the North-West University.

Division of chapters:

Chapter 1 provided the scope of the study, and explained the research methodology that was used to conduct the study. Chapter 2 provided a review of the current literature regarding Attention-Deficit/Hyperactivity Disorder (ADHD) in children and adolescents, prevalence, and comorbidities associated with ADHD. Chapter 3 contains the results in the form of two manuscripts. Chapter 4 includes the conclusions, recommendations, strengths and limitations of the study.

The supervisor and co-supervisor acted as co-authors in the manuscripts included in Chapter 3. Consent was given to include the manuscripts in the results chapter. The tables on the following pages provide the contributions made by each respective author.

AUTHORS' CONTRIBUTIONS (MANUSCRIPT 1)

The contribution of each author for Manuscript 1, entitled “Methylphenidate and atomoxetine prescribing patterns in the South African private health sector (2005-2013)” is stipulated in the following table:

Author	Role in studies
Mrs S de Villiers	Responsible for the literature review Planning and design of study projects and research presented in the manuscripts Responsible for the statistical analysis plan Interpretation of the results Primarily responsible for writing of the manuscripts
Prof MS Lubbe	Supervision of concept and design of study and manuscript Acquisition of data and complex programming for statistical analysis Supervision in the writing of the manuscripts and study Revising the manuscript critically for important intellectual content and final approval of the version to be published
Dr JR Burger	Co-supervision of concept and design of study and manuscript Supervision in the writing of the manuscripts and study Support of statistical analyses Guidance in the interpretation of results Review of the manuscript critically and final approval of the version to be published
Prof I Truter	Critical review of the dissertation
Mrs M Cockeran	Responsible for the verification of the research design, statistical analysis and interpretation of results.

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

I declare that I have approved the above-mentioned manuscripts and that my role in this study, as indicated above, is representative of my actual contributions and I hereby give my consent that it may be published as part of the MPharm study of S de Villiers.

Prof MS Lubbe

Prof I Truter

Dr JR Burger

Mrs M Cockeran

AUTHORS' CONTRIBUTIONS (MANUSCRIPT 2)

The contribution of each author for Manuscript 2, entitled “Prescribing patterns of other central nervous system medication in South African children and adolescents with/without treatment for ADHD and its potential drug-drug interactions” is stipulated in the following table:

Author	Role in studies
Mrs S de Villiers	Responsible for the literature review Planning and design of study projects and research presented in the manuscripts Responsible for the statistical analysis plan Interpretation of the results Primarily responsible for writing of the manuscripts
Prof MS Lubbe	Supervision of concept and design of study and manuscript Acquisition of data and complex programming for statistical analysis Supervision in the writing of the manuscripts and study Revising the manuscript critically for important intellectual content and final approval of the version to be published
Dr JR Burger	Co-supervision of concept and design of study and manuscript Supervision in the writing of the manuscripts and study Support of statistical analyses Guidance in the interpretation of results Review of the manuscript critically and final approval of the version to be published
Prof I Truter	Critical review of the dissertation
Mrs M Cockeran	Responsible for the verification of the research design, statistical analysis and interpretation of results

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

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Prof I Truter

Dr JR Burger

Mrs M Cockeran

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CHAPTER 1: INTRODUCTION AND SCOPE OF STUDY

1.1 Introduction

This chapter reflects on the general layout of this study, which includes the background and problem statement, research objectives, research methodology, data analysis, ethical considerations and division of chapters.

1.2 Background and problem statement

Attention-Deficit/Hyperactivity Disorder (ADHD) is defined by the American Psychiatric Association (APA) (2013:59) as “a *persistent pattern of inattention and/or hyperactivity/impulsivity*”. A practitioner needs to carry out a detailed interview regarding the DSM-IV symptoms in order to diagnose ADHD (APA, 2000:80). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (APA, 2013:59), three subtypes of ADHD can be defined (see Annexure A for specific inattention and hyperactive impulsive items), namely:

- ADHD, Predominately inattentive presentation (F90.0);
- ADHD, Predominately hyperactive/impulsive presentation (F90.1); and
- ADHD, Combined presentation (F90.2).

ADHD is the most common neurodevelopmental disorder in early childhood and adolescents (Ferguson, 2000:182; Polanczyk *et al.*, 2007:942). In a comprehensive systematic review of studies addressing ADHD conducted in 2007, Polanczyk *et al.* (2007:945) estimated a world-wide pooled prevalence of 5.3% in children 18 years of age and younger. In a survey of 6 094 primary school children in Limpopo, South Africa, Meyer *et al.* (2004:131) found that 19.7% of participants had ADHD.

There are numerous factors (e.g. culture, age and gender) that influence the prevalence of ADHD. Meyer *et al.* (2004:131) found small cultural differences in the prevalence of ADHD between various South African cultures as well as between South African and other ‘Western’ cultures. The prevalence of this disorder is higher in males than in females, with a ratio of 3:1 (Meyer & Sagvolden, 2006:2; Snyman & Truter, 2012:2995; Truter, 2005:63). In a study conducted by Castle *et al.* (2007:336), it was found that boys were 2.3 times more likely to use medication for ADHD than girls. According to the Centers for Disease Control and Prevention (CDC) (2013), males (4.2%) were more likely than females (2.2%) (aged 12 to 19 years) to use ADHD medication in the United States of America (USA). Although the diagnostic criteria are

neutral with respect to gender and age, the condition has been most closely associated with school-age boys, especially those with hyperactive-impulsive symptoms (Castle *et al.*, 2007:337). ADHD is not limited to childhood. Researchers have estimated that 30% to 60% of children who have ADHD will continue to be impaired by the condition as adults (Kessler *et al.*, 2006:718; Lee *et al.*, 2008:371; Markowitz & Patrick, 2001:754; Weiss & Murray, 2003:716; Wender *et al.*, 2001:4).

Methylphenidate is the most commonly prescribed medication for ADHD (Snyman & Truter, 2012:2996), whereas atomoxetine is the only non-stimulant pharmacologic treatment currently available for this disorder (Chamberlain *et al.*, 2007:977). The only non-ADHD indication for methylphenidate is narcolepsy in adults (Mitler *et al.*, 1986:264). Atomoxetine is used exclusively for ADHD (Snyman, 2009:1). In a study conducted by Castle *et al.* (2007:337), the estimated ADHD treatment prevalence in children (≤ 19 years) in 2000 was 2.8%, with an increase of 1.6% in 2005 using pharmacy claims data for a large population of commercially insured Americans.

In 2001, Kadesjö and Gillberg (2001:487) estimated that the prevalence of comorbidities associated with ADHD in Swedish school-aged children was as high as 87%. The most common comorbidities include oppositional defiant disorder (ODD), mood disorders, developmental co-ordination disorder (DCD) and substance use disorders. Meyer *et al.* (2004:123) found that ADHD in South Africa was further associated with depressive and anxiety disorders, as well as learning disabilities and school failure.

Previous studies suggest a strong correlation between ADHD and the use of central nervous system (CNS) medication in children (Hsia & MacLennan, 2009:215; Paulose-Ram *et al.*, 2007:567; Steffenak *et al.*, 2012:230; Zito *et al.*, 2006:797) and adolescents (CDC, 2013:4). This could be as a result of comorbidities associated with ADHD (Biederman, 2004:3). Furthermore, the CDC (2013) determined that the most used CNS medication was for the drug class antidepressants (3.2%) and ADHD drugs (3.2%). Although polypharmacy with antidepressants is recommended for the treatment of a wide range of disorders, such as depression with psychotic features, treatment resistant depression or obsessive compulsive disorder (OCD) and ADHD with comorbid depressive or anxiety disorders (AACAP, 2007a:1509; Geller & March, 2012:98; Pliszka *et al.*, 2006:648), the concurrent use of methylphenidate and CNS medication leads to an increased risk of drug-drug interactions. Methylphenidate is a cytochrome P450 enzyme inhibitor (CYP2D6) and interacts with monoamine oxidase inhibitors (MAOIs), such as psycho-stimulants (Markowitz & Patrick, 2001:754).

The presence of ADHD in children increases parenting stress and parental psychopathology (Johnston & Mash, 2001:183), and since ADHD has been proved to be a genetic disorder

(Brassett-Harknett & Butler, 2007:191; Faraone *et al.*, 2005:1320), there could also be CNS medication use in family members. Family tendencies regarding the use of methylphenidate and atomoxetine remain unclear. There is a lack of information about the use of CNS medication in children with ADHD in the private health sector in South Africa. This merits further research to determine the prevalence of CNS medication in ADHD children and their families.

The following research questions can be formulated on the basis of the foregoing discussion:

- What is the prevalence of ADHD on a national and international level?
- Do prescribers follow nationally accepted ADHD treatment guidelines for children in South Africa?
- Are there differences in the prescribing patterns of methylphenidate- and atomoxetine-containing products in different age and gender groups?
- Which other¹ CNS products are prescribed together with methylphenidate- and atomoxetine-containing products?
- What is the prevalence of comorbid diseases with regard to ADHD?
- What is the prevalence of possible drug-drug interactions between products containing methylphenidate or atomoxetine with other CNS products?
- Are there any differences in the medicine prescribing patterns of CNS medication for children and adolescents with/without treatment for ADHD?
- Are there family tendencies regarding the use of methylphenidate and atomoxetine between children and adolescents with/without treatment for ADHD?

1.3 Research aims and objectives

1.3.1 Research aim

The general aim of the project was to investigate possible differences in the prescribing patterns of CNS medication in children and adolescents who are being treated for ADHD vs. those not treated for ADHD in the South African private health sector, as well as family tendencies regarding methylphenidate and atomoxetine usage.

¹ For the purpose of this study, 'other' CNS medication refers to sections 1.1 (excluding methylphenidate and atomoxetine) to 1.6 in the MIMS®, which included CNS stimulants, sedative hypnotics and anxiolytics, antidepressants, antipsychotics and anti-epileptics.

1.3.2 Research objectives

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

1.3.2.1 Specific research objectives: Literature review

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

- To describe the prevalence of ADHD, nationally as well as internationally, stratified by age and gender;
- To conceptualise ADHD treatment in children and adolescents;
- To estimate from the literature the prevalence of CNS -related comorbid diseases with regard to ADHD; and
- To determine potential drug-drug interactions between methylphenidate- or atomoxetine-containing products and other CNS medication.

1.3.2.2 Specific research objectives: Empirical investigation

Specific research objectives of the empirical investigation were the following:

- To evaluate current prescribing patterns of methylphenidate and atomoxetine for children and adolescents with ADHD;
- To compare the prescribing patterns of other CNS medication between children and adolescents who are being treated for ADHD vs. those not treated for ADHD;
- To determine the prevalence of potential drug-drug interactions between methylphenidate- or atomoxetine-containing products and other CNS medication on prescriptions; and
- To determine the association of the prevalence of ADHD in families of ADHD children and adolescents.

Table 1-1: Research objectives outlined from the empirical investigation and article in which they are addressed

Empirical objectives	Article	Reference
To evaluate current prescribing patterns of methylphenidate and atomoxetine for children and adolescents with ADHD	Methylphenidate and atomoxetine prescribing patterns in the South African private health sector (2005-2013)	Prepared for submission in the <i>Journal of clinical pharmacy and therapeutics</i>
To compare the prescribing patterns of other CNS medication between children and adolescents with treatment for ADHD vs. those without treatment for ADHD	Prescribing patterns of central nervous system medication in South African children and adolescents with/without treatment for ADHD and its potential drug-drug interactions	Prepared for submission in the <i>Pharmacoepidemiology and drug safety</i>
To determine the prevalence of potential drug-drug interactions between methylphenidate- or atomoxetine-containing products and other CNS medication on prescriptions	Prescribing patterns of central nervous system medication in South African children and adolescents with/without treatment for ADHD and its potential drug-drug interactions	Prepared for submission in the <i>Pharmacoepidemiology and drug safety</i>
To determine the association of the prevalence of ADHD in families of ADHD children and adolescents	Methylphenidate and atomoxetine prescribing patterns in the South African private health sector (2005-2013)	Prepared for submission in the <i>Journal of clinical pharmacy and therapeutics</i>

1.4 Research methodology

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

1.4.1 Phase one: Literature review

The literature review focused on the most recent publications regarding the prevalence of ADHD in children and adolescents, comorbid diseases with regard to ADHD and possible drug-drug interactions between methylphenidate- or atomoxetine-containing products and other CNS medication.

1.4.2 Phase two: Empirical investigation

The empirical investigation was discussed under the following headings: research design, data source, target- and study population, selection of study population, selection process, study variables and reliability and validity of database and data.

1.4.3 Research design

A quantitative, descriptive, longitudinal study was performed using a medicine claims database from a national representative Pharmaceutical Benefit Management (PBM) company for the study period 2005 to 2013 (nine years). Quantitative research is based on the measurement of

quantity or amount (Given, 2008:22). Descriptive research includes surveys and fact-finding enquiries of different kinds (Brink *et al.*, 2012:88).

A longitudinal design can be defined as an investigation where the participant outcomes and possible treatments are collected at multiple follow-up times. The way in which variables change over time will be examined (Brink *et al.*, 2012:114).

1.4.4 Data source

- Database

Data were obtained from a PBM company that is dedicated to the effective management of medicine benefits. This database is a real-time, electronic pharmaceutical claims processing system that manages medicine benefits by acting as a link between pharmacies/doctors and medical insurers. The PBM provides medicine management services to 39 medical schemes and capitation plans in South Africa. The database currently contains longitudinal patient medicine claims data for more than 1.6 million medical scheme beneficiaries. The PBM is at present linked to all of South Africa's pharmacies and 98% of all dispensing doctors. The total database for nine years (1 January 2005 to 31 December 2013) consists of all the medicine claims data available on the database. Only data from this PBM were used for this study.

- Data fields

The following data fields were obtained from the PBM: prescription number, member number, dependent code, active ingredient, date of dispensing of the prescription, birth date of the patient (will be used to calculate the age of the patient on the date of prescription), gender of the patient, days' supply, and quantity of medicine items dispensed.

- Reliability and validity

Data for the nine years were obtained from one database only, thereby limiting external validity, implying that the results can be generalised to the specific database and study population only. The research study was conducted from the viewpoint that all data obtained from the database were correct and accurate. However, data were cleaned by deleting all duplicate claims and incomplete patient information. The dataset was verified after each cleaning process by performing random data checks.

The PBM has certain validation processes in place to ensure the **integrity, validity and reliability of the data**, such as data integrity validation, eligibility management, medicine utilisation and clinical management, fully-integrated pre-authorisation services, including exception management; management of medicines for the Chronic Disease List (CDL), Prescribed Minimum Benefits (PMB) and other conditions; medicine management in capitation

environments; on-line medicine expenditure reporting; and supplementary services which include network management, development and implementation of reference price lists, formulary management, and price and product file management (refer to Annexure B).

The checklist, adapted from Motheral *et al.* (2003:90) and Hall *et al.* (2012), which was used to evaluate the validity of the database, is provided in Table 1.2.

Table 1-2: Checklist to evaluate the validity of the database

Item	Variable	Description	Evaluation
Database selection	Population covered	Does the resource include an appropriate population in terms of size, coverage and representativeness?	Approximately 1.6 million South African citizens are currently benefiting from the pioneering PBM services. At present, the PBM provides pharmaceutical benefit management services to 32 medical schemes and five capitation provider clients, administered by 15 different healthcare administrators.
	Capture of study variables	Are all exposures, outcomes and other study variables captured in sufficient detail, without bias, and accessible for research?	The data are obtained from the PBM. The PBM does not have all the information and is therefore biased, since it only captures claims data.
	Continuous and consistent data capture	Are there any breaks or changes in data collection over time for either individual patients or the whole population during the study observation period? Are there any inconsistencies in provision of healthcare or capture of study variables across the database population?	The population can differ from year to year. Medical aids do not necessarily include contracts with the PBM. Longitudinal data ensure that only patients who are on the database every year are used.
	Record duration and data latency	Is the average patient record duration, and the time between the occurrence of the exposure and data collection, sufficiently long for the study event?	Data for a study period of nine years will be used. The study population will be limited to those patients for whom there are records for all eight years and who have received prescriptions for ADHD medication.
	Database expertise	Is the expertise required to use the resource available: in-house or elsewhere?	Expertise from the personnel from MUSA (Medicine Usage of South Africa) is available in-house.
Extraction and analysis of the study population	Specification of extraction	Are the following specified in detail: how to extract the study population and variables, code lists and non-coded systems, retrieval and merging of additional external data, output and final analysis?	The data are divided into groups according to the MIMS® classification system. When needed, data can be extracted from the data system using the MIMS® categories (Mainpharm, subpharm, pharm code). The data can also be extracted using the description or active ingredient information.
Privacy and security	Compliance with privacy and security policy	Have all relevant local, regional and national policies been complied with?	A contract between the North-West University (NWU) and the PBM ensures the confidentiality of information. Confidentiality agreements are signed by the researcher, study supervisor and co-supervisor, as well as the statistical consultant.

Item	Variable	Description	Evaluation
	Limited use of identifying information	Are all direct identifiers removed or masked? Whose responsibility is it to ensure privacy?	All identifying information about a beneficiary is changed or removed by the PBM to make sure that a person or specific medical scheme cannot be identified before the data are obtained.
	Secure data storage and transfer	Is there a formal data security policy, and has this been adhered to?	The primary responsibility to ensure that the identifiers are removed lies with the PBM and is done even before the data are sent to the NWU.
	Review of policy and procedures	Are regular privacy reviews adhered to? Has the use of a new database, collection of additional patient or physician data, use of multiple resources, or narrative data impacted confidentiality?	Data are only available to a person when the study leader of the research group gives her permission and when the contract is renewed.
Quality and validation procedures	Overall database	Have appropriate general quality checks been completed?	Data will be cleaned by deleting all non-paid claims, duplicate claims and other incomplete data fields will be left out from the data analysis. The datasets will be verified after each cleaning process by performing random data checks
	Study population	Which study-specific quality checks are needed: the extraction process, data merging, study variables, assumptions, etc.? Has the annotated programming code been reviewed by an independent programmer?	The extraction process: the data are extracted according to the MIMS® categories/active ingredient. Data are merged to produce a dataset that is an appropriate size.
	Testing	The checks can be external, logical or internal and should be cross-sectional, longitudinal and up to date.	Trade names, spelling etc. will be checked to ensure that all relevant data are extracted.
Documentation	Format	Are the rules of Guidelines for Good Pharmacoepidemiology Practices followed, including storage and indexing?	All data will be stored for a period of five to seven years at Medicine Usage of South Africa (MUSA).
	Specifics	Have extraction specification, output, quality testing, merging resources, responsibility for privacy and annotated programming code for data extraction and final analysis been documented?	Yes.

1.4.5 Target population

All ADHD patients belonging to a medical scheme in the private health sector of South Africa with the same benefit² profile.

1.4.6 Study population

This section entails a discussion of the rationale for the selection of the study population, as well as the processes followed in selecting these patients.

1.4.6.1 Selection of study population

The total population who met the inclusion criteria was selected, and the data were filtered by means of the application of exclusion criteria.

Table 1-3: Inclusion criteria

Study period	Criteria
2005-2013	All children and adolescents ≤18 years of age and their family of all age groups (indicated as dependents of the same main member number) who received one or more prescriptions for CNS medication (including methylphenidate and atomoxetine) were selected from the database (refer to Figure 1-1)

Table 1-4: Exclusion criteria

Study period	Criteria
2005-2013	Unknown gender and age

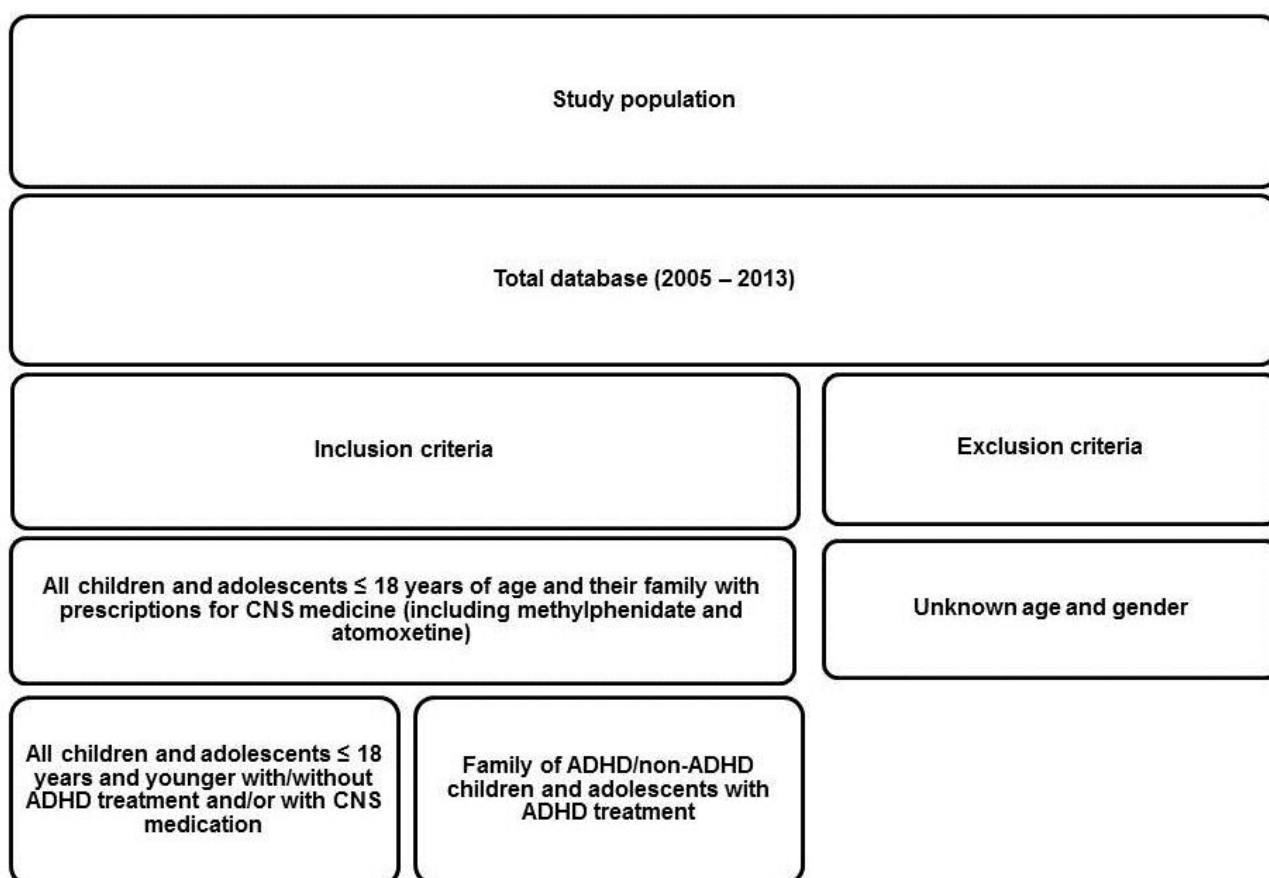
The Monthly Index of Medical Specialties (MIMS®) classification system was used to identify all the CNS medicine; therefore, sections 1.1 to 1.6 (refer to Annexure C) in the MIMS® were used (Snyman, 2009:1). For the purpose of this study, pharmacological groups anti-Parkinson's agents, antivertigo and anti-emetic agents, antimigraine agents, and Alzheimer's medication were excluded from the analysis, because they are neither related to any ADHD comorbidities, nor applicable to children under the age of 18 years (e.g. Alzheimer's medication and anti-Parkinson's agents).

The process that was followed, from obtaining the data to the selection of the study population, is depicted in Figure 1-1. The steps followed in this process were:

² The medical aid description/benefits/compilation should be similar.

- Data were obtained from PBM's central database.
- Data were cleaned by application of exclusion criteria to obtain individual datasets for 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012 and 2013, respectively.
- Application of inclusion criteria to obtain individual data subsets for 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012 and 2013, respectively and the categorisation of patients from each data subset into the study population.

The selection of the study population is illustrated in Figure 1.1.



*CNS – Central nervous system

Figure 1-1: Organogram illustrating the different data subsets

The study population included all children and adolescents ≤ 18 years of age and their family with prescriptions for CNS medicine and were divided into the following groups:

- All children and adolescents (≤ 18 years of age) with/without treatment for ADHD who received/did not receive CNS medication; and

- Family of children and adolescents with/without treatment for ADHD receiving ADHD medication.

The children and adolescents were the further divided into the following groups:

- ADHD children and adolescents who received CNS medication (ADHD-CNS group);
- ADHD children and adolescents who did not received CNS medication (ADHD-only group); and
- Non-ADHD children and adolescents who received CNS medication (CNS-only group).

The families were divided into the following groups:

- Families of ADHD children and adolescents who received ADHD treatment; and
- Families of non-ADHD children and adolescents who received ADHD treatment.

1.4.7 Study variables

The study variables were divided into independent- and dependent variables. According to Brink *et al.* (2012:90), an independent variable is “*a variable that influences other variables*”, and a dependent variable is the “*outcome variable*”.

1.4.7.1 Independent variables

The independent study variables that were used during the data analysis consisted of age and gender.

1.4.7.1.1 Age

Age is referred to as the period of time that has passed since the time of birth (Stedman's medical dictionary, 2000:34). The age of the person was calculated on the database from 1 January of the year following the date that the prescription was dispensed. Costello *et al.* (2007:2) define children as the age range between two and 11 years and adolescents in the age range between 12 and 18 years. There is limited information regarding the age of onset of ADHD (Kieling *et al.*, 2010:14; Todd, 2008:947) and therefore the age group two to 11 years was further divided into age groups 1 and 2 to simplify the data analysis. Data of family of patients were not analysed according to age groups.

For the purpose of this study, the children and adolescents were divided into three age groups, i.e.:

- Age group 1: ≤ 6 years
- Age group 2: >6 and ≤ 12 years
- Age group 3: >12 and ≤ 18 years

1.4.7.1.2 Gender

Gender is defined by the Cambridge Dictionaries Online (2015) as “*the physical and social condition of being male or female.*” For the purpose of this study, gender was divided into two categories, namely female and male. Patients for whom gender was not indicated were excluded from the analysis to ensure the quality of the data.

1.4.7.1.3 Different diagnoses groups

The study population was divided into three groups based on their diagnostic profile, i.e.:

ADHD-only group: All children and adolescents ≤ 18 years who either received prescriptions for methylphenidate and/or atomoxetine, or had an ICD10 diagnosis for ADHD;

ADHD-CNS group: All children and adolescents ≤ 18 years who either received prescriptions for methylphenidate and/or atomoxetine, or had an ICD10 diagnosis for ADHD and received prescriptions for other CNS medication; and

CNS-only group: All children and adolescents ≤ 18 years with prescriptions for other CNS medication.

1.4.7.2 Dependent variables

The dependent study variables that were used during the data analysis consisted of the prevalence, number of prescriptions dispensed, number of medicine items dispensed, the prescribed daily dose and the potential drug-drug interactions.

1.4.7.2.1 Prevalence

Prevalence (P) is defined as the number of existing cases of a disease (or any outcome, e.g. adverse drug reaction, drug use) in a population at a particular point in time (Waning & Montagne, 2001:108). The formula for the calculation of prevalence is as follows:

$p = \text{number of existing cases in a population} / \text{total number of people in that population}$

The prevalence of medicine usage was determined for the following categories:

- The prevalence of ADHD in the database according to parameters such as age and gender;
- The prevalence of methylphenidate and atomoxetine usage;
- The prevalence of CNS medication usage according to parameters such as age and gender;
- The prevalence of CNS medication usage in children and adolescents with treatment for ADHD according to parameters such as age and gender;
- The prevalence of potential drug-drug interactions; and
- Prevalence of ADHD in family of children and adolescents with/without ADHD.

1.4.7.2.2 Number of prescriptions dispensed

According to the Mosby's Dictionary (Myers & Kaemmerer, 2008:1357), prescriptions are an *"order for medication, therapy, or therapeutic device given by a properly authorized person"*. The number of prescriptions as well as the average number of prescriptions per patient per year were calculated, and were used as a measure of medicine usage.

1.4.7.2.3 Number of medicine items dispensed

According to the Mosby's Dictionary (Myers & Kaemmerer, 2008:1328), *"medicine is a drug or a remedy for illness"*. The Medicines and Related Substances Control Act (101 of 1965) of South Africa defines medicine as *"any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man"*.

The number of medicine items per prescription dispensed per patient per year for ADHD medication was calculated, and was used as a measure of the medicine usage.

1.4.7.2.4 Prescribed daily dose

The WHO (2003:4) defines the prescribed daily dose (PDD) as *"the average daily dose prescribed, as obtained from a representative sample or prescription"*. For the purpose of this study, the PDD was calculated as the milligrams of a specific active ingredient dispensed per day. This was calculated using the following formula:

$$\text{PDD} = (\text{strength} \times \text{quantity}) / \text{days' supply}.$$

Where:

Strength = strength per tablet (milligram)³

Quantity = the number of tablets dispensed/ claimed per medicinal item

Days' supply = the number of days' supply dispensed

The average PDD of specific active ingredients was compared to the recommended daily dose (RDD). The RDD recommended for children was determined by using the patient's weight. The dataset did not contain clinical data such as the weight and height of patients, which made it difficult to determine the exact RDD of methylphenidate and atomoxetine. The RDD for these medications was calculated using the Centre for Disease Control and Prevention's (CDC, 2000) growth charts for both genders. The growth charts are available for boys and girls (refer to Annexure E). Dose range was calculated by using the 75th percentile or other average weight-for-age percentiles for both genders from birth to 18 years.

Table 1-5 summarises the guidelines that were used to compare the average PDD with the RDD in the analysis of the data (Rossiter, 2014:508).

³ The strength is programmed into the dataset obtained from the PBM.

Table 1-5: Recommended daily dose

Active ingredient	Trade name	Recommended daily dose	Maximum RDD
Methylphenidate	Concerta®	Children: 54 mg/day	72 mg/day
	Methylphenidate HCL-Douglas®	Children: 1 mg/kg/day	60 mg/day
	Ritalin LA Capsules®	Children: 1 mg/kg/day	60 mg/day
	Ritalin Tablets®	Children: 1 mg/kg/day	60 mg/day
Atomoxetine	Strattera Capsules®	Children: 1.2 mg/kg/day	60 mg/day

1.4.7.2.5 Potential drug-drug interactions

According to Rossiter (2014:508), the drug-drug interactions of methylphenidate with other medication are the following: barbiturates, primidone, phenytoin, tricyclic antidepressants (TCAs), warfarin and MAOIs.

Potential drug-drug interactions with methylphenidate are phenelzine, tranylcypromine, carbamazepine, cyclosporine, guanethidine, phenytoin, amitriptyline, amoxapine, clomipramine, desipramine, dicumarol, doxepin, imipramine, nortriptyline, protriptyline, trimipramine and isocarboxazid (Tatro, 2012:950; 456; 665; 739; 1434; 118; 950).

Potential drug-drug interactions with atomoxetine are isocarboxazid, phenelzine, tranylcypromine (MAOIs), and fluoxetine and paroxetine (SSRIs) (Tatro, 2012: 213, 214).

Potential drug-drug interactions between different medicine items prescribed per prescription were identified and classified according to a clinical significance rating. The significance for potential drug-drug interactions was derived from the criteria formulated by Tatro (2012:xiv).

Tatro (2012:xiv) assigns a significance rating of 1 to drug-drug interactions classified as major, a significance rating of 2 signifies a drug-drug drug interaction of moderate severity, a drug-drug interaction of minor severity is assigned a significance rating of 3, a significance rating of 4 to drug-drug interactions classified as major/moderate and a significance rating of 5 to drug-drug interactions classified as minor/any (refer to Annexure D for the significance rating of the potential drug-drug interactions).

Tatro (2012:xiv) defines the degree of severity as follows:

- Major: *“The effects are potentially life-threatening or capable of causing permanent damage”.*

- Moderate: *“The effects may cause deterioration in a patient’s clinical status”*.
- Minor: *“The effects are usually mild; consequences may be bothersome or unnoticeable but should not significantly affect the therapeutic outcome”*.

1.5 Data analysis

In this project, a **retrospective drug utilisation study** was used. This type of review has a number of beneficial aspects.

- It can be performed quite easily using an administrative database (Truter, 2008:95);
- Inappropriate prescribing practices such as over- and underutilisation, appropriate generic use and the use of formulary medications can be identified and through educational interventions with the doctor, these problems can be eradicated. This can lead to rational prescribing and better quality treatment for the patient (Academy of Managed Care Pharmacy, 2009); and
- It is a relatively inexpensive type of Drug Utilisation Research (DUR) method with a variety of interesting applications such as identifying new relationships and problems among medications and disease (Truter, 2008:95).

In addition, the findings of these studies can provide valuable information to be employed by decision-makers in managed healthcare organisations, such as the South African PBM providing the data, to prevent recurrence of inappropriate medicine use.

The data were analysed using the Statistical Analysis System® program (SAS 9.3®) in consultation with a statistician. All study variables were analysed descriptively. All of the statistical tests/analyses conducted to attain each specific objective of the empirical investigation phase are provided here.

1.5.1 Descriptive statistics

1.5.1.1 Frequency

Frequency is described by the Oxford English Dictionary (2011) as “*the rate at which something occurs over a particular period of time or in a given sample*”. Denominators for frequency calculations therefore included all patients in the particular dataset or data subset, stratified by age and gender, as necessary.

1.5.1.2 Average (arithmetic mean)

According to Pagano and Gauvreau (2000:38), the mean is “*calculated by summing all the observations in a set of data and dividing by the total number of measurements*”. The sample average can be calculated by using the following formula (Pagano & Gauvreau, 2000:38):

$$A = \frac{1}{n} \times \sum_{i=1}^n x_i$$

Where:

A = average (or arithmetic mean)

n = the number of terms (e.g. the number of items or numbers being averaged)

x_i = the value of each individual item in the list of numbers being averaged

For the purpose of this study, the average (arithmetic mean) was used to determine:

- the average number of prescriptions claimed per year; and
- the average number of medicine items per prescription.

1.5.1.3 Standard deviation

The standard deviation (SD) is defined as “*a measurement of the degree to which each number in a set of numbers is different from the average*” (Cambridge Dictionaries Online, 2012). Ott and Longnecker (2010:93) further describe standard deviation as the positive square root of the deviation.

The sample standard deviation was calculated as follows (Pagano & Gauvreau 2000:47):

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

Where:

s = standard deviation

Σ = sum of

x = values of the variable

n = number of observations

1.5.1.4 Confidence Interval

Confidence interval (CI) quantifies the uncertainty in measurement (Straus *et al.*, 2011:269). It is usually reported as '95% CI', which is the range of values within which we can be 95% sure that the true value for the whole population lies (Joubert, 2007:142).

1.5.1.5 Ratio

In mathematics, a ratio is a relationship between two numbers of the same kind expressed as "*a*" to "*b*" or *a*:*b* (The American Heritage Science Dictionary, 2005).

1.5.2 Inferential statistics

1.5.2.1 The *t*-test

The independent *t*-test is defined as a test that "*tests if the population means estimated by two independent samples differ significantly*" (Banerjee, 2003:59). The *t*-test was used to determine whether differences between two groups' means were statistically significant.

According to Cohen (1988:24), the *d*-value is a "*degree with which the phenomenon is present in the population*". Cohen and Lea (2004:60) define the *d*-value as the difference between two means divided by the largest standard deviation of the two means. Cohen's *d*-value was used to evaluate the effect size between the means in order to determine the practical significance of

the differences (e.g. average PDD between the ADHD-only and the ADND-CNS group). The practical significance of the differences between two means was calculated when the p -value was statistically significant ($p \leq 0.0001$). The following formula was used to calculate the Cohen's d value:

$$d = \frac{\bar{x}_t - \bar{x}_c}{S_{max}}$$

Where:

d = effect size

$\bar{x}_t$ and $\bar{x}_c$ = mean

S_{max} = maximum standard deviation

For practical significance, Steyn (1999:3) recommends the following guidelines:

Cohen's $d = 0.2$: small effect - no significant difference

Cohen's $d = 0.5$: medium effect - observable and can be significant

Cohen's $d = 0.8$: large effect - significant and of practical importance

1.5.2.2 Chi-square test

The chi-square test (χ^2) is a non-parametric statistical method that is used to determine whether the proportion or event rates of two or more groups are different. It is used when data are expressed in frequencies or may be reduced to frequencies. It may be used to test whether a significant difference exists between the observed frequencies in certain categories and what could be expected to occur by chance (Jackson, 1981:99). The practical significance of the results were calculated when the p -value was statistically significant ($p \leq 0.0001$). The Cramer's V statistic was used to test the practical significance of this association (with Cramer's $V \geq 0.5$ defined as practically significant).

The following mathematical formula can be used to determine the Cramer's V :

$$V = \sqrt{\frac{\chi^2}{nt}}$$

Where:

V = Cramer's V value

χ^2 = chi-square statistic

n = sample size

t = minimum number of rows minus one or the number of columns minus 1

The Cramer's V value is interpreted as follows (Rea & Parker, 2005:189):

- negligible association: Cramer's $V > 0.0 \leq 0.1$;
- weak association: Cramer's $V > 0.1 \leq 0.2$;
- moderate association: Cramer's $V > 0.2 \leq 0.4$;
- relatively strong association: Cramer's $V > 0.4 \leq 0.6$;
- strong association: Cramer's $V > 0.6 \leq 0.8$;
- very strong association: Cramer's $V > 0.8 \leq 1.0$.

1.5.2.3 ANOVA

One-way analysis of variance (ANOVA) is defined as a “*test for assessing the contribution of more than two independent categorical variables to variations in the mean of a dependent continuous variable*” (Banerjee, 2003:99). ANOVA was used to test differences between more than two groups' means. It was operationalised with the general linear procedure of the SAS version 9.1.3 system (Schlotzhauer & Littell, 1997:244). If a difference was indicated, a second procedure, a Tukey multiple comparisons procedure, was performed to determine which groups most significantly influence the overall difference between the groups. Cohen's d -value was used to evaluate effect size between the different means (with Cohen's $d \geq 0.8$ defined as a large effect with practical significance) (refer to 1.5.2.1).

1.6 Ethical considerations

This study was conducted with the approval of the Health Research Ethics Committee of North-West University (Potchefstroom Campus) (NWU-00179-14-A1), and the board of directors of the PBM.

This study was considered to be a low-risk study since retrospective medicine claims data were used. The risk was low because there was no direct contact with patients. Risks can include

accidental disclosure of the data by the researcher. This can violate the privacy and security of the PBM. Access to data is therefore subject to the signing of a confidentiality agreement by all researchers, study leaders and statistician.

There was no physical contact with the patients, medical schemes, prescribers or pharmacies; therefore, these institutions or persons could not be identified. The PBM was not identified. The PBM assures confidentiality for their patients by means of the random allocation of a 'dummy' member number to each record. No patient could be identified, thereby ensuring that anonymity and confidentiality are maintained.

All data were stored in a secure environment and were only used for research purposes. Data privacy and confidentiality were maintained at all times. Furthermore, the PBM providing the data for the study is nowhere identified in the dissertation. Additionally, the researcher, study leader, co-supervisor and the statistical consultant signed confidentiality agreements. On completion of the study, all data will be kept by the North-West University, Faculty of Health Sciences, MUSA for five years, after which it will be discarded of appropriately.

1.7 Chapter summary

Chapter 1 provided the scope of the study, and discussed the methodology that was used. Chapter 2 will provide a broad overview of the existing literature, with the focus on the literature objectives stipulated in Chapter 1.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

In this chapter, the focus is on the nature of Attention-Deficit/Hyperactivity Disorder (ADHD). This includes the aetiology of ADHD; the prevalence of ADHD described in accordance with gender, age, ethnicity and socioeconomic characteristics; treatment, which includes methylphenidate and atomoxetine, comorbid diseases, and a summary of 'other' CNS drugs that are commonly co-prescribed with methylphenidate and/ or atomoxetine.

2.2 ADHD definition

ADHD is defined by the American Psychiatric Association (APA) (2013:61) as “a *persistent and age-inappropriate pattern of inattention and/ or hyperactivity/ impulsivity*”. The definition of ADHD has evolved over time and has been known previously as hyperkinetic reaction of childhood, hyperkinetic syndrome, hyperactive child syndrome, minimal brain damage, minimal brain dysfunction, minimal cerebral dysfunction, minor cerebral dysfunction, and attention deficit disorder with or without hyperactivity (Barkley *et al.*, 1992:163; Clements, 1966:5; Morrison & Stewart, 1971:189; Weiss & Trokenberg- Hechtman, 1993:3).

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria (APA, 2013:59), there are 18 symptoms (see Annexure A for specific inattention and hyperactive impulsive items) in total across the two domains (inattentive- and hyperactive/impulsive domain): nine in the inattentive domain and nine in the hyperactive/impulsive domain. The hyperactive/impulsive symptoms consist of behaviours such as 'often gets up from seat when remaining in seat is expected' and 'often talks excessively' (see Annexure A for the complete list of symptoms). The inattentive symptoms include behaviours such as 'often forgetful in daily activities' and is 'often easily distracted'. For individuals aged 17 years and younger, a diagnosis requires at least six or more of the inattentive symptoms and/or at least six or more hyperactive/impulsive symptoms to have been present for at least six months in order to diagnose ADHD. Because an individual can present with just inattentive symptoms, or with just hyperactive/impulsive symptoms, or with both, the following three subtypes corresponding to these patterns of presentation have been defined (APA, 2013:59):

- ADHD, predominately inattentive presentation (F90.0);
- ADHD, predominately hyperactive-impulsive presentation (F90.1); and
- ADHD, combined presentation (F90.2).

ADHD is distinguished from hyperkinetic disorder in that it can either be only 'inattention' or 'hyperactive/impulsive' or a combination of the subtypes, whereas hyperkinetic disorder requires that all three domains are present (WHO, 1992), which can roughly relate to the ADHD combined type.

2.3 Aetiology of ADHD

The exact aetiology of ADHD is unknown, although there are grounds for the dopamine deficit theory (Levy, 1991:277; Solanto, 1998:127). The presence of dopamine deficits, genes encoding for certain neurotransmitters and receptors of the catecholamine system and environmental factors that cause a shortage of dopamine (e.g. toxic substances or foetal adaptations) all contribute to this theory (Swanson *et al.*, 2007:39).

2.3.1 Presence of dopaminergic deficits: brain size

The brain regions implicated in the pathophysiology of ADHD include the prefrontal cortex/orbital frontal cortex (impulsive symptoms, disinhibition), dorsolateral prefrontal cortex (dopamine) (sustained attention problem-solving), supplementary motor area (hyperactive symptoms) and dorsal anterior cingulate cortex (selective attention) (Stahl & Mignon, 2009:3). This could affect the functioning of their respective cortical-striatal-thalamic-cortical (CSTC) loops, which has an influence on functioning and motor control (Stahl & Mignon, 2009:3; Seidman *et al.*, 2005:1268). These abnormalities are reflected by brain size (smaller-than-average components) and function (hypo-activation), and contribute to the dopamine deficit theory (Swanson *et al.*, 2007:39). ADHD is characterised by a 3% decrease in volume throughout the brain (Castellanos *et al.*, 2002:1747). Castellanos and associates (2002:1746) found that the respective brain regions implicated in ADHD are those that have a high density of dopamine receptors (e.g. the caudate nucleus and globus pallidus). Sub-regions involved in coordination of the different brain regions are smaller in size (e.g. the splenium and the rostrum of the corpus callosum, and the cerebellum vermis lobules VIIIX) as well as anterior regions of the brain (e.g. right frontal white matter).

2.3.2 Genetic aetiologies of dopaminergic deficits

ADHD has a complex genetic architecture and cannot be attributed to a single gene, but rather to a combination of individually low risk genes (Cortese, 2012:422; Faraone & Mick, 2010:159). There are a number of susceptible genes that have been proposed to be involved in the aetiology of ADHD (Cortese, 2012:422). Studies of dopaminergic genes, serotonergic genes, and other candidate genes have been conducted to investigate the association of the different genes and ADHD (Cheuk & Wong, 2006:651; Faraone *et al.*, 2001:1052; Li *et al.*, 2006:2276;

Lowe *et al.*, 2004:348; Yang *et al.*, 2007:541). The main site of action for stimulant medication (also indicates the presence of dopaminergic effects according to the dopamine deficit theory) used for ADHD is the dopaminergic system (Volkow & Swanson, 2003:1910). The genes encoding the dopamine transporter (density of dopamine transporter genes are higher than normal in ADHD individuals) and receptors were documented by Li *et al.* (2006:2276) as the “*most attractive*” candidate genes for ADHD, although association studies of other candidate genes have been conducted (Barr *et al.*, 2000:408; Faraone & Mick, 2010:168; Kim *et al.*, 2007:786; Kustanovich *et al.*, 2003:313). The following candidate genes of the catecholaminergic system have been shown to contribute to the heritability of ADHD:

- The dopamine transporter gene (DAT, SLC6A3) (Barkley *et al.*, 2006:497; Brown *et al.*, 2011:13; Franke *et al.*, 2008:1578; Franke *et al.*, 2010:658; Yang *et al.*, 2007:541);
- The dopamine D4 receptor (DRD4) (Arcos-Burgos *et al.*, 2004:255; Faraone *et al.*, 2001:1052; Lynn *et al.*, 2005:908; Muglia *et al.*, 2000:275);
- The dopamine 5 receptor (DRD5) (Lowe *et al.*, 2004:348);
- Monoamine oxidase A (MAO-A) (Lawson *et al.*, 2003:86);
- Catechol-O-methyltransferase (COMT) (Gothelf *et al.*, 2007:304; Reuter *et al.*, 2006:935); and
- The norepinephrine transporter (NET; SLC6A2) (Kim *et al.*, 2006:19168).

Other candidate genes that have been suggested to have an impact on ADHD heritability is the synaptosomal associated protein of 25Kd (SNAP25) (Barr *et al.*, 2000:408; Kim *et al.*, 2007:786; Kustanovich *et al.*, 2003:313).

2.3.3 Environmental factors of dopaminergic deficits

There are various environmental factors that can influence the brain development of a foetus and can contribute to the probability of the unborn child to develop ADHD. These are listed here:

- Toxic substances/ chemical exposures and heavy metals: lead, phthalates (DEHP) (Engel *et al.*, 2010:570; Tanida *et al.*, 2009:43), bisphenol A (BPA) (Braun *et al.*, 2011:878; Tanida *et al.*, 2009:43), polycyclic aromatic hydrocarbons (PAHs) (Perera *et al.*, 2011:1180) and poly-fluoroalkyl chemicals (PFCs) (Hoffman *et al.*, 2010:1766);
- Foetal adaptations and low birth weight (Lahti *et al.*, 2006:1171; Linnet *et al.*, 2006:656);

- Gene-environment interactions (Caspi & Moffitt, 2006:583);
- Nutritional factors (Motlagh, 2010:760; Nomura *et al.*, 2010: 279); and
- Psychosocial/lifestyle factors: Tobacco smoke (Motlagh, 2010:760; Nomura *et al.*, 2010: 279).

ADHD is a multifactorial disorder comprising a wide heterogeneity and complex manifestations (Nigg, 2006:175; Deault, 2010:170). Through theoretical studies, numerous researchers have suggested that ADHD should be looked at by means of a developmental psychopathological perspective, which provides predictions regarding how the different risk factors influence the development of ADHD (Deault, 2010:170; Johnston & Mash, 2001:184; Nigg, 2006:175). Therefore, the emergence of ADHD cannot be ascribed only to a single factor, but rather to genetic, as well as environmental risk factors (Deault, 2010:170).

2.4 Epidemiology of ADHD

ADHD is the most common neurodevelopmental disorder in early childhood and adolescence (Ferguson, 2000; Polanczyk *et al.*, 2007:942). Polanczyk *et al.* (2007:945) conducted the first comprehensive systematic review of studies addressing ADHD and estimated a world-wide pooled prevalence of 5.3% included in 102 studies comprising 171 756 patients. Polanczyk *et al.* (2014:8) ascribed increases in diagnosis and treatment to the increasing awareness, access to treatment and changing clinical practices.

In 2012, Willcutt (2012:498) reported a prevalence estimate of 5.9% to 7.1% in children and adolescents who met full DSM-IV diagnostic criteria for ADHD, which were in line with other prevalence studies (Willcutt, 2012: 498).

An increase of 21.8% in prevalence of ADHD in children four to 17 years of age was reported in the USA, from 2003 to 2007 (Getahun *et al.*, 2013). According to the CDC (2014), one in 11 children aged 4 to 17 years of age have a current diagnosis of ADHD, with an annual increase of 5% in diagnosed children and adolescents from 2003 to 2011 (CDC, 2014).

Polanczyk *et al.* (2007:946) warned that prevalence rates in Africa and the Middle East can be less accurate than those of the other continents due to a lack of sufficient numbers of epidemiological studies conducted in those regions.

In 2012, Bakare (2012) investigated the prevalence of ADHD in African continents. Bakare (2012:359) reported a total ADHD prevalence range of 5.4 to 8.7% among school-aged children according to the nine studies conducted in Africa (Bakare, 2012:360). From those nine studies,

four were conducted in South Africa, two from Nigeria and the Democratic Republic of Congo respectively, and one study from Ethiopia (Bakare, 2012:359). In Nigeria, researchers found that 8.7% of children (aged six to 12 years) had a diagnosis for ADHD (Adewuya & Famuyiwa, 2007:13). A prevalence of 6% was found in Kinshasa, Democratic Republic of Congo (Kashala *et al.*, 2005:179), and the lowest prevalence was documented in Ethiopia (Ashenafi *et al.*, 2001:310).

Willcutt (2012:490) identified several reasons from previous studies that may have contributed to lower prevalence rates of ADHD in the past, namely the criteria used to diagnose ADHD, method of ADHD-symptom assessment (Polanczyk & Rohde, 2007:387), the specific algorithm used to combine multiple sources of information, and the incorporation of functional impairment as part of the definition of ADHD (Willcutt, 2012:490). Polanczyk and colleagues also noted that prevalence estimates must be determined by using standardised procedures (e.g. patients diagnosed according to the DSM-V) in a population representative of the whole population (Polanczyk *et al.*, 2014:7), rather than methods based on parent- or teacher reporting.

2.4.1 The influence of gender on prevalence

According to Polanczyk and associates (2007:945), only 44 studies out of 102 distinguished ADHD prevalence according to gender. The results suggested that gender shows significant influences on prevalence, with an average 10% for males compared to the average 4% for females (Polanczyk *et al.*, 2007:945). Polanczyk and Rhode (2007:389) reported a pooled ADHD prevalence for both genders, and found that the prevalence for boys was 2.45 times higher than for girls.

Additionally, the CDC (2013) calculated the ratio of ADHD medication usage in the USA, stratified by gender, and reported a male to female ratio of 2:1 (community samples), which suggests a higher male to female prevalence of ADHD. They confirmed this in their 2014 report stating that 12.1% of boys versus 5.5% of girls have current ADHD (CDC, 2014). Although the diagnostic criteria are neutral with respect to gender and age, the condition has been most closely associated with school-age boys, especially those with hyperactive-impulsive symptoms (Castle *et al.*, 2007:337).

Erskine *et al.* (2013:1267) conducted a systematic review of global epidemiology, which included 44 studies that covered 21 world regions. They documented a global ADHD prevalence for males aged five to 19 years as 2.2% and for females 0.7%, which is also in line with other calculations (CDC, 2013; Erskine *et al.*, 2013:1267).

There are substantially fewer studies regarding epidemiological data in Africa, and prevalence estimates must therefore be carefully interpreted (Polanczyk *et al.*, 2007:946; Polanczyk *et al.*, 2014:8; Snyman & Truter, 2012:2995). Nevertheless, the prevalence of ADHD according to gender among African children is documented to be higher than the prevalence documented in other regions of the world (Bakare, 2012:360). In Kinshasa, Democratic Republic of Congo (Kashala *et al.*, 2005:175), 45% of the study sample (consisting of 286 school children) were boys and 55% were girls. Snyman and Truter (2012:2995) investigated the aetiology, diagnosis and treatment of youths with a diagnosis of ADHD in South Africa of which 73.6% of the patients were male.

Several reasons for the higher male to female ratio have been postulated. For example, Arnold (1996:556), Gaub and Carlson (1997:109), Egger *et al.* (2006:322) and Biederman *et al.* (2005:1087) suggested that this could be due to the likelihood of male referral for pharmacotherapy and psychotherapy and lack thereof in females. More recently, Biederman *et al.* (2002:39), Meyer *et al.* (2004:133) and Quinn and Wigal (2004) proposed that a difference in clinical presentation, e.g. inattentive subtype being predominant in females when compared with males. Furthermore, females with ADHD are less likely to have externalising disorders or show disruptive behaviour (Biederman & Faraone, 2005:238; Gershon, 2002:149), and lower rates of psychometrically defined learning disabilities which added to the high prevalence rate of ADHD in males (Quinn & Wigal, 2004). In addition, males are more likely to be exposed to environmental causes such as head injury (Biederman & Faraone, 2005:238). Another major contributing factor appears to be the presence of co-existing symptoms that often cloud the diagnostic feature (Quinn, 2008:422).

2.4.2 The influence of age on prevalence

According to the APA (2013:61), ADHD has an onset in early childhood (Biederman *et al.*, 2000:817). Previously, hyperactive-impulsive or inattentive symptoms had to be present before age seven years for an ADHD diagnosis, which led to the under-diagnosis of ADHD in older patients (APA, 2000:78; Todd *et al.*, 2008:945). In the study done by Todd and colleagues (2008:945), they found that the DSM-IV age of onset criterion complicated the diagnosis of ADHD, with 10% missed diagnoses due to age restrictions. Additionally, age of onset for ADHD has not yet been established, mainly because of difficulties in proving ADHD onset (APA, 2013:61; Barkley, 2008:80). Currently, the APA requires that symptoms must present before age 12 years, illustrating the importance of clinical presentation during childhood (APA, 2013:61).

With regard to children and adolescents, the CDC reported that 5.1 million children aged four to 17 years of age had a current diagnosis of ADHD in 2010, with the highest prevalence among children aged 11 to 14 years old (CDC, 2010). Adewuya and Famuyiwa (2007:13) found that 8.7% of Nigerian school children six to 12 years old had a diagnosis of ADHD. Snyman and Truter (2012:2994) analysed 51 questionnaires from pharmacies in the Eastern Cape Province in South Africa, and found that the average age of patients diagnosed with ADHD was 10.3 years (SD = 2.54).

In recent studies, researchers estimated that 30% to 60% of children who have ADHD will continue to be impaired by the condition as adults and that ADHD should be considered a chronic disorder (Biederman *et al.*, 2011:152; Faraone *et al.*, 2006:162; Kessler *et al.*, 2005b:1446; Lee *et al.*, 2008:371; Markowitz & Patrick, 2001:754; Michielsen *et al.*, 2012:303; Weiss & Murray, 2003:716; Wender *et al.*, 2001:4). According to a prevalence study conducted by Kessler *et al.* (2006:718), the prevalence of ADHD in adults (ages 18 to 44 years) was documented to be 4.4%, lower than the prevalence estimates for children.

2.4.3 Ethnic characteristics

The impact of race and culture on the prevalence estimates of ADHD have not yet received as much attention as have studies investigating the influence of age and gender on ADHD prevalence. To date, no work has examined ethnic differences in executive function in the general population or in children with ADHD (Martel, 2013:166). A few recent studies suggest that ADHD is not a cultural phenomenon, but rather a basic, neuro-behavioural disorder (Aase *et al.*, 2006; Adewuya & Famuyiwa, 2007:13).

Among white or non-Hispanic populations, Hispanic or Latino populations and black or African American populations, the latter has been identified to have the highest prevalence of ADHD among children, comprising 904 000 children of which 9.8% of children having a diagnosis for ADHD (CDC, 2010; Miller *et al.*, 2009:84). Similarly, Cuffe *et al.* (2005:) and Lee *et al.* (2008:378) found ADHD symptoms seem to be higher in African Americans compared to Caucasians (Cuffe *et al.*, 2005:397; Lee *et al.*, 2008:377). Martel (2013:171) concurs with these findings, regardless of whether symptoms were teacher or parent-rated.

Adewuya and Famuyiwa (2007:13) considered the cross-cultural phenomenon in their study with specific reference to school-aged children in Nigeria (Africa). They found the prevalence of ADHD in sub-Saharan cultures to be 8.7% in children 6 to 12 years old. Adewuya and Famuyiwa (2007:13) further described different prevalence ratings in different cultures, after which they concluded that ADHD is not a cultural construct, but rather due to methodological differences in criteria used to define ADHD. On the other hand, Meyer *et al.* (2004:131) found

small cultural differences in the prevalence of ADHD between various South African cultures, as well as between South African and other 'Western' cultures.

2.4.4 Socio-economic status

Low socio-economic status (SES) has been associated with high ADHD prevalence among children (Boyle *et al.*, 2011:1040; Cuffe *et al.*, 2005:398; Russell *et al.*, 2014:442). In the review by Russell *et al.* (2014:437), possible significant reasons for the higher prevalence among these children were suggested. These factors include increased exposure to risk factors, e.g. tobacco smoke during pregnancy (Linnet *et al.*, 2003:1035), unattached parenting and family conflict (Deault, 2010:181), heritability of ADHD (parents are therefore more likely to have ADHD symptoms themselves and lower levels of education, occupational achievement and therefore income), clinical identification bias and parent or teacher reporting bias (Russell *et al.*, 2014:437). Russell *et al.* (2014:437) identified another possible explanation for lower SES among families with ADHD children. They explained this by using a reverse causality model. Families of ADHD children tend to have lower incomes, due to limited ability to find work, sustain social networks in workplaces and within the family and social exclusion (Russell *et al.*, 2014:437). In addition, Johnston and Mash (2001:183) reported that the presence of ADHD in children often heightens levels of parenting distress and parental psychopathology.

2.5 Treatment of ADHD

The most commonly used treatment for ADHD consists of neuro-stimulants such as amphetamines and methylphenidate, and represent the first stage of medication intervention (Pliszka *et al.*, 2006:642), whereas atomoxetine is the only FDA-approved non-stimulant medication indicated for ADHD (FDA, 2015).

In this section, the mechanism of action, indications, recommended daily dose (RDD) and possible drug-drug interactions with other CNS medication will be discussed.

2.5.1 Methylphenidate

2.5.1.1 Mechanism of action

Methylphenidate is a piperidine derivative with mild CNS stimulatory effects mainly on mental activities (Westfall & Westfall, 2011:299). It acts mainly as a dopamine agonist and exerts its effects via the blockade of the reuptake of dopamine (blockade of the dopamine transporter (DAT) protein) and disinhibition of the dopamine-2 (DA₂) auto-receptors in the presynaptic region (Spencer *et al.*, 2005:1293). Methylphenidate also activates the dopamine-1 receptors (D₁) in the dorsal striatum, nucleus accumbens and in the prefrontal cortex (Arnston,

2006:2377; Spencer *et al.*, 2005:1293) by increasing the extracellular dopamine (Bymaster, 2002:704), which is responsible for executive functions, e.g. regulation of attention, planning, impulse control, mental flexibility, initiation- and monitoring of action (Aron & Poldrack, 2005:1289).

The agonist effects of methylphenidate on the α_{2A} -adrenoceptors increase norepinephrine in the hippocampus (Kuczenski & Segal, 2001:880) and the prefrontal cortex (Berridge *et al.*, 2006:1117; Bymaster, 2002:704). According to Bymaster *et al.* (2002:704), the released norepinephrine can bind to heteroreceptors on dopaminergic neurons in the frontal cortex to inhibit dopamine release and thereby inhibiting symptoms such as inattention and impulsivity.

2.5.1.2 Indications

Methylphenidate is primarily indicated for the treatment of ADHD in children, adolescents and adults, as well as narcolepsy in adults (Rossiter, 2014:508).

2.5.1.3 Recommended daily dose (RDD)

Table 1-5 shows the RDD of methylphenidate for the treatment of ADHD in children and adults. This table was composed using the South African Medicines Formulary (SAMF) (Rossiter, 2014:508).

2.5.1.4 Potential drug-drug interactions

Polypharmacy with antidepressants is recommended for the treatment of a wide range of disorders, such as depression with psychotic features, treatment resistant depression or OCD and ADHD with comorbid depressive or anxiety disorders (AACAP, 2007a:1509; Geller & March, 2012:98; Pliszka *et al.*, 2006:648); however, the concurrent use of methylphenidate and CNS medication may lead to an increased risk of drug-drug interactions.

According to Tatro (2012:1943), methylphenidate interacts with tricyclic antidepressants (TCAs) (Markowitz & Patrick, 2001:754), hydantoin derivatives (Tatro, 2012:955), and carboxamides (Tatro, 2012:1233) causing increased serum concentration of these agents by inhibiting its metabolism via CYP450. Although the mechanism by which methylphenidate interacts with the mono-amine oxidase inhibitors (MAOIs) (Markowitz & Patrick, 2001:754) is unknown (Tatro, 2012:1235), the concomitant use of these agents can lead to a hypertensive crisis (Tatro, 2012:1235). Refer to Annexure F for specific significant drug-drug interaction levels.

2.5.2 Atomoxetine

2.5.2.1 Mechanism of action

Atomoxetine is a non-stimulant noradrenergic reuptake inhibitor, with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors (Michelson *et al.*, 2001). It is also considered an atypical antidepressant (O'Donnell & Shelton, 2011:402). Atomoxetine is metabolised by the hepatic cytochrome P450 (CYP2D6) (Michelson *et al.*, 2001), but shows no inducing or inhibiting effects on this enzyme (Rossiter, 2010:493).

2.5.2.2 Indications

Atomoxetine is primarily indicated for the treatment of ADHD in children, adolescents and adults (Rossiter, 2014:508) and is considered as the first-line medication in patients with substance abuse problems, comorbid anxiety or patients with severe TD (Pliszka *et al.*, 2006:648).

2.5.2.3 Recommended daily dose (RDD)

Table 1-5 shows the RDD for atomoxetine for the treatment of ADHD in children and adults. This table was composed by using the South African Medicines Formulary (SAMF) (Rossiter, 2014:507).

2.5.2.4 Potential drug-drug interactions

Potential drug-drug interactions with atomoxetine are mono-amine oxidase inhibitors (MAOIs), e.g. isocarboxazid, phenelzine and tranylcypromine, as well as selective serotonin reuptake inhibitors (SSRIs), e.g. fluoxetine and paroxetine (Tatro, 2012: 213, 214).

The concurrent use of atomoxetine and MAOIs or SSRIs can increase the risk for adverse effects such as serotonin syndrome (Tatro, 2012:213). Refer to Annexure F for specific significant drug-drug interaction levels.

2.6 Central nervous system comorbidities/co-existing disorders associated with ADHD

Controversy regarding the use of the term 'comorbidity' has been debated among researchers. The use of 'comorbidity' in psychopharmacology can be problematic because it often refers to disease entities or morbid conditions. Psychopathology is not disease entities, but rather conditions or functional impairments and arrays of symptoms and diagnostic criteria that are not fundamental of a specific disease entity. 'Comorbidity' can also refer to the underlying aetiology of two or more diseases, one disease leading to another, or can be present when two or more independent disorders occur together (Caron & Rutter, 1991:1068; Gillberg *et al.*, 2004:80;

Steinhausen *et al.*, 2006:26). For the purpose of this study, 'comorbidity' will be regarded as simultaneous mental disorders co-occurring in one individual (Valderas *et al.*, 2009:357; Burgić-Radmanović & Burgić, 2010:298).

In 1991, Biederman *et al.* (1991:564) conducted a meta-analysis on comorbid disorders in children and adolescents with ADHD using data from cross-sectional, retrospective, and follow-up studies and found that youths with ADHD are at risk of developing other psychiatric disorders, including mood, anxiety and substance use disorders. Severe impairment of mental health, quality-of-life and social- and psychological adaptation result from psychiatric conditions (Taurines *et al.*, 2010:268).

ADHD is associated with a high percentage of co-existing disorders (Kadesjö, & Gillberg, 2001:490; Kessler *et al.*, 2006:718; Kooij *et al.*, 2004:980). The most common comorbidities include ODD, DCD, mood disorders (depression- and anxiety disorders) and SUD (Elia *et al.*, 2008; Ralston *et al.*, 2004:39). Recently, the CDC (2013) determined that the most used CNS medication in the American population was from the drug class antidepressants (3.2%) and ADHD drugs (3.2%), which can be due to the high prevalence of these comorbid conditions. A cogent relationship between ADHD and the use of CNS medication in children (Hsia & MacLennan, 2009:215; Paulose-Ram *et al.*, 2007:567; Steffenak *et al.*, 2012:230; Zito *et al.*, 2006:797) and adolescents (Biederman, 2004:3; CDC, 2013:4) was suggested to be a result of comorbidities associated with ADHD.

Taurines *et al.* (2010:269) outlined the temporal order of the comorbidities associated with ADHD. TD, GAD, OCD, depression, ODD, CD, SUD etc. were categorised as post-comorbid disorders, implying an onset in childhood and persistence into adult life (appearing after the onset of ADHD) (Taurines *et al.*, 2010:269).

Strong patterns of comorbidity are found within internalising (anxiety and mood) ranging from 13 to 51% (Jensen *et al.*, 2001:150) and externalising (disruptive behaviour and substance abuse) ranging from 43 to 93% (Jensen *et al.*, 2001:150) disorders, which are broad clusters of disorders referred to in childhood (Fayyad & Kessler, 2015:25). Internalising disorders tend to persist over lifetime, with incremental increases in prevalence with age. Externalising disorders have early onset in childhood, but often disappear into adulthood (Chan *et al.*, 2008:21). Depressive- and anxiety disorders, as well as ASD (Gillberg *et al.*, 2004:84), are considered as internalising disorders, while externalising disorders include ODD and CD (Diler *et al.*, 2007:127).

Between 65 and 89% of ADHD diagnosed adults have been documented to suffer from at least one psychiatric disorder during their lifetime (McGough *et al.*, 2005:1624; Sobanski, 2006:26).

Prevalence rates of between 35 and 50% for depression, 27% for anxiety disorders (Taurines *et al.*, 2010:269), 4.4% for autism spectrum disorder (ASD) (Nyden *et al.*, 2010:1666), 60 to 90% for bipolar disorder (West *et al.*, 1995:272) and up to 50% with substance abuse disorders (Biederman *et al.*, 1998:272; Jacob *et al.*, 2007:314; Wilens *et al.*, 1997:477) have been documented.

According to Chronis *et al.* (2003:1429), children are more likely to be diagnosed with ADHD if their parents have the same diagnosis due to its genetic and aetiological origin (Mick & Faraone, 2008:275). Research indicates that the approximate estimate of ADHD heritability is 76% (Biederman & Faraone, 2005:239; Spencer *et al.*, 2007:78).

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

ADHD is an externalising disorder and is consistently found to have a strong comorbidity with ODD and CD (Fayyad & Kessler, 2015:25). Estimates for the co-occurrence of either disorder range from 30 to 50% in clinical and epidemiological samples (Spencer, 2006:29). According to the APA (2013:91), the essential diagnostic feature of ODD is “*a recurrent pattern of negativity, hostility and defiance toward authority figures*”. ODD is considered the most prevalent co-existing disorder in ADHD and approximately half of the children with ADHD meet the DSM-V criteria for this externalising disorder (Alston, 2007; Gillberg *et al.*, 2004:81; Wilens *et al.*, 2002:266).

ADHD subtypes play a role when considering associated comorbidities. It was found that the subtype impulsivity-hyperactivity and the combined type have a higher comorbidity with ODD and CD than the inattentive type (Adewuya & Famuyiwa, 2007:14; Connor *et al.*, 2003:198). In a cohort study conducted by Takeda *et al.* (2012:423), results confirmed that children (ages 6 to 18 years) with comorbid ODD and CD are more impulsive than those with internalising disorders.

Different results regarding the influence of age and gender on ADHD comorbidities have been documented. For example, when Lahey and associates (2000:496) analysed parent reports, no age and gender differences were found, but when teacher reports were analysed, ODD was more common in boys than girls. Maughan *et al.* (2004:615) confirmed these findings from teacher reports when they found that 3.2% of boys compared to 1.4% of girls met the full DSM-IV criteria for ODD. On the contrary, Rowe *et al.* (2002:367) reported that the prevalence of ODD was the same in both genders.

CD is defined by the APA (2013:85) as “*a repetitive and persistent pattern of behaviour in which the basic rights of others or major age-appropriate societal norms or rules are violated*”.

Prevalence rates of ADHD with comorbid CD have been reported, with approximately 46% of children suffering from both disorders (Ralston *et al.*, 2004:39). Children and adolescents with CD often show behaviour ranging from physical aggression (e.g. aggression to people and animals by bullying, threatening or intimidating etc.), non-aggressive conduct problems (e.g. lying, stealing etc.) and status violations. In a cohort study of 1 478 children aged six to 18 years, Steinhausen *et al.* (2007:27) reported that children with ADHD and ODD/CD presented with higher ratings for total difficulties, which included conduct problems, peer relationship problems and social behaviour compared to ADHD-only children, and overlapping symptoms may heighten these symptoms (Keenan & Wakschlag, 2000:40; Lahey *et al.*, 2000:496; Maughan *et al.*, 2004:616; Rowe *et al.*, 2002:367).

CD becomes more prevalent with increases in age (Takeda *et al.*, 2012:423) and shows a more consistent pattern in males than in females (Lahey *et al.*, 2000:494; Maughan *et al.*, 2004:609; Rowe *et al.*, 2002:370; Spencer *et al.*, 2005:75). Consistent with these findings, Erskine *et al.* (2013:1269) reported that the prevalence of CD in males was 2.4 times higher than in females. Boys also tend to show more aggressive behaviour and property offenses than girls, and are more common in older ages (Lahey *et al.*, 2000:497). A cross-sectional epidemiological study conducted by Maughan *et al.* (2004:614) investigated age and gender ratios in ODD and CD, and reported an increase in the prevalence of CD in boys. They also found that the risk of developing CD symptoms increases with age and that boys are more prone to develop CD (Maughan *et al.*, 2004:614).

2.6.2 Depression

Depression is a common psychiatric, internalising disorder that is characterised by depressed mood or the diminished interest or pleasure in nearly all activities (APA, 2013:93). Depression can be classified as major/unipolar depression or bipolar depression (O'Donnell & Shelton, 2011:397). Unipolar depression is distinguished from bipolar depression in that the former exhibits mood swings towards depressive symptoms, and the latter displays a disorder in which depression and mania alternate (Pleuvry, 2004:354; Widmaier *et al.*, 2008:243). The following signs and symptoms of clinical depression are documented in the APA (2013:93): weight gain or loss, disturbed sleep, psychomotor activity (agitation and retardation), fatigue, poor concentration, feelings of worthlessness or guilt, decreased energy, difficulty thinking or concentrating and decision-making, and recurrent thoughts of death or suicidal pre-occupation, plans, or attempts. Diagnosis of depression in children is often difficult and can lead to misdiagnoses due to differences in symptom presentation, as well as overlap between ADHD and depression (such as restlessness and concentration problems) (Alston, 2007). Major depression in children can present as irritability rather than sadness or depression, and where

weight gain is expected, children usually show weight loss (APA, 2013:93; Spencer *et al.*, 2005:77). Features associated with depressed children include difficulties in school, refusal to attend school, withdrawal, somatic complaints, negativity, aggression and antisocial behaviour (Spencer *et al.*, 2007:77).

An estimated 32% of children and adolescents with ADHD have been reported to have a diagnosis for depression (Steinhausen *et al.*, 2006:27). Children and adolescents with ADHD are often diagnosed with comorbid depression, which, like ODD and CD, has overlapping symptoms with ADHD (Biederman *et al.*, 1996:1001; Wilens *et al.*, 2002:266), including distractibility, impaired, racing thoughts and irritability (APA, 2013:93). This overlap can contribute to a higher risk for greater psychiatric morbidity and disability in ADHD children and adolescents with comorbid depression than those without major depression when not treated effectively (Alston, 2007; Steinhausen *et al.*, 2006:28).

Different factors should be taken into consideration when examining the association between ADHD and depression as a comorbid condition (Alston, 2007), i.e. moderating variables (such as age, gender, comorbidities and ADHD subtype) (Brunsvold *et al.*, 2008). For example, when Brunsvold *et al.* (2008) considered gender, age, comorbid ODD, ADHD subtype and data source they found that the inattentive subtype was more likely to correlate with depression, but when only one moderating variable was taken into consideration, results tended to differ. Children and adolescents diagnosed with the inattentive subtype and even with the combined subtype of ADHD were found to be more at risk for depression than those diagnosed with the hyperactive-impulsive type (Adewuya & Famuyiwa, 2007:14). Lower prevalence rates of females have been reported by Biederman and colleagues (2008) when they controlled for these moderating variables. They also reported a higher association of the inattentive subtype of ADHD in females, with a likeliness of 2.2 (Biederman *et al.*, 2002:38). Kessler also reported a two-fold prevalence of depression in females (Kessler, 1994:11). Quin (2008:421) described the comorbidity of depression in girls as 5.4 times more likely, and that girls are more often treated for depression than boys.

According to Brunsvold *et al.* (2008), behaviours consistent with different age groups must also be considered when screening for comorbid depression. They found that boys younger than 10 years (opposite is true for girls) were more likely to have high levels of depression. Alston (2007) reported that diagnosis with depression increases with age, especially for females. They concluded that these results could explain why different researchers have come to different conclusions about whether comorbid depression is accounted for by a third variable. Spencer *et al.* (2007:77) reported a 16% increase of comorbid depression in children at an average age of 15 years.

Retrospective and prospective studies have shown that 35 to 50% of adults with ADHD suffer from one or more depressive disorders during their lifetime (Gittelman *et al.*, 1985:940). In fact, there is evidence to suggest that the comorbidity of depressive disorders is similar in children and young adults (Angold *et al.*, 1999:74; Biederman *et al.*, 1993:1793; Spencer *et al.*, 1999:918; Sobanski, 2006:27; Wilens *et al.*, 2002:266), which suggests that depressive disorders remain present into adulthood (Michielsen *et al.*, 2012:225). In addition, several studies reported an increase in the severity of ADHD symptoms with age (Michielsen *et al.*, 2012:225; Simon *et al.*, 2013:312).

2.6.3 Anxiety disorders

The APA (2013:189) classifies 12 subtypes of anxiety disorders, namely separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder, general anxiety disorder and substance-induced anxiety disorder. “*Excessive fear, anxiety and behavioural disturbances*” are common shared characteristics in anxiety disorders (APA, 2013:189). Anxiety disorders are considered internalising disorders (Jensen *et al.*, 2001:147), with an onset in childhood and persistence into adulthood. Anxiety frequently co-occurs with ADHD (Biederman *et al.*, 1991:574; Schatz & Rostain, 2006:148), and 28 to 50% of ADHD diagnosed youths have been documented to suffer from comorbid anxiety disorders (Wilens *et al.*, 2002:264; Biederman *et al.*, 1991:570; Ralston *et al.*, 2004:40).

Despite the fact that ADHD is considered an externalising disorder and anxiety an internalising disorder, their symptoms overlap (irritability, restlessness, sleep disturbances and difficulty in concentrating). When Tannock (2000:125) considered overlapping symptoms of ADHD and anxiety in clinical and epidemiological samples, he estimated the prevalence of anxiety in ADHD-patients aged five to 19 years to reach 25%.

The aetiology of anxiety disorders in patients with ADHD is controversial (Tannock, 2000:125). Some researchers suggest that anxiety problems in ADHD patients stems from poor social abilities, problems in performance at work or school and difficulties in peer interactions (Mikami *et al.*, 2011:480), while others support the hypothesis that attention problems are secondary to an anxiety disorder due to symptom overlap (Jarret & Ollendick, 2008:1267). Another explanation for this comorbidity is that it may represent another, distinct, unclassified disorder that involves dysregulation in both anxiety and ADHD domains (Menassis, 2007:981). The influence of family characteristics, e.g. overprotectiveness and lack of positive parenting, with regard to anxiety in children with ADHD have also been described as a possible reason for the comorbidity of ADHD and anxiety (Pfiffner & McBurnett, 2006:729). Maternal anxiety, overprotectiveness, and a lack of positive parenting were found to significantly affect child

anxiety (Pfiffner & McBurnett, 2006:729). Braaten *et al.* (2003:98) documented that children with ADHD are more susceptible to have an anxiety disorder than children without ADHD, especially when there were familial anxiety.

2.6.4 Autism spectrum disorder (ASD)

Autism spectrum disorder (ASD) is a lifelong pervasive developmental disorder and presents as abnormalities in social communication and interaction with restricted, repetitive patterns of behaviour, interests or activities (APA, 2013:50). A prevalence estimate of 1% in adult and child samples has been reported in recent years (APA, 2013:55), and a surprising 20 - 50% of ADHD-patients exhibit autistic traits or even meet the diagnostic criteria for autism (Kotte *et al.*, 2013:617; Rommelse *et al.*, 2010:288; Simonoff *et al.*, 2008:926), for which the reverse is also true (Lee & Ousley, 2006:742).

An additive co-occurrence (Tye *et al.*, 2013:1111) of ADHD and autism has been described, mainly due to similarities in social deficits, e.g. problems with peers and family (Kotte *et al.*, 2013:616). Difficulties in socialisation associated with autism include a wide spectrum of signs and symptoms, from basic aspects of social interactions (for example shortfall in emotional perception and lack of attention when communicating with others), to relationship deficits (problems in initiating and maintaining relationships with friends and family) (Cervantes *et al.*, 2013:1105). Similarly, children with ADHD are often perceived as socially incompetent by authority figures such as teachers (DuPaul *et al.*, 2004:298), and are frequently rejected by peers and struggle to maintain or initiate friendships (Blachman & Hinshaw, 2002:365; Hoza *et al.*, 2005:82). Whereas children with ADHD exhibit maladaptive social behaviour, ASD sufferers display a lack of adaptive social skills (Cervantes *et al.*, 2013:1107).

Genetic overlapping between ADHD and ASD have been investigated, mainly implicating the DAT1 and DRD3 genes (primarily associated with ADHD) (Gadow *et al.*, 2008:1338), and the serotonin transporter genes (SLC6A4, SERT, 5-HTT) (Huang & Sntangelo, 2008:1114). ASD symptoms are present in ADHD families, also suggestive of underlying genetic factors (Mulligan *et al.*, 2009:204). This could also explain the similarities between the social difficulties in ADHD and ASD, respectively.

Despite previous findings of a higher male to female ratio for ASD, and studies suggesting relatively few differences between genders (Rivet & Matson, 2011:962), a recent study by Kumazaki *et al.* (2015:3) reported that females are more likely to suffer from ASD. Rivet and Matson (2011:972) outlined various reasons for this phenomenon, and included, among others, problems in correct and early diagnosis of ASD in females, as well as difficulties in recognising behavioural differences in females.

2.6.5 Tic disorders (TD)

Tics are “*sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations*” and are brief/transitory in most cases (APA, 2013:82). Tourette’s disorder, chronic tic disorder (tics occurring for more than one year), transient tic disorder and tic disorder (not otherwise specified), are all classified as tic disorders (TDs) (APA, 2013:81), and commonly co-occur with ADHD (Spencer *et al.*, 2001:613). ADHD commonly precedes TD (Spencer *et al.*, 2001:613), and according to Taurines *et al.* (2010:269), TD is considered a post-comorbid disorder with an onset in middle childhood with a chronic outcome (Spencer *et al.*, 2001:614).

According to the APA (2013:84), the male to female ratio of TDs vary from 2:1 to 4:1. Approximately eight to 14% of patients with ADHD have concurrent comorbidity with TDs (Ralston *et al.*, 2004:140, Steinhausen *et al.*, 2006:27), and TD is found in 20 to 85% of children with ADHD (Biederman *et al.*, 2005:1086; Gillberg *et al.*, 2004:82). TD is documented not only to affect children, but also adults (Spencer *et al.*, 2001:614). In the study conducted by Spencer *et al.* (2001:615), 81% of the subjects who had a diagnosis of ADHD, as well as tics, were male.

ADHD is associated with disruptive behaviour, whereas TDs are more associated with anxiety and depression (Roessner *et al.*, 2007:82; Spencer *et al.*, 2001:614). According to findings from Robertson (2006:4) and Roessner *et al.* (2007:82), when a patient suffers from both ADHD and TD, it is most likely that ADHD will only contribute to the social and behavioural difficulties. Despite this, TD does not have an impact on ADHD outcome (Spencer *et al.*, 2001:611).

2.6.6 Substance use disorders (SUD)

Alcohol or drug dependence is referred to as substance use disorders, and include behavioural, cognitive and physiological symptoms, which are seen in individuals who persistently use substances despite its related problems (APA, 2013:483). SUD has a lifetime prevalence of 15.3 to 18% among 18 to 59 year old individuals in the US (Kessler *et al.*, 2005a:596).

Faraone *et al.* (2007:29) reported alcohol and cannabis to be the highest abused substances, followed by cocaine and amphetamines (Sullivan & Rudnik-Levin, 2001:257). For example, Arias *et al.* (2008:1204) found that 5.22% of their study sample that consisted of 1 761 children had cocaine and/or opioid dependence. Ohlmeier *et al.* (2011:156) reported that 39.3% of their study sample was alcohol dependent.

The relationship between ADHD and SUD entails a wide variety of factors and pathways. Kalbag and Levin (2005:1964) gave a brief outline of the possible explanations for this phenomenon, which includes the presence of CD, the most common comorbidity of ADHD,

genetic predisposition, the need for self-medicating ADHD symptoms, and the effect that poor school or work performance etc. can have on the individual's perception of success (Young & Bramham, 2012:244). Impulsivity, one of the core symptoms of ADHD, may also be an important mediating factor in considering the development of SUD (Dawe & Loxton, 2004:349).

Individuals with ADHD or comorbid CD have a higher risk for later substance use disorder, and individuals with both disorders carry an even higher risk to develop a substance use disorder (Looby, 2008:456, 457). When Arias *et al.* (2008:1205) analysed the effects of ADHD with comorbid CD on substance disorder risk, they found that individuals with both ADHD and CD had an earlier age of onset of substance use than individuals with only CD, or only ADHD, suggesting an additive effect on age of onset. In another study conducted by Abrantes and associates (2005:397), it was found that ADHD also had an impact on the frequency of substance use. Furthermore, Arias and colleagues (2008:1205) concluded that ADHD is associated with a greater number of substance disorder diagnoses. ADHD, CD and SUD are moderated by age (Abrantes *et al.*, 2005:397), but the frequency of substance use is related to ADHD symptoms in boys, whereas in girls, it is related to conduct symptoms (Abrantes *et al.*, 2005:397).

ADHD is considered a risk factor for SUD (Molina & Pelham, 2003:503; Wilens, 2004b:38), and contributes to the development of SUD in individuals (Looby *et al.*, 2008:460) as ADHD manifests earlier than SUD (Wilens, 2004a:285). SUD is commonly seen in patients with ADHD, with an overall prevalence of 15 to 25% of adults with concurrent ADHD (Wilens, 2004a:284). Some studies even reported comorbidity rates of approximately 50% (Biederman *et al.*, 1998:272; Jacob *et al.*, 2007:314; Ohlmeier *et al.*, 2011:157; Wilens *et al.*, 1997:477). Subsequently, the prevalence of ADHD is highest in individuals with SUD (Kalbag & Levin, 2005:1963), particularly males (Katusic *et al.*, 2003:772).

According to Barkley (2008:291) and Arias *et al.* (2008:1206), children with persistent ADHD are likely to suffer from SUD in adulthood. The risk for the development of SUD increases with age, and adults with ADHD tend to start abusing substances at earlier ages than peers without ADHD (Katusic *et al.*, 2003:772; Skoglund *et al.*, 2015:884; Wilens, 2004b:39; Wilens, 2004a:284), usually at ages 17 to 19 years (Wilens, 2004a:286, 298). SUD patients with ADHD tend to have a more severe form of SUD, with higher rates of relapse and experience more problems in remaining abstinent, resulting in a poorer treatment outcome (Wilens, 2004a:284). Additionally, Biederman and colleagues (1998:272) reported that persistent ADHD is associated with a two-fold increased (52% vs. 27%, respectively) risk to develop SUD. ADHD and comorbid SUD can cause greater psychiatric comorbidities (e.g. CD and bipolar disorder) and a longer duration of SUD (Wilens, 2004a:285).

According to Skoglund *et al.* (2015:883), there is a strong genetic familial association between ADHD and SUD. Shared genes that have been suggested to be involved in the aetiology of SUD as well as ADHD include the DRD2 gene, the dopamine β -hydroxylase gene, the DAT gene, the SNAP-25 gene and the DRD4 receptor gene (Bédard *et al.*, 2010:940; Ray *et al.*, 2010:121). As reviewed by Wilens (2004a:286), ADHD and SUD in parents cause higher incidence of ADHD in biological children.

Contrary to previous speculations regarding the effects that stimulant medication may have on later substance abuse, treatment of ADHD with stimulant medication protects against SUD (Fischer & Barkley, 2003:21; Katusic *et al.*, 2003:772; Wilens *et al.*, 2003:182). Treatment with stimulant medication is not associated with SUD development, and decreases the risk to develop SUD later in life (Barkley *et al.*, 2003:107; Dalsgaard *et al.*, 2014:327; Mannuzza *et al.*, 2008:607; Molina *et al.*, 2007:1037).

2.6.7 Obsessive compulsive disorder (OCD)

OCD is a chronic, internalising psychiatric disorder where the sufferers have obsessions or compulsions that negatively affect their day-to-day activities (APA; 2013:237). OCD differs from ADHD in that OCD is typically associated with restraint and harm or risk avoidance, in contrast to the impulsiveness associated with ADHD (Abramovitch *et al.*, 2015:4). This phenomenology is supported by respective neurobiological and neurochemical differences, namely dopamine pathways contributing to the impulsive behaviours of ADHD patients versus the serotonin pathways mediating compulsiveness (Abramovitch *et al.*, 2013:57; Carlsson, 2001:17).

OCD has an onset in childhood, usually before the age of 15 years (Goodman & Scott, 2012:131), and persists into adulthood, causing distress and disability (Carlsson, 2001:6). Comorbid OCD also tends to affect adult males more than it does adult females (APA, 2013:239; Masi *et al.*, 2006:45).

The reported prevalence of OCD in children with ADHD is reported to range from six to 18.8% (Geller *et al.*, 2003:28; Gillberg *et al.*, 2003:263). The prevalence of OCD in individuals with ADHD ranges from 11.8 to 25.5% (Brem *et al.*, 2014:177; De Mathis *et al.*, 2007:44). De Mathis *et al.* (2007:44) further found that males were more likely than females to have comorbid OCD, and that patients with ADHD had an earlier onset of OCD.

One of the main concerns regarding this comorbidity is the additive effect ADHD symptoms have on OCD, implicating the social and attention problems in these individuals (Masi *et al.*, 2006:46). Nevertheless, Masi *et al.* (2006:42) noted that comorbid ADHD had no impact on obsessions or compulsions. The same conclusions were drawn by De Mathis and colleagues

(2007:44), when they found that the phenomenology of ADHD was not affected by co-occurring OCD.

Concomitant ADHD-OCD as a familial subtype and the executive overload model of OCD have both been suggested as etiological accounts for the comorbidity of ADHD and OCD (Abramovitch *et al.*, 2015:12). The executive overload model suggests that obsessive thoughts in OCD may 'overload' the executive functions that result in neurocognitive impairment. In other words, individuals with OCD may present with ADHD-like symptoms due to OCD-related neurocognitive impairment (Abramovitch *et al.*, 2015:12). OCD is familial, with heritability of approximately 50% (Goodman & Scott, 2012:133). SLC1A1 has been suggested as a candidate gene that is involved in the neurotransmission of glutamate (Goodman & Scott, 2012:133). Geller and associates (2007:319) proposed that ADHD and OCD represent a "distinct familial subtype", suggesting that both disorders are inherited together. Furthermore, Geller *et al.* (2007:320) concluded that ADHD and OCD are independent conditions.

2.6.8 Developmental co-ordination disorder (DCD)

Developmental co-ordination disorder (DCD) is a neurodevelopmental motor disorder that is the DSM-V diagnosis used to describe the disorder in individuals who fail to obtain and execute fine motor coordination and that interferes with everyday tasks and academics (APA, 2013:32). Prevalence estimates of five to six percent in children aged five to 11 years old suggest that it is a fairly common psychiatric condition (APA, 2013:75), where ADHD is reported to occur in 50% of DCD diagnosed children (Kadesjö & Gillberg, 2001:491; Pitcher *et al.*, 2003:534). DCD more frequently occurs in the male population (APA, 2013:75).

According to recent studies, children with ADHD and DCD share common neurophysiological deficits in motor skills and attention (Kaiser *et al.*, 2015:535; McLeod *et al.*, 2014:573). Consequently, individuals with both disorders experience more impairment than those with only ADHD or DCD (APA, 2013:76; Kaiser *et al.*, 2015:353). A shared aetiology between ADHD and DCD has been proposed that may be distinct from the factors influencing either of the separate disorders (Martin *et al.*, 2006:112). For example, ADHD and DCD have been shown to have shared genes (Martin *et al.*, 2006:121), implicating the DAT1 (Chen *et al.*, 2003:394), DRD4 (Langley *et al.*, 2004:135), and MAO (Payton *et al.*, 2001:468) genes.

2.6.9 Specific learning disorder

Learning disabilities (LD) encompass a wide spectrum of learning disabilities, including reading disorder/dyslexia, mathematical disabilities/dyscalculia and disorder of writing expression (APA, 2013:66). This category of learning disorders refers to difficulties in learning and using

academic skills by the appropriate age and causes substantial interference with academic or occupational performance (APA, 2013:66). As noted by Pastor and Reuben (2008:237), an overall prevalence of LD and ADHD in an epidemiological study sample consisting of 23 051 children aged six to 17 years, was 3.7%, and that boys were twice as likely to be diagnosed with LD than girls (5.1% vs. 2.3%, respectively).

Although there may be overlapping characteristics between learning disorders and ADHD, for example motor skills, speed of information processing etc., it remains two distinct neurodevelopmental disorders (De Jong *et al.*, 2009:1014; Shanahan *et al.*, 2006:585; Tannock & Brown, 2000:237).

Reading disability (RD), or dyslexia, is the most common learning disability (Sexton *et al.*, 2012:538), and refers to difficulties in comprehension of what is read, poor spelling and inaccurate or inarticulate word recognition (APA, 2013:67; Lyon *et al.*, 2003:1).

There are three hypotheses that have been proposed for the co-occurrence of ADHD and reading disorders, namely, the 'phenocopy model', the 'cognitive subtype hypothesis', as well as the 'multiple deficit model'. The phenocopy model suggests that attention problems related to ADHD can result in RD, or that RD gives rise to inattention (Sexton *et al.*, 2012:544). The second hypothesis, the cognitive subtype hypothesis, is explained by different aetiologies that may give rise to a third disorder (Sexton *et al.*, 2012:544). Other researchers have proposed a third hypothesis that may also explain the comorbidity between LD and ADHD, which is based on shared genetic risk factors that may increase an individual's proneness to inherit both disorders (Shanahan *et al.*, 2006:598; Willcutt *et al.*, 2005:69).

2.7 Other central nervous system medication

An overview discussion of 'other' central CNS nervous system medication and their mechanism of action, indications and drug interactions associated with methylphenidate or atomoxetine is discussed in this section.

2.7.1 Central nervous system stimulants

CNS medication will be discussed under their respective pharmacological classifications.

2.7.1.1 Central analeptics

Drugs included in this class are sympathomimetic acting piracetam and modafinil.

Piracetam improves oxygen utilisation (Keil *et al.*, 2006:199), and is indicated for the treatment of pre-delirium, delirium tremens, toxicomanias, disorders of consciousness, consequences of head injury and cerebral acidosis (Snyman, 2014:1).

Modafinil is also considered a CNS analeptic, and is indicated for the treatment of narcolepsy and hyper-somnolence with cataplexy (Rossiter, 2014:508).

2.7.1.2 Respiratory stimulants

Doxapram and naloxone are considered respiratory stimulants.

Doxapram stimulates respiration through stimulation of peripheral carotid and aortic chemoreceptors (peripheral) and through brainstem respiratory centres (Yost, 2006:236). It is indicated for the treatment of respiratory failure resulting from COPD, post-anaesthesia respiratory depression or apnoea (Yost, 2006:236).

Naloxone is a pure, competitive opioid antagonist, and is used to reverse opioid-induced respiratory depression post-operatively (Rossiter, 2014:429), and opioid toxicity (Pharmacare limited, 1993).

2.7.1.3 Others

Flumazenil is used to treat benzodiazepine overdose or to reverse the sedative effects of benzodiazepines in anaesthesia by competitively binding to the GABA-A receptor (Rossiter, 2014; 416).

2.7.2 Sedative hypnotic- and anxiolytic agents

The term 'sedatives' refers to medication that is used to induce calmness and drowsiness, whereas 'hypnotics' can be defined as drugs that are used to induce sleep or unconsciousness (Absalom & Adapa, 2007:340; Mihic & Harris, 2011:457). Anxiolytic medication is used to reduce anxiety (Absalom & Adapa, 2007:340).

2.7.2.1 Benzodiazepine derivatives

Benzodiazepine derivatives are most commonly prescribed for short-term anxiety disorders and insomnia (Absalom & Adapa, 2007:340; Heeremans & Absalom, 2010:330; Rossiter, 2014:488). Drugs in this class include alprazolam, bromazepam, clobazam, chlorazepate, chlordiazepoxide, ketazolam, loprazolam, lorazepam, midazolam, oxazepam, prazepam, temazepam and triazolam.

Benzodiazepines exert their action by modulating the effects of γ -aminobutyric acid (GABA) at the γ -aminobutyric acid (GABA-A) receptor, which is a ligand-gated chloride channel that consists of five subunits (Absalom & Adapa, 2007:340; Heeremans & Absalom, 2010:330). When this receptor is activated, chloride ions flux through the GABA receptor, causing hyperpolarisation and inhibition of neuronal transmission (Widmaier *et al.*, 2008:170; Absalom & Adapa, 2007:340; Heeremans & Absalom, 2010:330).

Benzodiazepines are used for anxiolysis and sedation (Absalom & Adapa, 2007:340) and prevent seizures (Widmaier *et al.*, 2008:170). Benzodiazepines can also be used for status epilepticus (Mihic & Harris, 2011:465).

2.7.2.2 Barbiturates

The use of barbiturates has been replaced with benzodiazepines, which are much safer to use due to its safety profile (Mihic & Harris, 2011:469). Phenobarbitone (syn. phenobarbital) is the only barbiturate therapeutically used in South Africa (Rossiter, 2014:454).

Barbiturates function on the same principle mechanism as does benzodiazepines. Barbiturates heighten the effects of GABA on the GABA-A receptor, and unlike benzodiazepines, barbiturates prolong the opening of the chloride channels (Mihic & Harris, 2011:471).

Barbiturates are used for insomnia, pre-operative sedation with its consequential anterograde amnesia and the emergency management of seizures (Mihic & Harris, 2011:470).

2.7.2.3 Others (benzodiazepine-receptor agonists)

Zolpidem and zopiclone are considered as benzodiazepine-related drugs due to its GABA receptor-binding site (Rossiter, 2014:493). These drugs are preferred to benzodiazepines because they are associated with fewer side effects, e.g. sleep disturbances, and less likely to produce dependence and withdrawal effects (Rossiter, 2014:493). Zolpidem and zopiclone are indicated for sleep onset insomnia (Mihic & Harris, 2011:467).

2.7.3 Antidepressants

Antidepressant medication will be discussed under their respective pharmacological classifications.

2.7.3.1 Selective serotonin re-uptake inhibitors (SSRIs)

The selective serotonin re-uptake inhibitors are considered second-generation antidepressants and are the most commonly used medications due to their relatively selective nature (O'Donnell

& Shelton, 2011:405; Peretti, 2000:24). Agents included in this drug class are fluoxetine, citalopram, sertraline, fluvoxamine and paroxetine.

Selective serotonin re-uptake inhibitors (SSRIs) represent a chemically diverse class of agents that have as their primary action the inhibition of the neuronal transporter for serotonin (SERT) (DeBattista, 2009:513). SSRIs act mainly by selectively inhibiting the primary process by which serotonin neurotransmission is terminated (O'Donnell & Shelton, 2011:405; Rossiter, 2014:498). The mechanism by which SSRIs relieve depression is extrapolated from the different pathways by which serotonin is transported, and the adaptive actions of serotonin receptors. These mechanisms include the inhibition of SERT, and the adaptation of serotonin receptors. When SSRIs bind to its SERT binding site, it decreases the transporter's affinity for serotonin (negative allosteric modulation) (Stahl, 1998:218), which leads to an accumulation of serotonin in the synaptic cleft (Stahl, 1998:219). Somatodendritic 5-hydroxytryptamine 1A (5-HT_{1A}) autoreceptors act to reduce the firing rate of serotonergic autoreceptors in the dorsal raphe, as well as the release of serotonin (Nutt *et al.*, 1999:82). Initially, this leads to a prolonged and enhanced transmission of serotonin, which is then available to activate serotonin receptors and to stimulate somatodendritic- and presynaptic terminal receptors (O'Donnell & Shelton, 2011:405). The stimulation of HT_{1A} and 5-HT₇ autoreceptors on cell bodies in the raphe nucleus in the midbrain and of 5-HT_{1D} autoreceptors on serotonergic terminals is the one mechanism by which SSRI treatment relieves depression (O'Donnell & Shelton, 2011:405). With chronic SSRI treatment, these receptors become desensitised, leading to even more serotonin release (Stahl, 1998:221). The delay in therapeutic response of SSRIs is ascribed to the increased quantities of serotonin in the synapse after the transporter is blocked, which causes desensitisation and, in turn, down-regulation of receptors (Stahl, 1998:219).

The primary indication for SSRIs is the treatment of depression (DeBattista, 2009:509). In addition to their use as antidepressants, SSRIs are also indicated for a number of other CNS disorders such as general anxiety disorder (GAD), panic disorders, social anxiety disorder (SAD), OCD and post-traumatic stress disorder (PTSD) (DeBattista, 2009:513; Nutt *et al.*, 1999:S81).

2.7.3.2 Serotonin and norepinephrine re-uptake inhibitors (SNRIs)

Serotonin and norepinephrine re-uptake inhibitors (SNRIs) are considered second-generation antidepressants and are the most commonly prescribed (O'Donnell & Shelton, 2011:398). Agents in this class are duloxetine and venlafaxine.

Serotonergic and norepinephrine neurotransmission are enhanced by SNRIs (O'Donnell & Shelton, 2011:407). The SNRIs bind to and inhibit the serotonin- (SERT) and norepinephrine

(NET) transporters responsible for the re-uptake of serotonin and norepinephrine (noradrenalin) at presynaptic terminals (O'Donnell & Shelton, 2011:407). Initially, the 5-HT_{1A} and 5-HT_{1D} autoreceptors are activated, which then causes a decreased serotonergic neurotransmission by negative feedback until these autoreceptors are desensitised (O'Donnell & Shelton, 2011:407). This inhibition leads to an increased concentration of serotonin and norepinephrine in the brain available for the stimulation of postsynaptic serotonin receptors on serotonergic neurons (O'Donnell & Shelton, 2011:407). This mechanism relieves depression (O'Donnell & Shelton, 2011:407). Venlafaxine and duloxetine are also weak dopamine reuptake inhibitors (Rossiter, 2014:505).

SNRIs are primarily used in treating disorders associated with serotonin and norepinephrine, such as major depression and GAD (Rossiter, 2014:505). Off-label uses include stress urinary incontinence (Erdinc *et al.*, 2009:345; Mariappan *et al.*, 2007:72; Schagen van Leeuwen *et al.*, 2008:144), pain syndromes (fibromyalgia) (Sumpton & Moulin, 2001:558), autism (duloxetine) (Carminati, 2005:314), binge eating disorders (duloxetine) (Guerdjikova *et al.*, 2012:284), hot flushes (Nelson *et al.*, 2006), premenstrual dysphoric disorders (Freeman *et al.*, 2001:30) and PTSD (Davidson *et al.*, 2006). FDA-approved indications for duloxetine include: major depression, GAD, diabetic peripheral neuropathy, fibromyalgia, musculoskeletal pain and osteoarthritis (Sansone & Sansone, 2014:38).

FDA-approved indications for venlafaxine include: major depression, GAD, panic disorder and social phobia (Sansone & Sansone, 2014:38).

2.7.3.3 Mono-amine oxidase inhibitors (MAOIs)

Mono-amine oxidase inhibitors are classified as selective or non-selective, reversible or irreversible. Drugs in this class are moclobemide (reversible, selective MAO-A inhibitor), phenelzine, tranylcypromine (non-selective MAOI) and isocarboxazid (Pleuvry, 2004: 355).

The monoamine oxidase enzyme (MAO) consists of two distinct isoenzymes, namely monoamine oxidase enzyme A (MAO-A) (responsible for the metabolism of serotonin and norepinephrine), and monoamine oxidase enzyme B (MAO-B) (Pleuvry, 2004:354). These enzymes are responsible for the metabolism of catecholamines (dopamine, noradrenaline and adrenaline) in the nerve terminals and the synapse (O'Donnell & Shelton, 2011:404; Rossiter, 2014:502; Widmaier *et al.*, 2008:243). Monoamine oxidase inhibitors prevent the degradation of catecholamines and cause increases in concentrations of these neurotransmitters in the synapse (Block & Nemeroff, 2014:8).

MAOIs are mainly used to treat mood disorders, e.g. clinical depression (Widmaier *et al.*, 2008:243).

2.7.3.4 Tricyclic antidepressants (TCAs)

Tricyclic antidepressants (TCAs) are not used as first-line treatment for depression due to poor tolerability (multi-receptor blockade), difficulty of use and to lethality in overdose (DeBattista, 2009:514; O'Donnell & Shelton, 2011:407; Steffens *et al.*, 1997:17). TCAs are used primarily for treatment resistant depression (DeBattista, 2009:514; O'Donnell & Shelton, 2011:407). Agents classified as TCAs include: amitriptyline, amoxapine, clomipramine, desipramine, dothiepin, doxepin, imipramine, lofepramine, maprotiline, nortriptyline, protriptyline and trimipramine (DeBattista, 2009:514; O'Donnell & Shelton, 2011:407).

TCAs are multi-receptor blockers/inhibitors (H₁, 5-HT, α_1 , muscarinic, and dopaminergic receptors), but are mainly used as antidepressants due to its antagonism of norepinephrine (NET) and serotonin transporters (SERT) (DeBattista, 2009:514; O'Donnell & Shelton, 2011:408). This, in turn, increases the synaptic concentration of norepinephrine (NE) and serotonin (5-HT), which then enhances neurotransmission of these neurotransmitters (DeBattista, 2009:514; O'Donnell & Shelton, 2011:408). TCAs' non-selectively inhibits the re-uptake of 5-HT, DA and NE in the presynaptic vesicles in the brain and may contribute to its therapeutic effects (O'Donnell & Shelton, 2011:408).

TCAs are primarily indicated for the treatment of depression, anxiety disorders, chronic pain disorders and nocturnal enuresis in children over 11 years of age (Rossiter, 2014:496). Agents in this class suitable for use in children include amitriptyline, clomipramine and imipramine, and are indicated in depression, OCD (Snyman, 2014:12) and nocturnal enuresis.

2.7.3.5 Tetracyclic antidepressants

Maprotiline is a tetracyclic antidepressant whose mechanism of action is unknown (Drugs.com). According to Drugs.com, its pharmacologic action is achieved by blocking the reuptake of NE at nerve endings, thereby potentiating NE action at central adrenergic synapses (Drugs.com, 2015).

Mianserin is considered an atypical antidepressant and antagonises α_2 -receptors in the brain whereby norepinephrine turnover is increased (Rossiter, 2014:503). Mianserin is also an antagonist of serotonin autoreceptors (5-HT₂) in some parts of the brain (Pleuvry, 2004:355; Rossiter, 2014:503). Mianserin is indicated for major depression (Rossiter, 2014:503).

Mirtazapine elevates NE and 5-HT neurotransmission in the brain by acting as a presynaptic α_2 antagonist (Pharmacare Limited, 2007; Rossiter, 2014:504). It is also an antagonist at 5-HT_{2A}, 5-HT_{2C} and 5-HT₃ receptor subtypes, with the consequential down regulation of these receptors (Pharmacare Limited, 2007; Rossiter, 2014:504). Mirtazapine's sedative property stems from its antagonist effects on the histamine₁ (H₁) receptor (Pharmacare Limited, 2007; Rossiter, 2014:504). Mirtazapine is used to treat major depression (Pharmacare Limited, 2007; Rossiter, 2014:504).

2.7.3.6 Noradrenaline and/or dopamine re-uptake inhibitors

Drugs in this class inhibit the active re-uptake process of noradrenaline and/or dopamine into the presynaptic terminal by norepinephrine- (NET) and dopamine transporter (DAT) (Pleuvry, 2004:355; O'Donnell & Shelton, 2011:407), and includes bupropion and reboxetine.

Bupropion has a mixed neuropharmacological profile, with a chlorpropiphenone structure with weak uptake inhibitor properties of serotonin and noradrenalin (Dwoskin *et al.*, 2006:179; Rossiter, 2014:506). Furthermore, it also inhibits the re-uptake of dopamine (Rossiter, 2014:506). Bupropion is indicated to treat depression, and prophylaxis for seasonal depression, and is also used as a nicotine use cessation agent (Dwoskin *et al.*, 2006:181,182).

Reboxetine is a potent, selective noradrenaline re-uptake inhibitor, and has a weak effect on the re-uptake of serotonin (Rossiter, 2014:506). It is indicated for the treatment of major depressive disorder (Rossiter, 2014:506).

2.7.3.7 Melatonergic specific antidepressants

Agomelatine is a melatonergic receptor agonist, and a serotonergic antagonist, specifically on the 5-HT_{2C} receptor subtype (Cardinali *et al.*, 2012:18; San & Arranz, 2008:400). Melatonin is a hormone that is responsible for the regulation of an organism's biological clock, or circadian rhythm (Cardinali *et al.*, 2012:18; San & Arranz, 2008:400). As depression seems to be related to a dysregulation in melatonin concentration, a melatonergic agonist shows antidepressant-like actions (Cardinali *et al.*, 2012:18; San & Arranz, 2008:400). In addition, due to agomelatine's antagonist effects on 5-HT_{2C} receptor, it also relieves anxiety (Cardinali *et al.*, 2012:18; San & Arranz, 2008:400).

2.7.3.8 Lithium

Lithium is considered a mood stabiliser, because of its ability to prevent mood swings associated with depression (Pleuvry, 2004:355). Lithium has no effect on depression, but can reverse mania during an acute attack (Pleuvry, 2004:355).

Lithium's mode of action includes the depletion of membrane phosphatidyl inositol by blocking the phosphatidyl pathways (Pleuvry, 2004:355).

2.7.3.9 Others

Trazodone is a central acting noradrenaline re-uptake inhibitor, and acts by blocking the $\alpha 1$ -adrenoceptors in the brain (Brogden *et al.*, 2012; Rossiter, 2014:504). Trazodone also possesses antagonist effects on presynaptic 5-HT₁ receptors (Brogden *et al.*, 2012; Rossiter, 2014:504). Trazodone is commonly used as an anxiolytic in patients with depression (Brogden *et al.*, 2012).

2.7.4 Antipsychotic agents

The development of typical antipsychotics is based on the dopamine hypothesis, implicating the postsynaptic dopamine D₂-receptor and its psychotic effects (Meyer, 2011:417). Typical antipsychotics cause increased levels of prolactin, extrapyramidal symptoms and tardive dyskinesia, whereas the newer atypical antipsychotics elicit low or negligible side-effects (Seeman, 2002:28). Typical antidepressants are only useful for positive symptoms of psychosis (Pleuvry, 2004:356), and the second-generation antipsychotics are the first-line drug choice for newly diagnosed schizophrenia due to the side-effects of the traditional antipsychotics and its effect on positive, as well as negative symptoms of schizophrenia (Pleuvry, 2004:356).

Neuronal pathways that use dopamine to exert normal physiological functioning and that are part of dopamine deficient disorders include the mesolimbic and mesocortical pathways in the human brain (Pleuvry, 2004:356). Antipsychotic medications exert their therapeutic effect mainly by antagonism or partial agonism of the dopamine D₂-postsynaptic receptor in those pathways, but also have effects on glutamate, serotonin and muscarinic receptors (Meyer, 2011:429, 431).

Antipsychotic medication is mainly used to treat schizophrenia, manic depression and psychosis due to chemical or traumatic head injuries (Pleuvry, 2004:355). Typical antipsychotic drugs are classified in their respective chemical classes, namely: phenothiazines, butyrophenones, thioxanthene derivatives, benzamides, diphenylbutylpiperidine and the thiazepines. The newer atypical antipsychotic drugs are clozapine, olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole.

2.7.5 Anti-epileptic agents

Antiseizure medication acts by one of three mechanisms (Porter & Meldrum, 2009:400). The first mechanism involves the enhancement of the GABAergic neurotransmission (which is an inhibitory neurotransmitter) by either pre- or postsynaptic action (Porter & Meldrum, 2009:400).

Antiseizure drugs can also act by decreasing the neurotransmission of glutamate or modifying ionic conductances (inhibition of voltage-gated Ca^{2+} channels or promoting the inactivated state of voltage-gated Na^+ channels (Porter & Meldrum, 2009:400).

Phenytoin is the oldest anti-epileptic, and is indicated for the treatment of partial- and generalised tonic-clonic seizures (focal and grand mal seizures, respectively) (Lasoñ *et al.*, 2011:278; Porter & Meldrum, 2009:403). It acts by altering Na^+ , K^+ and Ca^{2+} ion channel conductance, influencing the membrane potential and the concentration of amino acids as well as the neurotransmitter NE, Ach, and GABA (Kwan *et al.*, 2001:24; Porter *et al.*, 2015:10; Porter & Meldrum, 2009:403).

The carboxamides, carbamazepine and oxcarbazepine, as well as primidone, have a mechanism of action similar to phenytoin (Goldberg, 2010:399; Lasoñ *et al.*, 2011:278; Porter & Meldrum, 2009:406).

Phenobarbitone potentiates phasic GABA_A receptor responses, and reduces excitatory synaptic responses (Goldberg, 2010:402). It is useful in the treatment in generalised tonic-clonic seizures, partial seizures, generalised seizures and neonatal seizures (Goldberg, 2010:401).

Vigabatrin is an irreversible GABA transaminase inhibitor, the primary enzyme for GABA catabolism (Goldberg, 2010:405; Greenfield, 2013:595; Lasoñ *et al.*, 2011:278; Porter & Meldrum, 2009:408). This causes increased GABA concentrations in the brain, with subsequent sensitisation of synaptic GABA_A receptors (Goldberg, 2010:405). Glutamine synthetase activity is decreased due to increased GABA concentrations (Porter & Meldrum, 2009:408). Vigabatrin is effective against complex partial seizures (Greenfield, 2013:595; Porter & Meldrum, 2009:408).

Gabapentin and pregabalin are GABA-enhancing agents. Gabapentin is a GABA-analog, and is used for generalised tonic-clonic, generalised and partial seizures (Greenfield, 2013:595; Porter & Meldrum, 2009:410). It acts by decreasing excitatory transmission of GABA and decreasing glutamate release by decreasing Ca^{2+} entry via voltage-gated channels (Greenfield, 2013:595; Porter & Meldrum, 2009:410). Pregabalin acts in the same mechanism as gabapentin, but is only approved for the adjunctive treatment of partial seizures (Greenfield, 2013:595; Porter & Meldrum, 2009:410).

Lamotrigine prevents sustained repetitive firing of action potentials by inactivating sodium channels and acting presynaptically on voltage-gated Ca^{2+} channels with subsequent decreased glutamate release (Goldberg, 2010:397; Kwan *et al.*, 2001:25; Porter & Meldrum, 2009:421). Valproic acid mainly alters GABA metabolism, and blocks voltage-gated Na^+

channels (Goldenberg, 2010:397; Greenfield, 2013:595; Porter *et al.*, 2015:11). Topiramate has multiple actions, including inhibition of Na⁺ and Ca²⁺ channels, inhibition of carbonic anhydrase, antagonising the AMPA subtype of the glutamate receptor and enhancing GABA-mediated inhibition (Goldberg, 2010:398; Greenfield, 2013:594; Lasoñ *et al.*, 2011:278; Porter *et al.*, 2015:11). Levetiracetam binds to synaptic protein SV2A (Porter *et al.*, 2015:11). Lamotrigine, valproic acid, levetiracetam and topiramate are effective in the treatment of generalised tonic-clonic seizures, generalised seizures and partial seizures with lamotrigine, valproic acid and topiramate being indicated for absence seizures. Valproic acid is also used in treating myoclonic seizures (Porter & Meldrum, 2009:421).

Ethosuximide is only indicated for the treatment of absence seizures, and acts by reducing low threshold Ca²⁺ currents (Goldberg, 2010:401; Lasoñ *et al.*, 2011:278; Porter & Meldrum, 2009:420).

The benzodiazepines (clonazepam, clobazam, diazepam, lorazepam and midazolam) potentiate GABA_A responses (Greenfield, 2013:591; Porter & Meldrum, 2009:420). It is effective in the treatment of status epilepticus, seizure clusters (diazepam, lorazepam), absence seizures, myoclonic seizures and infantile spasms (clonazepam, clobazam) (Porter & Meldrum, 2009:420).

2.8 Chapter summary

In this chapter, a broad overview of the existing literature was provided, whereby the objectives of the literature review were met. ADHD was discussed in terms of definition, aetiology, epidemiology, treatment and its comorbidities. This was followed by a summary of other CNS medication as defined in Chapter 1. The empirical investigation will be discussed in Chapter 3.

CHAPTER 3: RESULTS AND DISCUSSION

3.1 Introduction

This chapter contains the results of the empirical study and is presented in the form of two manuscripts, which will be submitted for consideration for publication.

Manuscript 1, entitled “Methylphenidate and atomoxetine prescribing patterns in the South African private health sector: 2005-2013” will be submitted to the journal “*Journal of clinical pharmacy and therapeutics*”. The author’s guidelines for this journal are included in Annexure G. [http://onlinelibrary.wiley.com/journal/10.1111/\(ISSN\)1365-2710/homepage/ForAuthors.html](http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1365-2710/homepage/ForAuthors.html)

Manuscript 2, entitled “Prescribing patterns of central nervous system medication in South African children and adolescents with/without treatment for ADHD and its potential drug-drug interactions” will be submitted to the journal “*Pharmacoepidemiology and drug safety*”. The author’s guidelines for this journal are included in Annexure H. [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)1099-1557/homepage/ForAuthors.html](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1099-1557/homepage/ForAuthors.html)

3.2 Manuscript 1

Methylphenidate and atomoxetine prescribing patterns in the South African private health sector: 2005-2013

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SUMMARY

What is known and objective

Children and adolescents are subject to increased diagnoses with Attention-Deficit/Hyperactivity Disorder (ADHD), with subsequent increases in the prescribing of methylphenidate and atomoxetine. ADHD in children increases parenting stress, and since ADHD has been proved to be a genetic disorder, the family of ADHD children could also use methylphenidate and atomoxetine. There is limited data on the use of ADHD medication, and family tendencies regarding the use of methylphenidate and/or atomoxetine remain unclear in South Africa. The aim of this study was to determine the prescribing patterns of methylphenidate and atomoxetine in South African children, adolescents and their families.

Methods

A retrospective, longitudinal study was performed using a medicine claims database from a national representative pharmaceutical benefit management (PBM) company for the study period 1 January 2005 to 31 December 2013. The study population consisted of children and adolescents ≤ 18 years and their family who received ≥ 1 prescriptions for either methylphenidate or atomoxetine or both. Children and adolescents were categorised into the following groups: ≤ 6 years, > 6 years and ≤ 12 years, and > 12 years and ≤ 18 years. The average prescribed daily doses (PDD) of both methylphenidate and atomoxetine prescribed to ADHD children were compared to: i) the recommended daily dose (RDD) in the different age groups; and ii) between ADHD children and adolescents with or without additional central nervous system (CNS) medication.

Results

ADHD prevalence in children and adolescents aged 18 years and younger increased from 2.11% in 2005 to 4.4% in 2013. ADHD prevalence in families of children and adolescents with ADHD increased from 14.94% to 29.09% over the nine-year study period. The average PDD for methylphenidate and atomoxetine was higher in patients who received treatment for other CNS disorders, than those who only claimed methylphenidate or atomoxetine. The highest number of methylphenidate- (16.69%) and atomoxetine- (13.75%) containing items that exceeded the RDD was for children six years and younger.

What is new and conclusions

ADHD prevalence in both children and adolescents and their family increased from 2005 to 2013. Most items prescribed to children and adolescents that exceeded the RDD were for

atomoxetine-containing products, especially in children six years and younger. The average PDD for methylphenidate- and atomoxetine-containing products was higher in patients who also received treatment for other CNS disorders.

WHAT IS KNOWN AND OBJECTIVE

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder, commonly affecting children and adolescents worldwide.¹ ADHD is characterised by inattention, hyperactivity and impulsivity.² According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria, three subtypes of ADHD are defined and include: predominately inattentive presentation, predominately hyperactive/impulsive presentation and combined presentation.² A diagnosis with ADHD requires a good clinical history and examination by a healthcare practitioner with sufficient experience.^{2,3}

The lifetime prevalence for ADHD in Africa is between 5.4% and 8.7% in school children,⁴ compared to the worldwide prevalence of 5.3%.^{5,6} Bakare refers to a few ADHD prevalence studies that have been conducted in South Africa, none of which have studied the total South African population.⁴ Nevertheless, these studies documented a prevalence of approximately 5%, which concurs with the prevalence rates across the world.^{4,5,6} In a study conducted by Castle *et al.* (2007), the estimated ADHD treatment prevalence in children and adolescents, younger than 20 years, in 2000 was 2.8%, with an increase of 1.6% in 2005 using pharmacy claims data for a large population of commercially insured Americans.⁷

Several factors influence the prevalence of ADHD, *inter alia*, age and gender. ADHD has an early childhood onset, and an onset before the age of 12 years is required by the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-V) to diagnose ADHD.² In 2010, the Center for Disease Control and Prevention (CDC) reported that the highest prevalence of ADHD was in children and adolescents aged 11 to 14 years.⁸ A study conducted in Nigeria reported a prevalence rate of 8.7% in school children between the ages of six and 12 years.⁹ A recent study from South Africa reported that the average age of children and adolescents who received medication for ADHD was 10 years old.¹⁰

Previous studies have all revealed higher ADHD prevalence rates for males than for females.^{5,11,12,13} For example, the CDC reported a male to female ratio of 2:1 in 2014.¹⁴ There are few studies regarding epidemiological data of ADHD in Africa, and prevalence estimates must therefore be carefully interpreted.^{5,10,11} However, the prevalence of ADHD according to gender among African children is documented to be higher than documented in other regions of the world.⁴ For example, in Kinshasa, Democratic Republic of Congo, 45% of a study sample (consisting of 286 school children) were boys and 55% were girls.¹² In South Africa, Snyman and Truter investigated the aetiology, diagnosis and treatment of the youth with a diagnosis of ADHD and found that 73.6% of the patients were male.¹⁰

Methylphenidate and atomoxetine are the only available pharmacological treatments for ADHD in South Africa.¹⁵ Methylphenidate is the most commonly used neuro-stimulant,¹⁰ whilst atomoxetine, exclusively used for ADHD,¹⁶ is the only FDA-approved non-stimulant indicated for this disorder.^{10,17}

There is limited information on prevalence rates and treatment of ADHD in South Africa.⁹ When considering the chronic^{15,18,19} and genetic^{20,21} nature of ADHD, the use of methylphenidate or atomoxetine must also be taken into consideration when assessing ADHD medication usage in families. Little is known regarding the prevalence of ADHD in families of ADHD children and adolescents in South Africa. The aim of this study was therefore to investigate the prescribing patterns of methylphenidate and atomoxetine in South African children and adolescents and their families.

METHOD

Research design and data source

We conducted a retrospective longitudinal study analysing medicine claims data from a national representative pharmaceutical benefit management (PBM) company for the study period 1 January 2005 to 31 December 2013. The PBM provides medicine management services to 39 medical schemes and capitation plans in South Africa and is linked to all community pharmacies and 98% of all dispensing doctors in South Africa. The PBM has the following internal validation processes in place to ensure the validity and reliability of the data: gate-keeping services, eligibility services, utilisation management services, clinical management services and pricing management along with real-time benefit management.

Patient demographic information (e.g. age, gender, diagnoses, encrypted patient member numbers and dependent codes) and medication information (e.g. prescription number, active ingredient, dispensing date, active ingredients, trade name of the medication, day's supply, quantity of medicine items dispensed, and tablet strength) were obtained from the PBM.

Study population

The study population consisted of all children and adolescents 18 years and younger who have received one or more prescriptions for methylphenidate or atomoxetine and their family (based on the same main member number profile). The study population was divided into the following four groups: i) children and adolescents who received only prescriptions for ADHD medication; ii) children and adolescents who received prescriptions for ADHD and other CNS medication; iii)

families of children and adolescents receiving ADHD treatment; and iv) families of children and adolescents not receiving ADHD treatment.

For the purpose of this study, the ADHD-only group included all patients with either an ICD10 diagnosis for ADHD, or who received prescriptions for methylphenidate or atomoxetine during the study period. The ADHD-CNS group included all patients with either an ICD10 diagnosis for ADHD or who received prescriptions for methylphenidate or atomoxetine and who received prescriptions for CNS medication. Family included patients of all age groups indicated as dependents of the same main member number. The Monthly Index of Medical Specialties (MIMS®) classification system was used to identify all the CNS medication. It included the CNS stimulants, sedative hypnotics and anxiolytics, antidepressants, antipsychotics and anti-epileptic drugs.¹⁵ Pharmacological groups anti-Parkinson's agents, antivertigo and anti-emetic agents, antimigraine agents, and Alzheimer's medication were excluded because they are not related to any ADHD comorbidities, or were not applicable to children under the age of 18 years (e.g. Alzheimer's medication and anti-Parkinson's agents).

Comparison between Prescribed Daily Dose (PDD) and Recommended Daily Dose (RDD)

The average PDD of methylphenidate and atomoxetine in the different age groups was compared to the RDD. The PDD for methylphenidate and atomoxetine was determined by multiplying the number of tablets by their strength in milligrams, and dividing it by the number of days covered by the prescription. The average PDD for methylphenidate and atomoxetine was compared between the ADHD-only group and the ADHD-CNS group.

The RDD for methylphenidate and atomoxetine in the different age groups is stipulated in Table 1. The RDD for methylphenidate and atomoxetine was determined using the South African Medicines Formulary (SAMF),²² the MIMS®¹⁶ and the Martindale²³. The RDD of methylphenidate (for patients < 6 years) and atomoxetine is subject to the weight of children.¹⁵ The dataset did not contain clinical data such as the weight and height of patients, which made it difficult to determine the exact RDD for methylphenidate and atomoxetine. The RDD for these medications was calculated using the Centre for Disease Control and Prevention's (CDC) growth charts for both genders. Dose ranges were calculated by using the 75th percentile on other average weight-for-age percentiles from birth to 18 years for both genders.¹ For the purpose of the data analysis, the maximum RDD for Concerta® (methylphenidate), e.g. 72 mg/day was used to determine PDD that exceeded the RDD.

Statistical analyses

Data management and analysis were performed using the SAS® program Version 9.3.²⁵ All statistically significant results were considered with a probability of $p < 0.0001$. Practical significance of results was computed when the p -value was statistically significant.

Study variables were expressed using descriptive statistics such as frequency, mean, standard deviation (SD), confidence interval (95% CI) and ratio.

Study variables included age groups, gender and diagnosis (ADHD or ADHD-CNS) as independent variables, and prevalence of ADHD or ADHD-CNS, number of prescriptions and PDD as the dependent variables. The ages of patients were calculated from 1 January of the year following the dispensing date and the birth date of the patient. Children and adolescents were categorised into the following age groups: ≤ 6 years, > 6 years and ≤ 12 years, and > 12 years and ≤ 18 years.

The chi-square (χ^2) test was used to determine whether an association existed between proportions of two or more groups. The Cramer's V statistic was used to test the practical significance of this association (practical significance was interpreted as follows: effect size of 0.1 was small; 0.3 effect size was medium and an effect size of 0.5 was large). One-way analysis of variance (ANOVA) was used to test for significant differences between the average number of methylphenidate and atomoxetine prescriptions per patient for the different years. If a difference was indicated, a Tukey multiple comparison test was performed to determine which groups most significantly influence the overall difference between groups.²⁶ A two-sample t -test was used to compare the PDD of methylphenidate and atomoxetine between the ADHD group and the ADHD-CNS group per age group per year. Cohen's d -value was used to evaluate the effect size between means.²⁷ For practical significance, the following were considered: ≤ 0.2 a small effect, with no significant difference, $> 0.2 \leq 0.5$ a medium effect with an observable significance, > 0.8 a large effect and significant difference.²⁷

Ethical considerations

Ethical approval from the Health Research Ethics Committee of the Faculty of Health Sciences, North-West University (Potchefstroom campus) (NWU-00179-14-A1), and a goodwill permission from the board of directors of the PBM were obtained.

RESULTS

Patient demographics

The prevalence of children and adolescents with ADHD increased from 2.11% in 2005 to 4.4% in 2013. A statistically significant association was found between the proportion of ADHD-only and the ADHD-CNS group per year over the study period, with an increasing trend in the prevalence of children and adolescents within the ADHD-only group and the ADHD-CNS group ($p < 0.0001$). This association, however, was weak (Cramer's $V = 0.0422$) (Table 2).

The same gender differences were observed within both the ADHD-only and ADHD-CNS group with an annual male to female ratio of 3:1. Statistically significant associations were found between the proportion of both ADHD-only ($p < 0.0001$) and ADHD-CNS ($p < 0.0001$) children and adolescents per gender group over the study period, with an increasing trend in the female groups. These associations in both the ADHD-only and ADHD-CNS group according to gender were weak (Cramer's $V = 0.0325$ and Cramer's $V = 0.0439$, respectively) (Table 2).

The majority of children and adolescents in both the ADHD-only and ADHD-CNS group fell in the $> 6 \leq 12$ years age group compilation. Statistically significant associations were found between the proportion of both ADHD-only ($p < 0.0001$) and ADHD-CNS ($p < 0.0001$) children and adolescents per age group over the study period, with an increasing trend in the > 12 and ≤ 18 years age group and a decreasing trend in the > 6 and ≤ 12 year age group. The effects of these associations were weak (Cramer's $V = 0.0446$ and Cramer's $V = 0.0596$) (Table 2).

>>>>Insert Table 2 here<<<<

ADHD medication use by family

For each year from 2006, statically significant associations ($p < 0.0001$) were found between the proportion of children and adolescents with/without ADHD and their family who used/did not use methylphenidate- or atomoxetine-containing products. It seems that there was an increasing trend in the prevalence of ADHD children and adolescents whose family also use methylphenidate- or atomoxetine-containing products: 14.94% in 2006 and 29% in 2013.

>>>>Insert Table 3 here<<<<

General prescribing patterns of methylphenidate and atomoxetine

A total number of 260 437 prescriptions, containing methylphenidate or atomoxetine, were claimed during the nine-year study period for the study population. This represented 0.37% of all prescriptions claimed during this period (Table 4). The average number of prescriptions for

ADHD medication per patient per year in 2005 (3.58 ± 2.71 ; 95% CI 3.51-3.64) was significantly lower than in 2013 (4.08 ± 2.91 ; 95% CI 4.01-4.14) ($p < 0.0001$). Compared to 2013, this increase was not of practical significance (Cohen's $d = 0.17$). The same trend was found with the average number of methylphenidate prescriptions per patient per year, which increased from 3.65 ± 2.75 (95% CI 3.59-3.72) in 2005 to 4.03 ± 2.86 (95% CI 3.97-4.1) in 2013 ($p < 0.0001$; Cohen's d -value = 0.13). The average number of atomoxetine prescriptions per patient per year increased significantly from 2.37 ± 1.54 (95% CI 2.22-2.52) in 2005 to 4.61 ± 3.47 (95% CI 4.33-4.89) in 2013 ($p < 0.0001$). This effect was moderate (Cohen's d -value = 0.65).

>>>>Insert Table 4 here<<<<

Prescribed daily dose (PDD) vs. recommended daily dose (RDD)

The largest percentage of medicine items that exceeded the maximum RDD was for atomoxetine-containing products (4.35% compared to the 1.10% for methylphenidate-containing items that exceeded the RDD). The highest increase in the number of medicine items that exceeded the maximum RDD was in the ≤ 6 years age group for both methylphenidate and atomoxetine. The majority of medicine items prescribed for children ≤ 6 years were for products containing 36 mg methylphenidate and 40 mg atomoxetine.

>>>>Insert Table 5 here<<<<

The average PDD for methylphenidate in the ADHD-CNS group was higher than the average PDD for methylphenidate in the ADHD-only group for all age groups. The average PDD for atomoxetine in the ADHD-only group was lower than in the ADHD-CNS group for all age groups. A practically significant and statistically significant difference between the average PDD of atomoxetine in the ADHD-only and the ADHD-CNS group in children six years and younger was observed from 2008 to 2013 ($p < 0.0001$; Cohen's $d > 0.8$). This group consisted of only 238 patients. Overall, a statistically significance of difference was found between the average PDD of methylphenidate in the ADHD-only or ADHD-CNS groups from 2005 to 2013 in all age groups ($p < 0.0001$). However, no practically significant difference was found (Cohen's d -value < 0.2). A practically significant difference between the average PDD for atomoxetine in the ADHD-CNS group per year for children aged six years and younger was found, with an increase from 17.62 ± 6.9 (95% CI 13.48-21.75) in 2005 to 48.33 ± 28.43 (95% CI 48.33-28.43) in 2013 (Cohen's d -value = 1.1). This association, however, was not of statistical significance ($p > 0.0001$). There was an increase in the average PDD of atomoxetine in the > 12 and ≤ 18 year age groups for both the ADHD-only and ADHD-CNS group. This association, however, was weak (Cohen's d -value < 0.5), and not of statistical significance ($p > 0.0001$).

>>>>Insert Table 6 here<<<<

>>>>Insert Table 7 here<<<<

DISCUSSION

This longitudinal study shows the annual trends of methylphenidate and atomoxetine prescribing in the private health sector of South Africa. The prevalence of ADHD in children and adolescents, 18 years and younger, was 4.4% in 2013. This confirms Castle and associates' results when they analysed pharmacy claims data for American children aged 0 to 19 years from 2000 to 2005.⁷ In Nigeria, the authors reported a 3.2% prevalence estimate of children with ADHD.²⁸ Bakare conducted a meta-analysis of prevalence studies conducted in Africa, which included four studies conducted in South Africa, two from Nigeria and the Democratic Republic of Congo respectively, and one study from Ethiopia.⁴ He reported the ADHD prevalence to range from 5.4% to 8.7% in school-aged children, and 1.5% in the general population.⁴ Although epidemiological data regarding ADHD prevalence in South Africa is limited, a prevalence of approximately four to five percent of children have been documented in previous studies.^{4,29,30}

The overall prevalence of patients who received ADHD treatment over the study period increased with 2.29% from 2005 to 2013. This trend is in line with previous studies conducted in the US,^{31,32,33,34} Europe,^{35,36} UK,³⁷ Oceania³⁸ and Africa⁴. For example, Zuvekas and Vitiello reported an increase in stimulant medication use over the study period of 1996 to 2008, with an annual increase of 3.4% in US children and adolescents 18 years and younger.³¹ These results were the same documented by Olfson and associates who analysed service use data for children aged three to 18 years in the US.³³ Sclar and colleagues reported a 4.9-fold increase in ADHD diagnosis and treatment rates in five to 18 year old children from 1991 to 2008 in the US.³⁴ In Europe, treatment prevalence rates of 2.21% in children and adolescents 18 years and younger were reported.³⁵ Prevalence estimates of stimulant treatment use in Western Australia were 2.4% (children aged 3 to 18 years) during 2004.³⁸ In South Africa, Truter documented a 3% treatment prevalence with methylphenidate in children.³⁹ Possible explanations for the increase in ADHD medication use can include the following: i) growing awareness of ADHD as a debilitating disorder, ii) recognition and acceptance of ADHD and its treatment by health care practitioners and the public, iii) the growing definition of ADHD, iv) educational instruments and programmes aiding teachers and parents to assess behaviour and attention problems, v) easy access to healthcare facilities, e.g. school-based health clinics; and vi) off-label use of stimulants.^{1,31,33,35,40,41}

The general prescribing patterns of methylphenidate and atomoxetine increased during the study period; however, with a more significant increase for atomoxetine than for methylphenidate. Atomoxetine was introduced in South Africa in 2005, and therefore it was not much prescribed initially.⁴²

This can also be as a result of the different side-effect profiles experienced with atomoxetine.⁷ Another possible explanation given by previous literature, is the effect that comorbid conditions may have on treatment choices. For instance, methylphenidate use in ADHD patients with tics and/or anxiety is contraindicated.^{43,44} Similarly, atomoxetine is contraindicated for use in ADHD patients with oppositional defiant disorder.⁴⁵ Although methylphenidate and atomoxetine have comparable efficacy and acceptability in the treatment of ADHD, extended release formulations of methylphenidate are reported to be more effective in the management of ADHD symptoms than atomoxetine.⁴⁶ Methylphenidate is therefore considered the drug of choice in the treatment of ADHD.⁴⁷

An annual male to female ratio of 3:1 was observed. This trend confirms previous population-based studies, both internationally,^{7,32,34} as well as in South Africa.^{47,48,49} Castle and colleagues reported that treatment rates for boys were 2.4 times higher than for girls, which was also confirmed by Sclar *et al.*^{7,34} Our findings are also in accordance with other male to female ratios in South Africa, ranging from 70 to 76% of the study samples being males.^{47,48,49} Females tend to show a different clinical presentation than males do, mainly because they are less likely to show disruptive behaviour, and tend to exhibit more inattentive than hyperactive symptoms.^{29,50,51,52} Moreover, males are more likely to be referred for pharmacotherapy than their female counterparts.^{52,53,54,55}

The highest increase in ADHD prevalence was observed in the $> 12 \leq 18$ years age group. A possible explanation may be due to changes in the DSM-V regarding age of onset.³ Previously, children had to be seven years or younger to be diagnosed, which has been changed to 12 years.³ Additionally, the American Academy of Pediatrics (AAP) recommends that all children aged four years through 18 years of age who present with academic or behavioural problems and symptoms of inattention, hyperactivity or impulsivity be evaluated by a primary care clinician, and that adolescents (12 to 18 years of age) be prescribed FDA-approved medications for ADHD, as well as behaviour therapy as treatment for ADHD.¹ Methylphenidate is not indicated for use in children six years and younger, except when the child is assessed by a specialist prior to commencement of treatment.^{1,22,23} This could explain the low prevalence rate of ADHD in the age group ≤ 6 years. This finding concurs with previous studies conducted in South Africa, where methylphenidate prescribing was the highest in patients between approximately 10 and 17 years of age.^{7,10, 47,48,49}

An increase in the prevalence of ADHD in families of ADHD children and adolescents was observed. Only one study previously conducted in South Africa indicated family relationships of ADHD, but they had a small study sample ($n = 21$).¹⁰ In their study, Snyman and Truter found that six children/adolescents had parents diagnosed with, or suspected of having ADHD as a child.¹⁰ Improved diagnostic rates, recognition of ADHD symptoms through their child's

experience with ADHD,¹⁰ and increased public awareness could all contribute to higher prevalence rates of the disorder in families of ADHD children.⁷ According to Chronis *et al.*,⁵⁶ children are more likely to be diagnosed with ADHD if their parents have the same diagnosis. An interesting occurrence was observed in 2005, where there were no family members of ADHD children/adolescents with prescriptions for ADHD medication recorded; however, we found that 0.16% (n = 36) of children/adolescents without ADHD had family members with ADHD. A possible explanation could be that methylphenidate and atomoxetine were not paid for by the medical scheme at the time and that they had to pay cash and not included on the database, or they used non-pharmacological treatments.

The average PDD for both methylphenidate and atomoxetine was in the recommended daily dose range for the ADHD-only and ADHD-CNS group. Although no practically significant difference was found between the PDD for methylphenidate in the ADHD-only and ADHD-CNS groups, the average PDD of methylphenidate in the ADHD-CNS group was slightly higher than in the ADHD-only group for all the age groups. A possible explanation for the trend observed here is that patients with comorbidities, e.g. oppositional defiant disorder, conduct disorder, depression, anxiety disorders etc. may need higher dosage titrations for the effective management of ADHD symptoms than patients without these comorbidities.⁴¹ A total of 4.35% of atomoxetine-containing products prescribed during the study period exceeded the RDD. Children six years and younger were the most exposed age group to have received prescriptions for methylphenidate- and atomoxetine-containing products that exceeded that RDD. The majority of medicine items prescribed for children six years and younger were for products containing 36 mg methylphenidate and 40 mg atomoxetine.

Limitations

Several limitations must be taken into account when interpreting these findings. Firstly, the results can only be generalised to the specific study population in the private health sector of South Africa. Secondly, due to the lack of clinical data such as weight and length, the RDD of methylphenidate and atomoxetine was calculated according to the CDC's growth charts. Thirdly, families of patients with ADHD were identified by the same main member number profile, assuming that all members are in fact biological family. ADHD patients were identified by either having an ICD10 diagnosis of ADHD or a paid claim for either methylphenidate or atomoxetine or both during the study period. Methylphenidate is also indicated for use in narcolepsy, but usually for older patients and not in adolescents for whom it was prescribed during the study.

WHAT IS NEW AND CONCLUSION

Methylphenidate and atomoxetine are increasingly being prescribed to children and adolescents younger than 18 years. This study also revealed increased prevalence of ADHD in adults who have children with or without ADHD. This may indicate increasing awareness of the disorder and its comorbidities. The highest percentage of the average PDD for methylphenidate and atomoxetine that exceeded the RDD was indicated for children six years and younger. The average PDD for methylphenidate and atomoxetine-containing products was higher in patients who also received treatment for other CNS disorders. Future studies should investigate the influence of prescriber speciality on the diagnosis and treatment of ADHD. It is also recommended that future studies should investigate dosages of CNS medication used to treat comorbid disorders in ADHD patients.

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Table 1: Recommended daily dose for methylphenidate and atomoxetine per age group

Daily dosage (mg/day)								
Age groups								
ADHD medication	≤ 6 years		> 6 ≤ 12 years		> 12 ≤ 18 years		Maximum RDD	
Methylphenidate	Ritalin®		Ritalin®		Ritalin®		Ritalin®	
	Ritalin LA®		Ritalin LA®		Ritalin LA®		Ritalin LA®	
	Methylphenidate HCL-Douglas®	± 22 mg/day	Methylphenidate HCL-Douglas®	60 mg/day	Methylphenidate HCL-Douglas®	60 mg/day	Methylphenidate HCL-Douglas®	60 mg/day
	Concerta®		Concerta®		Concerta®		Concerta®	
Atomoxetine	± 28 mg/day		± 55 mg/day		± 90 mg/day		120 mg/day	

Table 2: Patient demographic information

Study period	2005	2006	2007	2008	2009	2010	2011	2012	2013	Difference 2005 vs. 2013 (%)	<i>p</i> -value*	Cramer's <i>V</i> *
Total population (≤18 year) (n)	299 765	296 550	226 521	165 734	235 003	210 607	185 657	170 840	179 333			
Study population, n (%) ^a	6 322 (2.11)	6 665 (2.25)	5 916 (2.61)	5 069 (3.06)	6 814 (2.9)	6 888 (3.27)	6 849 (3.69)	7 063 (4.13)	7 883 (4.4)	2.29		
ADHD-only n (%)	5 198 (82.22)	5 333 (80.02)	4 524 (76.47)	3 849 (75.93)	5 298 (77.75)	5 319 (77.22)	5 404 (54.87)	5 514 (78.07)	6 136 (77.84)	-4.38	<i>p</i> <0.0001	0.0422
ADHD-CNS n (%)	1 124 (17.78)	1 332 (19.99)	1 392 (23.53)	1 220 (24.07)	1 516 (22.25)	1 569 (22.78)	1 445 (21.10)	1 549 (21.93)	1 747 (22.16)	4.38		
Gender, n (%)												
ADHD-only ^b												
Male	3 929 (75.59)	4 025 (75.47)	3 402 (75.2)	2 873 (74.64)	3 941 (74.39)	3 882 (72.98)	3 913 (72.41)	3 996 (72.47)	4 401 (71.72)	-3.87	<i>p</i> <0.0001	0.0325
Female	1 269 (24.41)	1 308 (24.53)	1 122 (24.80)	9 76 (25.36)	1 357 (25.61)	1 437 (27.02)	1 491 (27.59)	1518 (27.53)	1735 (28.28)	3.87		
ADHD-CNS ^c												
Male	825 (73.40)	1 005 (75.45)	985 (70.76)	863 (70.74)	1 100 (72.56)	1 124 (71.64)	1 007 (69.69)	1 066 (68.82)	1 212 (69.38)	-4.02	<i>p</i> <0.0016	0.0439
Female	299 (26.60)	327 (24.55)	407 (29.24)	357 (29.26)	416 (27.44)	445 (28.36)	438 (30.31)	483 (31.18)	535 (30.62)	4.02		

Study period	2005	2006	2007	2008	2009	2010	2011	2012	2013	Difference 2005 vs. 2013 (%)	p-value*	Cramer's V*
Age groups, (years) n (%)												
ADHD-only^b												
≤6	86 (1.65)	90 (1.69)	70 (1.55)	42 (1.09)	52 (0.98)	48 (0.90)	60 (1.11)	40 (0.73)	53 (0.86)	-0.79		
>6 and ≤12	3 143 (60.47)	3 167 (59.38)	2 556 (56.50)	2 134 (55.44)	2 991 (56.46)	2 953 (55.52)	2 920 (54.03)	2 912 (52.81)	3 271 (53.31)	-7.16	p<0.0001	0.0446
>12 and ≤18	1 969 (37.88)	2 076 (38.93)	1 898 (41.95)	1 673 (43.47)	2 255 (42.56)	2 318 (43.58)	2 424 (44.86)	2 562 (46.46)	2 812 (45.83)	7.95		
ADHD-CNS^c												
≤6	26 (2.31)	42 (3.15)	43 (3.10)	33 (2.70)	30 (1.98)	35 (2.23)	21 (1.45)	29 (1.87)	39 (2.23)	-0.08		
>6 and ≤12	655 (58.27)	739 (55.48)	760 (54.60)	651 (53.36)	775 (51.12)	781 (49.78)	720 (49.83)	740 (47.77)	808 (46.25)	-12.02	p<0.0001	0.0596
>12 and ≤18	443 (39.41)	551 (41.37)	589 (42.31)	536 (43.93)	711 (46.90)	753 (47.99)	704 (48.72)	780 (50.36)	900 (51.52)	12.11		

^aPercentages were calculated according to the total number of patients ≤18 years on the database in each respective year

^bPercentages were calculated according to the total number of patients claiming methylphenidate or atomoxetine

^cPercentages were calculated according to the total number of patients claiming methylphenidate or atomoxetine and a other CNS medication

*Chi-square test

Table 3: Prevalence of ADHD in family of children and adolescents with/without ADHD

Study period	Children and adolescents with ADHD and their family with ADHD n (%)	Children and adolescents without ADHD and their family with ADHD n (%)	<i>p</i> -value	Cramer's <i>V</i>
2005	0	36 (0.16)	$p < 0.4579$	-0.0049
2006	251 (14.94)	302 (0.44)	$p < 0.0001$	0.2508
2007	360 (14.05)	555 (0.58)	$p < 0.0001$	0.2235
2008	415 (14.96)	636 (0.67)	$p < 0.0001$	0.2301
2009	398 (34.10)	555 (1.37)	$p < 0.0001$	0.3613
2010	557 (41.72)	725 (1.72)	$p < 0.0001$	0.4080
2011	683 (46.34)	849 (2.08)	$p < 0.0001$	0.4344
2012	672 (46.63)	979 (2.60)	$p < 0.0001$	0.4126
2013	548 (29.09)	1093 (2.23)	$p < 0.0001$	0.2871

Table 4: Measurements of medication usage in the study population

Study period	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p-value*
Total prescriptions	8 391 836	8 906 344	7 911 071	6 775 863	9 023 205	8 515 428	7 371 213	6 770 703	6 794 490	70 460 153	
Total prescriptions for ADHD medication n (%)	23 438 (0.28)	26 464 (0.30)	27 114 (0.34)	24 590 (0.36)	32 761 (0.39)	32 876 (0.39)	29 487 (0.40)	30 620 (0.45)	33 087 (0.49)	260 437 (0.37)	
Average ADHD prescriptions per patient per year $\pm$SD (95% CI)	3.58 $\pm$ 2.71 (3.51-3.64)	3.80 $\pm$ 2.94 (3.76-3.87)	4.40 $\pm$ 3.14 (4.32-4.47)	4.64 $\pm$ 3.27 (4.55-4.73)	4.63 $\pm$ 3.26 (4.56-4.7)	4.60 $\pm$ 3.23 (4.53-4.68)	4.18 $\pm$ 3.02 (4.11-4.25)	4.20 $\pm$ 3.03 (4.13-4.27)	4.08 $\pm$ 2.91 (4.01-4.14)		p>0.0001
Total prescriptions MPH, n (%)	22 473 (95.88)	22 983 (86.85)	23 663 (87.28)	21 396 (87.01)	28 960 (88.40)	29 274 (89.04)	26 767 (90.78)	27 894 (91.10)	30 373 (91.80)	233 783 (89.77)	
Average prescription MPH per patient per year $\pm$SD (95% CI)	3.65 $\pm$ 2.75 (3.59-3.72)	3.74 $\pm$ 2.85 (3.67-3.81)	4.29 $\pm$ 3.01 (4.21-4.37)	4.52 $\pm$ 3.13 (4.43-4.61)	4.53 $\pm$ 3.15 (4.46-4.61)	4.5 $\pm$ 3.14 (4.42-4.57)	4.11 $\pm$ 2.94 (4.04-4.18)	4.15 $\pm$ 2.97 (4.08-4.22)	4.03 $\pm$ 2.86 (3.97-4.1)		p>0.0001
Total prescriptions atomoxetine, n (%)	965 (4.12%)	3 481 (13.15)	3 451 (12.73)	3 194 (12.99)	3 801 (11.6)	3 602 (10.96)	2 720 (9.22)	2 726 (8.9)	2 714 (8.2)	26 654 (10.23)	

Study period	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	p-value*
Average prescription atomoxetine per patient per year $\pm$ SD (95% CI)	2.37 $\pm$ 1.54 (2.22-2.52)	4.25 $\pm$ 3.49 (4.01-4.5)	5.26 $\pm$ 3.91 (4.96-5.56)	5.62 $\pm$ 4.11 (5.28-5.96)	5.56 $\pm$ 4.03 (5.25-5.86)	5.65 $\pm$ 3.96 (5.35-5.96)	5.03 $\pm$ 3.76 (4.7-5.35)	4.81 $\pm$ 3.59 (4.51-5.1)	4.61 $\pm$ 3.47 (4.33-4.89)		p>0.0001

MPH -Methylphenidate

SD - standard deviation, CI - confidence interval *ANOVA

Table 5: Medicine items with prescribed daily dose exceeding the recommended daily dose

ADHD medication	Methylphenidate			Atomoxetine		
Study period	≤ 6 years	>6 and ≤ 12 years	>12 and ≤ 18 years	≤ 6 years	>6 and ≤ 12 years	>12 and ≤ 18 years
	n (%) ^a	n (%) ^a	n (%) ^a	n (%) ^a	n (%) ^a	n (%) ^a
2005	33 (13.10)	347 (2.39)	241 (2.69)	1 (3.70)	53 (6.27)	2 (0.53)
2006	23 (7.85)	245 (1.65)	62 (0.66)	7 (20.0)	154 (6.32)	25 (1.76)
2007	66 (25.29)	234 (1.57)	1 (0.01)	3 (6.12)	98 (4.43)	1 (0.07)
2008	33 (20.25)	161 (1.22)	2 (0.02)	16 (20.78)	123 (5.60)	16 (1.26)
2009	12 (7.45)	333 (1.85)	27 (0.19)	3 (4.23)	219 (8.43)	2 (0.13)
2010	53 (25.0)	283 (1.64)	11 (0.08)	14 (33.33)	145 (6.40)	9 (0.67)
2011	44 (20.56)	203 (1.32)	4 (0.03)	0 (0)	111 (7.07)	0 (0)
2012	18 (12.08)	181 (1.17)	3 (0.02)	2 (7.41)	126 (8.17)	4 (0.28)
2013	44 (17.74)	98 (0.58)	20 (0.13)	2 (20.0)	146 (9.88)	1 (0.068)
Total	326 (16.69)	2085 (1.48)	371 (0.34)	48 (13.75)	1175 (6.85)	60 (0.50)

^aPercentages were calculated according to the total number of items for each respective year and age group.

Table 6: Prescribed daily dose for methylphenidate according to age groups: ADHD group vs. ADHD-CNS group

		Methylphenidate PDD								
		Age groups (years)								
		≤6			>6 and ≤12			>12 and ≤18		
Study period		ADHD-only	ADHD-CNS	<i>p</i> -value, Cohens' <i>d</i> *	ADHD-only	ADHD-CNS	<i>p</i> -value, Cohens' <i>d</i> *	ADHD-only	ADHD-CNS	<i>p</i> -value, Cohens' <i>d</i> *
2005	n	179	73	<i>p</i> = 0.4356	11449	3070	<i>p</i> = 0.3261	6997	1970	<i>p</i> < 0.0001
	Mean±SD	19.20±30.96	23.78±61.8	<i>d</i> = 0.07	23.76±35.35	25.7±34.26	<i>d</i> = 0.05	29.32±45.58	29.32±62.62	<i>d</i> = 0
	95% CI	14.64-23.77	9.34-28.2		23.11-24.4	24.48-26.91		28.25-30.39	33.32-38.86	
2006	n	158	135	<i>p</i> = 0.5638	11461	3360	<i>p</i> = 0.0093	7098	2234	<i>p</i> < 0.0001
	Mean±SD	15.32±9.35	15.9±8.2	<i>d</i> = 0.06	22.45±23.12	23.76±15.1	<i>d</i> = 0.056	27.66±20.97	32.34±35.5	<i>d</i> = 0.132
	95% CI	13.85-16.78	14.52-17.31		22.03-22.88	23.25-24.27		27.17-28.15	30.87-33.81	
2007	n	130	131	<i>p</i> = 0.7359	10988	3916	<i>p</i> < 0.0001	7347	2646	<i>p</i> < 0.0001
	Mean±SD	21.6±13.8	21.6±13.81	<i>d</i> = 0	22.67±11.68	23.93±11.72	<i>d</i> = 0.11	28.3±13.25	31.62±13.74	<i>d</i> = 0.24
	95% CI	19.2-23.99	18.62-23.42		22.46-22.89	23.57-24.3		27.99-28.60	31.1-32.15	
2008	n	77	86	<i>p</i> = 0.0004	9502	3689	<i>p</i> < 0.0001	7126	2591	<i>p</i> < 0.0001
	Mean±SD	14.89±9.25	21.73±13.89	<i>d</i> = 0.49	23.53±13.41	25.82±12.87	<i>d</i> = 0.17	29.88±13.92	32.81±15.61	<i>d</i> = 0.19
	95% CI	12.79-16.99	18.75-24.71		23.26-23.8	25.41-26.24		29.55-30.2	32.21-33.41	
2009	n	88	73	<i>p</i> = 0.0736	13420	4543	<i>p</i> < 0.0001	10077	3850	<i>p</i> < 0.0001
	Mean±SD	14.35±7.63	17.04±11.23	<i>d</i> = 0.24	23.17±12.35	26.72±13.78	<i>d</i> = 0.26	30.65±14	34.51±16.22	<i>d</i> = 0.24
	95% CI	12.74-15.97	14.42-19.66		22.97-23.38	26.32-27.12		30.38-30.92	33.99-35.02	
2010	n	92	120	<i>p</i> = 0.2800	12905	4335	<i>p</i> < 0.0001	10210	3947	<i>p</i> < 0.0001
	Mean±SD	18.46±11.71	20.41±13.92	<i>d</i> = 0.14	23.37±12.17	26.61±13.54	<i>d</i> = 0.24	31.31±15.69	34.42±15.65	<i>d</i> = 0.2
	95% CI	16.04-20.89	17.9-22.9		23.16-23.58	26.21-27.01		31-31.62	33.93-34.91	

		Methylphenidate PDD								
		Age groups (years)								
		≤6			>6 and ≤12			>12 and ≤18		
Study period		ADHD-only	ADHD-CNS	<i>p</i>-value, Cohens' <i>d</i>*	ADHD-only	ADHD-CNS	<i>p</i>-value, Cohens' <i>d</i>*	ADHD-only	ADHD-CNS	<i>p</i>-value, Cohens' <i>d</i>*
2011	n	154	60	$p = 0.3015$	11934	3485	$p = 0.0004$	9785	3423	$p < 0.0001$
	±SD	19.02±12.94	21.16±15.21	$d = 0.14$	23.39±11.51	25.7±12.89	$d = 0.179$	31.34±14.38	33.78±16.09	$d = 0.15$
	95% CI	16.96-21.08	17.23-25.09		23.19-23.6	25.27-26.12		31.06-31.63	33.24-34.32	
2012	n	101	48	$p = 0.0019$	11708	3751	$p < 0.0001$	10706	3920	$p < 0.0001$
	Mean±SD	17.12±9.81	12.31±5.40	$d = 0.49$	23.5±11.56	26.04±12.86	$d = 0.198$	31.7±14.44	34.56±15.57	$d = 0.18$
	95% CI	15.18-19.05	10.74-13.88		23.29-23.71	25.63-26.45		31.43-31.97	34.07-35.04	
2013	n	158	90	$p = 0.0803$	12881	4111	$p < 0.0001$	11289	4214	$p < 0.0001$
	Mean±SD	16.98±10.55	14.73±7.96	$d = 0.21$	22.65±11.02	25.23±12.59	$d = 0.21$	32.11±14.92	34.54±15.38	$d = 0.16$
	95% CI	15.32-18.64	13.07-16.4		22.46-22.84	24.85-25.62		31.84-32.39	34.07-35	

*t-test

Table 7: Prescribed daily dose for atomoxetine according to age groups: ADHD group vs. ADHD-CNS group

		Atomoxetine PDD								
		Age groups (years)								
		≤6			>6 and ≤12			>12 and ≤18		
Study period		ADHD-only	ADHD-CNS	<i>p</i> -value, Cohens' <i>d</i>	ADHD-only	ADHD-CNS	<i>p</i> -value, Cohens' <i>d</i>	ADHD-only	ADHD-CNS	<i>p</i> -value, Cohens'
2005	n	14	13	<i>p</i> = 0.9685	560	285	<i>p</i> = 0.0734	260	119	<i>p</i> = 0.0549
	Mean±SD	17.74±8.9	17.62±6.9	<i>d</i> = 0.01	34.85±46.56	29.4±30.27	<i>d</i> = 0.12	40.37±18.12	43.3±20.97	<i>d</i> = 0.14
	95% CI	12.6-22.88	13.48-21.75		30.98-38.71	25.87-32.93		38.15-42.58	39.49-47.1	
2006	n	29	6	<i>p</i> = 0.8972	1660	775	<i>p</i> = 0.5523	915	507	<i>p</i> < 0.0001
	Mean±SD	22.76±20.63	21.61±13.49	<i>d</i> = 0.056	32.35±28.83	33±14.81	<i>d</i> = 0.023	44.63±26.72	49.54±38.05	<i>d</i> = 0.13
	95% CI	14.92-30.61	7.45-35.77		30.96-33.74	31.96-34.04		42.9-46.36	46.22-52.86	
2007	n	17	32	<i>p</i> = 0.2	1478	734	<i>p</i> = 0.7303	899	617	<i>p</i> = 0.0129
	Mean±SD	21.59±10.6	18.72±4.9	<i>d</i> = 0.27	31.23±12.1	31.05±11.73	<i>d</i> = 0.098	47.48±18.15	50.07±18.91	<i>d</i> = 0.14
	95% CI	16.14-27.04	16.95-20.49		30.62-31.85	30.2-31.9		46.29-48.66	48.58-51.57	
2008	n	54	23	<i>p</i> = 0.0021	1382	813	<i>p</i> = 0.0385	746	526	<i>p</i> = 0.0001
	Mean±SD	26.65±11.34	18.62±6.13	<i>d</i> = 0.71	32.06±11.03	33.14±13.06	<i>d</i> = 0.083	45.8±18.61	49.89±18.53	<i>d</i> = 0.22
	95% CI	23.56-29.75	15.97-21.27		31.48-32.64	32.24-34.04		44.47-47.14	48.31-51.48	
2009	n	36	35	<i>p</i> = 0.0328	1642	952	<i>p</i> = 0.7322	958	559	<i>p</i> = 0.2128
	Mean±SD	17.61±6.36	21.11±7.18	<i>d</i> = 0.49	31.48±13.14	32.97±13.97	<i>d</i> = 0.11	48.19±19.3	46.97±16.4	<i>d</i> = 0.063
	95% CI	15.46-19.76	18.65-23.58		30.84-32.12	32.09-33.86		46.96-49.41	45.61-48.34	
2010	n	10	32	<i>p</i> = 0.0016	1422	845	<i>p</i> = 0.0045	980	610	<i>p</i> = 0.7927
	Mean±SD	18±0	28.27±9.48	<i>d</i> = 1.08	31.82±13.73	33.59±15.37	<i>d</i> = 0.12	48.17±20.21	48.44±18.77	<i>d</i> = 0.013
	95% CI	0	24.85-31.68		31.10-32.53	32.55-34.63		46.91-49.44	46.95-49.93	

		Atomoxetine PDD								
		Age groups (years)								
		≤6			>6 and ≤12			>12 and ≤18		
Study period		ADHD-only	ADHD-CNS	<i>p</i> -value, Cohens' <i>d</i>	ADHD-only	ADHD-CNS	<i>p</i> -value, Cohens' <i>d</i>	ADHD-only	ADHD-CNS	<i>p</i> -value, Cohens'
2011	n	10	1	<i>p</i> = 0.1716	1029	541	<i>p</i> = 0.3636	843	543	<i>p</i> = 0.0002
	Mean±SD	17.8±5	10±0	<i>d</i> = 1.56	31.75±13.52	32.42±14.15	<i>d</i> = 0.05	45.58±17.91	49.20±16.78	<i>d</i> = 0.20
	95% CI	14.22-21.38	-		30.93-32.58	31.22-33.61		44.37-46.79	47.79-50.61	
2012	n	5	22	<i>p</i> = 0.1105	963	580	<i>p</i> = 0.1090	849	597	<i>p</i> = 0.0023
	Mean±SD	16.2±6.34	22.35±7.70	<i>d</i> = 0.8	33.68±12.67	32.53±15.12	<i>d</i> = 0.076	47.73±20.37	50.83±16.86	<i>d</i> = 0.15
	95% CI	8.33-24.07	18.93-25.76		32.88-34.8	31.3-33.77		46.35-49.1	49.47-52.18	
2013	n	7	3	<i>p</i> = 0.0192	976	501	<i>p</i> = 0.007	889	568	<i>p</i> = 0.0914
	Mean±SD	17.71±6.13	48.33±28.43	<i>d</i> = 1.07	32.33±14.13	34.86±12.51	<i>d</i> = 0.18	48.66±17.05	50.24±18.04	<i>d</i> = 0.088
	95% CI	12.05-23.38	-22.29-118.96		31.44-33.22	33.77-35.96		47.53-49.78	48.75-51.73	

*t-test

3.3 Manuscript 2

Prescribing patterns of central nervous system medication in South African children and adolescents with/without treatment for ADHD and its potential drug-drug interactions

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Key points:

- The prevalence of children and adolescents 18 years and younger who use central nervous system (CNS) medication is decreasing;
- Anxiolytic agents are the most prevalent CNS medication prescribed to children and adolescents without ADHD;
- CNS medication prescribing in children and adolescents with ADHD are increasing;
- Antidepressant drugs are the most prevalent active ingredient prescribed to ADHD-CNS children and adolescents; and
- The most severe potential drug-drug interactions were found on prescriptions of atomoxetine prescribed with escitalopram and citalopram.

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Conflict of Interest

None of the authors have any conflicts to declare.

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Abstract

Purpose: To compare the prescribing patterns of other central nervous system (CNS) medication in South African children and adolescents receiving methylphenidate and atomoxetine treatment (ADHD-CNS), or not (CNS-only), and to determine the prevalence of potential drug-drug interactions between methylphenidate or atomoxetine and other CNS medication.

Methods: A quantitative, descriptive, longitudinal study was performed using medicine claims data from the period 1 January 2005 to 31 December 2013. Potential drug-drug interactions on prescriptions were determined between methylphenidate and atomoxetine and other CNS medication on prescriptions using the *Drug Interaction Facts Compendia* of Tatro 2012.

Results

Prevalence of children and adolescents, aged 18 years and younger, who used CNS medication decreased from 5.12% in 2005 to 4.48% in 2013. Overall, ADHD children and adolescents who received CNS medication increased, whereas prescribing decreased in CNS only children and adolescents. Antidepressants were the most common CNS medication prescribed to ADHD children and adolescents (41.51%). Anxiolytic agents were the most frequently prescribed subclass to children and adolescents without ADHD (39.12%).

Potential significant level 1, 4 and 5 drug-drug interactions were observed on 4 530 (1.94%) methylphenidate prescriptions. The highest prevalence of potential drug-drug interactions on methylphenidate prescriptions occurred with imipramine (51.79%) and amitriptyline (37.00%). Potential significant levels 1 and 2 drug-drug interactions were observed in 1 038 (3.89%) prescriptions for atomoxetine. Escitalopram (37.67%) and citalopram (29.58%) in combination with atomoxetine accounted for the most frequent potential drug-drug interactions.

Conclusion

The study highlights the difference in prescribing patterns of CNS medicine for children and adolescents receiving treatment for ADHD versus those who do not. ADHD children and adolescents are more likely to use other CNS medication, and to experience potentially severe drug-drug interactions.

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder, commonly affecting young children.^{1,2} Youths with ADHD are at risk for developing other psychiatric disorders, with consequent impairment in mental health, quality-of-life and social- and psychological adaptation.^{3,4,5} Oppositional defiant disorder, developmental coordination disorder, mood disorders (depression- and anxiety disorders) and substance use disorders are among the most common comorbidities associated with ADHD.^{6,7}

Previous studies have suggested a cogent relationship between ADHD and the use of CNS medication in children^{8,9,10,11} and adolescents^{12,13} as a result of these comorbidities. This can be attributed to the increasing treatment rates of CNS medication in children and adolescents.

With an increase in the prescribing of CNS medication for individuals receiving treatment for ADHD, an increase in the probability of drug-drug interactions may follow.¹⁴ Drug-drug interactions may have severe consequences and can result in possible hospitalisation or death.¹⁵ Methylphenidate in combination with monoamine oxidase inhibitors (MAOIs) such as phenelzine, rasagiline, selegiline and tranylcypromine, may have severe consequences and the effects can be life-threatening or cause permanent damage.¹⁵ Atomoxetine in combination with MAOI and selective serotonin reuptake inhibitors (SSRIs) also have debilitating effects on patients' health.¹⁵

The prevalence of CNS medication usage and its potential drug-drug interactions with methylphenidate or atomoxetine-containing products among South African children and adolescents is unknown. This study aimed to determine the prevalence of CNS medication usage among children and adolescents. A secondary aim was to identify the prevalence and significance of potential drug-drug interactions on prescriptions of methylphenidate or atomoxetine and CNS medication for children and adolescents, 18 years and younger, in the private health sector in South Africa.

METHODS

Data source and study population

A retrospective longitudinal study was performed on nationally representative medicine claims data that was submitted for reimbursement from 1 January 2005 to 31 December 2013. The Pharmaceutical Benefit Management (PBM) company that provided the data is dedicated to the effective management of medicine benefits for members of 39 medical schemes and capitation plans in South Africa. The PBM is linked to all South Africa's pharmacies and 98% of all

dispensing doctors. The reliability and validity of the data obtained from the PBM was ascertained by the PBM's internal validation processes.

Patient demographics (such as age, gender, diagnosis, and encrypted patient member numbers) and pertinent prescription information data (such as prescription number, active ingredient, pharmacological group, date of dispensing of the prescription) were extracted for analysis.

Study population

The study population included all patients on the database, 18 years and younger, with paid claims for medicine classified in the following CNS pharmacological groups: i) CNS stimulants; ii) sedative hypnotic agents; iii) anxiolytic agents; iv) antidepressants; v) antipsychotic agents; and vi) anti-epileptic agents.¹⁶ The study population was then divided into two groups, namely children and adolescents who either received prescriptions for methylphenidate or atomoxetine, or had an ICD10 diagnosis for ADHD (referred to as the ADHD-CNS group); and children and adolescents who did not receive prescriptions for methylphenidate and/or atomoxetine nor had an ICD10 diagnosis for ADHD (referred to as the CNS-only group).

For the purpose of this study, the pharmacological classes of anti-Parkinson's agents, antivertigo and anti-emetic agents, antimigraine agents, and Alzheimer's medication were excluded from analysis, because they are neither related to any ADHD comorbidities, nor applicable to children under the age of 18 years (e.g. Alzheimer's medication and anti-Parkinson's agents).

Identification of potential drug-drug interactions

Potential drug-drug interactions between methylphenidate or atomoxetine and other CNS medication were determined by using *Drug Interaction Facts Compendia* of Tatro 2012.¹⁵ Drug-drug interactions were divided into five groups depicting the five different significant levels and measure of severity. Tatro assigns a significance rating of 1 to drug-drug interactions classified as major, a significance rating of 2 signifies a drug-drug interaction of moderate severity, a drug-drug interaction of minor severity is assigned a significance rating of 3, a significance rating of 4 to drug-drug interactions classified as major/moderate and a significance rating of 5 to drug-drug interactions classified as minor/any.¹⁵ Drug-drug interactions on prescriptions that may result in a severity rating of 1 to 5 for either methylphenidate or atomoxetine in a potentially interacting combination with other CNS medication were counted during the study period.

Statistical analysis

Data management and analysis were performed using the SAS® program version 9.3.¹⁷

Practical significance of results were calculated when the p -value was statistically significant ($p \leq 0.0001$).

Study variables included age, gender, diagnosis, prevalence of ADHD-CNS or CNS patients, number of prescriptions for CNS medication and number of potential drug-drug interactions.

Three patient age strata were used, namely; ≤ 6 years, > 6 years and ≤ 12 years and > 12 years and ≤ 18 years. Study variables were expressed using descriptive statistics.

The chi-square (χ^2) test was used to determine whether an association existed between proportions of two or more groups. The Cramer's V statistic was used to test the practical significance of associations (practical significance was interpreted as follows: effect size of 0.1 was small; 0.3 effect size was medium and an effect size of 0.5 was large). A two-sample t -test was used to test for statistically significant differences between the average number of CNS prescriptions per ADHD-CNS or CNS-only patient per year. Cohen's d -value was used to evaluate the effect size between the difference in means.¹⁸ For practical significance, the following were considered: ≤ 0.2 a small effect, with no significant difference, $> 0.2 \leq 0.5$ a medium effect with an observable significance, > 0.8 a large effect and significant difference.¹⁸

Ethical considerations

Ethical approval from the Health Research Ethics Committee of the Faculty of Health Sciences, North-West University (Potchefstroom Campus) (NWU-00179-14-A1), and goodwill permission from the board of directors of the PBM, were obtained.

RESULTS

General prescribing patterns/patient demographic information

During the study period, the percentage of children and adolescents, 18 years and younger, who received prescriptions for CNS medication decreased with 0.64% from 5.12% ($n = 15\,334$) in 2005 to 4.48% ($n = 8\,037$) 2013. A statistically significant association was found between the proportion of children and adolescents in the ADHD-CNS and the CNS-only group per year over the study period, with an increase of 14.39% in the ADHD-CNS group, and a similar decrease in the CNS-only group. This association was weak (Cramer's $V = 0.1288$).

The majority of children and adolescents in the ADHD-CNS group were females, with a male to female ratio of 1:1 in the CNS-only group. No statistically significant associations were found between gender and the proportion of ADHD-CNS ($p = 0.0017$) or CNS ($p = 0.0305$) children and adolescents groups over the study period, with an increasing trend in the female groups. These associations in both the CNS-only and ADHD-CNS group were weak (Cramer's $V = 0.0438$ and Cramer's $V = 0.0138$, respectively).

The majority of children and adolescents in the ADHD-CNS group were distributed between the > 6 and ≤ 12 years and > 12 and ≤ 18 years age groups, whereas the majority of children and adolescents in the CNS-only group were in the $> 12 \leq 18$ years age group. Statistically significant associations were found between the proportion of both ADHD-CNS and CNS-only children and adolescents per age group over the study period ($p < 0.0001$). An increase was found in the prevalence of ADHD-CNS and CNS-only children and adolescents within the $> 12 \leq 18$ years age group; however, the effect of these associations was weak (Cramer's $V = 0.0595$ and Cramer's $V = 0.0458$).

>>>Insert Table 1 here<<<

Comparison of CNS medication usage between ADHD-CNS group and CNS group

A total of 257 702 CNS prescriptions were claimed during the study period for children and adolescents, which represented 0.37% of all prescriptions claimed during the study period on the database. Of all CNS prescriptions claimed during the study period, 0.11% ($n = 74\,931$) prescriptions were for patients also treated for ADHD. For each year, the average number of CNS prescriptions claimed per ADHD-CNS patient was statistically significantly higher than the average number of CNS prescriptions claimed per patient for the CNS-only patient ($p < 0.0001$). The effect of these differences was moderate for all study years (Cohen's d -value between 0.36 and 0.48).

Antidepressants were the most frequently prescribed CNS medication in the ADHD-CNS group, with a total number of 7 866 (41.54%) prescriptions from 2005 to 2013. Among the antidepressants, the SSRIs were the most frequently prescribed antidepressant medicine class (20.99%), followed by tricyclic antidepressants (17.31%). Imipramine (10.00%) and amitriptyline (6.68%) were the most prescribed antidepressants within the ADHD-CNS group.

The pharmacological group of anxiolytic agents were the most frequent CNS medication prescribed to children and adolescents, 18 years and younger, within the CNS-only group, representing 39.12% (n = 43 175) of all prescriptions for CNS medication. Antidepressants accounted for 27.67% (n = 30 531) of all prescriptions prescribed to children and adolescents within the CNS-only group.

>>>Insert Table 2 here<<<

>>>Insert Table 3 here<<<

Identification of potential drug-drug interactions

A potentially significant level one interaction between methylphenidate and moclobemide was observed for 63 (1.39%) prescriptions. The 427 cases of level four potential drug-drug interactions with methylphenidate were composed of phenytoin (0.02%), carbamazepine (9.10%) and oxcarbazepine (0.35%). A total number of 4 102 (90.56%) cases of level five interactions were composed of interactions between antidepressants and methylphenidate, of which amitriptyline (37.00%) and imipramine (51.79%) were the most prevalent.

A total number of 1 038 (3.89%) prescriptions contained atomoxetine in a potentially significant level one or two drug-drug interaction combination with other CNS medication. Prescriptions containing potentially significant level one interactions represented 0.39% (n = 4) of prescriptions, and were for moclobemide in combination with atomoxetine. Escitalopram was the most prevalent potentially significant level two interacting medication prescribed with atomoxetine, accounting for 391 (37.67%) cases of potential drug-drug interactions with atomoxetine.

>>>Insert Table 4 here<<<

>>>Insert Table 5 here<<<

DISCUSSION

This longitudinal study investigated the prescribing patterns of CNS medication in ADHD and non-ADHD children and adolescents and the potential drug-drug interactions between methylphenidate or atomoxetine and other CNS medication in the private health sector of South Africa.

The overall prevalence of children and adolescents, 18 years and younger, who claimed CNS medication was 4.48% of the total database in 2013. Differences in psychotropic medication prevalence rates exist between continents and countries,^{19,20} ranging from as high as 7.2% in the USA²¹ to 2.0% in Europe¹⁹. In 2013, the United States Centers for Disease Control and Prevention (CDC) reported that approximately 6.3% of adolescents aged 12 to 19 years of age had used CNS medication between 2005 and 2010.¹³ Lower estimates were reported in France, with a treatment prevalence rate of 2.5% in children and adolescents.²²

Psychotropic prescription rates similar to that in France have been reported in the United Kingdom.²³ According to Zoëga and associates (2009), 4.87% of Icelandic children and adolescents 17 years and younger, used CNS drugs in 2007.²⁴ When Olfson and associates (2013) examined a 12-month prevalence of psychotropic drug use in adolescents, 7% of the adolescents had at least used one psychotropic medication during the study period.²⁵ These differences in the prevalence estimates of CNS drug use can be attributed to any of the following factors: nosology of psychopathology; ethnic, economic, regulatory and other related factors that may play a role in the physician or parents' decision to medicate children and adolescents with emotional or behavioural disorders; increased public awareness of mental health problems and treatment options for disorders in children; development of medications that are considered safe in treating young children; increased behavioural expectations of children in controlled settings, e.g. school or childcare; over diagnosis of psychotropic disorders and overuse of psychotropic drugs in children; national and international variations in diagnostic guidelines; shortage of child and adolescent psychiatrists; and access to mental healthcare.^{20,26,27,28,29}

A significant change was observed in the prevalence of patients within the ADHD-CNS and the CNS-only group over the study period with an increase in the ADHD-CNS group and a decrease in the CNS-only group. Additionally, the percentage of CNS prescriptions prescribed to children and adolescents in the ADHD-CNS group increased (0.08%), while the percentage of CNS prescriptions prescribed to children and adolescents within the CNS-only group decreased (0.09%). A possible explanation for this finding might be that comorbidities are increasingly being recognised in patients with ADHD, and that ADHD without comorbidity is viewed as an exception rather than the rule.³⁰ In addition, the American Academy of Pediatrics' guidelines

state that clinicians should consider ADHD comorbidities in ADHD children and adolescents for the diagnosis of ADHD.³¹ On the other hand, fewer evidence concerning the efficacy of drug combinations to treat complex comorbid disorders exists.^{29,32} These combinations are frequently used either to address side effects of effective drugs or to enhance the efficiency of drugs in patients with partial response to first-line agents, or to address symptoms associated with neurotransmitter abnormalities.^{29,33}

An increasing trend was observed in female patients and adolescents within both the ADHD-CNS- and CNS-only groups; however, with a higher prevalence of males within the ADHD-CNS group. According to the CDC's National Center for Health Statistics' data brief, males were more likely to report ADHD medication use, whereas females were more likely to report the use of CNS medication.¹³ Betts and colleagues (2014) studied the prevalence of the co-prescribing of CNS medication in ADHD children and adolescents in the USA, and found higher concomitant psychotropic medication use in females.³⁴

The majority of children and adolescents in the ADHD-CNS group were distributed between the > 6 and ≤ 12 years and > 12 and ≤ 18 years age groups, whereas the majority of children and adolescents in the CNS-only group were in the > 12 ≤ 18 years age groups.

Antidepressants were the most prevalently prescribed CNS medication prescribed to patients within the ADHD-CNS group during the study period (41.51%). Depression is considered one of the most common comorbid disorders of ADHD.^{6,7} An estimated 32% of children and adolescents with ADHD have been reported to have a diagnosis for depression,³⁵ which can contribute to the high prescribing prevalence of antidepressants in children and adolescents. The SSRIs were the most prevalent prescribed antidepressant drugs (20.99%), which is in line with the findings from Beck *et al.* (2005) and Betts *et al.* (2014) reporting a prevalence of 17.8% and 17.6% respectively.^{21,34} Children with ADHD tend to be more vulnerable to various forms of urinary problems, such as nocturnal enuresis.^{36,37} Amitriptyline and imipramine are indicated for the treatment of nocturnal enuresis,^{16,38} which can contribute to the high prevalence rate of imipramine (10%) and amitriptyline (6.68%) prescribing.

The pharmacological group of anxiolytic agents were the most frequent CNS medication prescribed to children and adolescents 18 years and younger within the CNS-only group. This prevalence is considerably higher than the prevalence reported in similar studies. For instance, Kovess *et al.* (2015) reported that the anxiolytic agents were the most prescribed psychotropic medication used in French children and adolescents, at a prevalence of 1.9%.³⁹ Furthermore, Ohayon and Lader (2002) found that 4.3% of the sample was for the anxiolytic agents.⁴⁰ It should be noted, however, that the study by Ohayon and Lader was conducted in the general population. Furthermore, the same trend was not reported in all prevalence studies, for

instance, the pharmacological drug class of antidepressants was the most prevalent prescribed drugs to adolescents, with a prevalence rate of 3.2% from 2005 to 2010.¹³ Likewise, Olfson *et al.* (2013) reported a 3.9% treatment prevalence of antidepressants in adolescents.²⁵

Twenty percent of patients were exposed to significance level one or two potential drug-drug interactions. Approximately 19% of these interactions were level two significance interactions between atomoxetine and the SSRIs paroxetine, fluvoxamine, citalopram escitalopram and sertraline.^{15,38} These agents are inhibitors of the cytochrome P450 enzyme (CYP2D6), which is responsible for the metabolism of atomoxetine.^{15,38} This can lead to increased concentrations of atomoxetine in the brain with consequent serious or fatal adverse reactions and deterioration of the patient's clinical outcome.^{15,38}

Possible significance level five drug-drug interactions between methylphenidate and the tricyclic antidepressants (TCAs), amitriptyline, imipramine, clomipramine, dothiepin and lofepramine accounted for approximately 74% of potential drug-drug interactions on prescriptions. This interaction can cause increased serum concentration of tricyclic antidepressants by inhibiting its metabolism via the cytochrome P450 enzyme in the liver.¹⁵ Consequentially, this can lead to increased plasma concentrations of the TCAs, with increased risk of precipitation of adverse reactions.¹⁵ However, the effects of this drug-drug interaction are usually mild, and should not significantly alter the therapeutic outcome.¹⁵

Limitations

This study was conducted using medicine claims data, which is associated with several limitations. The generalisability of the results is limited to the specific database used and study population in the private health sector of South Africa. The data were subject to the accuracy of the claimed data as processed by service providers, which opened the possibility of faulty or inaccurate claims. The lack of clinical data made it impossible to determine the reasons for the co-prescribing of the agents included. ADHD patients were identified by either having an ICD10 diagnosis of ADHD or a paid claim for either methylphenidate or atomoxetine or both during the study population. Methylphenidate is also indicated for use in narcolepsy, but usually for older patients and not for children and adolescents for which it were prescribed during the study.

CONCLUSION

The study concluded that CNS medication prescribing, with specific reference to antidepressant medication, is increasing in patients with ADHD. Anxiolytic agents were the most prevalent prescribed CNS medication for children and adolescents without treatment for ADHD. Severe drug-drug interactions were found on prescriptions of methylphenidate and atomoxetine, the highest prevalence being prescriptions containing atomoxetine in combination with escitalopram

or citalopram. Future studies should explore the full extent of polypharmacy prescribing to children and adolescents with ADHD, as well as resources available to clinicians for prescribing in the ADHD population.

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Table 1: Demographic information of the study population

Study period	2005	2006	2007	2008	2009	2010	2011	2012	2013	Difference 2005 vs. 2013 (%)	p- value	Cramer's V*
Total population (≤18 year) (n)	299 765	296 550	226 521	165 734	235 003	210 607	185 657	170 840	179 333			
Study population, n (%) ^a	15 334 (5.12)	15 431 (5.20)	12 504 (5.52)	9 414 (5.68)	12 478 (5.31)	11 273 (5.35)	9 020 (4.86)	7 958 (4.66)	8 037 (4.48)	-0.64		
ADHD-CNS n (%)	1 124 (7.33)	1 332 (8.63)	1 392 (11.13)	1 220 (12.96)	1 516 (12.15)	1 569 (13.92)	1 445 (16.02)	1 549 (19.46)	1 746 (21.72)	14.39	<i>p</i> < 0.0001	0.1288
CNS-only n (%)	14 210 (92.67)	14 099 (91.37)	11 112 (88.87)	8 194 (87.04)	10 962 (87.85)	9 704 (86.08)	7 575 (83.98)	6 409 (80.54)	6 291 (78.28)	-14.39		
Gender, n (%)												
ADHD-CNS group ^b												
Male	825 (73.40)	1 005 (75.45)	985 (70.76)	863 (70.74)	110 (72.56)	1 124 (71.64)	1 007 (69.69)	1 066 (68.82)	1 212 (69.42)	-6.03	0.0017	0.0438
Female	299 (26.60)	327 (24.55)	407 (29.24)	357 (29.26)	416 (27.44)	445 (28.36)	438 (30.31)	483 (31.18)	534 (30.58)	6.03		
CNS-only group ^c												
Male	6 739 (52.58)	6 671 (47.32)	5 186 (46.67)	3 724 (45.45)	5 091 (46.44)	4 555 (46.94)	3 483 (45.98)	2 910 (45.41)	2 907 (46.21)	-1.11	0.0305	0.0138
Female	7 471 (52.58)	7 428 (52.68)	5 926 (53.33)	4 470 (54.55)	5 871 (53.56)	5 149 (53.06)	4 092 (54.02)	3 499 (54.60)	3 384 (53.79)	1.11		

Study period	2005	2006	2007	2008	2009	2010	2011	2012	2013	Difference 2005 vs. 2013 (%)	p-value	Cramer's χ^2 *
Age groups, (years) n (%)												
ADHD-CNS group ^b												
≤6	26 (2.31)	42 (3.15)	43 (30.9)	33 (2.70)	30 (1.98)	35 (2.23)	21 (1.45)	29 (1.87)	39 (2.23)	-0.92	$p < 0.0001$	0.0595
>6 and ≤12	655 (58.27)	739 (55.48)	760 (54.60)	651 (53.36)	775 (51.12)	781 (49.78)	720 (49.83)	740 (47.77)	808 (46.28)	-9.2		
>12 and ≤18	443 (39.41)	551 (41.37)	589 (42.31)	536 (43.93)	711 (46.90)	753 (47.99)	704 (48.72)	780 (50.36)	899 (51.49)	10.12		
CNS-only group ^c												
≤6	3 640 (25.62)	3 486 (24.73)	2 599 (23.39)	1 463 (17.85)	2 933 (26.76)	2 716 (27.99)	2 085 (27.52)	1 539 (24.01)	1 477 (23.48)	-1.25	$p < 0.0001$	0.0458
>6 and ≤12	3 937 (27.71)	3 808 (27.01)	2 918 (26.26)	2 316 (28.26)	2 827 (25.79)	2 479 (25.55)	2 012 (26.56)	1 707 (26.63)	1 679 (26.69)	0.32		
>12 and ≤18	6 633 (46.68)	6 805 (48.27)	5 595 (50.35)	4 415 (53.88)	5 202 (47.45)	4 509 (46.47)	3 478 (15.91)	3 164 (49.37)	3 135 (49.83)	1.56		

^aPercentages were calculated according to the total number of patients ≤18 years on the database in each respective year

^bPercentages were calculated according to the total number of patients claiming methylphenidate or atomoxetine and CNS medication

^cPercentages were calculated according to the total number of patients claiming CNS medication

*Chi-square

Table 2: Medicine usage during the study period

Study period	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	<i>p</i> -value
Total prescriptions on database	8 391 836	8 906 344	7 911 071	6 775 863	9 023 205	8 515 428	7 371 213	6 770 703	6 794 490	70 460 153	
CNS patients											
Total nr of CNS prescriptions, n (%)	34 762 (0.41)	36 495 (0.41)	31 800 (0.40)	24 896 (0.37)	34 200 (0.38)	30 165 (0.35)	23 334 (0.32)	20 592 (0.30)	21 458 (0.32)	257 702 (0.37)	
Average nr of CNS prescriptions per patient $\pm$SD (95% CI)	2.45 $\pm$ 4.06 (2.38-2.51)	2.59 $\pm$ 4.28 (2.52-2.66)	2.86 $\pm$ 4.82 (2.77-2.95)	3.03 $\pm$ 5.14 (2.92-3.15)	3.12 $\pm$ 5.36 (3.02-3.22)	3.12 $\pm$ 5.2 (3-3.2)	3.08 $\pm$ 5.22 (2.96-3.2)	3.21 $\pm$ 5.27 (3.08-3.34)	3.41 $\pm$ 5.61 (3.27-3.55)		<i>p</i> <0.0001
ADHD-CNS patients											
Total nr of CNS prescriptions, n (%)^a	5 728 (0.07)	6 989 (0.08)	7 854 (0.10)	7 661 (0.11)	9 550 (0.11)	9 818 (0.12)	8 416 (0.12)	9 031 (0.13)	9 884 (0.15)	74 931 (0.11)	
Average nr of CNS prescriptions per patient $\pm$SD (95% CI)	5.1 $\pm$ 5.83 (4.75-5.43)	5.25 $\pm$ 5.63 (4.94-5.55)	5.64 $\pm$ 6.32 (5.31-5.97)	6.28 $\pm$ 7.10 (5.88-6.67)	6.3 $\pm$ 6.64 (5.97-6.63)	6.26 $\pm$ 6.89 (5.92-6.6)	5.82 $\pm$ 6.74 (5.48-6.17)	5.83 $\pm$ 6.85 (5.49-6.17)	5.66 $\pm$ 6.3 (5.36-5.96)		<i>p</i> <0.0001
<i>p</i>-value	<i>p</i> < 0.0001	<i>p</i> < 0.0001	<i>p</i> < 0.0001	<i>p</i> < 0.0001	<i>p</i> < 0.0001	<i>p</i> < 0.0001	<i>p</i> < 0.0001	<i>p</i> < 0.0001	<i>p</i> < 0.0001		
Cohen' <i>d</i>-value*	<i>d</i> = 0.45	<i>d</i> = 0.47	<i>d</i> = 0.44	<i>d</i> = 0.46	<i>d</i> = 0.48	<i>d</i> = 0.46	<i>d</i> = 0.41	<i>d</i> = 0.38	<i>d</i> = 0.36		

^aExcluding prescriptions for methylphenidate and atomoxetine

SD - standard deviation, CI - confidence interval

*t-test

Table 3: Comparison of CNS medication usage between ADHD-CNS- and CNS patient group

Pharmacological classification	ADHD-CNS, n (%) ^a	CNS, n (%) ^a	Subclass	ADHD-CNS, n (%) ^a	CNS, n (%) ^a	Active ingredient	ADHD-CNS, n (%) ^a	CNS n, (%) ^a
Sedative hypnotic agents	593 (3.13)	9 637 (8.73)	Benzodiazepines	297 (1.57)	3 785 (3.83)	Midazolam	225 (1.19)	3 069 (2.78)
Anxiolytic agents	1989 (10.50)	43 175 (39.12)	Benzodiazepine derivatives	1 018 (5.37)	12 079 (10.95)	Alprazolam	283 (1.49)	3 538 (3.21)
						Clobazam	262 (1.38)	1 712 (1.55)
			Other	1 128 (5.96)	27 621 (26.57)	Hydroxyzine	792 (4.18)	27 540 (24.96)
Antidepressants	7 866 (41.51)	30 531 (27.67)	Tricyclic	3 260 (17.31)	16 286 (14.96)	Amitriptyline	1 267 (6.68)	7 746 (7.02)
						Imipramine	1 894 (10.00)	8 140 (7.38)
			SSRI	3 975 (20.99)	11 667 (2.84)	Fluoxetine	920 (4.86)	3 133 (2.84)
						Citalopram	1 142 (6.03)	3 202 (2.90)
						Escitalopram	991 (5.23)	3 193 (2.89)
						Sertraline	670 (3.54)	1 207 (1.09)
Antipsychotic agents	4 516 (23.85)	7 717 (6.99)	Benzamides	271 (1.43)	1 882 (1.7)	Sulpiride	240 (1.27)	1 847 (1.67)
			Atypical antipsychotics	4 134 (21.68)	4 675 (4.09)	Risperidone	3 841 (20.29)	3 803 (3.45)
Anti-epileptic agents	3 890 (20.54)	19 002 (17.22)	Carboxamides	501 (2.65)	3 048 (2.77)	Carbamazepine	463 (2.45)	2 910 (2.64)
			Fatty acid derivatives	1 655 (60.42)	8 497 (39.89)	Valproic acid	1 655 (8.74)	8 497 (7.7)
			Other	1 627 (8.9)	5 983 (5.36)	Lamotrigine	1 321 (6.98)	3 862 (3.50)
						Topiramate	207 (1.09)	1 230 (1.11)

^aPercentages were calculated according to the total number of CNS prescriptions

Table 4: Frequency of potential drug-drug interactions with methylphenidate over the study period

CNS medication	Frequency of prescriptions with interactions with methylphenidate n (%)^a	Level of interaction
Amitriptyline	1 676 (37.00)	5 (Tatro, 2012:1943)
Imipramine	2 346 (51.79)	
Clomipramine	62 (1.37)	
Dothiepin	5 (0.11)	
Lofepramine	13 (0.29)	
Moclobemide	63 (1.39)	1 (Tatro, 2012:1235)
Phenytoin	1 (0.02)	4 (Tatro, 2012:955, 1233)
Carbamazepine	410 (9.1)	
Oxcarbazepine	16 (0.35)	
Total number of prescriptions	4 530	

^aPercentages were calculated according to the total number of prescription with potential drug-drug interactions with methylphenidate

Table 5: Frequency of potential drug-drug interactions with atomoxetine over the study period

CNS medication	Frequency of prescriptions with interactions with atomoxetine n (%)^a	Level of interaction
Moclobemide	4 (0.39)	1 (Tatro, 2012:213)
Fluoxetine	55 (5.30)	2 (Tatro, 2012:214)
Paroxetine	26 (2.51)	
Fluvoxamine	59 (5.68)	
Citalopram	307 (29.58)	
Escitalopram	391 (37.67)	
Sertraline	196 (18.89)	

Total number of prescriptions	1 038
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^aPercentages were calculated according to the total number of prescription with potential drug-drug interactions with atomoxetine

3.4 Chapter summary

This chapter contained the results in the form of manuscripts. Chapter 4 will discuss the strengths, limitations, recommendations and the conclusions derived from the study.

CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS

4.1 Introduction

In this chapter, the conclusions and key findings of the current study will be discussed, and recommendations regarding future studies will be provided. The limitations of the study will also be listed.

The general aim of this study was to investigate possible differences in the prescribing patterns of CNS medication in children and adolescents with treatment for ADHD vs. those without treatment for ADHD in the South African private health sector, as well as family tendencies regarding methylphenidate and atomoxetine usage.

4.2 Content of dissertation

This dissertation consisted of four chapters. Chapter 1 provided a general overview of the study, which included the background, problem statement and research questions, aims, objectives and the methodology used to conduct this study. Chapter 2 provided a review of the available literature regarding the prevalence of ADHD in children and adolescents, the treatment for ADHD, prevalence of comorbid diseases and the potential drug-drug interactions of ADHD medication and other CNS medication. The results and discussion of the empirical investigation were presented in the form of two manuscripts. The manuscripts were presented with the following titles:

- Manuscript 1: Methylphenidate and atomoxetine prescribing patterns in the South African private health sector (2005-2013).
- Manuscript 2: Prescribing patterns of other CNS medication in South African children and adolescents with/without treatment for ADHD and its potential drug-drug interactions.

4.3 Conclusions from the study

The aim was approached *via* the literature review objectives and the empirical investigation objectives. A quantitative, descriptive and longitudinal design was followed using retrospective, longitudinal medicine claims data from a nationally representative Pharmaceutical Benefit Management (PBM) company. The conclusions from the specific research objectives follow in the subsequent paragraphs.

4.3.1 Conclusions from the literature review

The literature review objectives, as outlined in paragraph 1.3.2.1, Chapter 1, were achieved in Chapter 2 of this dissertation. The following paragraphs summarise the key findings:

4.3.1.1 Prevalence of ADHD, nationally as well as internationally, stratified by age and gender

This research objective was approached via a broad overview of the prevalence of ADHD nationally as well as internationally with specific reference to children and adolescents (refer to Chapter 2, section 2.4). A world-wide pooled prevalence of ADHD of 5.3% (Polanczyk *et al.*, 2007:945) was established from the literature (refer to Chapter 2, section 2.4). These prevalence estimates were reported to be higher in African countries, with a range of 5.4 to 8.7% (Bakare, 2012:360).

Gender showed significant influences on prevalence, with an average of 10% for males compared to an average of 4% for females (Polanczyk *et al.*, 2007:945). Additionally, the prevalence of ADHD in African children, stratified by gender, was documented to be higher than the prevalence documented in other countries. Finally, it was established from the literature that the highest prevalence of ADHD was in children between the ages of four to 17 years (CDC, 2010).

4.3.1.2 Conceptualise ADHD treatment in children and adolescents

This objective was approached via an appraisal of the literature of the treatment of ADHD (refer to Chapter 2, section 2.5). The aim of ADHD treatment is to increase dopamine levels in the brain (Bymaster, 2002:704), especially in the dorsal striatum, nucleus accumbens and in the prefrontal cortex (Arnston, 2006:2377; Spencer *et al.*, 2005:1293), which is responsible for executive function such as regulation of attention (Aron & Poldrack, 2005:1289). It also acts on adrenoceptors, increasing norepinephrine in the hippocampus (Kuczenski & Segal, 2001:880) and the prefrontal cortex (Berridge *et al.*, 2006:1117; Bymaster, 2002:704). This, in turn, prevents dopamine release in the prefrontal cortex, which is responsible for inattention and impulsivity (Bymaster, 2002:704).

Although the exact mechanism for atomoxetine is not yet known, it was established from the literature that atomoxetine plays a key role in the management of ADHD symptoms.

4.3.1.3 Prevalence of CNS-related comorbid diseases with regard to ADHD

Through the literature review, the CNS comorbidities associated with ADHD were investigated. CNS comorbidities are common in children, adolescents and adults with ADHD (Jacob *et al.*,

2007:314; Nyden *et al.*, 2010:1666; Taurines *et al.*, 2010:269; West *et al.*, 1995:272). Youths with ADHD are at risk of developing other psychiatric disorders, which include mood, anxiety and substance use disorders, with severe impairment in mental health, quality of life as well as social and psychological adaptation (Biederman *et al.*, 1991:564). CNS comorbidities that usually occur in patients with ADHD include oppositional defiant disorder (ODD), conduct disorder (CD), depression, anxiety disorders, autism spectrum disorder (ASD), tic disorders (TD), substance use disorders (SUD), obsessive compulsive disorder (OCD), developmental coordination disorder (DCD) and specific learning disorder (Taurines *et al.*, 2010:269) (refer to Chapter 2, section 2.6).

4.3.1.4 Potential drug-drug interactions between methylphenidate- or atomoxetine-containing products and other CNS drugs

This objective was approached via referencing Tatro's *Drug Interaction Facts Compendia*, and a number of interactions were identified. Both methylphenidate and atomoxetine's possible interactions were tabulated in Annexure F.

Methylphenidate has a significance level 1 drug-drug interaction with the MAOIs. The mechanism of this interaction is unknown; however, concomitant use of these agents can cause a severe increase in blood pressure and may lead to a stroke (known as a hypertensive crisis) (Aggarwal & Khan, 2006:139; Tatro, 2012:1235). This interaction may lead to hospitalisation or possible death of the patient (Tatro, 2012:xiv). A significance level 4 potential drug-drug interaction is assigned to drug-drug interactions with hydantoin derivatives and carboxamides (anti-epileptic agents). The mechanism of these interactions is also unknown, but according to Tatro (2012:1943), methylphenidate interacts with hydantoin derivatives (Tatro, 2012:955), and carboxamides (Tatro, 2012:1233) causing increased serum concentration of these agents by inhibiting its metabolism via CYP450. Methylphenidate and the TCAs are assigned a significance level 5 potential drug-drug interaction (Tatro, 2012:1943), which can lead to the inhibition of the TCAs metabolism causing increased risk for side-effects associated with the TCAs (Markowitz & Patrick, 2001:754).

Atomoxetine shows significance level 1 drug-drug interactions with the MAOIs. When atomoxetine and MAOIs are co-administered, possible monoamine concentrations alterations in the brain can occur. This interaction has a rapid onset and demands immediate medical intervention due to increased risk of severe reactions and may cause death (Tatro, 2012:xiv, 213). SSRIs inhibit the CYP2D6 iso-enzyme in the liver, the primary metabolism pathway of atomoxetine. When these two agents are co-administered, increased atomoxetine plasma concentrations can cause an increased risk of adverse effects and possible hospitalisation (Tatro, 2012:214).

This objective concluded that there were significant potential drug-drug interactions between methylphenidate and atomoxetine and other CNS medications, as defined in Chapter 1.

4.3.2 Conclusions from the empirical study objectives

The empirical study objectives, as outlined in 1.3.2.2, Chapter 1, were achieved in Chapter 3 of this dissertation. The following paragraphs summarise the key findings:

4.3.2.1 Current prescribing patterns of methylphenidate and atomoxetine for children and adolescents with ADHD

During the study, an increase of 2.29% in the prevalence of ADHD in children and adolescents, 18 years and younger, from 2.11% in 2005 to 4.40% in 2013 was observed. The prevalence of children and adolescents with ADHD in 2013 was 0.90% lower than the prevalence estimate reported by Polanczyk's systematic review of studies addressing ADHD world-wide in 2007 (Polanczyk, 2007:945). From previous prevalence studies, it is clear that the prevalence of ADHD is increasing; for example, in 2012, Willcutt (2012:498) reported an ADHD prevalence estimate of 5.9% to 7.1% in children and adolescents. The increase in the treatment and diagnosis of ADHD may be attributed to increasing awareness, acceptance and recognition of ADHD; educational instruments employed to assess behaviours and attention problems; and possible off-label use of stimulants (APA, 2013:12; Olfson *et al.*, 2003:1075; Polanczyk *et al.*, 2014:8; Schubert *et al.*, 2010:620; Zuvekas & Vitiello, 2012:164).

From the study, an annual male to female ratio of 3:1 in children and adolescents with ADHD was observed. International studies reported findings similar to ours: Polanczyk and associates (2007:389) reported an estimated 10.00% prevalence for males vs. a mere 4.00% prevalence estimate for females. In 2013, the CDC (2013) calculated the ratio of ADHD medication usage from community samples in the USA, and reported a male to female ratio of 2:1. Differences in male to female prevalence rates may be due to differences in the clinical presentation of girls and referral bias towards boys (Egger & Angold, 2006:322; Meyer *et al.*, 2004:133).

ADHD prevalence was the highest among school-aged children (between 6 and 18 years of age). According to the CDC (2011), an annual average of 9.00% of children and adolescents (aged 5 to 17 years) had ever been diagnosed with ADHD. This finding may be explained by the increasing demands of academic achievement and behavioural outcomes in school structures (Currie *et al.*, 2014:64).

A total of 89.77% of prescriptions for ADHD medication was for methylphenidate, whereas atomoxetine accounted for the remaining prescriptions. According to the literature, methylphenidate is the most commonly used drug used to aid ADHD (Truter, 2014:1157). This

study found no differences between the average prescribed daily dose (PDD) for methylphenidate and atomoxetine compared to the recommended daily dose (RDD) range for methylphenidate and atomoxetine in both the ADHD-only and the ADHD-CNS group during the study period. A total of 4.35% of atomoxetine-containing products prescribed during the study period exceeded the RDD. Children six years and younger were the most exposed age group to have received prescriptions for methylphenidate- and atomoxetine-containing products that exceeded that RDD. The majority of medicine items prescribed to children six years and younger were for products containing 36 mg methylphenidate and 40 mg atomoxetine (refer to manuscript 1).

4.3.2.2 The prescribing patterns of other CNS medication between children and adolescents with treatment for ADHD vs. those without treatment for ADHD

During the study period, a decrease in the prevalence of children and adolescents with treatment for CNS medication was observed (5.12% in 2005 to 4.48% in 2013). This finding was different to the prevalence rates of CNS medication use in the literature (Vitiello, 2012:16; Zito, 2008). These variations could be explained by a number of different factors as outlined in manuscript 2, for example, variations in diagnostic- and treatment guidelines nationally and internationally or cultural, economic or regulatory differences that may play a role in a clinician's decision-making process etc. (AACAP, 2009:962; Vitiello, 2012:16).

Of all the patients 18 years and younger, those who received treatment for ADHD showed the highest increase in the use of CNS medication from 2005 to 2013. Additionally, a 0.08% increase in the prescribing of CNS medication to children and adolescents with ADHD from 2005 to 2013 was found. A possible explanation for this finding might be that comorbidities are increasingly being recognised in patients with ADHD, and that ADHD without comorbidity is viewed as the exception rather than the rule (Jarret & Ollendick, 2008:1276). Increased awareness and changing diagnostic guidelines may explain this finding (AAP, 2011:7). On the other hand, there is evidence to suggest that CNS medication may be co-prescribed to address side effects of effective drugs, or to enhance the efficacy of drugs (AACAP, 2009:963).

Females within both the ADHD-CNS and CNS-only groups increased during the study period, with the highest increase observed within the ADHD-CNS group. This finding is in accordance with the study from Betts and colleagues (2014:264), who also reported higher concomitant psychotropic medication use in ADHD females.

The majority of children and adolescents in the ADHD-CNS group were distributed between the > 6 and ≤ 12 years and > 12 and ≤ 18 years age groups. This could be due to increasing demands for academic performance and age-inappropriate discipline required by children in

structured settings (Magellan Health, Inc., 2013:2). The majority of children and adolescents in the CNS-only group were in the $> 12 \leq 18$ years age groups.

Antidepressants (41.54%) were the most common CNS medication prescribed to children and adolescents within the ADHD-CNS group, among which the SSRIs (20.99%) were the most frequently prescribed pharmacological class. Depression is considered one of the most common comorbidities of ADHD (Elia *et al.*, 2008; Ralston, 2004:39; Steinhausen *et al.*, 2006:27) and could explain this finding. Within the antidepressant pharmacological class, the SSRIs (20.99%) were the most frequently prescribed, which is in line with the findings from Beck *et al.* (2005:605) and Betts *et al.* (2014:260), who reported a prevalence rate of 17.8% and 17.6% respectively. Urinary problems, such as nocturnal enuresis, is commonly associated with ADHD children (Robson *et al.*, 1997; Shreeram *et al.*, 2009), and may explain the high percentage of prescriptions for amitriptyline (10%) and imipramine (6.68%) (Rossiter, 2014:482, 483; Snyman, 2014:13).

Anxiolytic agents were the most commonly prescribed to children and adolescents within the CNS-only group (39.12%). This prevalence rate is considerably higher than prevalence rates reported in the literature, and range from 1.9% (Kovess *et al.*, 2015:168) to 4.3% (Ohayon & Lader, 2002:817). It is important to note that the same trend was not reported in all prevalence studies; for example, the CDC (2013) and Olfson *et al.* (2013:378) reported the most common prescribed drug class to be the antidepressants (refer to manuscript 2).

4.3.2.3 The prevalence of potential drug-drug interactions between methylphenidate- or atomoxetine-containing products and other CNS medication on prescriptions

A total number of 1 038 (3.89%) prescriptions contained atomoxetine in a potentially significant level one or two drug-drug interaction combination with other CNS medication. Out of these interactions, 99.63% were for prescriptions containing atomoxetine in combination with selective serotonin reuptake inhibitors (SSRIs). The SSRIs are CYP2D6 inhibitors (O'Donnell & Shelton, 2011:412), the primary enzyme in the liver responsible for the metabolism of atomoxetine (Rossiter, 2014:508). When co-administered, the inhibition of this metabolic enzyme may cause increased plasma concentrations of atomoxetine, and could lead to serious or fatal reactions (e.g. serotonin syndrome) or deterioration of the patient's clinical outcome (O'Donnell & Shelton, 2011:405; Tatro, 2012:213, 214).

In 1.93% ($n = 4\,530$) of prescriptions, methylphenidate was indicated in a potentially significant drug-drug interaction. Approximately 91% of these drug-drug interactions were found on prescriptions for which methylphenidate and tricyclic antidepressants (TCAs) were indicated. According to Tatro (2012:1943), methylphenidate interacts with TCAs (Markowitz & Patrick,

2001:754), causing increased serum concentration of these agents by inhibiting its metabolism via CYP450. Increased serum concentrations of the TCAs may lead to an increased risk of side-effects (Tatro, 2012:1943). This interaction is assigned a significant level 5 drug-drug interactions with possible effects on the patient's clinical outcome (Tatro, 2012:1943).

4.3.2.4 Association of the prevalence of ADHD in families of ADHD children and adolescents

From this study, it was concluded that families of children with ADHD are increasingly being prescribed ADHD treatment (refer to manuscript 1). Although the exact aetiology of ADHD is unknown (Levy, 1991:277; Solanto, 1998:127), previous studies have suggested a number of factors, of which genetic- and environmental factors may play a role (Cortese, 2012:422; Deault, 2010:170; Faraone & Mick, 2010:159; Johnston & Mash, 2001:184; Nigg, 2006:175; Swanson *et al.*, 2007:39). Serotonergic- and dopaminergic genes have previously been implicated in the genetic aetiology of ADHD (Cheuk & Wong, 2006:651; Yang *et al.*, 2007:541), whereas toxic substances (Engel *et al.*, 2010:570), foetal adaptations (Lahti *et al.*, 2006:1171), nutritional factors (Motlagh, 2010:760) etc. can also play a role in its aetiology. In conclusion, our finding may be related to the genetic or environmental aetiology of ADHD.

4.4 Limitations

The following limitations and shortcomings were taken into account when the results and conclusions of this study were evaluated.

External validity was limited, implying that the results could only be generalised to the specific database and study population in the private health sector of South Africa.

Due to the lack of clinical data such as the patient's weight and height, the RDD for methylphenidate and atomoxetine was calculated by using the Centre for Disease Control and Prevention's growth charts for both genders (refer to section 1.4.7).

- Patients for whom gender was not indicated were excluded to ensure the quality of the data.
- Families of patients with ADHD were identified when they were dependents of the same main member number, assuming that all members are in fact biological family.
- The data were subject to the accuracy of the claimed data as processed by service providers, which opened the possibility of faulty or inaccurate claims

4.5 Strengths

The strengths of the study include the following:

- Data from a large, nationally representative pharmaceutical claims dataset with a large number of patients at baseline were used, thereby increasing the power of subgroup analysis.
- Data quality was ascertained by several automated validation processes that were applied in-house by the PBM, such as gate-keeping services, eligibility services, utilisation management services, clinical management services and pricing management along with real-time benefit management.
- The study may contribute to the understanding of ADHD with regard to treatment and comorbidities.
- The possible publication of results in medical journals and conferences can improve healthcare practitioners' knowledge regarding ADHD and CNS disorders comorbid with ADHD. Therefore, it may also improve the current prescribing patterns of ADHD and CNS medicine prescribed to patients by raising awareness of potential drug-drug interactions of polypharmacy with CNS medicine through feedback from the PBM.

4.6 Recommendations

This study recommends that future studies be conducted to investigate the medicine treatment cost of psychiatric comorbidities in ADHD patients. Further research should be done on adherence to ADHD therapy medication use and adherence to medicine treatment of CNS comorbidities in these patients.

4.7 Chapter Summary

Chapter 4 provided a brief summary of the study, including the strengths and limitations of the study as well as recommendations for future studies.

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ANNEXURE A

Diagnostic criteria for ADHD

A: A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterised by (1) and/or (2):

- (1) Six (or more) of the following symptoms of **inattention** have persisted for at least six months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Note: The symptoms are not solely a manifestation of oppositional behaviour, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (aged 17 and older), at least five symptoms are required.

Inattention

- (a) Often fails to pay close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g. overlooks or misses details, work is inaccurate).
 - (b) Often has difficulty sustaining attention in tasks or play activities (e.g. has difficulty remaining focused during lectures, conversations, or lengthy reading).
 - (c) Often does not seem to listen when spoken to directly (e.g. mind seems elsewhere, even in the absence of any obvious distraction).
 - (d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g. starts tasks but quickly loses focus and is easily side-tracked).
 - (e) Often has difficulty organising tasks and activities (e.g. difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganised work; has poor time management; fails to meet deadlines).
 - (f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework; for older adolescents and adults; preparing reports, completing forms, reviewing lengthy papers).
 - (g) Often loses things necessary for tasks or activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
 - (h) Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
 - (i) Is often forgetful in daily activities (e.g. doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).
- (2) Six (or more) of the following symptoms have persisted for at least six months to a degree that is inconsistent

with developmental level and that negatively impacts directly on social and academic/occupational activities:

Note: The symptoms are not solely a manifestation of oppositional behaviour, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (aged 17 and older), at least five symptoms are required.

Hyperactivity and impulsivity

- (a) Often fidgets with hands or feet or squirms in seat.
- (b) Often leaves seat in situations when remaining seated is expected (e.g. leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
- (c) Often runs about or climbs excessively in situations where it is inappropriate (Note: In adolescents or adults, may be limited to feeling restless).
- (d) Often unable to play or engage in leisure activities quietly.
- (e) Is often 'on the go' acting as if 'driven by a motor' (e.g. is unable to be or uncomfortable being still for extended time, as in restaurants, meetings, may be experienced by others as being restless or difficult to keep up with).
- (f) Often talks excessively
- (g) Often blurts out answers before questions have been completed (e.g. completes people's sentences, cannot wait for turn in conversation).
- (h) Often has difficulty waiting turn (e.g. while waiting in line).
- (i) Often interrupts or intrudes on others (e.g. butts into conversations, games or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

B: Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C: Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g. at home, school, or work; with friends or relatives; in other activities).

D: There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

E: The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:

314.01 (F90.2) Attention-Deficit/Hyperactivity Disorder, Combined Type: if both criterion A1 (inattention) and criterion A2 (hyperactive-impulsivity) have been met for the past six months

314.00 (F90.0) Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if criterion A1

(inattention) has been met, but criterion A2 (hyperactive-impulsivity) has not been met for the past six months

314.01 (F90.1) Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive, Impulsive Type: if criterion A2 has been met and criterion A1 (inattention) has not been met for the past six months

Specify if:

In partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past six months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.

Moderate: Symptoms or functional impairment between 'mild' and 'severe' are present.

Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

ANNEXURE B

Validation processes to ensure the validity and reliability of data

Validation processes: Examples	Validation processes: Examples
Data integrity validation & eligibility management	• Claim field format checks • Provider validation checks • Member validation checks • Verify dependant code • Waiting period check • Duplicate check
Medicine utilisation management (checked at active ingredient level against patient history)	• Refill limits (e.g. 12 fills per year for chronic medication) • Fill limitations per period (e.g. 1 fill per 26 days) • Product quantity limits (e.g. 200 analgesics/365 days) • Products requiring pre-authorisation (e.g. immune-modulating agents) • Patient-specific exclusions (e.g. for pre-existing conditions and general waiting periods) • Pre-existing conditions (e.g. patient specific as advised by scheme) • Drug-to-age range limitations (e.g. RitalinTM and generics will pay for patients 16 years and younger) • Drug-to-gender limitations (e.g. hormone replacement therapy in women) • Invalid prescriber specialty (e.g. DianeTM prescribed by dermatologists) • Broad category exclusions (e.g. soaps/shampoos excluded) • Specific products excluded (e.g. urinary antiseptics) • Waiting periods (e.g. patient specific as advised by scheme)
Clinical management	• Ingredient duplication • Maximum daily dose exceeded • Therapeutic duplication • Drug-drug interactions • Drug-allergy interactions • Drug-age interactions • Drug-gender interactions • Drug-disease interactions • Drug-inferred health state interactions
Pricing management	• Continuous price file maintenance • Apply reference pricing, e.g. generic

	reference pricing and therapeutic reference pricing (i.e. formulary based pricing for chronic diseases)
Formulary management	• Management of Chronic Disease List prescribed minimum benefits and non-chronic disease list conditions • Daily real-time benefit validation

ANNEXURE C

Pharmaceutical classification of central nervous system medication

Pharmaceutical classification	
1.1. Central nervous system stimulants	Central analeptics 1.1.1. Respiratory stimulants 1.1.2. Others
1.2. Sedative hypnotic agents	1.2.1. Benzodiazepines 1.2.2. Barbiturates 1.2.3. Others
1.3. Anxiolytic agents	1.3.1. Benzodiazepines 1.3.2. Others
1.4. Anti-depressants	1.4.1. Tricyclic 1.4.2. Non-Tricyclic 1.4.3. Mono-Amine Oxidase inhibitors 1.4.3.1. Non-selective mono-amine oxidase inhibitors 1.4.3.2. Selective mono-amine oxidase inhibitors 1.4.4. Selective serotonin re-uptake inhibitors 1.4.5. Serotonin and noradrenaline re-uptake inhibitors 1.4.6. Lithium 1.4.7. Others
1.5. Anti-psychotic agents	1.5.1. Phenothiazines 1.5.2. Butyrophenones 1.5.3. Others
1.6. Anti-epileptic agents	-

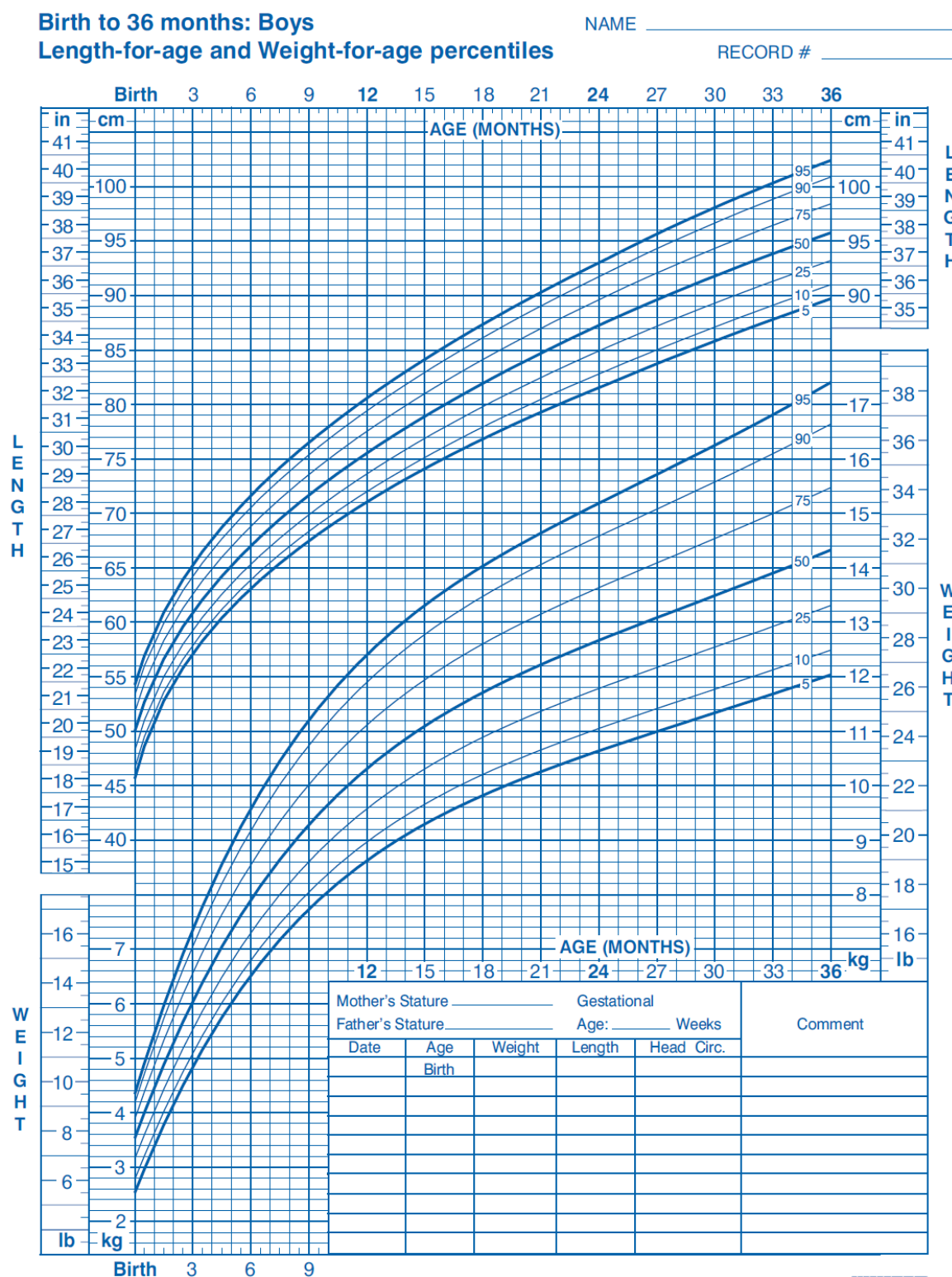
ANNEXURE D

Tatro's significance ratings for drug-drug interactions

Significance rating	Severity	Documentation
1	Major	Suspected or >
2	Moderate	Suspected or >
3	Minor	Suspected or >
4	Major/Moderate	Possible
5	Minor	Possible
	Any	Likely

ANNEXURE E

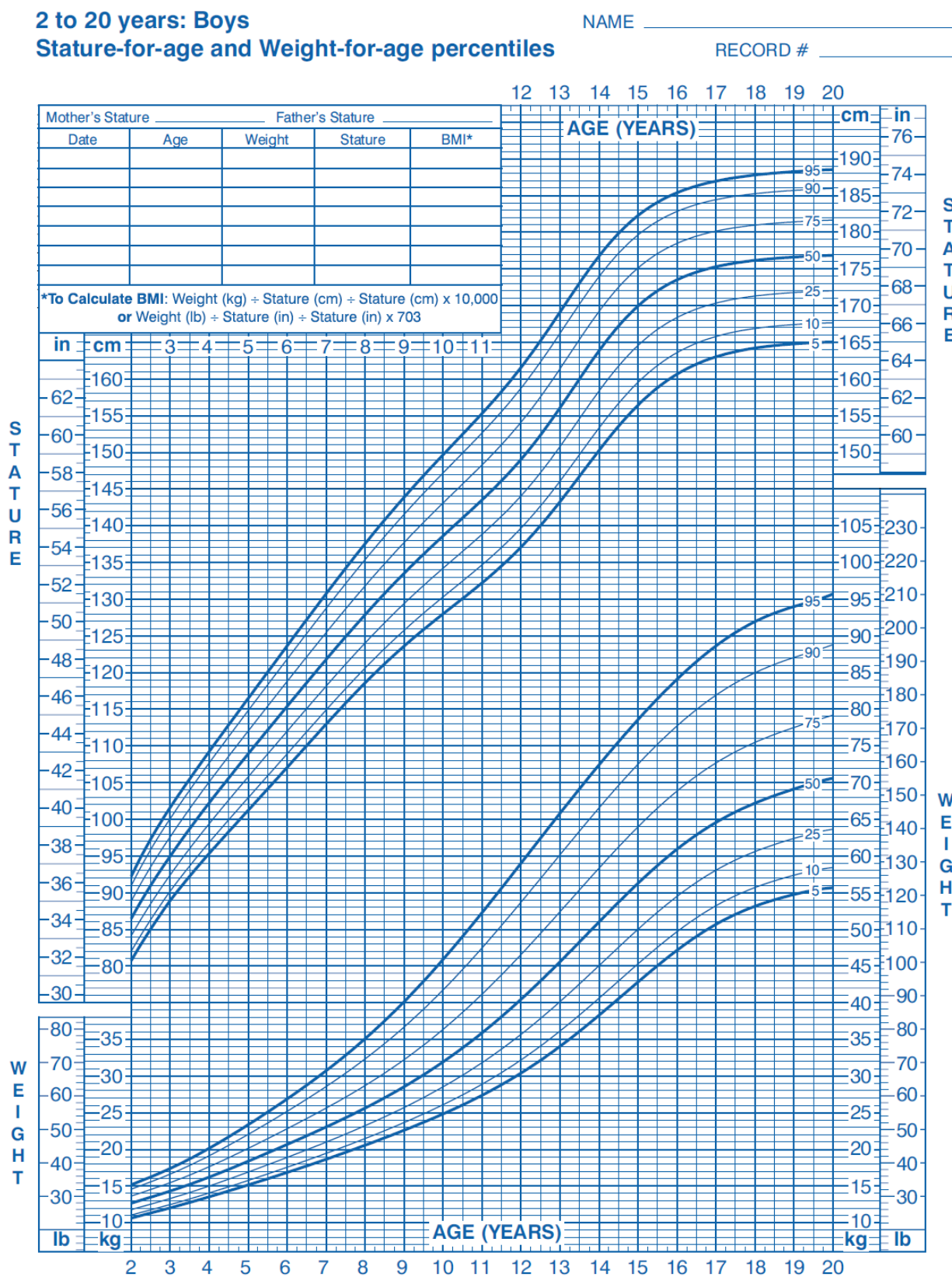
Figure 1: CDC Growth chart for boys (birth to 36 months)



Published May 30, 2000 (modified 4/20/01).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
<http://www.cdc.gov/growthcharts>



Figure 2: CDC Growth chart for boys aged 2 to 20 years



Published May 30, 2000 (modified 11/21/00).

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
<http://www.cdc.gov/growthcharts>



SAFER • HEALTHIER • PEOPLE™

Birth to 36 months: Girls

NAME _____ RECORD # _____

Length-for-age and Weight-for-age percentiles

The growth chart displays two sets of percentile curves for girls aged 0 to 36 months. The top section shows Length-for-Age Percentiles, with the y-axis ranging from 15 to 41 inches (cm) and the x-axis representing Age in Months. The bottom section shows Weight-for-Age Percentiles, with the y-axis ranging from 2 to 16 kg (lb) and the x-axis representing Age in Months. Both sections include percentile curves at 5%, 10%, 25%, 50% (median), 75%, 90%, and 95%. A vertical dashed line indicates the child's current age.

L E N G T H

W E I G H T

AGE (MONTHS)

Mother's Stature _____
Father's Stature _____

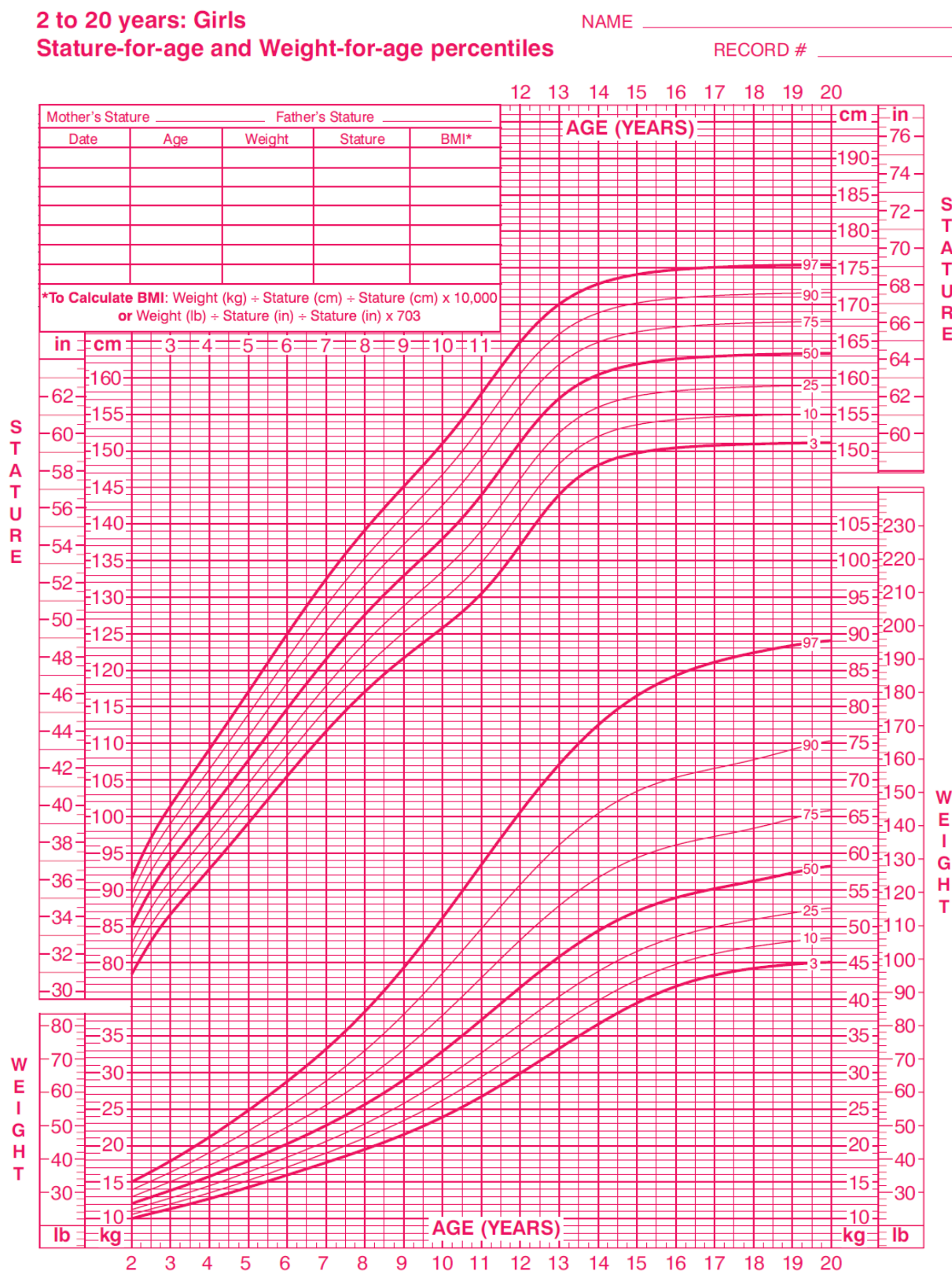
Gestational Age: _____ Weeks

Date	Age Birth	Weight	Length	Head Circ.	Comment

Published May 30, 2000 (modified 4/20/01).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
National Institutes for Clinical Research, Prevention and Health Promotion ©2000

CDC

Figure 4: CDC Growth chart for girls aged 2 to 20 years



Published May 30, 2000 (modified 11/21/00).

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
<http://www.cdc.gov/growthcharts>



ANNEXURE F

Drug-drug interactions of methylphenidate and atomoxetine with other central nervous system medication

Pharmacological classification	Subclass	Drug	Significance rating	
			Methylphenidate	Atomoxetine
Antidepressants	Tricyclic antidepressants (TCAs)	Amitriptyline	5 (Tatro, 2012:1943)	No interaction
		Amoxapine		
		Imipramine		
		Clomipramine		
		Desipramine		
		Doxepin		
		Dothiepin		
		Lofepramine		
		Maprotiline		
		Nortriptyline		
		Protriptyline		
		Trimipramine		

Pharmacological classification	Subclass	Drug	Significance rating	
			Methylphenidate	Atomoxetine
Antidepressants	Monoamine Oxidase Inhibitors (MAOIs)	Tranylcypromine	1 (Tatro, 2012:1235)	1 (Tatro, 2012:213)
		Moclobemide		
		Isocarboxazid		
		Phenelzine		
		Selegiline		
	Selective Serotonin Reuptake Inhibitors (SSRIs)	Fluoxetine	No interaction	2 (Tatro, 2012:214)
		Paroxetine		
		Fluvoxamine		
		Citalopram		
		Escitalopram		
		Sertraline		
Antiepileptic agents	Hydantoin derivatives	Phenytoin	4 (Tatro, 2012:955)	No interaction
		Fosphenytoin		
	Carboxamides	Carbamazepine	4 (Tatro, 2012:1233)	No interaction
		Oxcarbazepine		

ANNEXURE G

Author Guidelines - Journal of Clinical Pharmacy and Therapeutics

1. General

The *Journal of Clinical Pharmacy and Therapeutics (JCPT)* provides a forum for clinicians, pharmacists and pharmacologists to explore and report on issues of common interest. It welcomes five main types of articles

- Editorials
- Original research
- Review articles (including Mini-reviews)
- Commentaries
- Case reports

As our main interest is on novelty, irrespective of the type of contribution, the sub-headings should identify what is known and what is new. A clear description of these aspects is important as they are used by us to filter submissions at the very first stage. This helps us to return manuscripts quickly to authors for submission elsewhere.

Please read the instructions below carefully for details on the submission of manuscripts, the Journal's requirements and standards as well as information concerning the procedure after a manuscript has been accepted for publication in *JCPT*.

2. Ethical Guidelines

JCPT has adopted the following ethical guidelines for publication and research.

2.1 Authorship and Acknowledgements

Authorship: Authors submitting a paper do so on the understanding that the manuscript has been read and approved by all authors and that all authors agree to the submission of the manuscript to the Journal.

JCPT adheres to the definition of authorship set up by The International Committee of Medical Journal Editors (ICMJE). According to the ICMJE authorship criteria, all named authors should meet the following conditions: 1) substantial contributions to conception and design of, or acquisition of data or analysis and interpretation of data, 2) drafting the article or revising it critically for important intellectual content and 3) final approval of the version to be published. Participation solely in the acquisition of funding or the collection of data does not justify authorship. All people who fulfil the criteria for authorship should be listed as authors. Contributors who do not qualify as authors should be mentioned in Acknowledgements.

The Editors recognise that complex, large-scale and multi-centre research will often result in a significant number of people fulfilling the authorship criteria. However, they reserve the right to ask the lead author to justify the inclusion of more than six authors.

Acknowledgements: Under Acknowledgements please specify contributors to the research/article other than the authors accredited. Please note that research funders are now listed separately under Source of Funding.

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JCPT requires that sources of financial support for the work reported within the manuscript are fully acknowledged, and any potential conflicts of interest noted.

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Source of Funding: Authors are required to specify the sources of funding for their research when submitting a manuscript. These include the individuals and organisations that supplied resources for interventions as well as those that funded researcher time and other research costs. All sources of funding should be named and their location (town, state/county, country) included. The information should be provided on the title page of the manuscript and will be disclosed in the published article.

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The Editors make careful judgements about the selection of manuscripts for publication, taking into account the extent to which the manuscript is consistent with the aims and scope of the Journal and their own and referees' assessments of the quality of the work and the contribution it is likely to make to knowledge, policy and practice. We are able to accept only a proportion of the manuscripts that are submitted to the Journal, and recognise that authors are often disappointed when we decline to publish their manuscripts. We strongly discourage routine appeals against such decisions. Authors who believe there were serious flaws in our editorial judgement may appeal decisions by e-mailing the editorial office with a detailed explanation of their concerns.

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4. Manuscripts Types Accepted

Original research: Reports in this section should have a structured summary and a main text, both of which must have the following sub-headings: What is known and Objective; Methods; Results and discussion; What is new and Conclusion.

The maximum word-length for reports of original research is 3000 words excluding tables, figures, references and summary. We encourage submission of additional supporting material for online-only publication but this should be clearly identified and labeled as 'Online appendix A1' etc. within the text.

Review articles: These contributions should have a structured summary and a main text both of which must have the following sub-headings: What is known and Objective; Methods; Results and discussion; What is new and Conclusion. **If your review is not a systematic review, then it should be submitted as a commentary. A mini-review can be submitted either as a commentary or as a systematic review depending on the methodology used.**

The maximum word-length for a Review is 5000 words excluding tables, figures, references and summary. A mini-review is by definition shorter than this but we impose no specific word-length.

We encourage submission of additional supporting material for online-only publication but this should be clearly identified and labeled as 'Online appendix A1' etc. within the text.

Commentaries: A commentary should have:

- (i) a structured summary of no more than 150 words with the following subheadings: What is known and Objective; Comment; What is new and Conclusion.
 - (ii) a main text with the same sub-headings as the summary but with a maximum of 2000 words excluding references.
- In both the summary and the main text, the Comment section should make up the bulk of the contribution (> 90%).

Editorials: Generally these are contributed by our own Editors to describe specific developments at the Journal but may also include invited contributions from leading experts on highly topical subjects for which the novelty is obvious. These expert contributions may vary considerably in length and style so as to ensure particularly rapid publication.

Case reports: A case report should have:

- (i) a summary of not more than 100 words
- (ii) a main text of not more than 1500 words excluding references.

Both sections should have the following sub-headings: What is known and objective; Case description; What is new and Conclusion. In both sections the case-description should make up the bulk (> 90%) of the contribution. We encourage submission of additional supporting material for online-only publication but this should be clearly identified and labelled as 'Online appendix A1' etc. within the text.

Letters: Correspondence is invited. Letters will only be considered if they contain constructive comments on published articles and if they are received in time to allow the authors a right of reply. Publication of correspondence is at the discretion of the Editor.

5. Manuscript Format and Structure

5.1 Format

Language: The language of publication is English. Authors for whom English is a second language should have their manuscript professionally edited by an English speaking person before submission to make sure the English is of high quality. A list of independent suppliers of editing services can be found at http://authorservices.wiley.com/bauthor/english_language.asp. All services are paid for and arranged by the author, and use of one of these services does not guarantee acceptance or preference for publication.

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The typescript should be on A4 paper on one side only, double spaced with a wide margin on each side. The title and short title (to be printed at the head of alternate pages), authors' names, qualifications and the department(s) where the work was carried out, and the name and full postal address of the author to whom all correspondence should be sent, should be typed on a separate sheet. Please include a telephone, a fax number and an e-mail address.

5.2 References

The Journal follows the Vancouver style.

References should be numbered sequentially as they occur in the text and identified in the main text by numbers in superscript after the punctuation. The reference list should be prepared on a separate sheet from the main text, and references should be listed numerically. The following are examples of the style.

1. Finkelstein E, Quintillani R, Lee R, Bracci A, Nightingale CH. Pharmacokinetics of oral cephalosporins: cephadrine and cephalixin. *Journal of Pharmaceutical Sciences*, 1978; 67, 1447-1450.
2. Aikawa R, Nakamo M, Arita TC. Fluorimetric determination of cephalixin in urine. *Chemical and Pharmaceutical Bulletin*, 1976; 24, 235-2355.

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We recommended the use of a tool such as Reference Manager for reference management and formatting. Reference Manager reference styles can be searched for here: <http://www.refman.com/support/rmstyles.asp>.

5.3 Figures and Tables

Figures: All graphs, drawings and photographs are considered figures and should be numbered in Arabic numerals e.g. Fig. 1, Fig. 2, etc. in order of appearance. Each figure should have a legend and all legends should be typed together on a separate sheet and numbered correspondingly. If all or parts of previously published illustrations are used, permission must be obtained from the copyright holder concerned. It is the author's responsibility to obtain these in writing and provide copies to the Publisher.

In the full-text online edition of the Journal figure legends may be truncated in abbreviated links to the full screen version. Therefore the first 100 characters of any legend should inform the reader of key aspects of the figure.

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ANNEXURE H

Author Guidelines – Pharmacoepidemiology and drug safety

1. AIMS AND SCOPE

The aim of *Pharmacoepidemiology and Drug Safety* is to provide an international forum for the communication and evaluation of data, methods and opinion in the discipline of pharmacoepidemiology, defined broadly.

Particular areas of interest include:

- design, analysis, results, and interpretation of studies looking at the benefit or safety of specific pharmaceuticals, biologics, or medical devices, including studies in pharmacovigilance, postmarketing surveillance, pharmacoeconomics, patient safety, molecular pharmacoepidemiology, or any other study within the broad field of pharmacoepidemiology;
- comparative effectiveness research relating to pharmaceuticals, biologics, and medical devices. Comparative effectiveness research is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, as these methods are truly used in the real world;
- methodologic contributions of relevance to pharmacoepidemiology, whether original contributions, reviews of existing methods, or tutorials for how to apply the methods of pharmacoepidemiology;
- assessments of harm versus benefit in drug therapy;
- patterns of drug utilization;
- relationships between pharmacoepidemiology and the formulation and interpretation of regulatory guidelines;
- evaluations of risk management plans and programmes relating to pharmaceuticals, biologics and medical devices.

2. MANUSCRIPT CATEGORIES

Pharmacoepidemiology and Drug Safety invites the following types of submission:

Original Reports

Original Reports are the Journal's primary mode of scientific communication. Original Reports typically do not exceed **3000** words of body text, excluding abstract, tables, figures and references.

Reviews

Reviews of 'hot topics', controversies, and pharmacoepidemiologic methods are welcome. Reviews should be of a critical nature, discussing all sides of a question in a balanced manner. Experts considering offering such a review should feel free to contact one of the Regional Editors, as appropriate, in order to avoid unnecessary effort. All reviews will be peer-reviewed. Reviews typically should not exceed **3000** words of body text (excluding abstract, figures, tables and references), and be limited to **150** references.

Brief Reports

Succinct data papers, and in highly unusual situations case reports (*Pharmacoepidemiol Drug Saf* 2007; **16** :473), will be considered for publication as Brief Reports. Brief Reports should not exceed **1500** words excluding abstract, and be limited to 1 table, 1 figure and **15** references.

Commentaries

Commentaries cover a variety of topics of current interest in pharmacoepidemiology and pharmacovigilance, and the intersection between these disciplines and society. The Journal welcomes submissions and proposals. Commentaries are limited to **1500** words and **15** references. No abstract is required for a commentary.

Letters to the Editor

Letters to the Editor are encouraged, and may be in response to issues arising from recently published articles, or short, free-standing pieces expressing an opinion. No abstract is required, and text should be formatted in one continuous section. Letters are limited to 1000 words.

Research Protocol

PDS does not ordinarily publish study protocols without results. Rather, we strongly recommend that investigators post their research protocols in a publicly available archive such as [ClinicalTrials.gov](http://clinicaltrials.gov/) (<http://clinicaltrials.gov/>) or ENCePP (<http://www.encepp.eu/encepp/studiesDatabase.jsp>) and ask that they describe that posting in their manuscripts submitted to PDS. However, in unusual circumstances, PDS will consider publishing descriptions of the design and rationale of pharmacoepidemiologic studies, before study results are available. Characteristics of such descriptions that support consideration for publication include:

- the study is of unusually high public health importance and interest to the readership of PDS
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The format for the manuscript should be: Introduction, Design and Research Plan, Results (optional), and Discussion. Data describing the study population recruited can be included, if available, in the Results section of the publication. Please select 'Research Protocol' as the category for submission of the manuscript. The remainder of the format should be the same as that of Original Articles.

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The first page of the manuscript should contain the following information:

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- names of the institutions at which the research was conducted;
- name, address, telephone and fax number, and email address of corresponding author;
- 2–6 article keywords;
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Authors should note that structured abstracts (maximum **250** words) are required. The structured abstract should adopt the format: Purpose, Methods, Results, Conclusions. Abstracts should not contain citations to other published work.

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This should in general, but not necessarily, be divided into sections with the headings: Introduction, Methods, Results, Discussion.

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- Emerson A, Martin RM, Tomlin M, *et al.* Prospective cohort study of adverse events monitored by hospital pharmacists. *Pharmacoepidemiol Drug Saf* 2001; 10: 85–92. DOI:10.1002/pds.574
- Meichenbaum D and Turk D. *Facilitating Transplant Adherence: A Practitioner's Guide*. Plenum Press: New York, NY, 1987;44.
- Cramer JA and Mattson RH. Monitoring compliance with antiepileptic drug therapy. In *Patient Compliance in Medical Practice and Clinical Trials*. Cramer JA and Spiker B (eds). Raven Press: New York, NY, 1991; 123–138.
- FDA. Guidance for industry. Premarketing risk assessment. FDACDER/CBER, Rockville; March 2005. <http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0187-gdl0002.pdf> (accessed 1 January 2007).

Supporting Information

Supplementary materials are not proofed, so the contents should be considered final at the time the manuscript is accepted. Appendices will be treated as supplementary materials, so will be published online only as well. Supplementary files or appendices should be uploaded separately as Supplementary Material for Review.

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