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

S de Villiers

22116966

BPharm

Dissertation submitted in partial fulfilment of the requirements for the degree Magister Pharmaciae at the Potchefstroom campus of the North-West University

Supervisor: Prof MS Lubbe
Co-supervisors: Dr JR Burger
               Prof I Truter

October 2015
ACKNOWLEDGEMENTS

I thank our heavenly Father for the opportunity to have studied and completed my MPharm degree, and for providing me with the self-discipline and capability I needed to persevere and succeed.

Thank you to my parents, Johan and Heloise van Tonder. Without the example you set for me through your continuous hard work, I would not have been able to come this far. Thank you for always helping me achieve my goals, motivating me, having faith in me, and waiting for me at the finish line. It is your prayers that guided me through this dissertation.

Thirdly, to my husband, Braam de Villiers. Thank you for all your constant support and motivation from the beginning to the end.

I would like to acknowledge the following people for their hard work and time they sacrificed in completing this study.

- To my supervisor, Prof MS Lubbe, thank you for your patience, time and effort.
- To Dr JR Burger, in her capacity as co-supervisor of this study for your support and for your excellent explaining skills.
- To Prof I Truter for your expertise regarding ADHD.
- To Mrs M Cockeran for your expertise in the statistical analysis.
- To Mrs E Oosthuizen for your help with technical editing of the dissertation.
- To Ms A Bekker for your assistance with the analysis of the data and administrative support regarding the database.
- To Ms A Pretorius for all your help regarding references
- To Mrs C van Zyl for the language editing of the dissertation.
- To all my friends. Thank you for your support, friendship, and completing the race with me.
- The National Research Fund, for financial support.
- The Pharmaceutical Benefit Management company for providing the database for this dissertation.
“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

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AACAP</td>
<td>American Academy of Child and Adolescent Psychiatry</td>
</tr>
<tr>
<td>AAP</td>
<td>American Academy of Pediatrics</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention-Deficit/Hyperactivity Disorder</td>
</tr>
<tr>
<td>AMPA</td>
<td>α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid</td>
</tr>
<tr>
<td>ANOVA</td>
<td>One-way analysis of variance</td>
</tr>
<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
</tr>
<tr>
<td>ASD</td>
<td>Autism spectrum disorder</td>
</tr>
<tr>
<td>BPA</td>
<td>Bisphenol A</td>
</tr>
<tr>
<td>CD</td>
<td>Conduct disorder</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CDL</td>
<td>Chronic Disease List</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COMT</td>
<td>Catechol-O-methyltransferase</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>DA</td>
<td>Dopamine</td>
</tr>
<tr>
<td>DAT</td>
<td>Dopamine Transporter</td>
</tr>
<tr>
<td>DCD</td>
<td>Developmental co-ordination disorder</td>
</tr>
<tr>
<td>DEHP</td>
<td>di (2-ethylhexyl) phthalate</td>
</tr>
<tr>
<td>DRD2</td>
<td>Dopamine D2 receptor</td>
</tr>
<tr>
<td>DRD4</td>
<td>Dopamine D4 receptor</td>
</tr>
<tr>
<td>DRD5</td>
<td>Dopamine 5 receptor</td>
</tr>
<tr>
<td>DSM-V</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, version-5</td>
</tr>
<tr>
<td>DUR</td>
<td>Drug Utilisation Research</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GABA</td>
<td>γ-aminobutyric acid</td>
</tr>
<tr>
<td>GAD</td>
<td>General Anxiety disorder</td>
</tr>
<tr>
<td>H</td>
<td>Histamine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>ICD10</td>
<td>International Classification of Diseases, 10th Revision</td>
</tr>
<tr>
<td>LD</td>
<td>Learning Disabilities</td>
</tr>
<tr>
<td>MAO</td>
<td>Monoamine Oxidase enzyme</td>
</tr>
<tr>
<td>MAOI</td>
<td>Monoamine Oxidase Inhibitor</td>
</tr>
<tr>
<td>MUSA</td>
<td>Medicine Usage in South Africa</td>
</tr>
<tr>
<td>NE</td>
<td>Norepinephrine/ Noradrenalin</td>
</tr>
<tr>
<td>NET</td>
<td>Norepinephrine transporter</td>
</tr>
<tr>
<td>OCD</td>
<td>Obsessive compulsive disorder</td>
</tr>
<tr>
<td>ODD</td>
<td>Oppositional defiant disorder</td>
</tr>
<tr>
<td>PAH</td>
<td>Polycyclic aromatic hydrocarbon</td>
</tr>
<tr>
<td>PBM</td>
<td>Pharmaceutical Benefit Management company</td>
</tr>
<tr>
<td>PDD</td>
<td>Prescribed daily dose</td>
</tr>
<tr>
<td>PFC</td>
<td>Poly-fluoroalkyl chemical</td>
</tr>
<tr>
<td>PMB</td>
<td>Prescribed Minimum Benefits</td>
</tr>
<tr>
<td>PTSD</td>
<td>Post-traumatic stress disorder</td>
</tr>
<tr>
<td>RD</td>
<td>Reading disability</td>
</tr>
<tr>
<td>RDD</td>
<td>Recommended daily dose</td>
</tr>
<tr>
<td>SAD</td>
<td>Social anxiety disorder</td>
</tr>
<tr>
<td>SAMF</td>
<td>South African Medicines Formulary</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical Analysis System® program</td>
</tr>
<tr>
<td>SERT</td>
<td>Serotonin transporter</td>
</tr>
<tr>
<td>SES</td>
<td>Socio-economic status</td>
</tr>
<tr>
<td>SNAP25</td>
<td>Synaptosomal Associated Protein of 25Kd</td>
</tr>
<tr>
<td>SNRI</td>
<td>Serotonin and norepinephrine re-uptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>SUD</td>
<td>Substance use disorder</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic antidepressant</td>
</tr>
<tr>
<td>TD</td>
<td>Tic disorder</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>5-HT</td>
<td>5-Hydroxytryptamine</td>
</tr>
</tbody>
</table>
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 familiere neigings ten opsigte van metielfenidaat- en atomoksitien-verbruik. ’n Retrospektiewe, longitudinale studie is uitgevoer wat medikasie-eise-data van ’n nasionale verteenwoordigende farmaseutiese voordelebestuursmaatskappy analyseer 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 geanalyser is, was daar ’n toename vanaf 2005 (14.94%) tot 2013 (29.09%). ADHD-kinders en -adolessente wat ook voorskrifte ontvang vir ander SSS-medikasie, het hoër gemiddelde voorgeskrewe daaglike dosisse (VDD) ontvang as ADHD-kinders en -adolessente wat nie enige SSS-medikasie ontvang nie. Die hoogste hoeveelheid metielfenidaat- (16.69%) en atomoksitien-bevattende (13.75%) items wat die voorgeskrewe daaglike 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-kinders en -adolessente wat SSS-medikasie gebruik, het toegeneem, terwyl die voorskrif van slegs SSS-medikasie vir kinders en adolessente afgeneem het. Antidepressante was die mees algemene SSS-aktiewe bestanddeel voorgeskrif aan ADHD-kinders, en die 41.51% van alle SSS-voorskrifte uitgemaak. Tussen die antidepressante is die selektiewe serotonin-heropname-inhibeerders (SSHI) meeste voorgeskrif (20.99%). Die mees algemene voorgeskrewe SSS-medikasie voorgeskryf aan nie-ADHD-kinders 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.

viii
Ten slotte het hierdie studie die voorkomsstatistieke van ADHD in Suid-Afrikaanse kinders en adolessente, sowel as die voorkoms van SSS-mediakasiegebruik 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 voorskrippatrone in kinders en adolessente is bepaal. Metielfenidaat- en atomoksitien voorskrippatrone 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-mediakasiegebruik tussen ADHD- en nie-ADHD-kinders en -adolessente met spesifieke verwysing na ouderdoms- en geslagsgroepe en die mees algemene voorgeskrewe SSS-mediakasie 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-mediakasie.

**SLEUTELWOORDE:** Aandaggebrek-hyperaktiwiteitsteuring, kinders, adolessente, familie, sentrale senuweestelselmedikasie, potensiële geneesmiddel-geneesmiddel-interaksies
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:

<table>
<thead>
<tr>
<th>Author</th>
<th>Role in studies</th>
</tr>
</thead>
</table>
| 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

Dr JR Burger

Prof I Truter

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:

<table>
<thead>
<tr>
<th>Author</th>
<th>Role in studies</th>
</tr>
</thead>
</table>
| 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     Dr JR Burger

_________________________  ________________________
Prof I Truter      Mrs M Cockeran
TABLE OF CONTENTS

ACKNOWLEDGEMENTS ........................................................................................................... I
LIST OF ACRONYMS .................................................................................................................. III
ABSTRACT AND KEYWORDS ...................................................................................................... VI
OPSOMMING EN SLEUTELWOORDE ........................................................................................... VIII
PREFACE ..................................................................................................................................... X
AUTHORS’ CONTRIBUTIONS (MANUSCRIPT 1) ....................................................................... XI
AUTHORS’ CONTRIBUTIONS (MANUSCRIPT 2) ....................................................................... XIII

CHAPTER 1: INTRODUCTION AND SCOPE OF STUDY ................................................................. 1
1.1 Introduction .......................................................................................................................... 1
1.2 Background and problem statement .................................................................................... 1
1.3 Research aims and objectives ............................................................................................. 3
1.3.1 Research aim .................................................................................................................. 3
1.3.2 Research objectives ........................................................................................................ 4
1.3.2.1 Specific research objectives: Literature review .......................................................... 4
1.3.2.2 Specific research objectives: Empirical investigation .................................................. 4
1.4 Research methodology ....................................................................................................... 5
1.4.1 Phase one: Literature review .......................................................................................... 5
1.4.2 Phase two: Empirical investigation .................................................................................. 5
1.4.3 Research design .............................................................................................................. 5
1.4.4 Data source .................................................................................................................... 6
1.4.5 Target population .......................................................................................................... 10
1.4.6 Study population .......................................................................................................... 10
1.4.6.1 Selection of study population .................................................................................. 10
1.4.7 Study variables.......................................................... 12
1.4.7.1 Independent variables ............................................. 12
1.4.7.1.1 Age.......................................................................... 12
1.4.7.1.2 Gender ..................................................................... 13
1.4.7.1.3 Different diagnoses groups ...................................... 13
1.4.7.2 Dependent variables.................................................. 13
1.4.7.2.1 Prevalence ............................................................... 13
1.4.7.2.2 Number of prescriptions dispensed......................... 14
1.4.7.2.3 Number of medicine items dispensed ..................... 14
1.4.7.2.4 Prescribed daily dose .............................................. 14
1.4.7.2.5 Potential drug-drug interactions ............................. 16
1.5 Data analysis................................................................. 17
1.5.1 Descriptive statistics.................................................... 18
1.5.1.1 Frequency ................................................................. 18
1.5.1.2 Average (arithmetic mean) ......................................... 18
1.5.1.3 Standard deviation..................................................... 18
1.5.1.4 Confidence Interval................................................... 19
1.5.1.5 Ratio ......................................................................... 19
1.5.2 Inferential statistics...................................................... 19
1.5.2.1 The $t$-test ................................................................. 19
1.5.2.2 Chi-square test .......................................................... 20
1.5.2.3 ANOVA..................................................................... 21
1.6 Ethical considerations ..................................................... 21
1.7 Chapter summary........................................................................................................... 22

CHAPTER 2: LITERATURE REVIEW ..................................................................................... 23
2.1 Introduction .................................................................................................................. 23
2.2 ADHD definition ......................................................................................................... 23
2.3 Aetiology of ADHD .................................................................................................... 24
  2.3.1 Presence of dopaminergic deficits: brain size ......................................................... 24
  2.3.2 Genetic aetiologies of dopaminergic deficits ......................................................... 24
  2.3.3 Environmental factors of dopaminergic deficits .................................................. 25
2.4 Epidemiology of ADHD ............................................................................................. 26
  2.4.1 The influence of gender on prevalence ................................................................. 27
  2.4.2 The influence of age on prevalence ....................................................................... 28
  2.4.3 Ethnic characteristics ........................................................................................... 29
  2.4.4 Socio-economic status .......................................................................................... 30
2.5 Treatment of ADHD .................................................................................................. 30
  2.5.1 Methylphenidate ................................................................................................. 30
    2.5.1.1 Mechanism of action ....................................................................................... 30
    2.5.1.2 Indications ....................................................................................................... 30
    2.5.1.3 Recommended daily dose (RDD) ................................................................. 31
    2.5.1.4 Potential drug-drug interactions ..................................................................... 31
  2.5.2 Atomoxetine ......................................................................................................... 32
    2.5.2.1 Mechanism of action ....................................................................................... 32
    2.5.2.2 Indications ....................................................................................................... 32
    2.5.2.3 Recommended daily dose (RDD) .................................................................. 32
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5.2.4</td>
<td>Potential drug-drug interactions</td>
<td>32</td>
</tr>
<tr>
<td>2.6</td>
<td>Central nervous system comorbidities/co-existing disorders associated with ADHD</td>
<td>32</td>
</tr>
<tr>
<td>2.6.1</td>
<td>Oppositional defiant disorder (ODD) and conduct disorder (CD)</td>
<td>34</td>
</tr>
<tr>
<td>2.6.2</td>
<td>Depression</td>
<td>35</td>
</tr>
<tr>
<td>2.6.3</td>
<td>Anxiety disorders</td>
<td>37</td>
</tr>
<tr>
<td>2.6.4</td>
<td>Autism spectrum disorder (ASD)</td>
<td>38</td>
</tr>
<tr>
<td>2.6.5</td>
<td>Tic disorders (TD)</td>
<td>39</td>
</tr>
<tr>
<td>2.6.6</td>
<td>Substance use disorders (SUD)</td>
<td>39</td>
</tr>
<tr>
<td>2.6.7</td>
<td>Obsessive compulsive disorder (OCD)</td>
<td>41</td>
</tr>
<tr>
<td>2.6.8</td>
<td>Developmental co-ordination disorder (DCD)</td>
<td>42</td>
</tr>
<tr>
<td>2.6.9</td>
<td>Specific learning disorder</td>
<td>42</td>
</tr>
<tr>
<td>2.7</td>
<td>Other central nervous system medication</td>
<td>43</td>
</tr>
<tr>
<td>2.7.1</td>
<td>Central nervous system stimulants</td>
<td>43</td>
</tr>
<tr>
<td>2.7.1.1</td>
<td>Central analeptics</td>
<td>43</td>
</tr>
<tr>
<td>2.7.1.2</td>
<td>Respiratory stimulants</td>
<td>44</td>
</tr>
<tr>
<td>2.7.1.3</td>
<td>Others</td>
<td>44</td>
</tr>
<tr>
<td>2.7.2</td>
<td>Sedative hypnotic- and anxiolytic agents</td>
<td>44</td>
</tr>
<tr>
<td>2.7.2.1</td>
<td>Benzodiazepine derivatives</td>
<td>44</td>
</tr>
<tr>
<td>2.7.2.2</td>
<td>Barbiturates</td>
<td>45</td>
</tr>
<tr>
<td>2.7.2.3</td>
<td>Others (benzodiazepine-receptor agonists)</td>
<td>45</td>
</tr>
<tr>
<td>2.7.3</td>
<td>Antidepressants</td>
<td>45</td>
</tr>
<tr>
<td>2.7.3.1</td>
<td>Selective serotonin re-uptake inhibitors (SSRIs)</td>
<td>45</td>
</tr>
<tr>
<td>2.7.3.2</td>
<td>Serotonin and norepinephrine re-uptake inhibitors (SNRIs)</td>
<td>46</td>
</tr>
</tbody>
</table>
2.7.3.3 Mono-amine oxidase inhibitors (MAOIs) .......................................................... 47
2.7.3.4 Tricyclic antidepressants (TCAs) ................................................................. 48
2.7.3.5 Tetracyclic antidepressants ............................................................................ 48
2.7.3.6 Noradrenaline and/or dopamine re-uptake inhibitors .................................. 49
2.7.3.7 Melatonergic specific antidepressants .......................................................... 49
2.7.3.8 Lithium ............................................................................................................. 49
2.7.3.9 Others ............................................................................................................. 50
2.7.4 Antipsychotic agents ...................................................................................... 50
2.7.5 Anti-epileptic agents ...................................................................................... 50
2.8 Chapter summary .............................................................................................. 52

CHAPTER 3: RESULTS AND DISCUSSION .................................................................. 53
3.1 Introduction ......................................................................................................... 53
3.2 Manuscript 1 ...................................................................................................... 54
3.3 Manuscript 2 ...................................................................................................... 83
3.4 Chapter summary .............................................................................................. 106

CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS .................................... 107
4.1 Introduction ......................................................................................................... 107
4.2 Content of dissertation ...................................................................................... 107
4.3 Conclusions from the study ............................................................................. 107
4.3.1 Conclusions from the literature review .......................................................... 108
4.3.1.1 Prevalence of ADHD, nationally as well as internationally, stratified by age and gender .......................................................... 108
4.3.1.2 Conceptualise ADHD treatment in children and adolescents .................. 108
4.3.1.3 Prevalence of CNS-related comorbid diseases with regard to ADHD .......... 108
4.3.1.4 Potential drug-drug interactions between methylphenidate- or atomoxetine-containing products and other CNS drugs .................................................. 109
4.3.2 Conclusions from the empirical study objectives........................................ 110
4.3.2.1 Current prescribing patterns of methylphenidate and atomoxetine for children and adolescents with ADHD....................................................... 110
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.. 111
4.3.2.3 The prevalence of potential drug-drug interactions between methylphenidate- or atomoxetine-containing products and other CNS medication on prescriptions .................................................. 112
4.3.2.4 Association of the prevalence of ADHD in families of ADHD children and adolescents ........................................................................................................ 113
4.4 Limitations ....................................................................................................... 113
4.5 Strengths ........................................................................................................ 114
4.6 Recommendations .......................................................................................... 114
4.7 Chapter Summary ............................................................................................. 114
REFERENCES ......................................................................................................... 115
ANNEXURE A ....................................................................................................... 150
ANNEXURE B ....................................................................................................... 153
ANNEXURE C ....................................................................................................... 155
ANNEXURE D ....................................................................................................... 156
ANNEXURE E ....................................................................................................... 157
ANNEXURE F ....................................................................................................... 161
ANNEXURE G ....................................................................................................... 163
ANNEXURE H ....................................................................................................... 170
ANNEXURE H ....................................................................................................... 179
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table 1-1:</th>
<th>Research objectives outlined from the empirical investigation and article in which they are addressed</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1-2:</td>
<td>Checklist to evaluate the validity of the database</td>
<td>8</td>
</tr>
<tr>
<td>Table 1-3:</td>
<td>Inclusion criteria</td>
<td>10</td>
</tr>
<tr>
<td>Table 1-4:</td>
<td>Exclusion criteria</td>
<td>10</td>
</tr>
<tr>
<td>Table 1-5:</td>
<td>Recommended daily dose</td>
<td>16</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

Figure 1-1: Organogram illustrating the different data subsets ........................................ 11
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 worldwide 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 Sates 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 (Mitter 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 other 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

<table>
<thead>
<tr>
<th>Empirical objectives</th>
<th>Article</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>To compare the prescribing patterns of other CNS medication between children and adolescents with treatment for ADHD vs. those without treatment for ADHD</td>
<td>Prescribing patterns of central nervous system medication in South African children and adolescents with/without treatment for ADHD and its potential drug-drug interactions</td>
<td>Prepared for submission in the Pharmacoepidemiology and drug safety</td>
</tr>
<tr>
<td>To determine the prevalence of potential drug-drug interactions between methylphenidate- or atomoxetine-containing products and other CNS medication on prescriptions</td>
<td>Prescribing patterns of central nervous system medication in South African children and adolescents with/without treatment for ADHD and its potential drug-drug interactions</td>
<td>Prepared for submission in the Pharmacoepidemiology and drug safety</td>
</tr>
</tbody>
</table>

### 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>
<thead>
<tr>
<th>Item</th>
<th>Variable</th>
<th>Description</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Database selection</td>
<td>Population covered</td>
<td>Does the resource include an appropriate population in terms of size, coverage and representativeness?</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Capture of study variables</td>
<td>Are all exposures, outcomes and other study variables captured in sufficient detail, without bias, and accessible for research?</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Continuous and consistent data capture</td>
<td>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?</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Record duration and data latency</td>
<td>Is the average patient record duration, and the time between the occurrence of the exposure and data collection, sufficiently long for the study event?</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Database expertise</td>
<td>Is the expertise required to use the resource available: in-house or elsewhere?</td>
<td>Expertise from the personnel from MUSA (Medicine Usage of South Africa) is available in-house.</td>
</tr>
<tr>
<td>Extraction and analysis of the study population</td>
<td>Specification of extraction</td>
<td>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?</td>
<td>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.</td>
</tr>
<tr>
<td>Privacy and security</td>
<td>Compliance with privacy and security policy</td>
<td>Have all relevant local, regional and national policies been complied with?</td>
<td>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.</td>
</tr>
<tr>
<td>Item</td>
<td>Variable</td>
<td>Description</td>
<td>Evaluation</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Limited use of identifying information</td>
<td>Are all direct identifiers removed or masked? Whose responsibility is it to ensure privacy?</td>
<td>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.</td>
</tr>
<tr>
<td>Secure data storage and</td>
<td>Secure data storage and transfer</td>
<td>Is there a formal data security policy, and has this been adhered to?</td>
<td>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.</td>
</tr>
<tr>
<td>transfer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review of policy and</td>
<td>Review of policy and procedures</td>
<td>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?</td>
<td>Data are only available to a person when the study leader of the research group gives her permission and when the contract is renewed.</td>
</tr>
<tr>
<td>procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality and validation</td>
<td>Overall database</td>
<td>Have appropriate general quality checks been completed?</td>
<td>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</td>
</tr>
<tr>
<td>procedures</td>
<td>Study population</td>
<td>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?</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testing</td>
<td></td>
<td>The checks can be external, logical or internal and should be cross-sectional, longitudinal and up to date.</td>
<td>Trade names, spelling etc. will be checked to ensure that all relevant data are extracted.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documentation</td>
<td>Format</td>
<td>Are the rules of Guidelines for Good Pharmacoepidemiology Practices followed, including storage and indexing?</td>
<td>All data will be stored for a period of five to seven years at Medicine Usage of South Africa (MUSA).</td>
</tr>
<tr>
<td></td>
<td>Specifics</td>
<td>Have extraction specification, output, quality testing, merging resources, responsibility for privacy and annotated programming code for data extraction and final analysis been documented?</td>
<td>Yes.</td>
</tr>
</tbody>
</table>
1.4.5 Target population

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

<table>
<thead>
<tr>
<th>Study period</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005-2013</td>
<td>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)</td>
</tr>
</tbody>
</table>

### Table 1-4: Exclusion criteria

<table>
<thead>
<tr>
<th>Study period</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005-2013</td>
<td>Unknown gender and age</td>
</tr>
</tbody>
</table>

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.


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:

\[ p = \frac{\text{number of existing cases in a population}}{\text{total number of people in that population}} \]

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:

\[ PDD = \frac{\text{strength} \times \text{quantity}}{\text{days’ supply}}. \]

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

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Trade name</th>
<th>Recommended daily dose</th>
<th>Maximum RDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>Concerta®</td>
<td>Children: 54 mg/day</td>
<td>72 mg/day</td>
</tr>
<tr>
<td></td>
<td>Methylphenidate HCL-Douglas®</td>
<td>Children: 1 mg/kg/day</td>
<td>60 mg/day</td>
</tr>
<tr>
<td></td>
<td>Ritalin LA Capsules®</td>
<td>Children: 1 mg/kg/day</td>
<td>60 mg/day</td>
</tr>
<tr>
<td></td>
<td>Ritalin Tablets®</td>
<td>Children: 1 mg/kg/day</td>
<td>60 mg/day</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Strattera Capsules®</td>
<td>Children: 1.2 mg/kg/day</td>
<td>60 mg/day</td>
</tr>
</tbody>
</table>

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):

\[
A = \frac{1}{n} \sum_{i=1}^{n} x_i
\]

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
\( \Sigma \) = 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 (\( \chi^2 \)) 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 \( V \):

\[
V = \frac{\sqrt{\chi^2}}{nt}
\]
Where:

\[ V = \text{Cramer's } V \text{ value} \]

\[ x^2 \text{ = chi-square statistic} \]

\[ n = \text{sample size} \]

\[ t = \text{minimum number of rows minus one or the number of columns minus 1} \]

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 VIII IX) 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, serotoninergic 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 polyfluoroalkyl 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. The 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<sub>2A</sub>-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”.

34
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 (Menassi, 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 (Pfliffner & 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.
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, flunitrazepam, 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 & Harrs, 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-HT1A) 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 HT1A and 5-HT7 autoreceptors on cell bodies in the raphe nucleus in the midbrain and of 5-HT1D 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\textsubscript{1A} and 5-HT\textsubscript{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)


TCAs are multi-receptor blockers/inhibitors (H1, 5-HT, α1, 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 α2-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 α₂ antagonist (Pharmacare Limited, 2007; Rossiter, 2014:504). It is also an antagonist at 5-HT₂A, 5-HT₂C 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 chlorpropiophenone 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-HT₂C 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-HT₂C 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 α1-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, thioxanthenes 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 catalysis (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-analogue, 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

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
3.2 Manuscript 1


Authors: S de Villiers¹, MS Lubbe¹, JR Burger¹, I Truter², M Cockeran¹

Institution: ¹Medicine Usage in South Africa, Faculty of Health Sciences, North-West University, Potchefstroom Campus, Potchefstroom, South Africa, 2520.

²Drug Utilization Research Unit, Department of Pharmacy, Nelson Mandela Metropolitan University, Port Elizabeth, South Africa, 6031.

Corresponding author: MS Lubbe

Mailing address: North-West University, Potchefstroom Campus, Private Bag, X6001, Potchefstroom, 2520

Phone: +2718-2992288

E-mail address: Martie.Lubbe@nwu.ac.za

Keywords: Attention-Deficit/Hyperactivity Disorder, children, adolescents, family relationships.

Source of funding: This work was funded by the National Research Foundation and the North-West University, Potchefstroom, South Africa. The funder had no role in the design and conduct of the study, collection, management, analysis, or interpretation of the data and preparation, review, or approval of the manuscript for publication.

Conflict of interest: The authors declare that they have no conflict of interest.
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 dose (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. ADHD is characterised by inattention, hyperactivity and impulsivity. 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. A diagnosis with ADHD requires a good clinical history and examination by a healthcare practitioner with sufficient experience.

The lifetime prevalence for ADHD in Africa is between 5.4% and 8.7% in school children, compared to the worldwide prevalence of 5.3%. 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. Nevertheless, these studies documented a prevalence of approximately 5%, which concurs with the prevalence rates across the world. 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.

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. 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. A study conducted in Nigeria reported a prevalence rate of 8.7% in school children between the ages of six and 12 years. A recent study from South Africa reported that the average age of children and adolescents who received medication for ADHD was 10 years old.

Previous studies have all revealed higher ADHD prevalence rates for males than for females. For example, the CDC reported a male to female ratio of 2:1 in 2014. There are few studies regarding epidemiological data of ADHD in Africa, and prevalence estimates must therefore be carefully interpreted. However, the prevalence of ADHD according to gender among African children is documented to be higher than documented in other regions of the world. For example, in Kinshasa, Democratic Republic of Congo, 45% of a study sample (consisting of 286 school children) were boys and 55% were girls. 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.
Methylphenidate and atomoxetine are the only available pharmacological treatments for ADHD in South Africa.\textsuperscript{15} Methylphenidate is the most commonly used neuro-stimulant,\textsuperscript{15} whilst atomoxetine, exclusively used for ADHD,\textsuperscript{16} is the only FDA-approved non-stimulant indicated for this disorder.\textsuperscript{10,17}

There is limited information on prevalence rates and treatment of ADHD in South Africa.\textsuperscript{9} When considering the chronic\textsuperscript{15,18,19} and genetic\textsuperscript{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. 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), the MIMS®, and the Martindale. The RDD of methylphenidate (for patients < 6 years) and atomoxetine is subject to the weight of children. 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. 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. 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 (\( \chi^2 \)) 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. 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. For practical significance, the following were considered: ≤ 0.2 a small effect, with no significant difference, > 0.2 ≤ 0.5 a medium effect with an observable significance, > 0.8 a large effect and significant difference.

**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 $\leq 18$ years age group and a decreasing trend in the $> 6$ and $\leq 12$ year age group. The effects of these associations were weak (Cramer’s $V = 0.0446$ and Cramer’s $V = 0.0596$) (Table 2).

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.

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).

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 \( \leq 6 \) years age group for both methylphenidate and atomoxetine. The majority of medicine items prescribed for children \( \leq 6 \) years were for products containing 36 mg methylphenidate and 40 mg atomoxetine.

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 \( \leq 18 \) 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 \( (p > 0.0001) \).
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. In Nigeria, the authors reported a 3.2% prevalence estimate of children with ADHD. 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. He reported the ADHD prevalence to range from 5.4% to 8.7% in school-aged children, and 1.5% in the general population. 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.

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, Europe, UK, Oceania and Africa. 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. 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. 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. In Europe, treatment prevalence rates of 2.21% in children and adolescents 18 years and younger were reported. Prevalence estimates of stimulant treatment use in Western Australia were 2.4% (children aged 3 to 18 years) during 2004. In South Africa, Truter documented a 3% treatment prevalence with methylphenidate in children. 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.

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.
This can also be as a result of the different side-effect profiles experienced with atomoxetine. 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. Similarly, atomoxetine is contraindicated for use in ADHD patients with oppositional defiant disorder. 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. Methylphenidate is therefore considered the drug of choice in the treatment of ADHD.

An annual male to female ratio of 3:1 was observed. This trend confirms previous population-based studies, both internationally, as well as in South Africa. Castle and colleagues reported that treatment rates for boys were 2.4 times higher than for girls, which was also confirmed by Solar et al. 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. 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. Moreover, males are more likely to be referred for pharmacotherapy than their female counterparts.

The highest increase in ADHD prevalence was observed in the > 12 ≤ 18 years age group. A possible explanation may be due to changes in the DSM-V regarding age of onset. Previously, children had to be seven years or younger to be diagnosed, which has been changed to 12 years. Additionally, the American Academy of Pediatrics (AAP) recommends that all children aged four 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. 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. 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.

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). In their study, Snyman and Truter found that six children/adolescents had parents diagnosed with, or suspected of having ADHD as a child. Improved diagnostic rates, recognition of ADHD symptoms through their child’s
experience with ADHD, and increased public awareness could all contribute to higher prevalence rates of the disorder in families of ADHD children. According to Chronis et al., 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. 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.

ACKNOWLEDGEMENTS

The authors wish to thank the South African PBM company that provided this data. The interpretation of the results does not necessarily reflect that of the PBM. We thank Ms A Bekker for administrative support regarding the database.
REFERENCES


<table>
<thead>
<tr>
<th>ADHD medication</th>
<th>≤ 6 years</th>
<th>&gt; 6 ≤ 12 years</th>
<th>&gt; 12 ≤ 18 years</th>
<th>Maximum RDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>Ritalin®</td>
<td>Ritalin®</td>
<td>Ritalin®</td>
<td>Ritalin®</td>
</tr>
<tr>
<td></td>
<td>Ritalin LA®</td>
<td>Ritalin LA®</td>
<td>Ritalin LA®</td>
<td>Ritalin LA®</td>
</tr>
<tr>
<td></td>
<td>± 22 mg/day</td>
<td>60 mg/day</td>
<td>60 mg/day</td>
<td>60 mg/day</td>
</tr>
<tr>
<td></td>
<td>Methylphenidate HCL-Douglas®</td>
<td>Methylphenidate HCL-Douglas®</td>
<td>Methylphenidate HCL-Douglas®</td>
<td>Methylphenidate HCL-Douglas®</td>
</tr>
<tr>
<td></td>
<td>Concerta®</td>
<td>Concerta®</td>
<td>Concerta®</td>
<td>Concerta®</td>
</tr>
<tr>
<td></td>
<td>54 mg/day</td>
<td>72 mg/day</td>
<td>72 mg/day</td>
<td>72 mg/day</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>± 28 mg/day</td>
<td>± 55 mg/day</td>
<td>± 90 mg/day</td>
<td>120 mg/day</td>
</tr>
</tbody>
</table>
Table 2: Patient demographic information

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (≤18 year) (n)</td>
<td>299 765</td>
<td>296 550</td>
<td>226 521</td>
<td>165 734</td>
<td>235 003</td>
<td>210 607</td>
<td>185 657</td>
<td>170 840</td>
<td>179 333</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study population, n (%)</td>
<td>6.322 (2.11)</td>
<td>6.665 (2.25)</td>
<td>5.916 (2.61)</td>
<td>5.069 (3.06)</td>
<td>6.814 (2.9)</td>
<td>6.888 (3.27)</td>
<td>6.849 (3.69)</td>
<td>7.063 (4.13)</td>
<td>7.883 (4.4)</td>
<td>2.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD-only n (%)</td>
<td>5.198 (82.22)</td>
<td>5.333 (80.02)</td>
<td>4.524 (76.47)</td>
<td>3.849 (75.93)</td>
<td>5.298 (77.75)</td>
<td>5.319 (77.22)</td>
<td>5.404 (54.87)</td>
<td>5.514 (78.07)</td>
<td>6.136 (77.84)</td>
<td>-4.38</td>
<td>p&lt;0.0001</td>
<td>0.0422</td>
</tr>
<tr>
<td>ADHD-CNS n (%)</td>
<td>1.124 (17.78)</td>
<td>1.332 (19.99)</td>
<td>1.392 (23.53)</td>
<td>1.220 (24.07)</td>
<td>1.516 (22.25)</td>
<td>1.569 (22.78)</td>
<td>1.445 (21.10)</td>
<td>1.549 (21.93)</td>
<td>1.747 (22.16)</td>
<td>4.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD-only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.929 (75.59)</td>
<td>4.025 (75.47)</td>
<td>3.402 (75.2)</td>
<td>2.873 (74.64)</td>
<td>3.941 (74.39)</td>
<td>3.882 (72.98)</td>
<td>3.913 (72.41)</td>
<td>3.996 (71.72)</td>
<td>4.401 (71.72)</td>
<td>-3.87</td>
<td>p&lt;0.0001</td>
<td>0.0325</td>
</tr>
<tr>
<td>Female</td>
<td>1.269 (24.41)</td>
<td>1.308 (24.53)</td>
<td>1.122 (24.80)</td>
<td>0.976 (25.36)</td>
<td>1.357 (25.61)</td>
<td>1.437 (27.02)</td>
<td>1.491 (27.59)</td>
<td>1.518 (27.53)</td>
<td>1.735 (28.28)</td>
<td>3.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD-CNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>825 (73.40)</td>
<td>1.005 (75.45)</td>
<td>985 (70.76)</td>
<td>863 (70.74)</td>
<td>1.100 (72.56)</td>
<td>1.124 (71.64)</td>
<td>1.007 (69.69)</td>
<td>1.066 (68.82)</td>
<td>1.212 (69.38)</td>
<td>-4.02</td>
<td>p&lt;0.0016</td>
<td>0.0439</td>
</tr>
<tr>
<td>Female</td>
<td>299 (26.60)</td>
<td>327 (24.55)</td>
<td>407 (29.24)</td>
<td>357 (29.26)</td>
<td>416 (27.44)</td>
<td>445 (28.36)</td>
<td>438 (30.31)</td>
<td>483 (31.18)</td>
<td>535 (30.62)</td>
<td>4.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>----------------------------</td>
<td>----------</td>
<td>------------</td>
</tr>
<tr>
<td>Age groups, (years) n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD-onlyb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>86 (1.65)</td>
<td>90 (1.69)</td>
<td>70 (1.55)</td>
<td>42 (1.09)</td>
<td>52 (0.98)</td>
<td>48 (0.90)</td>
<td>60 (1.11)</td>
<td>40 (0.73)</td>
<td>53 (0.86)</td>
<td>-0.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6 and ≤12</td>
<td>3,143</td>
<td>3,167</td>
<td>2,556</td>
<td>2,134</td>
<td>2,991</td>
<td>2,953</td>
<td>2,920</td>
<td>2,912</td>
<td>3,271</td>
<td>-7.16</td>
<td>p&lt;0.0001</td>
<td>0.0446</td>
</tr>
<tr>
<td>&gt;12 and ≤18</td>
<td>1,969</td>
<td>2,076</td>
<td>1,898</td>
<td>1,673</td>
<td>2,255</td>
<td>2,318</td>
<td>2,424</td>
<td>2,562</td>
<td>2,812</td>
<td>7.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD-CNSc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>26 (2.31)</td>
<td>42 (3.15)</td>
<td>43 (3.10)</td>
<td>33 (2.70)</td>
<td>30 (1.98)</td>
<td>35 (2.23)</td>
<td>21 (1.45)</td>
<td>29 (1.87)</td>
<td>39 (2.23)</td>
<td>-0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6 and ≤12</td>
<td>655</td>
<td>739</td>
<td>760</td>
<td>651</td>
<td>775</td>
<td>781</td>
<td>720</td>
<td>740</td>
<td>808</td>
<td>-12.02</td>
<td>p&lt;0.0001</td>
<td>0.0596</td>
</tr>
<tr>
<td>&gt;12 and ≤18</td>
<td>443</td>
<td>551</td>
<td>589</td>
<td>536</td>
<td>711</td>
<td>753</td>
<td>704</td>
<td>780</td>
<td>900</td>
<td>12.11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Percentages 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

<table>
<thead>
<tr>
<th>Study period</th>
<th>Children and adolescents with ADHD and their family with ADHD n (%)</th>
<th>Children and adolescents without ADHD and their family with ADHD n (%)</th>
<th>p-value</th>
<th>Cramer’s V</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>0</td>
<td>36 (0.16)</td>
<td>p &lt; 0.4579</td>
<td>-0.0049</td>
</tr>
<tr>
<td>2006</td>
<td>251 (14.94)</td>
<td>302 (0.44)</td>
<td>p &lt; 0.0001</td>
<td>0.2508</td>
</tr>
<tr>
<td>2007</td>
<td>360 (14.05)</td>
<td>555 (0.58)</td>
<td>p &lt; 0.0001</td>
<td>0.2235</td>
</tr>
<tr>
<td>2008</td>
<td>415 (14.96)</td>
<td>636 (0.67)</td>
<td>p &lt; 0.0001</td>
<td>0.2301</td>
</tr>
<tr>
<td>2009</td>
<td>398 (34.10)</td>
<td>555 (1.37)</td>
<td>p &lt; 0.0001</td>
<td>0.3613</td>
</tr>
<tr>
<td>2010</td>
<td>557 (41.72)</td>
<td>725 (1.72)</td>
<td>p &lt; 0.0001</td>
<td>0.4080</td>
</tr>
<tr>
<td>2011</td>
<td>683 (46.34)</td>
<td>849 (2.08)</td>
<td>p &lt; 0.0001</td>
<td>0.4344</td>
</tr>
<tr>
<td>2012</td>
<td>672 (46.63)</td>
<td>979 (2.60)</td>
<td>p &lt; 0.0001</td>
<td>0.4126</td>
</tr>
<tr>
<td>2013</td>
<td>548 (29.09)</td>
<td>1093 (2.23)</td>
<td>p &lt; 0.0001</td>
<td>0.2871</td>
</tr>
</tbody>
</table>
Table 4: Measurements of medication usage in the study population

<table>
<thead>
<tr>
<th>Study period</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>Total</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>8 391 836</td>
<td>8 906 344</td>
<td>7 911 071</td>
<td>6 775 863</td>
<td>9 023 205</td>
<td>8 515 428</td>
<td>7 371 213</td>
<td>6 770 703</td>
<td>6 794 490</td>
<td>70 460 153</td>
<td>p&gt;0.0001</td>
</tr>
<tr>
<td>Total</td>
<td>23 438</td>
<td>26 464</td>
<td>27 114</td>
<td>24 590</td>
<td>32 761</td>
<td>32 876</td>
<td>29 487</td>
<td>30 620</td>
<td>33 087</td>
<td>260 437</td>
<td>260 437</td>
</tr>
<tr>
<td>Total</td>
<td>3.58±2.71</td>
<td>3.80±2.94</td>
<td>4.40±3.14</td>
<td>4.64±3.27</td>
<td>4.63±3.26</td>
<td>4.60±3.23</td>
<td>4.18±3.02</td>
<td>4.20±3.03</td>
<td>4.08±2.91</td>
<td>p&gt;0.0001</td>
<td>p&gt;0.0001</td>
</tr>
<tr>
<td>Average</td>
<td>22 473</td>
<td>22 983</td>
<td>23 663</td>
<td>21 396</td>
<td>28 960</td>
<td>29 274</td>
<td>26 767</td>
<td>27 894</td>
<td>30 373</td>
<td>233 783</td>
<td>233 783</td>
</tr>
<tr>
<td>MPH, n (%)</td>
<td>(95.88)</td>
<td>(86.85)</td>
<td>(87.58)</td>
<td>(87.01)</td>
<td>(88.40)</td>
<td>(89.04)</td>
<td>(90.78)</td>
<td>(91.10)</td>
<td>(91.80)</td>
<td>(89.77)</td>
<td>(89.77)</td>
</tr>
<tr>
<td>Average</td>
<td>3.65±2.75</td>
<td>3.74±2.85</td>
<td>4.29±3.01</td>
<td>4.52±3.13</td>
<td>4.53±3.15</td>
<td>4.53±3.14</td>
<td>4.12±2.94</td>
<td>4.15±2.97</td>
<td>4.03±2.86</td>
<td>p&gt;0.0001</td>
<td>p&gt;0.0001</td>
</tr>
<tr>
<td>MPH, n (%)</td>
<td>(95.72)</td>
<td>(86.37)</td>
<td>(87.31)</td>
<td>(87.01)</td>
<td>(88.40)</td>
<td>(89.04)</td>
<td>(90.78)</td>
<td>(91.10)</td>
<td>(91.80)</td>
<td>(89.77)</td>
<td>(89.77)</td>
</tr>
<tr>
<td>Total</td>
<td>965</td>
<td>3 481</td>
<td>3 451</td>
<td>3 194</td>
<td>3 801</td>
<td>3 602</td>
<td>2 720</td>
<td>2 726 (8.9)</td>
<td>2 714 (8.2)</td>
<td>26 654</td>
<td>(10.23)</td>
</tr>
<tr>
<td>atomoxetine</td>
<td>(4.12%)</td>
<td>(13.15)</td>
<td>(12.73)</td>
<td>(12.99)</td>
<td>(11.6)</td>
<td>(10.96)</td>
<td>(9.22)</td>
<td>(9.22)</td>
<td>(9.22)</td>
<td>(9.22)</td>
<td>(9.22)</td>
</tr>
</tbody>
</table>
### Average prescription atomoxetine per patient per year ± SD (95% CI)

<table>
<thead>
<tr>
<th>Study period</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>Total</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.37±1.54</td>
<td>4.25±3.49</td>
<td>5.26±3.91</td>
<td>5.62±4.11</td>
<td>5.56±4.03</td>
<td>5.65±3.96</td>
<td>5.03±3.76</td>
<td>4.81±3.59</td>
<td>4.61±3.47</td>
<td></td>
<td>p&gt;0.0001</td>
</tr>
<tr>
<td></td>
<td>(2.22-2.52)</td>
<td>(4.01-4.5)</td>
<td>(4.96-5.56)</td>
<td>(5.28-5.96)</td>
<td>(5.25-5.86)</td>
<td>(5.35-5.96)</td>
<td>(4.7-5.35)</td>
<td>(4.51-5.1)</td>
<td>(4.33-4.89)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MPH - Methylphenidate  
SD - standard deviation, CI - confidence interval *ANOVA

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

<table>
<thead>
<tr>
<th>ADHD medication</th>
<th>Methylphenidate</th>
<th>Atomoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study period</td>
<td>≤6 years</td>
<td>&gt;6 and ≤12 years</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>2005</td>
<td>33 (13.10)</td>
<td>347 (2.39)</td>
</tr>
<tr>
<td>2006</td>
<td>23 (7.85)</td>
<td>245 (1.65)</td>
</tr>
<tr>
<td>2007</td>
<td>66 (25.29)</td>
<td>234 (1.57)</td>
</tr>
<tr>
<td>2008</td>
<td>33 (20.25)</td>
<td>161 (1.22)</td>
</tr>
<tr>
<td>2009</td>
<td>12 (7.45)</td>
<td>333 (1.85)</td>
</tr>
<tr>
<td>2010</td>
<td>53 (25.0)</td>
<td>283 (1.64)</td>
</tr>
<tr>
<td>2011</td>
<td>44 (20.56)</td>
<td>203 (1.32)</td>
</tr>
<tr>
<td>2012</td>
<td>18 (12.08)</td>
<td>181 (1.17)</td>
</tr>
<tr>
<td>2013</td>
<td>44 (17.74)</td>
<td>98 (0.58)</td>
</tr>
<tr>
<td>Total</td>
<td>326 (16.69)</td>
<td>2085 (1.48)</td>
</tr>
</tbody>
</table>

*Percentages were calculated according to the total number of items for each respective year and age group.
<table>
<thead>
<tr>
<th>Study period</th>
<th>ADHD-only</th>
<th>ADHD-CNS</th>
<th>p-value, Cohens' d*</th>
<th>ADHD-only</th>
<th>ADHD-CNS</th>
<th>p-value, Cohens' d*</th>
<th>ADHD-only</th>
<th>ADHD-CNS</th>
<th>p-value, Cohens' d*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>179</td>
<td>73</td>
<td>0.4356</td>
<td>11449</td>
<td>3070</td>
<td>0.3261</td>
<td>6997</td>
<td>1970</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2005 95% CI</td>
<td>14.64-23.77</td>
<td>9.34-28.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>158</td>
<td>135</td>
<td>0.5638</td>
<td>11461</td>
<td>3360</td>
<td>0.0093</td>
<td>7098</td>
<td>2234</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2006 Mean±SD</td>
<td>15.32±9.35</td>
<td>15.9±8.2</td>
<td></td>
<td>22.45±23.12</td>
<td>23.76±15.1</td>
<td>23.25-24.27</td>
<td>27.17-28.15</td>
<td>30.87-33.81</td>
<td>53.25-61.74</td>
</tr>
<tr>
<td>2006 95% CI</td>
<td>13.85-16.78</td>
<td>14.52-17.31</td>
<td></td>
<td>22.03-22.88</td>
<td>23.25-24.27</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>130</td>
<td>131</td>
<td>0.7359</td>
<td>10988</td>
<td>3916</td>
<td>0.0001</td>
<td>7347</td>
<td>2646</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2008</td>
<td>77</td>
<td>86</td>
<td>0.0004</td>
<td>9502</td>
<td>3689</td>
<td>0.0001</td>
<td>7026</td>
<td>2591</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2009</td>
<td>88</td>
<td>73</td>
<td>0.0736</td>
<td>13420</td>
<td>4543</td>
<td>0.0001</td>
<td>10077</td>
<td>3850</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2010</td>
<td>92</td>
<td>120</td>
<td>0.2800</td>
<td>12905</td>
<td>4335</td>
<td>0.0001</td>
<td>10210</td>
<td>3947</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2010 Mean±SD</td>
<td>18.46±11.71</td>
<td>20.41±13.92</td>
<td></td>
<td>23.37±12.17</td>
<td>26.61±13.54</td>
<td>26.21-27.01</td>
<td>31.31-15.69</td>
<td>34.42±15.65</td>
<td>53.25-61.74</td>
</tr>
<tr>
<td>2010 95% CI</td>
<td>16.04-20.89</td>
<td>17.9-22.9</td>
<td></td>
<td>23.16-23.58</td>
<td>26.21-27.01</td>
<td></td>
<td>31.31-15.69</td>
<td>33.93-34.91</td>
<td>53.25-61.74</td>
</tr>
</tbody>
</table>
# Methylphenidate PDD

## Age groups (years)

<table>
<thead>
<tr>
<th>Study period</th>
<th>ADHD-only</th>
<th>ADHD-CNS</th>
<th>( p )-value, Cohens' ( d )</th>
<th>ADHD-only</th>
<th>ADHD-CNS</th>
<th>( p )-value, Cohens' ( d )</th>
<th>ADHD-only</th>
<th>ADHD-CNS</th>
<th>( p )-value, Cohens' ( d )</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>154</td>
<td>60</td>
<td>( p = 0.3015 ) ( d = 0.14 )</td>
<td>11934</td>
<td>3485</td>
<td>( p = 0.0004 ) ( d = 0.179 )</td>
<td>9785</td>
<td>3423</td>
<td>( p &lt; 0.0001 ) ( d = 0.15 )</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>19.02±12.94</td>
<td>21.16±15.21</td>
<td>23.39±11.51</td>
<td>23.19-23.6</td>
<td>25.7±12.89</td>
<td>25.27-26.12</td>
<td>31.34±14.38</td>
<td>31.06-31.63</td>
<td>33.78±16.09</td>
</tr>
<tr>
<td>95% CI</td>
<td>16.96-21.08</td>
<td>17.23-25.09</td>
<td>23.1-23.6</td>
<td>25.27-26.12</td>
<td>31.06-31.63</td>
<td>33.24-34.32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>101</td>
<td>48</td>
<td>( p = 0.0019 ) ( d = 0.49 )</td>
<td>11708</td>
<td>3751</td>
<td>( p &lt; 0.0001 ) ( d = 0.198 )</td>
<td>10706</td>
<td>3920</td>
<td>( p &lt; 0.0001 ) ( d = 0.18 )</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>17.12±9.81</td>
<td>12.31±5.40</td>
<td>23.5±11.56</td>
<td>23.29-23.71</td>
<td>26.04±12.86</td>
<td>25.63-26.45</td>
<td>31.7±14.44</td>
<td>31.43-31.97</td>
<td>34.56±15.57</td>
</tr>
<tr>
<td>95% CI</td>
<td>15.18-19.05</td>
<td>10.74-13.88</td>
<td>23.29-23.71</td>
<td>25.63-26.45</td>
<td>31.43-31.97</td>
<td>34.07-35.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>158</td>
<td>90</td>
<td>( p = 0.0803 ) ( d = 0.21 )</td>
<td>12881</td>
<td>4111</td>
<td>( p &lt; 0.0001 ) ( d = 0.21 )</td>
<td>11289</td>
<td>4214</td>
<td>( p &lt; 0.0001 ) ( d = 0.16 )</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>16.98±10.55</td>
<td>14.73±7.96</td>
<td>22.65±11.02</td>
<td>22.46-22.84</td>
<td>25.23±12.59</td>
<td>24.85-25.62</td>
<td>32.11±14.92</td>
<td>31.84-32.39</td>
<td>34.54±15.38</td>
</tr>
<tr>
<td>95% CI</td>
<td>15.32-18.64</td>
<td>13.07-16.4</td>
<td>22.46-22.84</td>
<td>24.85-25.62</td>
<td>31.84-32.39</td>
<td>34.07-35.04</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^*\)t-test
Table 7: Prescribed daily dose for atomoxetine according to age groups: ADHD group vs. ADHD-CNS group

<table>
<thead>
<tr>
<th>Study period</th>
<th>ADHD-only</th>
<th>ADHD-CNS</th>
<th>ADHD-only</th>
<th>ADHD-CNS</th>
<th>ADHD-only</th>
<th>ADHD-CNS</th>
<th>ADHD-only</th>
<th>ADHD-CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age groups (years)</td>
<td>ADHDO only</td>
<td>ADHD-CNS</td>
<td>p-value, Cohens’ d</td>
<td>ADHDO only</td>
<td>ADHD-CNS</td>
<td>p-value, Cohens’ d</td>
<td>ADHDO only</td>
</tr>
<tr>
<td></td>
<td>≤6</td>
<td>&gt;6 and ≤12</td>
<td>&gt;12 and ≤18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>n</td>
<td>Mean±SD</td>
<td>95% CI</td>
<td>n</td>
<td>Mean±SD</td>
<td>95% CI</td>
<td>n</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>17.74±8.9</td>
<td>12.6-22.88</td>
<td>13</td>
<td>17.62±6.9</td>
<td>13.48-21.75</td>
<td>560</td>
<td>34.85±46.56</td>
</tr>
<tr>
<td>2006</td>
<td>n</td>
<td>29</td>
<td>22.76±20.63</td>
<td>14.92-30.61</td>
<td>6</td>
<td>21.61±13.49</td>
<td>7.45-35.77</td>
<td>1660</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>17</td>
<td>21.59±10.6</td>
<td>16.14-27.04</td>
<td>32</td>
<td>18.72±4.9</td>
<td>16.95-20.49</td>
<td>1478</td>
</tr>
<tr>
<td>2007</td>
<td>n</td>
<td>54</td>
<td>26.65±11.34</td>
<td>23.56-29.75</td>
<td>23</td>
<td>18.62±6.13</td>
<td>15.97-21.27</td>
<td>1382</td>
</tr>
<tr>
<td>2009</td>
<td>n</td>
<td>36</td>
<td>17.61±6.36</td>
<td>15.46-19.76</td>
<td>35</td>
<td>21.11±7.18</td>
<td>18.65-23.58</td>
<td>1642</td>
</tr>
<tr>
<td>2010</td>
<td>n</td>
<td>10</td>
<td>18±0</td>
<td>28.27±9.48</td>
<td>32</td>
<td>24.85±31.68</td>
<td>1422</td>
<td>31.82±13.73</td>
</tr>
</tbody>
</table>

95% CI
## Atomoxetine PDD

### Age groups (years)

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

* 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

Authors: S de Villiers¹, MS Lubbe¹, JR Burger¹, I Truter², M Cockeran¹

Institution: ¹Medicine Usage in South Africa, Faculty of Health Sciences, North-West University, Potchefstroom Campus, Potchefstroom, South Africa, 2520.

²Drug Utilization Research Unit, Department of Pharmacy, Nelson Mandela Metropolitan University, Port Elizabeth, South Africa, 6031.

Corresponding author: MS Lubbe

Mailing address: North-West University, Potchefstroom Campus, Private Bag, X6001, Potchefstroom, 2520

Phone: +27-18-299-2288

E-mail address: Martie.Lubbe@nwu.ac.za

Keywords:
Attention-Deficit/Hyperactivity Disorder, children, adolescents, central nervous system medication, South Africa

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.
Funding

This work was funded by the National Research Foundation and the North-West University, Potchefstroom, South Africa. The funder had no role in the design and conduct of the study, collection, management, analysis, or interpretation of the data and preparation, review, or approval of the manuscript for publication.

Conflict of Interest

None of the authors have any conflicts to declare.

Word count text: 3 019 words
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. 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 AHDH-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. 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. 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.\textsuperscript{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; $\leq 6$ years, $> 6$ years and $\leq 12$ years and $> 12$ years and $\leq 18$ years. Study variables were expressed using descriptive statistics.

The chi-square ($\chi^2$) 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.\textsuperscript{18} For practical significance, the following were considered: $\leq 0.2$ 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.\textsuperscript{18}

\textit{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 ≤ 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 ≤ 18 years age group; however, the effect of these associations was weak (Cramer’s $V = 0.0595$ and Cramer’s $V = 0.0458$).

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.

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.
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, ranging from as high as 7.2% in the USA to 2.0% in Europe. 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. Lower estimates were reported in France, with a treatment prevalence rate of 2.5% in children and adolescents.

Psychotropic prescription rates similar to that in France have been reported in the United Kingdom. According to Zoëga and associates (2009), 4.87% of Icelandic children and adolescents 17 years and younger, used CNS drugs in 2007. When Olsson 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. 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.

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. 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. On the other hand, fewer evidence concerning the efficacy of drug combinations to treat complex comorbid disorders exists. 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.

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. 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.

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. An estimated 32% of children and adolescents with ADHD have been reported to have a diagnosis for depression, 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. Children with ADHD tend to be more vulnerable to various forms of urinary problems, such as nocturnal enuresis. Amitriptyline and imipramine are indicated for the treatment of nocturnal enuresis, 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%. Furthermore, Ohayon and Lader (2002) found that 4.3% of the sample was for the anxiolytic agents. 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. Likewise, Olfson et al. (2013) reported a 3.9% treatment prevalence of antidepressants in adolescents.

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. These agents are inhibitors of the cytochrome P450 enzyme (CYP2D6), which is responsible for the metabolism of atomoxetine. 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.

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. Consequentially, this can lead to increased plasma concentrations of the TCAs, with increased risk of precipitation of adverse reactions. However, the effects of this drug-drug interaction are usually mild, and should not significantly alter the therapeutic outcome.

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.

ACKNOWLEDGEMENTS

The authors wish to thank the South African PBM company that provided this data. The interpretation of the results does not necessarily reflect that of the PBM. We thank Ms A Bekker for administrative support regarding the database.
REFERENCES


13. CDC (Centers for Disease Control and Prevention). Psychotropic medication use among 
   [Accessed 26 March 2014].

14. Nevels RM, Weiss NH, Killebrew AE, Gontkovsky ST. Methylphenidate and its under- 
   recognized, under-explained, and serious drug interactions: a review of the literature with 


   2014.


   Potchefstroom, North-West University. 1999. Available from: 

19. Zito JM, Safer DJ, de Jong-van den Berg LTW, Janhsen K, Fegert JM, Gardner JF, 
   Glaeske G & Valluri SC. A three-country comparison of psychotropic medication 
   Available from: http://www.researchgate.net/publication/23281489_A_three- 
   country_comparison_of_psychotropic_medication_prevalence_in_youth [Accessed: 20 
   September 2015].

   JM. (ed.) IACAPAP e-Textbook of child and adolescent mental health, Geneva: 
   International Association for child and adolescent psychiatry and allied professions; 2012. 

   Patten SB. Psychotropic medication use in Canada. *Canadian journal of psychiatry*. 2005; 

22. Kovess V, Choppin S, Gao F, Pivette M, Husky M, Leray E. Psychotropic medication use 
   in French children and adolescents. *Journal of child and adolescent psychopharmacology*. 
   2015; 25(2):168-175.


31. AAP (American Academy of Pediatrics). ADHD: clinical practice guideline for the
diagnosis, evaluation, and treatment of Attention-Deficit/Hyperactivity Disorder in children
and adolescents. *Pediatrics*. 2011; 128(5). Available from:

32. McCellan JM, Werry, JS. Evidence-Based treatments in child and adolescent psychiatry:
42(12):1388-1400.

33. Wilens TE, Spencer T, Biederman J, Wozniak J, Connor D. Combined pharmacotherapy:
an emerging trend in pediatric psychopharmacology. *Journal of the American Academy of

prevalence of concomitant psychotropic medication usage among children and
adolescents with Attention-Deficit/Hyperactivity Disorder during 2009. *Journal of child and

SJ, Rothenberger A. Co-existing psychiatric problems in ADHD in the ADORE cohort.

36. Robson WL, Jackson HP, Blackhurst D, Leung AK. Enuresis in children with attention-

37. Shreeram S, He JP, Kalaydjian A, Brothers S, Merikangas KR. Prevalence of enuresis
and its association with attention-deficit/hyperactivity disorder among U.S. children: results
from a nationally representative study. *Journal of the American Academy of Child &

38. Rossiter D. South African medicines formulary. 11th ed. Cape Town: Health and Medical

2015; 25(2):168-175.

40. Ohayon MM, Lader MH. Use of psychotropic medication in the general population of
63(9):817-825.
## Table 1: Demographic information of the study population

<table>
<thead>
<tr>
<th>Study period</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th><strong>Difference</strong></th>
<th><strong>P-value</strong></th>
<th><strong>Cramer’s V</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total population</strong> (≤18 year) (n)</td>
<td>299 765</td>
<td>296 550</td>
<td>226 521</td>
<td>165 734</td>
<td>235 003</td>
<td>210 607</td>
<td>185 657</td>
<td>170 840</td>
<td>179 333</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study population, n (%)</td>
<td>15 334 (5.12)</td>
<td>15 431 (5.20)</td>
<td>12 504 (5.52)</td>
<td>9 414 (5.68)</td>
<td>12 478 (5.31)</td>
<td>11 273 (5.35)</td>
<td>9 020 (4.86)</td>
<td>7 958 (4.66)</td>
<td>8 037 (4.48)</td>
<td>-0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD-CNS n (%)</td>
<td>1 124 (7.33)</td>
<td>1 332 (8.63)</td>
<td>1 392 (11.13)</td>
<td>1 220 (12.96)</td>
<td>1 516 (11.15)</td>
<td>1 569 (13.92)</td>
<td>1 445 (16.02)</td>
<td>1 549 (19.46)</td>
<td>1 746 (21.72)</td>
<td>14.39</td>
<td><em>p &lt; 0.0001</em></td>
<td>0.1288</td>
</tr>
<tr>
<td>CNS-only n (%)</td>
<td>14 210 (92.67)</td>
<td>14 099 (91.37)</td>
<td>11 112 (88.87)</td>
<td>8 194 (87.04)</td>
<td>10 962 (86.08)</td>
<td>9 704 (83.98)</td>
<td>7 575 (80.54)</td>
<td>6 409 (78.28)</td>
<td>6 291 (78.28)</td>
<td>-14.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD-CNS group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>825 (73.40)</td>
<td>1 005 (75.45)</td>
<td>985 (70.76)</td>
<td>863 (70.74)</td>
<td>110 (72.56)</td>
<td>1 124 (71.64)</td>
<td>1 007 (69.69)</td>
<td>1 066 (68.82)</td>
<td>1 212 (69.42)</td>
<td>-6.03</td>
<td><em>0.0017</em></td>
<td>0.0438</td>
</tr>
<tr>
<td>Female</td>
<td>299 (26.60)</td>
<td>327 (24.55)</td>
<td>407 (29.24)</td>
<td>357 (29.26)</td>
<td>416 (27.44)</td>
<td>445 (28.36)</td>
<td>438 (30.31)</td>
<td>483 (31.18)</td>
<td>534 (30.58)</td>
<td>6.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS-only group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 739 (52.58)</td>
<td>6 671 (47.32)</td>
<td>5 186 (46.67)</td>
<td>3 724 (45.45)</td>
<td>5 091 (46.44)</td>
<td>4 555 (46.94)</td>
<td>3 483 (45.98)</td>
<td>2 910 (45.41)</td>
<td>2 907 (46.21)</td>
<td>-1.11</td>
<td><em>0.0305</em></td>
<td>0.0138</td>
</tr>
<tr>
<td>Female</td>
<td>7 471 (52.58)</td>
<td>7 428 (52.68)</td>
<td>5 926 (53.33)</td>
<td>4 470 (54.55)</td>
<td>5 871 (53.56)</td>
<td>5 149 (53.06)</td>
<td>4 092 (54.02)</td>
<td>3 499 (54.60)</td>
<td>3 384 (53.79)</td>
<td>1.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>--------</td>
<td>--------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>-------------------------------</td>
<td>----------</td>
<td>------------</td>
</tr>
<tr>
<td>ADHD-CNS group b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>26 (2.31)</td>
<td>42 (3.15)</td>
<td>43 (30.9)</td>
<td>33 (2.70)</td>
<td>30 (1.98)</td>
<td>35 (2.23)</td>
<td>21 (1.45)</td>
<td>29 (1.87)</td>
<td>39 (2.23)</td>
<td>-0.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6 and ≤12</td>
<td>655 (58.27)</td>
<td>739 (55.48)</td>
<td>760 (54.60)</td>
<td>651 (53.36)</td>
<td>775 (51.12)</td>
<td>781 (49.78)</td>
<td>720 (49.83)</td>
<td>740 (47.77)</td>
<td>808 (46.28)</td>
<td>-9.2</td>
<td>p &lt; 0.0001</td>
<td>0.0595</td>
</tr>
<tr>
<td>&gt;12 and ≤18</td>
<td>443 (39.41)</td>
<td>551 (41.37)</td>
<td>589 (42.31)</td>
<td>536 (43.93)</td>
<td>711 (46.90)</td>
<td>753 (47.99)</td>
<td>704 (48.72)</td>
<td>780 (50.36)</td>
<td>899 (51.49)</td>
<td>10.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS-only group c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>3 640 (25.62)</td>
<td>3 486 (24.73)</td>
<td>2 599 (23.39)</td>
<td>1 463 (17.85)</td>
<td>2 933 (26.76)</td>
<td>2 716 (27.99)</td>
<td>2 085 (27.52)</td>
<td>1 539 (24.01)</td>
<td>1 477 (23.48)</td>
<td>-1.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6 and ≤12</td>
<td>3 937 (27.71)</td>
<td>3 808 (27.01)</td>
<td>2 918 (26.26)</td>
<td>2 316 (26.26)</td>
<td>2 827 (25.79)</td>
<td>2 479 (25.55)</td>
<td>2 012 (26.56)</td>
<td>1 707 (26.63)</td>
<td>1 679 (26.69)</td>
<td>0.32</td>
<td>p &lt; 0.0001</td>
<td>0.0458</td>
</tr>
<tr>
<td>&gt;12 and ≤18</td>
<td>6 633 (46.68)</td>
<td>6 805 (48.27)</td>
<td>5 595 (50.35)</td>
<td>4 415 (53.88)</td>
<td>5 202 (47.45)</td>
<td>4 509 (46.47)</td>
<td>3 478 (15.91)</td>
<td>3 164 (49.37)</td>
<td>3 135 (49.83)</td>
<td>1.56</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

*Excluding 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

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

<sup>a</sup>Percentages were calculated according to the total number of CNS prescriptions
Table 4: Frequency of potential drug-drug interactions with methylphenidate over the study period

<table>
<thead>
<tr>
<th>CNS medication</th>
<th>Frequency of prescriptions with interactions with methylphenidate n (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>1 676 (37.00)</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>2 346 (51.79)</td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>62 (1.37)</td>
<td>5 (Tatro, 2012:1943)</td>
</tr>
<tr>
<td>Dothiepin</td>
<td>5 (0.11)</td>
<td></td>
</tr>
<tr>
<td>Lofepramine</td>
<td>13 (0.29)</td>
<td></td>
</tr>
<tr>
<td>Moclobemide</td>
<td>63 (1.39)</td>
<td>1 (Tatro, 2012:1235)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>1 (0.02)</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>410 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>16 (0.35)</td>
<td></td>
</tr>
<tr>
<td><strong>Total number of prescriptions</strong></td>
<td><strong>4 530</strong></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Percentages 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

<table>
<thead>
<tr>
<th>CNS medication</th>
<th>Frequency of prescriptions with interactions with atomoxetine n (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moclobemide</td>
<td>4 (0.39)</td>
<td>1 (Tatro, 2012:213)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>55 (5.30)</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>26 (2.51)</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>59 (5.68)</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>307 (29.58)</td>
<td>2 (Tatro, 2012:214)</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>391 (37.67)</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>196 (18.89)</td>
<td></td>
</tr>
<tr>
<td>Total number of prescriptions</td>
<td>1038</td>
<td></td>
</tr>
</tbody>
</table>

*Percentages 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:


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.,
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; Olsson 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 ≤ 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% (Koves 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,
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.
REFERENCES


http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654.full.pdf+html
Date of access: 29 Sep. 2015.


Biederman, J., Ball, S.W., Monuteaux, M.C., Mick, E., Spencer, T.J., McCreary, M., Cote, M. & Faraone, S.V. 2008. New insights into the comorbidity between ADHD and major depression in


Center for Mental Health in Schools at UCLA. 1999? Common psychosocial problems of school aged youth: developmental variations, problems, disorders and perspectives for prevention and treatment. https://www.google.co.za/?gfe_rd=cr&ei=0aMLVqC3G--o8wfGgJaYAw&gws_rd=ssl#q=common+psychosocial+problems+od+school+aged+youth Date of access: 30 Sep. 2015.


138


http://eds.a.ebscohost.com.nwulib.nwu.ac.za/ehost/detail/detail?vid=2&sid=503c0048-797b-44da-bd23-0f6b79cd040e%40sessionmgr4004&hid=4105&bdata=#AN=9706225086&db=aph
Date of access: 2 Oct. 2015.


Tanida, T., Warita, K., Ishihara, K., Fukui, S., Mitsuhashi, T., Sugawara, T., Tabuchi, Y., Nanmori, T., Qi, W., Inamoto, T., Yokoyama, T., Kitagawa, H. & Hoshi, N. 2009. Fetal and neonatal exposure to three typical environmental chemicals with different mechanisms of action: mixed exposure to phenol, phthalate, and dioxin cancels the effects of sole exposure on mouse midbrain dopaminergic nuclei. Toxicology letters, 189(1):40-47.


United States Food and Drug Administration.  2015.  Atomoxetine (marketed as Strattera®) Information.  


http://www.researchgate.net/publication/23281489_A_three-

### 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**

<table>
<thead>
<tr>
<th>Validation processes: Examples</th>
<th>Validation processes: Examples</th>
</tr>
</thead>
</table>
| **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 |
<table>
<thead>
<tr>
<th>Formulary management</th>
<th>reference pricing and therapeutic reference pricing (i.e. formulary based pricing for chronic diseases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Management of Chronic Disease List prescribed minimum benefits and non-chronic disease list conditions</td>
</tr>
<tr>
<td></td>
<td>• Daily real-time benefit validation</td>
</tr>
</tbody>
</table>
ANNEXURE C

Pharmaceutical classification of central nervous system medication

<table>
<thead>
<tr>
<th>Pharmaceutical classification</th>
<th>Central analeptics</th>
<th>1.1.</th>
<th>Respiratory stimulants</th>
<th>1.1.1.</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2. Sedative hypnotic agents</td>
<td>1.2.1.</td>
<td>Benzodiazepines</td>
<td>1.2.2.</td>
<td>Barbiturates</td>
<td>1.2.3.</td>
</tr>
<tr>
<td>1.3. Anxiolytic agents</td>
<td>1.3.1.</td>
<td>Benzodiazepines</td>
<td>1.3.2.</td>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>1.4. Anti-depressants</td>
<td>1.4.1.</td>
<td>Tricyclic</td>
<td>1.4.2.</td>
<td>Non-Tricyclic</td>
<td>1.4.3.</td>
</tr>
<tr>
<td></td>
<td>1.4.3.1.</td>
<td>Non-selective mono-amine oxidase inhibitors</td>
<td>1.4.3.2.</td>
<td>Selective mono-amine oxidase inhibitors</td>
<td>1.4.4.</td>
</tr>
<tr>
<td></td>
<td>1.4.5.</td>
<td>Serotonin and noradrenaline re-uptake inhibitors</td>
<td>1.4.6.</td>
<td>Lithium</td>
<td>1.4.7.</td>
</tr>
<tr>
<td>1.5. Anti-psychotic agents</td>
<td>1.5.1.</td>
<td>Phenothiazines</td>
<td>1.5.2.</td>
<td>Butyrophenones</td>
<td>1.5.3.</td>
</tr>
<tr>
<td>1.6. Anti-epileptic agents</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## ANNEXURE D

Tatro’s significance ratings for drug-drug interactions

<table>
<thead>
<tr>
<th>Significance rating</th>
<th>Severity</th>
<th>Documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Major</td>
<td>Suspected or &gt;</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Suspected or &gt;</td>
</tr>
<tr>
<td>3</td>
<td>Minor</td>
<td>Suspected or &gt;</td>
</tr>
<tr>
<td>4</td>
<td>Major/Moderate</td>
<td>Possible</td>
</tr>
<tr>
<td>5</td>
<td>Minor</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>Likely</td>
</tr>
</tbody>
</table>
ANNEXURE E

Figure 1: CDC Growth chart for boys (birth to 36 months)
Figure 2: CDC Growth chart for boys aged 2 to 20 years

2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

Mother’s Stature: [ ]
Father’s Stature: [ ]

Date | Age | Weight | Stature | BMI*
--- | --- | --- | --- | ---

*To Calculate BMI: Weight (kg) = Stature (cm) × Stature (cm) × 10,000
or Weight (lb) = Stature (in) + Stature (in) × 703

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
Figure 3: CDC Growth chart for girls (birth to 36 months)
Figure 4: CDC Growth chart for girls aged 2 to 20 years

2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles

Mother’s Stature  Father’s Stature

Date  Age  Weight  Stature  BMI*

*To Calculate BMI: Weight (kg) = Stature (cm) - Stature (cm) x 10,000 or Weight (lb) = Stature (in) - Stature (in) x 703

Published May 30, 2000 (modified 11/21/06).
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

<table>
<thead>
<tr>
<th>Pharmacological classification</th>
<th>Subclass</th>
<th>Drug</th>
<th>Significance rating</th>
<th>Methylphenidate</th>
<th>Atomoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td>Tricyclic antidepressants (TCAs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amitriptyline</td>
<td>5 (Tatro, 2012:1943)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amoxapine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipramine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clomipramine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desipramine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doxepin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dothiepin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lofepramine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maprotiline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nortriptyline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protriptyline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trimipramine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacological classification</td>
<td>Subclass</td>
<td>Drug</td>
<td>Significance rating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------------------------------</td>
<td>-------------------</td>
<td>---------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylphenidate</td>
<td>Atomoxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td>Monoamine Oxidase Inhibitors (MAOIs)</td>
<td>Tranylcypromine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moclobemide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isocarboxazid</td>
<td>1 (Tatro, 2012:1235)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenelzine</td>
<td>1 (Tatro, 2012:213)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Selegiline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Selective Serotonin Reuptake Inhibitors (SSRIs)</td>
<td>Fluoxetine</td>
<td>No interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paroxetine</td>
<td>2 (Tatro, 2012:214)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluvoxamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Citalopram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Escitalopram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sertraline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiepileptic agents</strong></td>
<td>Hydantoin derivatives</td>
<td>Phenytoin</td>
<td>4 (Tatro, 2012:955)</td>
<td>No interaction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fosphenytoin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carboxamides</td>
<td>Carbamazepine</td>
<td>4 (Tatro, 2012:1233)</td>
<td>No interaction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxcarbazepine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.

2.2 Conflict of Interest and Source of Funding

JCPT requires that sources of financial support for the work reported within the manuscript are fully acknowledged, and any potential conflicts of interest noted.
**Conflict of Interest:** All manuscripts submitted to the Journal require a statement about authors’ conflicts of interest. Please disclose any possible conflict of interest under the heading ‘Conflicts of Interest’ on the title page of your manuscript. Any reported conflicts of interest will be published in a highlighted box as part of the article. If no conflicts of interest are reported, the box will include the statement "No conflicts of interest have been declared". Possible conflicts of interest include financial interests relating to issues discussed in the manuscript (e.g. patent ownership, stock ownership, consultancies and speaker’s fees).

**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.

2.3 Appeal of Editorial Decisions
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.

2.4 Permissions
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 permissions in writing and provide copies to the Publishers.

2.5 Copyright Assignment
If your paper is accepted, the author identified as the formal corresponding author for the paper will receive an email prompting them to login into Author Services; where via the Wiley Author Licensing Service (WALS) they will be able to complete the license agreement on behalf of all authors on the paper.

For authors signing the copyright transfer agreement
If the OnlineOpen option is not selected the corresponding author will be presented with the copyright transfer agreement (CTA) to sign. The terms and conditions of the CTA can be previewed in the samples associated with the Copyright FAQs below:

For authors choosing OnlineOpen
If the OnlineOpen option is selected the corresponding author will have a choice of the following Creative Commons License Open Access Agreements (OAA):
Creative Commons Attribution Non-Commercial License OAA
Creative Commons Attribution Non-Commercial -NoDerivs License OAA

To preview the terms and conditions of these open access agreements please visit the Copyright FAQs hosted on Wiley Author Services [http://authorservices.wiley.com/bauthor/faqs_copyright.asp](http://authorservices.wiley.com/bauthor/faqs_copyright.asp) and visit [http://www.wileyopenaccess.com/details/content/12f25db4c87/Copyright-License.html](http://www.wileyopenaccess.com/details/content/12f25db4c87/Copyright-License.html).
If you select the OnlineOpen option and your research is funded by The Wellcome Trust and members of the Research Councils UK (RCUK) you will be given the opportunity to publish your article under a CC-BY license supporting you in complying with Wellcome Trust and Research Councils UK requirements. For more information on this policy and the Journal’s compliant self-archiving policy please visit: http://www.wiley.com/go/funderstatement.

For RCUK and Wellcome Trust authors click on the link below to preview the terms and conditions of this license: Creative Commons Attribution License OAA.

To preview the terms and conditions of these open access agreements please visit the Copyright FAQs hosted on Wiley Author Services http://authorservices.wiley.com/bauthor/faqs_copyright.asp and visit http://www.wileyopenaccess.com/details/content/12f25db4c87/Copyright--License.html.

3. Submission of Manuscripts
Manuscripts should be submitted electronically via http://mc.manuscriptcentral.com/jcpt. Authors may track the status of their own manuscripts. Complete instructions for submitting papers are available online and a user ID and password can be obtained from the first visit. Further assistance can be obtained from: support@scholarone.com. If you cannot submit online or have a general query, please contact Professor Alain Li Wan Po (Editor-in-Chief) at alainliwanpo@yahoo.com

Papers do not attract page charges. OnlineOpen is available to authors of primary research articles who wish to make their article available to non-subscribers on publication, or whose funding agency requires grantees to archive the final version of their article. With OnlineOpen, the author, the author's funding agency, or the author's institution pays a fee (currently $3000) to ensure that the article is made available to non-subscribers upon publication via Wiley Online Library, as well as deposited in the funding agency’s preferred archive. For the full list of terms and conditions, see http://olabout.wiley.com/WileyCDA/Section/id-406241.html.

Prior to acceptance you should not inform the Editorial Office that you intend to publish your paper OnlineOpen. All OnlineOpen articles are treated in the same way as any other article. They go through the Journal's standard peer-review process and will be accepted or rejected based on their own merit.

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](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.

**Units and Spellings:** Système International (SI) units should be used, as given in *Units, Symbols and Abbreviations* (4th edition, 1988), published by the Royal Society of Medicine Services Ltd, 1 Wimpole Street, London W1M 8AE, UK. Other abbreviations should be used sparingly and only if a lengthy name or expression is repeated throughout the text. Spelling should conform to that used in *The Concise Oxford Dictionary*, published by Oxford University Press. Authors should strenuously avoid the use of jargon or obscure technical terms.

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.


The Editor and Publisher recommend that citation of online published papers and other material should be done via a DOI (digital object identifier), which all reputable online published material should have — see [www.doi.org](http://www.doi.org) for more information. If an author cites anything which does not have a DOI they run the risk of the cited material not being traceable.

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](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.

**Tables:** Clear tables presenting relevant data are welcome. If tables of important data are particularly lengthy (e.g. tables reporting details of a large number of studies included in a systematic review), the Editors may suggest that some are published as supporting online material. Each table must be typewritten on a separate sheet and should be numbered consecutively with Arabic numerals, e.g. Table 1, and given a short caption. No vertical rules should be used. Units should appear in parentheses in the column headings and not in the body of the table. All abbreviations should be defined in a footnote.

**Electronic Artwork:** We would like to receive your artwork in electronic form. Please save vector graphics (e.g. line artwork) in Encapsulated Postscript format (EPS), and bitmap files (e.g. half-tones) in Tagged Image File Format (TIFF). Ideally, vector graphics that have been saved in metafile (.WMF) or pict (.PCT) format should be embedded within the body of the text file.


5.4 Colour Artwork

It is the policy of the JCPT for authors to pay the full cost for the reproduction of their colour artwork. Therefore, please note that if there is colour artwork in your manuscript when it is
accepted for publication, Wiley Blackwell require you to complete and return a Colour Work Agreement form before your paper can be published.

Any article received by Wiley Blackwell with colour work will not be published until the form has been returned. If you are unable to access the Internet, or are unable to download the form, please contact the Production Editor for a form. In compliance with the Payment Card Industry Data Security Standard, the Colour Work Agreement Form should be sent by post or courier to the address below, should you require colour:

Customer Services (OPI)
John Wiley & Sons Ltd
European Distribution Centre
New Era Estate
Oldlands Way
Bognor Regis
West Sussex PO22 9NQ8

5.5 Supporting Information
Supporting Information can be a useful way for an author to include important but ancillary information with the online version of an article. Examples of Supporting Information include additional tables, data sets, figures, movie files, audio clips, 3D structures, and other related nonessential multimedia files. Supporting Information should be cited within the article text, and a descriptive legend should be included. It is published as supplied by the author, and a proof is not made available prior to publication; for these reasons, authors should provide any Supporting Information in the desired final format.

For further information on recommended file types and requirements for submission, please visit: http://authorservices.wiley.com/bauthor/suppinfo.asp.

6. After Acceptance
Upon acceptance of a paper for publication, the manuscript will be forwarded to the Production Editor who is responsible for the production of the Journal.

Online Production Tracking: Online production tracking is available for your article through Wiley Blackwell's Author Services. Author Services enables authors to track their article — once it has been accepted — through the production process to publication online and in print. Authors can check the status of their articles online and choose to receive automated e-mails at key stages of production. Authors will receive an e-mail with a unique link that enables them to register and have their article automatically added to the system. Please ensure that a complete e-mail address is provided when submitting the manuscript. Visit http://authorservices.wiley.com/ for more details on online production tracking and for a wealth of resources including FAQs and tips on article preparation, submission and more.

Proof Corrections: The corresponding author will receive an e-mail alert containing a link to a website. A working e-mail address must therefore be provided for the corresponding author. The proof can be downloaded as a PDF (portable document format) file from this site.

Acrobat Reader will be required in order to read this file. This software can be downloaded (free of charge) from the following website: www.adobe.com/products/acrobat/readstep2.html. This will enable the file to be opened, read on screen, and printed out in order for any corrections to be added. Further instructions will be sent with the proof. Hard copy proofs will be posted if no e-mail address is available; in your absence, arrange for a colleague to access your e-mail to retrieve the proofs.
**Early View Publication:** JCPT is covered by Wiley Blackwell’s Early View service. Early View articles are complete full-text articles published online in advance of their publication in a printed issue. Early View articles are complete and final. They have been fully reviewed, revised and edited for publication, and the authors’ final corrections have been incorporated. Because they are in final form, no changes can be made after online publication. The nature of Early View articles means that they do not yet have volume, issue or page numbers, so these articles cannot be cited in the traditional way. They are given a Digital Object Identifier (DOI), which allows the article to be cited and tracked before it is allocated to an issue. After print publication, the DOI remains valid and can continue to be used to cite and access the article.

**Search Engine Optimization for Your Paper:** By optimizing your article for search engines, you will increase the chance of someone finding it. This in turn will make it more likely to be viewed and/or cited in another work. Consult our SEO Tips for Authors page in order to maximize online discoverability for your published research. Included are tips for making your title and abstract SEO-friendly, choosing appropriate keywords, and promoting your research through social media.

**Offprints:** Free access to the final PDF offprint of your article will be available via Author Services only. Please therefore sign up for Author Services if you would like to access your article PDF offprint and enjoy the many other benefits the service offers. Additional paper offprints may be ordered online. Please click on this link, fill in the necessary details and ensure that you type information in all of the required fields.

If you have queries about offprints, please email offprint@cosprinters.com.

**Note to NIH Grantees:** Pursuant to NIH mandate, Wiley Blackwell will post the accepted version of contributions authored by NIH grant-holders to PubMed Central upon acceptance. This accepted version will be made publicly available 12 months after publication. For further information, see www.wiley.com/nihmandate.

**Author Material Archive Policy:** Please note that unless specifically requested, Wiley Blackwell will dispose of all hardcopy or electronic material submitted two months after publication. If you require the return of any material submitted, please inform the Editorial Office or Production Editor as soon as possible if you have not yet done so.

**Clinical Case Reports:** We work together with Wiley’s Open Access Journal, Clinical Case Reports, to enable rapid publication of good quality case reports that we are unable to accept for publication in our Journal. Authors of case reports rejected by our Journal will be offered the option of having their case report, along with any related peer reviews, automatically transferred for consideration by the Clinical Case Reports Editorial Team. Authors will not need to reformat or rewrite their manuscript at this stage, and publication decisions will be made a short time after the transfer takes place. Clinical Case Reports will consider case reports from every clinical discipline including Medicine, Nursing, Dentistry, and Veterinary Science and may include clinical images or clinical videos. Clinical Case Reports is a Wiley Open Access journal and article publication fees apply. For more information please go to www.clinicalcasesjournal.com.
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/) 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
- the study is of a scale that is likely to lead to multiple different subsequent results-oriented publications, each then able to refer to this original methods paper, rather than having to repeat the methods in detail
- the rationale for important aspects of the research design is discussed in more depth than could be accommodated in a paper reporting the results, and in more detail than would usually be included in the protocol that would be posted on ClinicalTrials.gov or the ENCePP database.
- the description will serve as an instructive teaching example

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.

Other

Reviews of books and other media may be submitted only at the invitation of the Editors. However, suggestions are welcome.

3. EDITORS AND PEER-REVIEW
The Editor-in-Chief (Brian Strom) will apportion manuscripts to a Regional Editor based on location, unless there are conflicts of interest between the paper's authors and that regional office.

Papers from The Americas will be handled by:

Sean Hennessy
University of Pennsylvania Perelman School of Medicine, Center for Pharmacoepidemiology Research and Training, 824 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021, USA
Tel: 215-898-1489. E-mail: kinman@pobox.upenn.edu

Papers from Europe and UK will be handled by:

Joerg Hasford
Ludwig Maximilian University of Munich, Marchioninistr. 15, D-81377 Munich, Germany
Tel: 49 89 7095 7480. E-mail: has-pds@ibe.med.uni-muenchen.de

Papers from Asia, Africa, the Middle East, and Oceania will be handled by:

Byung Joo Park
28 Yongon-Dong, 103 Daehakno, Chongno-Gu, Seoul 110-799, Korea
Tel: 44 23 9259 7220. E-mail: bipark@snu.ac.kr

A fast-track review and publication process is in place for particularly time-sensitive findings of urgent public health importance. The Editor-in-Chief should be contacted to begin this process.

Authors are encouraged to propose reviewers who have special competence to review their work. Authors may also ask that, due to a possible conflict of interest, named members of the Editorial Board or other individuals should not be selected to review a particular submission. The Editors will pay close attention to such requests, but must reserve to themselves the final choice of reviewers.

4. SUBMISSION OF MANUSCRIPTS

All submissions should be made online at the Pharmacoepidemiology and Drug Safety ScholarOne Manuscripts site—http://mc.manuscriptcentral.com/pds. New users should first create an account. Once a user is logged onto the site, submissions should be made via the ‘Author Centre’.

Authors must also supply:

- Completed Conflict of Interest Disclosure Form(s). Conflict of Interest (COI) disclosure forms must be uploaded with your manuscript files at submission. Please choose the file designation ‘Conflict of Interest form’ when submitting each of your forms. Please note: a separate COI form must be completed by the corresponding author and each co-author. If you do not submit separate COI forms for each of the authors, your manuscript will be unsubmitted back to you.
- Copyright and Permissions - If your paper is accepted, the author identified as the formal corresponding author for the paper will receive an email prompting them to login into Author Services; where via the Wiley Author Licensing Service (WALS) they will be able to complete the license agreement on behalf of all authors on the paper.
For authors signing the copyright transfer agreement
If the OnlineOpen option is not selected the corresponding author will be presented with the copyright transfer agreement (CTA) to sign. The terms and conditions of the CTA can be previewed in the samples associated with the Copyright FAQs below:

CTA Terms and Conditions http://authorservices.wiley.com/bauthor/faqs_copyright.asp

For authors choosing OnlineOpen
If the OnlineOpen option is selected the corresponding author will have a choice of the following Creative Commons License Open Access Agreements (OAA):

Creative Commons Attribution License OAA
Creative Commons Attribution Non-Commercial License OAA
Creative Commons Attribution Non-Commercial -NoDerivs License OAA

To preview the terms and conditions of these open access agreements please visit the Copyright FAQs hosted on Wiley Author Services and visit http://www.wileyopenaccess.com/details/content/12f25db4c87/Copyright--License.html.

If you select the OnlineOpen option and your research is funded by The Wellcome Trust and members of the Research Councils UK (RCUK) you will be given the opportunity to publish your article under a CC-BY license supporting you in complying with Wellcome Trust and Research Councils UK requirements. For more information on this policy and the Journal’s compliant self-archiving policy please visit: http://www.wiley.com/go/funderstatement.

5. PREPARATION OF MANUSCRIPTS

Manuscripts must be written in English.

Text should be supplied in a format compatible with Microsoft Word for Windows (PC). Charts and tables are considered textual and should also be supplied in a format compatible with Word. All figures (illustrations, diagrams, photographs) should be supplied in jpg, tiff or eps format.

All manuscripts must be typed in 12pt font with margins of at least 2.5 cm.

Submissions must comply with the word limits defined in section 2, and include:

Title Page

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

- the title of the paper;
- a running head not exceeding 50 characters;
- names of authors;
- 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;
- up to 5 bulleted 'take-home' messages, or key points;
• name(s) of any sponsor(s) of the research contained in the paper, along with grant number(s);
• a Conflict of Interest statement, summarizing the information from each author (see section 4);
• word count excluding abstract, tables, figures and references
• a statement about prior postings and presentations.

Abstracts

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.

Letters and Commentaries do not require abstracts.

Text

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

Letters should be formatted in one continuous section. Commentaries should be formatted as appropriate to content.

Tables and Figures

Tables and figures should not be inserted in the appropriate place in the text but should be included at the end of the paper, each on a separate page.

Tables and figures should be referred to in text as follows: Figure 1, Figure 2; Table 1, Table 2. The place at which a table or figure is to be inserted in the printed text should be indicated clearly on a manuscript. Each table and/or figure must have a legend that explains its content without reference to the text.

Any figure submitted as a colour original will appear in colour in the Journal's online edition free of charge. Colour figures will be printed in the Journal on condition that authors contribute to the associated costs.

Authors are responsible for obtaining permission to reproduce previously published figures or tables (see section 4).

Abbreviations

All abbreviations should be preceded the first time they appear by the full name except the SI symbols for units which are to be used without explanation. If systems other than SI units of measurement are employed, give conversion factors.

Nomenclature

Use generic names of drugs unless the specific trade name of a drug is essential to the discussion. Indicate sources of unusual materials and chemicals, and the manufacturer and model of equipment used.
Reference Style

PDS prefers references to primary sources when appropriate rather than reviews, and to permanent, archival sources when available rather than references to the web. Citations of sources that are continually changing are particularly problematic.

References should be indicated in the text by superscript Arabic numbers and listed at the end of the paper in the order in which they appear in the text. All references must be complete and accurate. Where possible the DOI for the reference should be included at the end of the reference. Online citations should include the date of access.


If necessary, cite unpublished or personal work in the text but do not include it in the reference list.

References should be listed in the following style:


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.

6. DECLARATION

Original Publication

Submission of a manuscript will be held to imply that it contains original unpublished work and is not being submitted for publication elsewhere at the same time.

Prior posting on the internet normally constitutes publication. However, manuscripts based on reports to government agencies that are posted on the government agency’s website can be considered for publication. Similarly, manuscripts based on theses published on university websites can be considered for publication. The author must supply a full
statement to the respective Editor about all postings, providing a link to the related report. If accepted for publication, a link to the published article on the journal website may then be inserted on the government or university website. The final published article, under copyright agreement, may not be posted on any other website without permission from the publisher.

A statement about prior postings (with link to website) and public presentations must be included on the title page of the submitted manuscript.

PDS encourages authors to release results of studies of public health importance to regulators as appropriate. This reporting is the responsibility of the author and the sponsor, however, not the journal. When relevant, it should be specified in the report that the manuscript is in press in PDS.

**Conflict of Interest**

Authors are responsible for disclosing all financial and personal relationships between themselves and others that might appear to bias their work. To prevent ambiguity, authors must state explicitly in the Conflict of Interest form whether potential conflicts do or do not exist. Authors should describe the role of the study sponsor(s), if any, in study design, in the collection, analysis and interpretation of data, in the writing of the report and in the decision to submit the report for publication. If the supporting source(s) had no such involvement, the authors should so state. (See section 4.)

**Clinical Trials Registration**

In accordance with the trials registration policy of the International Committee of Medical Journal Editors ([http://www.icmje.org](http://www.icmje.org)), Pharmacoepidemiology and Drug Safety encourages the registration of all interventional trials, whether early or late phase. The registry must be electronically searchable and accessible to the public at no charge (see [http://www.who.int/ictrp/en/](http://www.who.int/ictrp/en/)).

**Ethical Approval of Studies and Informed Consent**

For all manuscripts reporting data from studies involving human participants (i.e., human subjects research), formal review and approval by an appropriate institutional review board (IRB) or ethics committee is required, and should be confirmed in the Methods section. That board should be named in the paper. The authors should also state whether informed consent was obtained, or whether this requirement was waived by the IRB/ethics committee. Authors should be able to submit, upon request, a statement from the IRB/ethics committee indicating approval of the research, as well as either a sample of a patient consent form or a statement from the IRB/ethics board waiving the requirement for informed consent. For studies judged by the authors not to constitute human subjects research (e.g., computer simulations or epidemiologic studies performed in persons who cannot be identified or have the study information associated with them), the authors should specify the reason they believe the study is not human subjects research, and whether this determination was confirmed by an IRB/ethics committee.

Authors are expected to follow the Guidelines for Good Pharmacoepidemiology Practices as described in Pharmacoepidemiol Drug Saf. 2008 Feb;17(2):200-8. (link to article, with free access) PDS recommends that authors use STROBE ([http://www.strobe-statement.org](http://www.strobe-statement.org)) as a guideline for the reporting of observational studies and CONSORT ([http://www.consort-statement.org](http://www.consort-statement.org)) as a guideline for the reporting of randomized controlled clinical trials.
Authorship

All persons designated as authors should qualify for authorship and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One or more authors should take responsibility for the integrity of the work as a whole, from inception to published article. Authorship credit should be based only on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published. Conditions 1, 2 and 3 must all be met. Acquisition of funding, the collection of data or general supervision of the research group, by themselves, do not justify authorship.

Committee on Publication Ethics (COPE)

As a member of the Committee on Publication Ethics (COPE), adherence to the aforementioned submission criteria is considered essential for publication in *Pharmacoepidemiology and Drug Safety*; mandatory fields are included in the online submission process to ensure this. If, at a later stage in the submission process or even after publication, a manuscript or authors are found to have disregarded these criteria, it is the duty of the Editor-in-Chief to report this to COPE. COPE may recommend that action be taken, including but not exclusive to, informing the authors' professional regulatory body and/or institution of such a dereliction.

The website for COPE may be accessed at: [http://www.publicationethics.org.uk](http://www.publicationethics.org.uk)

7. ADDITIONAL INFORMATION ON ACCEPTANCE

Proofs

Proofs of accepted articles will be sent to the corresponding author for checking. This stage is to be used only to correct errors that may have been introduced during the production process. Prompt return of the corrected proofs, preferably within two days of receipt, will minimise the risk of the paper being held over to a later issue.

Offprints

Free access to the final PDF offprint or your article will be available via Author Services. Please therefore sign up for Author Services if you would like to access your article PDF offprint and enjoy the many other benefits the service offers.

Early View

Early View is Wiley's exclusive service presenting individual articles online as soon as they are ready before the release of the compiled print issue. Early View articles are complete, citable and are published in an average time of 6 weeks from acceptance.

Note to NIH grantees

Pursuant to NIH mandate, Wiley Blackwell will post the accepted version of contributions authored by NIH grant-holders to PubMed Central upon acceptance. This accepted version will be made publicly available 12 months after publication. For further information, click here.
Best Paper Award

Pharmacoepidemiology and Drug Safety provides an annual Best Paper Award to the first author of the strongest contribution within a given volume, as determined by the Editors and a representative of the International Society for Pharmacoepidemiology (ISPE). The Award is open to all authors. Certificates and prizes are awarded at ISPE's annual meeting.

PLEASE NOTE: PDS employs a plagiarism detection system. By submitting your manuscript to this journal you accept that your manuscript may be screened for plagiarism against previously published works.
ANNEXURE H

Proof of language editing