Antidepressant usage by South African children and adolescents:

A drug utilisation review

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B.Pharm

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

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November 2013

ACKNOWLEDGEMENTS

This study would not have been possible without the guidance and the help of several persons who, in one way or another, contributed and extended their assistance in the preparation and completion of this study. I would like to extend my heartfelt appreciation, especially to the following:

- First and foremost, my **Heavenly Father** for giving me guidance, patience, direction and the capability to embark on this journey in my life!
- My amazing supervisor, **Dr Johanita Burger**, for the incredible amount of support, guidance, patience and for believing in me from the first day.
- My co-supervisor, **Prof dr Martie Lubbe**, for the statistical analysis, all the insight, assistance and guidance.
- The **NWU** for funding this study and giving me this opportunity.
- My Mother, **Magda van Rooyen,** Father, **Kobus van Rooyen,** and my sister, **Dune van Rooyen** for their incredible amount of love, laughs and support!!
- The rest of my **family** for their never-ending support and love. They say you can't choose your family, and I am happy to say it doesn't matter to me.
- My **friends** for sticking by me through the good and bad times, for their support.
- **Prof Schalk Vorster** for the English editing of the dissertation.
- **Mrs Anriëtte Pretorius** at the library for all the assistance in the literature review.
- **Ms Anne-Marie Bekker** for assistance in the statistical analysis of the data.

Joshua 1:9

"Have not I commanded thee? Be strong and of good courage; be not afraid, neither be thou dismayed: for the LORD thy GOD is with thee whithersoever thou goest"

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LIST OF ACRONYMS AND ABBREVIATIONS

5HT – 5-Hydroxytryptamine

ADHD – Attention deficit hyperactivity disorder
ATC – Anatomical Therapeutic Chemical classification system
AUC – Area under the curve

COPD – Chronic obstructive pulmonary disease
CYP2D6 – Cytochrome P450-2D6

DSM – Diagnostic and statistical manual

ECG – Electrocardiogram
EMEA – European Medicines Agency
EU – European Union

FDA – Food and Drug Administration, United States of America

GAD – General anxiety disorder

ICD-10 – The International Statistical Classification of Diseases and Related Health Problems 10th Revision

LSD – Lysergic acid diethylamide

MAO-A – Monoamine oxidase enzyme isoform A
MAO-B – Monoamine oxidase enzyme isoform B
MAOI – Mono-amine oxidase inhibitor
MCC – Medicines Control Council, South Africa
MHRA – Medicines and Healthcare Products Regulatory Agency
MIMS – Monthly Index of Medical Specialities
MIS – Malahyde Information Systems

LIST OF ACRONYMS AND ABBREVIATIONS (CONTINUED)

NAPPI – National Pharmaceutical Pricing Index code
NSAID – Non-steroid anti-inflammatory drug
NWU – North-West University

OCD – Obsessive compulsive disorder

PBM – Pharmaceutical Benefit Management
PDD – Prescribed daily dosage
PI – Phosphatidylinositol
PTSD – Post-traumatic stress disorder

RDD – Recommended daily dosage

SAD – Social anxiety disorder
SAMF – South African medicines formulary
SAS – Statistical analysis system for Windows
SNRI – Serotonin and noradrenalin reuptake inhibitor
SSRI – Selective serotonin reuptake inhibitor

TCA – Tricyclic antidepressant

UK – United Kingdom
USA – United States of America

WHO – World Health Organization

ABSTRACT

Keywords: antidepressants, prescribing patterns, children, adolescents, drug-drug interactions, prescribed daily dosages

This study set out to review and analyse aspects of antidepressant prescribing in children and adolescents in a section of the private health care sector of South Africa. The research was conducted in two phases, namely a literature review and an empirical investigation. The aim of the literature review was to provide background to the study by conceptualising antidepressants. The empirical review followed a retrospective, descriptive, observational design. The data employed in the study was obtained from the medicine claims database of a South African Pharmaceutical Benefit Management (PBM) company. The study population consisted of 3 611 children and adolescents receiving ≥1 antidepressants from 1 January 2010 to 31 December 2010.

Basic descriptive statistics, such as frequency, prevalence, average, weighted average, standard deviation, weighted standard deviation, median, effect sizes, prescribed daily dosages and DU95% methodology were used to characterise the study sample, and were calculated using the Statistical Analysis System SAS® for Windows 9.3® program. The data were used to determine the prescribing patterns of antidepressants with regard to age, gender, geographic area, type of prescriber, the comparison of prescribed daily dosages vs. recommended daily dosages, and the prevalence of potential drug-drug interactions. Potential drug-drug interactions were identified and compiled by using various interaction compendia, whereas recommended daily dosages were identified by cross-referencing various dosage compendia. The study population consisted of 1 850 girls and 1 761 boys. The mean age of girls was 13.7 ± 3.9 years, vs. 12.3 ± 3.8 years for boys (d = 0.4).

A total of 11 735 prescriptions containing 12 272 antidepressants were documented in 2010. Results of the study furthermore showed that the average number of prescriptions claimed per patient increased with age, from an average of 1.0 ± 0.28 among those up to the age of 2 years, to an average of 3.4 ± 3.21 among those 16 to 18 years of age. Prescribing with regard to age groups differed, rising gradually from birth and peaking at middle childhood for boys, whereas antidepressant use in girls increased from birth up to 6 years of age, reaching a plateau and increases again from age 13 and onward.

Approximately 25% (n = 12 272) of antidepressants prescribed were either not indicated in children, or the dosages were deemed too high. More than 50% (n = 12 272) of antidepressants prescribed were in the Gauteng province.

The SSRIs (selective serotonin re-uptake inhibitors) and the TCAs (tricyclic antidepressants) were the most prescribed antidepressants in both gender groups. The male-to-female ratio for the selective serotonin re-uptake inhibitors was 0.9, compared to 1.2 for the tricyclic antidepressants. The top three antidepressants prescribed were imipramine (21.8%), citalopram (15.3%) and escitalopram (14.7%, n = 12 272).

Potential DDIs were observed on 284 (2.4%) (n = 11 743) prescriptions. The drug pairs with potential drug-drug interactions prescribed most, were imipramine with methylphenidate [43 cases (15.1%)] and valproic acid [38 cases (13.4%)], and followed by methylphenidate in combination with fluoxetine and sertraline [both documenting 32 cases (11.3%), respectively. The TCAs accounted for 182 (64.1%) cases of possible DDIs (drug-drug interactions), whereas combination therapy of SSRIs and TCAs accounted for 21.4% of potential DDIs.

In conclusion, this study determined that there were a number of differences with regard to antidepressant prescribing in children and adolescents. Recommendations for future studies were made.

UITTREKSEL

Trefwoorde: antidepressante, voorskryfpatrone, kinders, adolessente, geneesmiddel-geneesmiddel-interaksies, voorgeskrewe daaglikse dosisse

Die doel van die studie was die hersiening en ontleding van aspekte van die voorskryfpatrone vir antidepressante in kinders en tieners, in 'n gedeelte van die private gesondheidsorgsektor van Suid-Afrika. Die navorsing is in twee fases gedoen, naamlik 'n literatuurstudie en 'n empiriese ondersoek. Die doel van die literatuuroorsig was om agtergrond te gee vir die studie deur die konseptualisering van antidepressante. Die empiriese hersiening volg op 'n retrospektiewe, beskrywende, observasie-ontwerp. Die data is verkry vanuit die medisyne-eise databasis van 'n Suid-Afrikaanse farmaseutiesevoordele-bestuursmaatskappy. Die studiepopulasie het bestaan uit 3 611 kinders en tieners wat ≥1 antidepressant ontvang het vanaf 1 Januarie 2010 tot 31 Desember 2010.

Basiese beskrywende statistiek soos frekwensie, voorkoms, gemiddelde, geweegde gemiddelde, standaard afwyking, geweegde standaard afwyking, mediaan, effekgroottes, voorgeskrewe daaglikse dosisse en DU95%-metodologie is gebruik om die studiepopulasie te karakteriseer, en is bereken met behulp van die statistiese analisesisteem SAS ® vir Windows 9.3 ®-program. Die data is gebruik om die voorskryfpatrone van antidepressante te bepaal met betrekking tot ouderdom, geslag, geografiese aspekte, tipe voorskrywer, die vergelyking van voorgeskrewe daaglikse dosisse teenoor aanbevole daaglikse dosisse, en die voorkoms van potensiële geneesmiddel-geneesmiddel interaksies (GGI). Potensiële GGIs is geïdentifiseer en saamgestel deur die gebruik van verskillende bronne wat spesialiseer in interaksies, terwyl aanbevole daaglikse dosisse geïdentifiseer is deur kruisverwysing van verskeie bronne t.o.v. geneesmiddel-dosisse. Die studiepopulasie het bestaan uit 1 850 meisies en 1 761 seuns. Die gemiddelde ouderdom van die meisies was 13.7 ± 3.9 jaar teenoor 12.3 ± 3.8 jaar vir seuns (d = 0.4).

'n Totaal van 11 735 voorskrifte met 12 272 antidepressante was gedokumenteer vir 2010. Resultate van die studie het ook getoon dat die gemiddelde aantal voorskrifte geëis per pasiënt verhoog het met die ouderdom, van 'n gemiddeld van 1.0 ± 0.28 onder diegene vanaf geboorte tot op die ouderdom van 2 jaar, tot 'n gemiddeld van 3.4 ± 3.21 onder die 16 tot 18 jarige ouderdomsgroep. Voorskryfpatrone met betrekking tot ouderdomsgroepe het verskil, met

geleidelike styging vanaf geboorte tot ‘n hoogtepunt tydens die middelkinderjare vir seuns, terwyl antidepressantgebruik in meisies geleidelik gestyg het vanaf geboorte tot en met 6-jarige ouderdom, 'n plato bereik het en weer verhoog vanaf het vanaf ouderdom 13 en ouer.

Ongeveer 25% (n = 12 272) van die voorgeskrewe antidepressante is óf nie in kinders geïndikeer nie of die dosisse is geag te hoog te wees. Meer as 50% (n = 12 272) van antidepressante wat voorgeskryf is, was in die Gauteng provinsie.

Die SSHIs (selektiewe serotonien heropname-inhibeerders) en die TSAs (trisikliese antidepressante) was die mees voorgeskrewe antidepressante vir beide geslagte. Die man-tot-vrou-verhouding vir die selektiewe serotonien heropname-inhibeerders was 0.9, in vergelyking met 1.2 vir die trisikliese antidepressante. Die top drie antidepressante wat voorgeskryf is, was imipramine (21.8%), sitalopram (15.3%) en essitalopram (14.7%, n = 12 272).

Potensiële GGIs was waargeneem op 284 (2.4%) (n = 11 743) voorskrifte. Die geneesmiddelkombinasies met die meeste potensiële GGIs voorgeskryf, was imipramine met metielfenidaat [43 gevalle (15.1%)] en valproïensuur [38 gevalle (13.4%)], en gevolg deur metielfenidaat in kombinasie met fluoksetien en sertraline [beide met 32 gevalle (11.3%), onderskeidelik]. Die TSAs was verantwoordelik vir 182 (64.1%) gevalle van moontlike GGIs, terwyl kombinasieterapie van SSHIs en TSAs verantwoordelik was vir 21.4% van die potensiële GGIs.

Ten slotte, hierdie studie het bevind dat daar 'n aantal verskille met betrekking tot die voorskryf van antidepressante in kinders en tieners was. Aanbevelings is gemaak vir toekomstige studies.

PREFACE

This study has been conducted in an article format. The chapter containing the results, Chapter 3, is in the form of manuscripts as required by the regulations of the North-West University, in addition to additional results documented but not included in the manuscripts. Two manuscripts will be submitted for publishing in the following journals:

- *Pharmacoepidemiology and drug safety*
- *Journal of clinical pharmacy and therapeutics*

The references for the individual manuscripts are cited according to the instructions for authors as required by the different journals. However, a complete reference list is included at the end of the dissertation according to the reference style of the North-West University.

The division of chapters is stipulated as follows. Chapter 1 will give a brief introduction, accompanied by the methodology used to conduct this study. Chapter 2 will entail a literature review of antidepressants, potential drug-drug interactions and recommended daily dosages of the antidepressants in children and adolescents. The results and discussion will be included in Chapter 3 in article format with additional results whereas Chapter 4 will hold the conclusions, recommendations and limitations drawn from this study. The references and annexures will follow at the end.

The co-authors named in the manuscripts acted as supervisor and co-supervisor during the study. They gave consent that both articles may be used as part of this dissertation. The specific contributions of each author are stipulated on the next few pages.

AUTHORS' CONTRIBUTIONS

The contribution of each author to the study and Manuscript 1, entitled "Assessment of potential drug-drug interactions among South African children and adolescents receiving antidepressants" is stipulated in the following table.

Author	**Role in studies**
Mr C.J. van Rooyen	Responsible for the literature review Planning and design of manuscript Interpretation of results Writing of manuscript
Dr J.R. Burger (Supervisor)	Supervision of conception and design of study and manuscript Statistical analysis Guidance in the interpretation of results Supervision in the writing of the manuscript and study Revising the manuscript critically for important intellectual content and final approval of the version to be published
Prof dr M.S. Lubbe (Co-supervisor)	Co-supervision of conception and design of study and manuscript Acquisition of data Complex programming for statistical analysis Revising the manuscript critically for important intellectual content and final approval of the version to be published

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

I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is representative of my actual contributions and I hereby give my consent that it may be published as part of the M.Pharm study of C.J. van Rooyen.

Dr J.R. Burger

Prof dr M.S. Lubbe

AUTHORS' CONTRIBUTIONS (CONTINUED)

The contribution of each author for Manuscript 2, entitled "Antidepressant prescribing patterns to children and adolescents in South African private health sector: focus on variations in age, gender and dosage prescribed" is stipulated in the following table.

Author	**Role in studies**
Mr. C.J. van Rooyen	Responsible for the literature review Planning and design of manuscript Interpretation of results Writing of manuscript
Dr J.R. Burger (Supervisor)	Supervision of original planning conception and design of study and manuscript Statistical analysis Guidance in the interpretation of results Supervision in the writing of the manuscript Revising the manuscript critically for important intellectual content and final approval of the version to be published
Prof dr M.S. Lubbe (Co-supervisor)	Co-supervision of conception and design of the manuscript Acquisition of data Complex programming for statistical analysis Revising the manuscript critically for important intellectual content and final approval of the version to be published

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 manuscript, as indicated above, is representative of my actual contributions and I hereby give my consent that it may be published as part of the M.Pharm study of C.J. van Rooyen

Dr J.R. Burger

Prof dr M.S. Lubbe

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 methods and division of chapters.

1.2 BACKGROUND AND PROBLEM STATEMENT

According to Murray *et al.* (2004:1102) antidepressants are increasingly being prescribed to children and adolescents in populations worldwide, especially combined with psychotropic medications, increasing the odds for poly-pharmacy (Chen *et al.,* 2011:1450). Pratt *et al.* (2011:1) found in a study of antidepressant use in people aged 12 and over in the United States that 11% of Americans aged 12 years and over, took antidepressant medication, and 3.7% were between 12 and 17 years of age. South Africa is no exception to these observed prescribing patterns, as illustrated by recent reports indicating prevalence rates increasing from 3.8% in 1996 to 8.7% in 2002-2003 (Truter *et al.*, 2006:303). Another study found that 6.4% of all patients who received antidepressants in 2006 were aged ≤19 years (van der Westhuizen *et al.*, 2007:92); together with the prescribing of certain agents (i.e. sulpiride 50mg) to children even as young as six weeks (Burger *et al.,* 2009). A point of concern is the rate of off-label antidepressant prescribing in children and adolescents. High rates are reported worldwide in various populations (Burger *et al.,* 2009; Ma *et al.,* 2005; Volkers *et al.,* 2007: 1060; Zullino *et al.*, 2008:23).

Several explanations for the increase in the use of antidepressants are put forward in the literature. For instance, Kelly *et al.* (2003) list the rise in younger suicides as a possible reason, whilst Morrison (2008) and Currie (2005:19) are of the opinion that the lack of alternative medicine, availability of the antidepressants, as well as fierce marketing initiatives of new antidepressants as the selective serotonin reuptake inhibitors (Mancini *et al.,* 2002:494) may be the cause. The World Health Organization (2001:1) lists more reliable and accurate diagnoses of mental and neurological disorders as the main cause of increased prevalence rates. Munoz-Arroyo *et al.* (2006) furthermore speculate that the main conditions antidepressants are

commonly used for may have increased or that patients may be presenting with related problems more frequently.

The main indication for the use of antidepressants is depression, but there are other ailments/conditions besides that, which antidepressants are being prescribed for. These include obsessive compulsive disorder (OCD), child behaviour disorders, nocturnal enuresis, autism, attention deficit hyperactivity disorder (ADHD), bulimia nervosa, prophylaxis for headache, hyperactivity, neuropathic pain, anorexia nervosa, general and social anxiety disorders and smoking cessation (Snyman, 2007; Sweetman, 2008). Weismann *et al.* (1999:1709) indicated that the prevalence of the main indication for antidepressants *i.e.* depression, in America, was 4% of 12 to 17-year olds and 9% of 18-year olds. OCD in adolescents ranges from 0.35–4% (Fogel, 2003:34). The prevalence of bulimia and anorexia nervosa differs between Western and non-Western countries with prevalence rates in Western countries for anorexia nervosa ranging from 0.1–5.7% in female subjects. Prevalence rates for bulimia nervosa ranges from 0–2.1% in males and from 0.3–7.3% in female subjects in Western countries, compared to 0.46–3.2% in female patients in non-Western countries (Makino *et al.*, 2004:49). The worldwide pooled ADHD prevalence was 5.29% in 2007 (Polanczyk *et al.*, 2007:942); and approximate age-distributed prevalence of nocturnal enuresis is as follows: 15% of 5-year olds, 7% of 8 year-olds, 5% of 10-year olds, and 2% of 15-year olds (Clinical knowledge summaries, 2005).

Antidepressant prescribing is increasing, and there are only a few recent studies reporting on the prescribing patterns in South Africa. A point of concern is potential drug-drug interactions to which children and adolescents may be exposed. Some interactions' outcomes are of a severe nature and may lead to hospitalisation or in some cases even death. One may assume that with an increase in indications an increase in prescribing will follow, and this in turn may lead to a widening of the probability of drug-drug interaction taking place. Another concern is the appropriate dosing of medicine in pediatric patients. The risk of error is higher in these patients because dosages are subject to body weight, height, surface area or the age of a patient (Zhang *et al.,* 2012:2).

Drug utilisation is defined as "*The marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences*" (World Health Organization, 2003). Drug utilisation studies have been used to determine a number of different factors with regard to prescribing patterns, such as off-label usage (Burger *et al.,* 2009:7), fluctuations in medicine prescribing with regard to newer products (Cohen *et al.,* 2011:494) and the prevalence of potential drug-drug interactions (Katende-

Kyenda *et al.*, 2008:397). The DU90% methodology is a "*simple, inexpensive and flexible method to determine the quality of a drug*" or a group of drugs prescribed in routine health care (Bergman *et al.*, 1998:116). Bergman *et al.* (1998:117) further state that the number of products together with prescription guideline adherence in the DU90% may serve as general qualitative indicators. By analysing prescribing patterns utilising drug utilisation review methodology, it can be determined whether there are appropriate antidepressant dosages being prescribed to children and adolescents in South Africa. It can also be utilised to determine the number of potential drug-drug interactions and to which extent children and adolescents are exposed to these interactions. The following research questions can be formulated based on the before mentioned discussion:

- To what extent are South African children and adolescents exposed to potentially life-threatening drug-drug interactions?
- To what extent are prescribers adhering to the recommendations of appropriate antidepressant prescribing in South Africa, specifically with regard to recommended daily dosage?

1.3 RESEARCH OBJECTIVE

This research includes a general objective, as well as various specific objectives.

1.3.1 GENERAL OBJECTIVE

The general objective of this study is to review and analyse aspects of antidepressant prescribing in children and adolescents in a section of the private health care sector of South Africa.

1.3.2 SPECIFIC OBJECTIVES

The study will be conducted in two phases. The specific objectives are divided according to the phase of the study, namely the literary review objectives and the empirical study objectives. The literary review objectives are as follows:

- To review from the literature antidepressants as a pharmacological treatment class in children and adolescents.
- To identify possible drug-drug interactions and consequences in children and adolescents.

- To establish factors influencing antidepressant medicine usage patterns in children and adolescents.
- To determine the recommended daily dosages for antidepressants in children and adolescents by cross-referencing various dosage compendia.

The objectives of the empirical phase of the study are as follows:

- To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to age and gender, using medicine claims data.
- To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to type of prescriber, using medicine claims data.
- To establish the prescribed daily dosages of antidepressants prescribed to children and adolescents in South Africa, using medicine claims data.
- To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to geographical area, using medicine claims data.
- To determine the number of potential drug-drug interactions in children and adolescents receiving antidepressant therapy, using medicine claims data.

Table 1.1 lists the aforementioned specific objectives and which chapter, section or paragraph holds the relevant data to achieve the objective.

Table 1.1 Specific objectives and the sections in which they were met

Objective	Chapter, Section or Paragraph
To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to age and gender, using medicine claims data	Paragraph 4.2.1
To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to type of prescriber, using medicine claims data	Paragraph 4.2.2
To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to prescribed daily dosages, using medicine claims data	Paragraph 4.2.3
To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to geographical data, using medicine claims data	Paragraph 4.2.4
To determine the number of potential drug-drug interactions in children and adolescents receiving antidepressant therapy, using medicine claims data	Paragraph 4.2.5

1.4 RESEARCH METHODS

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

1.4.1 PHASE ONE: LITERATURE REVIEW

The literature review consists of a review of antidepressants, including the definition, indications, interactions, outcomes of possible interactions and dosages. The definition of a child and adolescent, as well as the factors which influence antidepressants' prescribing patterns in children and adolescents will be discussed.

To achieve the specific objectives of the literature review, a number of books, websites and articles from different fields of research and practices i.e. pharmacology and pharmacy practice were used.

Several older references were included in the review because of their significance in terms of their original contribution to the subject of antidepressant indication in a number of ailments such as Shapiro (1975), Young *et al.* (1979), Schachter *et al.* (1980), Thorén *et al.* (1980), Flament *et al.* (1985), Eberhard *et al.* (1988), Leonard *et al.* (1990), Trott *et al.* (1992), Versiani *et al.* (1992), Apter *et al.* (1994), Ayuso-Gutierrez *et al.* (1994), Black *et al.* (1994), Goldstein *et al.* (1995), Ikeguchi *et al.* (1995), Fowler *et al.* (1996), Tanum *et al.* (1996), Koponen *et al.* (1997), Lecrubier *et al.* (1997), Rocca *et al.* (1997), Wade *et al.* (1997), Yonkers *et al.* (1997), Ballenger *et al.* (1998), Hudson *et al.* (1998), March *et al.* (1998), Schneier *et al.* (1998), Stein *et al.* (1998), Brannon *et al.* (1999), Connor *et al.* (1999), Jorenby *et al.* (1999), Sindrup *et al.* (1999). Other older references assited in the identification of potential drug-drug interactions such as Raab *et al.* (1950), Goldberg *et al.* (1964), Lloyd *et al.* (1965), Aderhold *et al.* (1970), Hunter *et al.* (1970), Fann *et al.* (1971), Ciocatto *et al.* (1972), Boakes *et al.* (1973), Jounela *et al.* (1973), Logie *et al.* (1976), Gerson *et al.* (1977), Spaulding *et al.* (1977), Davies *et al.* (1978), Ghose (1980a), Ghose (1980b), MacCallum (1980), Nawishy *et al.* (1981), Silverglat (1981), Tung, *et al.* (1981), Bruckner *et al.* (1983), Richens *et al.* (1983), Rauch *et al.* (1984), Thomas *et al.* (1984), Tollefson *et al.* (1984), Glassman *et al.* (1987), Miller *et al.* (1987), Ventafridda *et al.* (1987), Sovner *et al.* (1988), Alvine *et al.* (1990), Zubieta *et al.* (1991), Toutoungi (1992), Härtter *et al.* (1993), Ketai (1993), Graber *et al.* (1994), Markel *et al.* (1994), Rasheed *et al.* (1994), Zogno *et al.* (1994), Coulter *et al.* (1995), Hernandez *et al.* (1995), Ketter *et al.* (1995), Spinda *et al.* (1995), Barrett *et al.* (1996), Mathew *et al.* (1996), Self *et al.* (1996), Sylvester *et al.*

(1996), Thomas *et al.* (1996), Blanche (1997), Alderman *et al.* (1997), Mekler *et al.* (1997), Normann *et al.* (1997), Benazzi (1998a), Benazzi (1998b), Gardner *et al.* (1998), Gordon (1998), Mattes (1998), Michalets (1998), Soutullo *et al.* (1998), Weiner *et al.* (1998).

1.4.2 PHASE TWO: EMPIRICAL INVESTIGATION

The discussion in this section focuses on the particulars of the empirical investigation phase of the study.

1.4.3 STUDY DESIGN

This study followed a retrospective, descriptive, and observational design.

Kirk (2013:9) defines a **retrospective** study as a study which uses "*historical records to look backward in time".* This study can thus be classified as retrospective due to the data dating from 1 January 2010 to 31 December 2010. A **descriptive** study is a study which usually describes characteristics of a group being investigated and the statistic goal is usually simple data descriptions or an estimate of a characteristic in the study population (Katzellenbogen, 2007:62). In the present study, the descriptive design will be applied through the description of the prescribing patterns of antidepressants in children and adolescents, focusing on drug interactions and dosages. **Observational** studies are studies where "*the researcher records information concerning the subjects under study without any interference with the process that is generating the information"* (Ott *et al.*, 2010:20). In the present study medicine claims data (secondary data) will be analysed — the investigator therefore had no effect on the claims processed.

1.4.4 DATA SOURCE

The data employed in the study were obtained from the medicine claims database of a South African Pharmaceutical Benefit Management (PBM) company. This PBM, which provided the data for this study, is a privately owned South African managed care organisation which has been in business for more than 24 years. The PBM currently provides real-time electronic pharmaceutical claims processing services to approximately 36 medical schemes in South Africa, or more than 1.6 million medical scheme beneficiaries. The identity of the company may not be disclosed due to ethical consideration. Data for a one year period, from January 1, 2010 to December 31, 2010 were obtained.

1.4.5 STUDY POPULATION

This section entails a discussion of the rationale for the selection of the study population, as well as the steps followed in the patient selection process.

1.4.5.1 Selection process for the study population

The process followed from obtaining the data to the selection of the study population (i.e. children and adolescents) is depicted in Figure 1.1. The following steps were in this process:

- Step 1: Data (refer to Table 3.1) were obtained from PBM's central database.
- Step 2: Application of exclusion criteria to obtain an individual data subset for patients aged 18 and younger.
- Step 3: Application of inclusion criteria to obtain an individual data subset for patients receiving antidepressants.

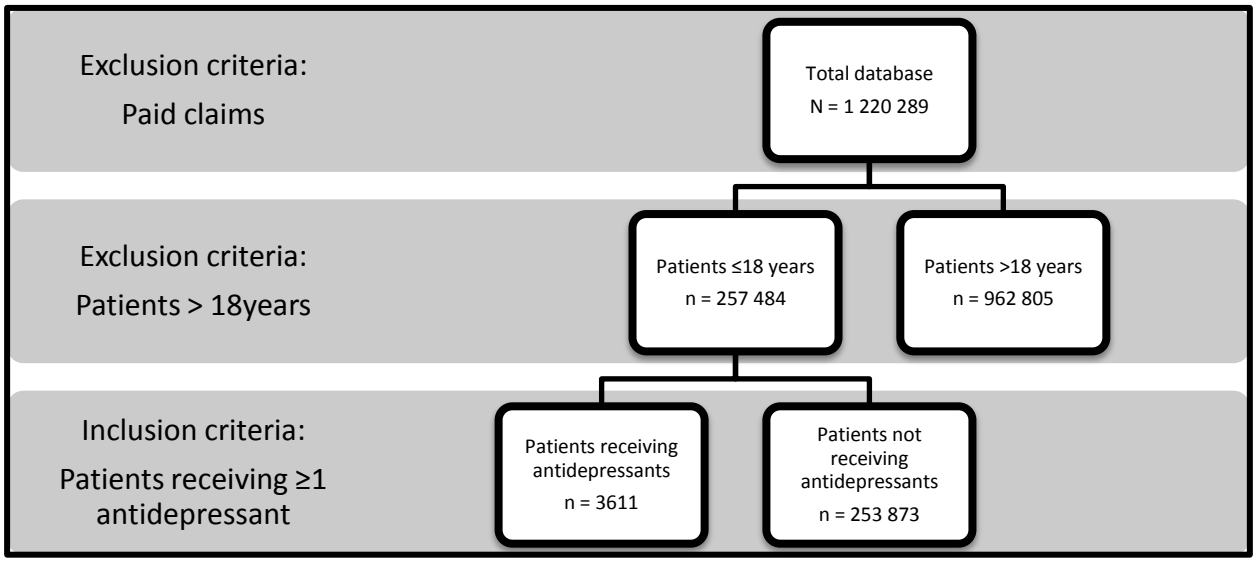

Figure 1.1: Selection process of the study population

Step 1: Obtaining data from the PBM's central database

The data elements available from the PBM's central database selected for research are shown in Table 1.2. A data field was added to the database at this stage, containing the Monthly Index of Medical Specialities (MIMS®) classification code for each active ingredient that appeared on the specific dataset.

Table 1.2: Data elements included in the PBM's database selected for research

Type of data	Selected data element
Membership	Date of birth
	Gender
	Encrypted membership identifier
	Encrypted member dependant identifier
	Postal codes
Medicine claims	Encrypted prescriber type identifier
	Drug trade name
	Quantity dispensed
	Days' supply
	Date filled

A discussion of the variables analysed during the study derived or computed from the available elements from the database (Table 1.2) follows in section 1.4.6.

Step 2: Application of exclusion criteria

Data for a total of 1 220 289 patients were obtained from the PBM. These patients represented 14.7% (N = 8 315 718) of the total number of beneficiaries of medical aid schemes in South Africa during 2010 (Council of Medical Schemes, 2010:158). The male-to-female ratio for the total private health sector for 2010 was 1.1. The average age of beneficiaries in the South African private health sector for 2010, was 31.5 years (Council of Medical Schemes, 2010:159).

The number of patients aged ≤18 years was obtained by applying the exclusion criteria (refer to Figure 1.1) which was any patient older than 18 years. The number of patients ≤18 years comprised 21.1% (n = 1 220 289) of the total number of patients from the PBM. Girls under the age of 18 years represented 19.0% (n = 661 007) of all female patients on the database, compared to 23.5% (n = 559 282) represented by boys.

Step 3: Application of inclusion criteria

The data subset was obtained by applying the inclusion criterion (refer to Figure 1.1) to obtain the number of patients receiving ≥1 antidepressants prescribed at any given time during the specific study period. The antidepressants were identified from pharmacological medicine classes based on the MIMS® classification code. The data subset was narrowed down to 3 611 patients. These patients encompassed 1.4% (n = 257 484) of the total number of children and

adolescents from the data received for 2010. Female patients represented 51.2% (n = 3 611) of the study population (male: female ratio 1). Female patients in the study population were slightly older than the male patients, at 13.7 ± 3.9 years for females and 12.3 ± 3.8 years for males (*d* = 0.4).

1.4.6 STUDY VARIABLES

The discussion in this section entails a description of the various dependent and independent variables (derived or computed from the available elements from the database as shown in Table 3.1), analysed during the study.

1.4.6.1 Demographic variables

These are demographics related to the patients on the database.

1.4.6.1.1 Age

Age can be defined as "*stage of development at which the body has arrived as measured by physical and laboratory standards"* (Myers, 2009:55). In this study "age" was calculated by computing the age of the patient on the first day of the following year. The age groups were divided into 6 different categories (Needlman, 2004:31):

- Age group 1: infants
- Age group 2: preschool
- Age group 3: middle childhood
- Age group 4: early adolescence
- Age group 5: middle adolescence
- Age group 6: late adolescence

The motivation for this categorisation of patients is due to the differences in child and adolescent growth and development. Needlman (2004:31) classify paediatric growth and development into three stages namely: "early childhood", "middle childhood" and "adolescence". There are a number of factors which determine these stages, i.e. physical, cognitive and emotional development (in early and middle childhood), communication (in children 6-12 months of age), linguistic development (children 1-2 years), and play and social development (in children 2–5 years). Adolescence is classified by somatic factors, sexual, cognitive and moral

factors, self-concept, family, peers and relationship to society.

The factor which is present throughout all the development stages is physical/somatic development. These factors were used to determine the age groups of the study. Needlman (2004:31-58) categorises ages as follows <1 year; 1–2 years; 2–5 years; 6–12 years and 10–20 years. Based on Needlman's classification for age, age group assignment for the purpose of this study was adapted to include infants (>0, ≤2 years), preschool (>2, ≤6 years), middle childhood (>6, ≤10 years), early adolescence (>10, ≤13 years), middle adolescence (>13, ≤16 years) and late adolescence (>16, ≤18 years).

The reason for the inclusion of age as an independent study variable can be derived from the number of studies which have found a significant difference in the prescribing patterns of antidepressants in different age groups in children and adolescents (Hsia *et al.,* 2009:214; Leslie *et al.,* 2000:472; Mancini *et al.,* 2006:497) (refer to paragraph 2.5.5.4).

1.4.6.1.2 Gender

Mosby's dictionary of Medicine, Nursing and Health Professions (Myers, 2009:784) describes the term "gender" as the classification of a person according to the sex of the person being male, female or ambivalent (typically used with reference to social and cultural differences rather than biological ones). For the purpose of this study "gender" is used to include biological sex, as well as gender in its strict sense.

The motivation for the inclusion of "gender" as an independent study variable is due to the fact that a number of studies showed a significant difference in both the number of prescriptions and number of medicinal items between male and female patients (Burger *et al.,* 2009:6; Cox *et al.,* 2008:1059; Dekker *et al.,* 2007:663; Kairuz *et al.* 2003:380-381; Mancini *et al.,* 2006: 499; Shireman *et al.,* 2002:1446; Wu *et al.,* 2001:193) (refer to paragraph 2.5.5.3).

1.4.6.2 Prescription related measurements

These variables are related to the prescriptions as recorded on the claims data.

1.4.6.2.1 Number of prescriptions and medicine items

Mosby's dictionary of Medicine, Nursing and Health Professions (Myers, 2009:1509) defines a prescription as "*an order for medication, therapy or therapeutic device given by a properly authorised person, which ultimately goes to a person properly authorised to dispense or perform this order".* Prescriptions in South Africa may contain one or more medicine items. The Medicines and Related Substances Control Act (101/1965) describes the term "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*". For the purpose of this study, the term "medicine" refers to any product (substance, active ingredient or mixture) which was prescribed to, or claimed by a service provider and recorded on the medicine claims database.

By analysing the number of prescriptions and number of medicine items as dependant variables, this study could evaluate the prescribing patterns by comparing the prevalence of prescriptions and/or items of either gender or age groups.

1.4.6.2.2 Speciality of prescriber

"Prescriber" is defined as "*A person who writes or authorises a medical prescription"* whereas "speciality" is described in relation to a person registered in respect of any profession under the Health Professions Act (56/1974). This means any particular discipline, division or subdivision of a profession which is recognised under this Act as a speciality in which such person specialises or intends to specialise. Speciality of prescriber thus refers to the type of prescriber who prescribed the antidepressant to the patient.

The speciality of the prescriber as a dependent variable allows this study to determine the type of prescriber prescribing antidepressants to children and adolescents. It also assists in describing certain dosages prescribed to patients.

1.4.7 MEASUREMENTS

The discussion in this section entails a description of the various measures of medication utilisation employed during the data analysis.

1.4.7.1 Prevalence and nature of potential drug-drug interactions (DDIs)

Two compendia were used in identifying possible drug-drug interactions, namely Tatro's drug interactions (2002) and Stockley's Drug Interactions (Baxter, 2008). Potential drug interactions between different medicine items prescribed per prescription will be identified and classified according to a clinical significance rating. The significance for potential interactions was derived from the criteria formulated by Tatro (2002: xiv).

Tatro (2002:xiv) classifies drug interactions in five significance ratings determined by the severity of the outcome and supporting documentation. This classification states level one is a severe interaction with suspected documentation, level two a moderate interaction with suspected documentation, level three a minor interaction with suspected documentation, level four a major/moderate interaction with possible documentation and level five a minor interaction with possible or unlikely proof of documentation. Interactions labelled with significance ratings of either one or two were documented and used for the purpose of this study because these interactions tend to have very severe or fatal outcomes.

A number of the potential drug-drug interactions with severe consequences documented in Baxter (2008) were based on individual case reports. These interactions are also mentioned in the literature review, due to the severe outcomes of these case reports.

1.4.7.2 Prescribed daily dosages (PDDs) *vs.* recommended daily dosages (RDDs)

The prescribed daily dose (PDD) is the "*average daily dose prescribed, as obtained from a representative sample of prescriptions*" (WHO, 2012). The recommended daily dose (RDD) is the dose recommended by various reference books to aid prescribers. The PDDs were calculated from the dataset, whilst a table (Table 2.2) of RDDs for all antidepressants was formulated by reviewing the MIMS® (Snyman, 2012), electronic package inserts (MIS, 2009), the British National Formulary for Children (Martin, 2007) and Martindale (Reynolds, 2002).

Some RDDs are determined by using the patient's weight. The dataset does not contain clinical data such as the weight and height of patients, which makes it difficult to determine the exact RDD of some antidepressants. The RDDs for these antidepressants were calculated by using the Centre for Disease Control and Prevention's (Centre for Disease Control and Prevention, 2000) growth charts for both genders. The growth charts are available for boys (Annexure A) and girls (Annexure B). Dosage range was calculated by using the 25^{th} and 75^{th} percentile on

the average weight-for-age percentiles for both genders aged 2–18 years. An example of the calculations follows in Annexure A.

1.4.8 DATA ANALYSIS

The data were analysed using the Statistical Analysis System® SAS 9.3® programme (SAS institute Inc., 2003) in consultation with the Statistical Consultation Services of the North-West University. Microsoft® Office Excel 2010 was used for general computations.

A descriptive analysis was conducted on all study variables. A summary of these statistics is provided here, followed by a summary of the statistical tests/analysis conducted to attain each specific objective of the empirical investigation phase.

1.4.8.1 Frequency and prevalence

"Frequency" is described as the rate at which something occurs in a given sample or over a specific period of time (Cambridge dictionaries online, 2012), whereas prevalence is described as "*the count of cases (new and old) at a point in time in a population size defined by characteristics (i.e. age and gender), and place"* (Bhopal, 2002:317). Prevalence can further be described as the number of people with a condition divided by the number of people at risk (McKenzie *et al.,* 2011:67).

Denominators for frequency and prevalence calculations therefore included the total number of patients ≤18 years on the database.

1.4.8.2 Average (arithmetic mean)

The Oxford English Dictionary (2012) define the average (arithmetic mean) as the "*quotient of the sum of several quantities and their number"*, and is also used to provide a measure of central location for the data (Anderson *et al.,* 2009:83; Ott *et al.*, 2010:81). The following quotation (Anderson *et al.,* 2009:83) was used for the calculation of the sample average:

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

Where:

$\bar{x}$ = average

$\sum xi$ = sum of all given x values

n = number of observations in the sample

This statistic was used to determine the average age of patients receiving antidepressants in the study population.

1.4.8.3 Weighted average

Weighted average according to Petrie and Sabin (2005:16) can be described as similar to an arithmetic mean, where instead of each of the data points contributing equally to the final average, certain values of the variable of interest, are more important or larger than others. For the purpose of this study, the weighted average was calculated using Microsoft® Office Excel 2010. The following formula (Microsoft®, 2011a) was used:

Weighted average = SUMPRODUCT (Xi:Xn,Yi:Yn)/SUM(Yi:Yn)

Where:
Xi = average of first observation
Xn = average of the last observation
Yi =frequency of the first observation
Yn = frequency of the last observation

The weighted average was used to determine the average prescribed daily dosage per active ingredient, taking all the different strengths into account.

1.4.8.4 Standard deviation

"Standard deviation" 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 *et al.* (2010:93) further describe standard deviation as the positive square root of the variance. The sample standard deviation (Anderson *et al.,* 2009:95) was calculated as follows:

$$\mathcal{S} = \frac{\sqrt{\sum(x - \bar{x})}}{n - 1}$$

Where:
$\mathcal{S}$ = standard deviation

x = any value in the dataset

$\bar{x}$ = average

n = number of observations in the sample

The standard deviation was used in the analysis of the age of patients receiving antidepressants in the study population, as well as determining the extent of possible dosage fluctuations prescribed to patients.

1.4.8.5 Weighted standard deviation

Kozak *et al.* (2008:27) defined weighted standard deviation as the positive square root of the variance, though, employing the weighted variance of the weighted average. The weighted standard deviation was calculated using Microsoft® Office Excel 2010 with the formula (Microsoft®, 2011b):

Weighted standard deviation = SQRT(SUMPRODUCT((Xi:Xn-Z)^2,Yi:Yn)/(SUM(Yi:Yn)-1))

Where:

Xi = average of first observation

Xn = average of the last observation

Yi = frequency of the first observation

Yn = frequency of the last observation

Z = weighted average

The weighted standard deviation was used in accordance with the weighted average in determining the prescribed daily dosages of the different antidepressants.

1.4.8.6 Median

The median, as a measure of central tendency, is the middle value when measurements are arranged from lowest to highest (Ott *et al.*, 2010:79).

1.4.8.7 Effect sizes (Cohen's *d* values)

The effect sizes are described as the extent of the differences between group averages or other test statistics (Marczyk *et al.,* 2005:92). Steyn (2009) calculated effect size with the following

formula:

$$d \equiv \delta = \frac{\bar{x}1 - \bar{x}2}{\mathcal{S}max}$$

Where:

$d \equiv \delta$ = effect size

$\bar{x}1$ = average age a

$\bar{x}2$ = average age of b

$\mathcal{S}max$ = Maximum standard deviation between a and b

The following guidelines are used to evaluate the value of *d* (Steyn, 2009):

$|\delta|$ = 0.2: small effect size

$|\delta|$ = 0.5: medium effect size

$|\delta|$ = 0.8: large effect size

Cohen's *d* value was used to determine the practical significance in difference between averages. Effect sizes ≥0.8 were deemed practically significant (Steyn, 2009).

1.4.8.8 Prescribed daily dosages (PDDs)

The antidepressants prescribed were analysed according to active ingredient and strength. A prescribed daily dosage was calculated by substituting the trade name with the active ingredient and determining the mean dosage of the particular antidepressant. The specific antidepressant's PDD and standard deviation will be calculated.

1.4.8.9 DU95% methodology

Based on the DU90% principle, in the present study the antidepressants and different prescribers that form part of the DU95% (i.e. 95% of antidepressants prescribed according to active ingredient and according to the type of prescriber) will be determined.

1.4.9 EMPIRICAL INVESTIGATION: RELIABILITY AND VALIDITY

This section entails the processes followed to ensure reliability and validity of the data.

1.4.9.1 Data quality

The PBM providing the data for the study has the following validation process in place to ensure the validity and reliability of data: gate-keeping services, eligibility services, utilisation management services, clinical management services and pricing management, along with real-time benefit management (refer to Table 1.3 for data validation techniques).

These validation processes ensure that claiming standards are met, for example, in the case of a missing or invalid product or member number, such a claim would be rejected. The PBM also conducts supplementary services such as integrated pre-authorisation services (including exception management), management of medicines for the Chronic Disease List (CDL), Prescribed Minimum Benefits (PMBs) and other conditions, and medicine management in capitation environments.

Data were additionally cleaned by deleting all duplicate claims, non-paid claims and claims for non-medicine items. The datasets were verified after each cleaning process by performing random data checks.

Table 1.4 was compiled from a checklist to assist any study conducted with regard to health-related retrospective databases, like this study, by covering a wide range of issues found in these types of studies and applying the criteria published (Motheral *et al.*, 2003:90-97).

Table 1.3: Validation processes to insure the validity and reliability of data employed by the PBM

Validation process	Example
Validation and eligibility management	• Claim field format checks • Provider validation checks • Member validation checks • Verify dependent codes • Waiting period check • Duplicate check
Medicine utilisation management (patient history checks at active ingredient level)	• 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. Ritalin™ and generics will pay for patients 16 years and younger) • Drug to gender limitations (e.g. hormone replacement therapy in women) • Invalid prescriber speciality (e.g. Diane™ prescribed by dermatologists) • Broad category exclusions (e.g. soaps/shampoos excluded) • Specific products excluded (e.g. urinary antiseptics) • Waiting periods (e.g. patient specific as advised by scheme)
Clinical management	• Ingredient duplication • Maximum daily dose exceeded • Therapeutic duplication • Drug-drug interactions • Drug-allergy interactions • Drug-age interactions • Drug-gender interactions • Drug-disease interactions • Drug-inferred health state interactions
Pricing management	• Continuous price file maintenance • Apply reference pricing e.g. generic reference pricing and therapeutic reference pricing (i.e. formulary based pricing for chronic disease)
Formulary management	• Management of Chronic disease List prescribed minimum benefits and non-chronic disease list conditions • Daily real-time benefit validation

Table 1.4: Checklist for retrospective database studies (compiled from Motheral *et al.*, 2003:90)

Aspect	Description	Answer	Explanation
Data Sources			
Relevance	Have the data attributes been described in sufficient detail for decision makers to determine whether there was a good rationale for using the data source, the data's overall generalisability, and how the findings can be interpreted in the context of their own organisation?	Yes	Refer to paragraphs 1.4.4, 1.4.5.1 and 1.4.9
Reliability and validity	Have the reliability and validity of the data been described, including any data checks and cleaning procedures?	Yes	Refer to paragraph 1.4.9
Linkages	Have the necessary linkages among data sources and/or different care sites been carried out appropriately, taking into account differences in coding and reporting across resources?	Not applicable	Not applicable
Eligibility	Have the authors described the type of data used to determine member eligibility?	Not applicable	Refer to paragraphs 1.4.5, 1.4.6 and 1.4.9
Methods *Research population*			
Data analysis plan	Was a data analysis plan, including hypotheses, developed a priori?	No	No hypotheses were generated, however an analysis plan is shown in Figure 1.1
Design selection	Has the investigator provided a rationale for the particular research design?	Yes	Refer to paragraph 1.4.3
Research design limitations	Did the author identify and address potential limitations of that design?	Yes	Refer to paragraph 4.3
Treatment effect	For studies that are trying to make inferences about the effects of an intervention, does the study include a comparison group and have the authors described the process for identifying the comparison group and the characteristics of the comparison group as they relate to the intervention group?	Not applicable	The study followed a descriptive, observational, retrospective design (paragraph 1.4.3)
Study population and variables			
Sample selection	Have the inclusion and exclusion criteria and the steps used to derive the final sample from the initial population been described?	Yes	Refer to paragraph 1.4.5
Eligibility	Are subjects eligible for the time period over which measurement is occurring?	Yes	The study followed a descriptive, observational, retrospective design (paragraphs 1.4.3 and 1.4.9)
Censoring	Were inclusion/exclusion or eligibility criteria used to address censoring and was the impact on study findings discussed?	Not applicable	
Operational definitions	Are case (subjects) and end point (outcomes) criteria explicitly defined using diagnosis, drug markers, procedure codes, and/or other criteria?	Yes	Refer to paragraph 1.4.5.1
Definition validity	Have the authors provided a rationale and/or supporting literature for the definitions and criteria used and were sensitivity analyses performed for definitions or criteria that are controversial, uncertain, or novel?	Not applicable	

Table 1.4: Checklist for retrospective database studies (compiled from Motheral *et al.*, 2003:90) (Continued)

Aspect	Description	Answer	Explanation
Timing of outcome	Is there a clear temporal (sequential) relationship between the exposure and outcome?	Not applicable	The study followed a descriptive, observational, retrospective design (paragraphs 1.4.3 and 1.4.9)
Event capture	Are the data, as collected, able to identify the intervention and outcomes if they actually occurred?	Not applicable	The study followed a descriptive, observational, retrospective design (paragraphs 1.4.3 and 1.4.9)
Disease history	Is there a link between the natural history of the disease being studied and the time period for analysis?	Not applicable	The study followed a descriptive, observational, retrospective design (paragraphs 1.4.3 and 1.4.9)
Resource valuation	For the studies that examine costs, have the authors defined and measured an exhaustive list of resources affected by the intervention given the perspective of the study and have resource prices been adjusted to yield a consistent valuation that reflects the opportunity cost of the resource?	Not applicable	
Statistics			
Control variables	If the goal of the study is to examine treatment effects, what methods have been used to control for other variables that may affect the outcome of interest?	Not applicable	
Statistical model	Have the authors explained the rationale for the statistical method used?	Yes	Refer to paragraphs 1.4.6 and 1.4.8
Influential cases	Have the authors examined the sensitivity of the results to influential cases?	Not applicable	
Relevant variables	Have the authors identified all variables hypothesised to influence the outcome of interest and included all available variables in their model?	Yes	Refer to paragraph 1.4.6
Testing statistical assumptions	Do the authors investigate the validity of the statistical assumptions underlying their analysis?	Not applicable	Refer to paragraph 1.4.3
Multiple tests	If analyses of multiple groups are carried out, are the statistical tests adjusted to reflect this?	Not applicable	Refer to paragraph 1.4.3
Model prediction	If the authors utilise multivariate statistical techniques in their analysis, do they discuss how well the model predicts what it is intended to predict?	Not applicable	The study followed a descriptive design (refer to paragraph 1.4.3)
Discussion/Conclusion			
Theoretical basis	Have the authors provided a theory for the findings and have they ruled out other plausible alternative explanations for the findings?	Yes	Refer to chapter 3 and chapter 4
Practical versus statistical significance	Have the statistical findings been interpreted in terms of their clinical or economic relevance?	Yes	Refer to chapter 3 and chapter 4
Generalisability	Have the authors discussed the populations and settings to which the results can be generalised?	Yes	Refer to paragraph 4.4

1.4.10 ETHICAL CONSIDERATIONS

Permission to conduct the study was obtained from the board of directors of the PBM, as well as the Ethical Committee of the North-West University (NWU-00005-07-A5).

Data privacy and confidentiality were maintained at all times. Therefore, no patient or medical scheme/administrator could be traced and it was also not possible to determine which prescribers or providers (i.e. name of the prescriber/provider) were involved in the prescribing/dispensing of the medicine items. The PBM providing the data for the study is not identified anywhere in the study. The researcher, study supervisor and co-supervisor further signed confidentiality agreements.

1.4.11 DIVISION OF CHAPTERS

The division of chapters is stipulated as follows. Chapter 1 gives a brief introduction accompanied by the methodology used to achieve this study. Chapter 2 entails a literature review of antidepressants, potential drug-drug interactions and recommended daily dosages of the antidepressants in children and adolescents. The results and discussion are included in Chapter 3, accompanied by additional results, whereas Chapter 4 will contain the conclusions, recommendations and limitations drawn from this study.

1.5 CHAPTER SUMMARY

This chapter stated the outline of this study and what methods were used to achieve the outcomes of this study. Chapter 2 gives a review of the literature with regard to antidepressants. It also focuses on potential drug-drug interactions and recommended daily dosages for children and adolescents.

CHAPTER 2
LITERATURE REVIEW

2.1 INTRODUCTION

Chapter 1 gave a brief introduction to the purpose and objectives of the study. This chapter provides a discussion on antidepressant drugs and their working mechanisms, indications, drug interactions and recommended daily dosages, with emphasis on children and adolescents. The chapter concludes with an overview of factors influencing prescribing patterns of the antidepressants in children and adolescents.

2.2 DEFINITIONS AND TERMINOLOGY

This literature review focuses on the use of **antidepressants** in **children** and **adolescents**. Needlman (2004:31) classifies paediatric growth and development into three stages namely: "early childhood", "middle childhood" and "adolescence". There are a number of factors which determine these stages, i.e. physical, cognitive and emotional development (in early and middle childhood), communication (in children 6–12 months of age), linguistic development (children 1–2 years), and play and social development (in children 2–5 years). Adolescence is classified by somatic factors, sexual, cognitive and moral factors, self-concept, family, peers and relationship to society.

Mosby's dictionary of Medicine, Nursing and Health Professions (Myers, 2009:357) defines a child as: "*a person of either sex between the time of birth and adolescence*", and an adolescent as a person who shows "*characteristics of adolescence*". Mosby's (Myers, 2009:47) further defines adolescence as: "*the period in development between the onset of puberty and adulthood"..."usually begin(ning) between 11 and 13 years of age with the appearance of secondary sex characteristics and spans the teenage years terminating at 18–20 years of age.*" The Free Dictionary (2010) defines puberty as "*the stage in the development of humans and other primates marked by the development of secondary sex characteristics, including menarche in females".* Menarche ensues at a median age of 12.4 (95% CI: 12.2–12.6) years in South African females of African descent and 12.5 (95% CI 11.7–13.3) years for Caucasians (Jones *et al.,* 2009:131). A child can thus be described as a person of either gender from the time of birth up to the time puberty starts to show, and an adolescent is a person of either

gender from the onset of puberty up to adulthood.

For the purpose of this study a child will be classified as a person from age 0≤13 years and an adolescent from age 13–18 years (refer to paragraph 1.4.6.1.1).

According to the Mayo Clinic (2011), antidepressants are medications used in the treatment of depression. MacPherson (1995:30) defines antidepressants as "*drugs which relieve depressive illness, characterized by depressed or absent effect, poor concentration, loss of interest, low self-esteem and changes in sleep & appetite*". Even though the definition states that antidepressants are indicated for depression, antidepressants may also be indicated for other conditions including agoraphobia, fibromyalgia, irritable bowel syndrome, and multiple sclerosis (Porter *et al.*, 2011). For the purpose of this study, antidepressants will be regarded as all medicines registered as such, based on the MIMS classification system (refer to section 2.3).
The following section presents an overview of antidepressants.

2.3 ANTIDEPRESSANT CLASSIFICATION SYSTEMS

This section contains an overview of four classification systems for antidepressants, namely those of Katzung (2004), the British National Formulary (Metha, 2006), the World Health Organization's (WHO) Anatomical Therapeutic Chemical (ATC) system and the Monthly Index of Medical Specialities (MIMS) (Snyman, 2012).

The WHO classifies medications according to the ATC classification system. Based on this system, each pharmaceutical product has its own code. This code is divided into 5 levels: 1st level represents the anatomical main group and the 2nd level represents the therapeutic group. A 3rd level further classifies the medication's pharmacological subgroup, whereas the 4th level indicates the chemical subgroup and the 5th level shows the chemical substance (WHO, 2003:34). Based on the ATC system, all antidepressants have the same first three codes, namely "N06A", where the code "N" designates nervous system agents, the code "06" designates "psychoanaleptics" and "A" designates "antidepressants". The WHO classifies antidepressants further into five 4th level groups which are listed as:

- N06AA: Non-selective monoamine re-uptake inhibitors (e.g. amitriptyline, clomipramine, dothiepin, imipramine, lofepramine, trimipramine and maprotiline)
- N06AB: Selective serotonin re-uptake inhibitors (e.g. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline)

- N06AF: Non-selective monoamine oxidase inhibitors (e.g. tranylcypromine)
- N06AG: Monoamine oxidase A inhibitors (e.g. moclobemide)
- N06AX: Other antidepressants (e.g. mianserin, mirtazapine, duloxetine, venlafaxine, reboxetine, bupropion, agomelatine and trazodone)

Based on the ATC-classification system, lithium is classified as an antipsychotic psycholeptic drug, signified with the code N05AN01.

Katzung (2004:483-485) classifies antidepressants into four different groups based on their pharmacological action and their chemical structure. These groups are tricyclic antidepressants (TCAs), heterocyclic antidepressants (heterocyclic antidepressants, selective serotonin re-uptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). The British National Formulary (Metha, 2006:198-209) classifies antidepressants into four pharmacological classes. These classes are tricyclic and related antidepressants, mono-amine oxidase inhibitors, selective serotonin re-uptake inhibitors, and "other antidepressants drugs". (The British National Formulary also combined the MIMS's non-tricyclic group, SNRIs, and certain "other" antidepressants in one group, designated as "other antidepressants drugs"). The MIMS (Snyman, 2012:11-26) classifies antidepressants into 7 different classes, based on the pharmacological mechanism of action, as depicted in Table 2.1. Based on this classification system, only clomipramine and imipramine are indicated for use in children and adolescents.

Table 2.1 MIMS® classification of antidepressants (Snyman, 2012:11-26)

Antidepressant group	Pharmacological agent
Tricyclic	• Amitriptyline • Clomipramine* • Dothiepin • Imipramine* • Lofepramine • Trimipramine
Non-tricyclic	• Maprotiline • Mianserin • Mirtazapine
Monoamine oxidase inhibitors (MAOIs)	• Non-selective (e.g. tranylcypromine) • Selective (e.g. moclobemide)

Table 2.1 MIMS® classification of antidepressants (Snyman, 2012:11-26) (continued)

Antidepressant group	Pharmacological agent
Selective serotonin re-uptake inhibitors (SSRIs)	• Citalopram • Escitalopram • Fluoxetine • Fluvoxamine • Paroxetine • Sertraline
Serotonin and noradrenalin re-uptake inhibitors (SNRIs)	• Duloxetine • Venlafaxine
Noradrenalin and Dopamine re-uptake inhibitors	• Reboxetine • Bupropion
Melatonergic Specific agonist	• Agomelatine
Lithium	• Lithium
Others	• Trazodone

**indicated for children and adolescents*

For the purpose of this study, the classification of antidepressants will be conducted according to the MIMS®-classification system.

2.3.1 TRICYCLIC ANTIDEPRESSANTS

In this section the tricyclic antidepressants will be discussed under the following headings: definition, working mechanism, indications, drug interactions and recommended daily dosages (RDDs).

2.3.1.1 Definition

The Princeton University's online dictionary (WordNet®, 2009.) defines a tricyclic antidepressant as an "*antidepressant drug that acts by blocking the re-uptake of noradrenalin and serotonin thus making more of those substances available to act on receptors in the brain*". Katzung (2004:483) adds that tricyclic antidepressants (TCAs) are antidepressant drugs named as such because of their characteristic three-ring nucleus. Based on these definitions tricyclic antidepressants are evidently named according to their chemical structure, the three-ring nucleus, and its pharmacological effect, i.e. relieving depression. Agents included in this class are amitriptyline, clomipramine, imipramine, lofepramine, and trimipramine (refer to Table 2.1).

2.3.1.2 Working mechanism

TCAs block the uptake of the neurotransmitters noradrenalin and serotonin in the brain (Katzung *et al.*, 2009:514; Kee *et al.,* 2000:346; Rang *et al.,* 2003:542), leading to amine neurotransmission termination (Katzung, 2004:483), thereby increasing the level of the amines. A rise in either of these transmitters leads to the relieving of depression (Rang *et al.,* 2003:537).

2.3.1.3 Indications

TCAs are primarily indicated for the treatment of depression (Snyman, 2012:11); this indication, however, does not extend to children and adolescents. Clomipramine, amitriptyline and imipramine may be used in children and adolescents for the treatment of depression, obsessive compulsive disorder (OCD), as well as nocturnal enuresis (Kardash *et al.,* 1968:265; Nevéus *et al.,* 2007:265; Rossiter, 2010:483; Reynolds, 2002:282-291; Snyman, 2012:11). The treatment for nocturnal enuresis should be limited to short courses in combination with a full physical examination. Amitriptyline is further indicated for the treatment of anxiety disorder and pain relief in chronic pain syndrome (Reynolds, 2002:275; Sindrup *et al.,* 1999:398), whereas imipramine is also indicated for the treatment of panic disorder (Barlow *et al.,* 2000:2533). Kapczinski *et al.* (2009:6) also found imipramine to show superior efficacy compared to placebo in the treatment of generalised anxiety disorder.

Clomipramine is furthermore indicated for the treatment of cataplexy with accompanied narcolepsy (Ristanovic *et al.*, 2009:420; Schachter *et al.,* 1980:171; Shapiro, 1975:256) and obsessive compulsive disorder (OCD) (Foa *et al.,* 2005:158; Thorén *et al.,* 1980:1285) in children and adolescents (Flament *et al.,* 1985:981; Leonard *et al.,* 1990:926).

Lofepramine, dothiepin and trimipramine are only indicated for the treatment of depression in adults (Trick *et al.*, 2004:212; Young *et al.,* 1979:1317).

2.3.1.4 Drug-drug interactions

All TCAs interact severely with clonidine, the mono-amine oxidase inhibitors (MAOIs) and cisapride. These interactions have a significance rating of one based on Tatro's classification system (refer to paragraph 1.4.7.1). The interaction with clonidine leads to impairment of blood pressure control and possibly life-threatening elevated blood pressure levels (Hui, 1983:164), whereas the interactions with the MAOIs lead to a hyperpyretic crises, convulsions and death

(Ciocatto *et al.,* 1972:69). Thomas *et al.* (1996:77) reported a rise in the risk of life-threatening cardiac arrhythmias, including *torsades de pointes* [a specific type of arrhythmia characterised by the increased beating of the two lower heart ventricles, causing a "twisted" electrocardiogram (ECG) wave (Mayo clinic, 2012)] with the concurrent administration of the TCAs with cisapride. During the arrhythmia blood volume is decreased, which may lead to fainting. The condition is self-limiting in short term cases (i.e. arrhythmias continuing less than a minute). Long term effects of *torsades de pointes* include life-threatening ventricular fibrillation (Mayo clinic, 2012).

Interactions with a significance rating of two on Tatro's scale include the interactions with the histamine H_2-antagonists, valproic acid, certain SSRIs, activated charcoal, dicumarol, rifampin and rifabutin. The H_2-antagonists, valproic acid, the SSRIs, inhibit TCA metabolism, leading to an increased TCA-level in circulation, and subsequently an increased possibility for TCA toxicity and adverse effects (Tatro, 2002). The interaction with sertraline may also lead to the development of serotonin syndrome (a condition where high concentrations of serotonin accumulate in the brain) (Mayo clinic, 2012). Symptoms of this syndrome include an agitation or restlessness, confusion, rapid heart rate and high blood pressure, dilated pupils, loss of muscle coordination or twitching muscles, heavy sweating, diarrhoea, headache, shivering and goose bumps. Severe serotonin syndrome may be life-threatening, and are characterised by a high fever, seizures, irregular heartbeat and unconsciousness (Mayo clinic, 2012). The SSRI, venlafaxine, has also been shown to cause serotonin syndrome in combination with the TCAs (Dougherty *et al.,* 2002:1647).

Activated charcoal, and the antituberculosis drugs rifampin and rifabutin decrease the absorption of TCAs significantly, leading to a sub-therapeutic effect of the latter agent (Self *et al.,* 1996:80; Vale *et al.,* 1993:78) whereas the interaction with dicumarol may lead to a potentially fatal increase of dicumarol's anticoagulant effects. Fatal cardiac arrhythmias have also been documented as a result of the interaction between ketanserine and the TCAs (Distler, 1990:79).

2.3.1.4.1 Amitriptyline

There are no interactions with a significance rating of one based on Tatro's scale documented specifically for amitriptyline. There are three interactions with a significance rating of two though, with the sympathomimetics guanethidine and carbamazepine. For example, according to Ghose (1980a:233), amitriptyline potentiates the pressor effects of direct-acting sympathomimetics, whilst decreasing that of the indirectly-acting sympathomimetics. The change in pressor effect

causes a rise in blood pressure and may lead to other cardiac conditions (Raab *et al.,* 1950:1401). Amitriptyline furthermore inhibits the hypotensive action of guanethidine (Fann *et al.,* 1971:111), whereas a decrease in amitriptyline levels occurs if co-administered with carbamazepine (Spinda *et al.,* 1995:413).

Baxter (2008) lists a number of case reports regarding amitriptyline. One such report entails the level of circulatory amitriptyline increases when administered in combination with St. John's Wort (Borrelli *et al.,* 2009:723). Concurrent therapy with morphine increases the area under the curve (AUC) of morphine (Ventafridda *et al.,* 1987:1204), whereas *torsades de pointes* and prolonged QTc levels occur when co-administered with fluconazole (Dorsey *et al.,* 2000:228). Other relevant effects of interactions with amitriptyline include:

- Toxic psychosis and hyperactivity with furazolidone (Aderhold *et al.,* 1970: 2080).
- Life-threatening orthostatic hypotension with altretamine (Bruckner *et al.,* 1983:516).

2.3.1.4.2 Clomipramine

Clomipramine shows no interactions with significance ratings of one or two based on Tatro's scale. According to Baxter (2008), however, clomipramine has relevant interactions including increased clomipramine levels with escitalopram, enalapril (Toutoungi, 1992:346) and carbamazepine (Gerson *et al.,* 1977:107), which may lead to toxicity (especially with enalapril and carbamazepine). Other outcomes of interactions with clomipramine include:

- An increase in the area under the curve of morphine (Ventafridda *et al.,* 1987:1204).
- An increased antimuscarinic adverse effect of clomipramine if co-administered with venlafaxine (Benazzi, 1998b:181).

2.3.1.4.3 Imipramine

Imipramine's drug-drug interactions include interactions with paroxetine, carbamazepine, guanethidine and the sympathomimetics (Tatro, 2002). These interactions are all given a significance rating of two according to Tatro's scale.

Imipramine levels will either increase if co-administered with paroxetine, leading to imipramine toxicity and increased adverse effects, or decrease if co-administered with carbamazepine (Spinda *et al.,* 1995:413), which may lead to a decrease in the desired effects of imipramine. Imipramine causes the inhibition of guanethidine's hypotensive action (Fann *et al.,* 1971:111).

Imipramine may further potentiate the pressor effects of the direct-acting sympathomimetic and decrease the pressor effect of the indirectly-acting sympathomimetic (Ghose, 1980a:233).

Baxter (2008) lists other cardiac interactions with imipramine in combination with altretamine (Bruckner *et al.,* 1983:516), which induces possible life-threatening orthostatic hypotension, and halothane (Tung, *et al.,* 1981:48) in which prolonged tachyarrhythmia are expected. Other relevant interactions with imipramine include:

- Atropine-like psychoses in combination with chlorpromazine (Rasheed *et al.,* 1994:233).
- A two- to threefold increase of the effects of intravenous infusions of adrenalin or noradrenalin (Boakes *et al.,* 1973:313).
- Serotonin syndrome in combination with dihydroergotamine (Mathew *et al.,* 1996: 235).
- Loss in muscle tone with baclofen (Silverglat, 1981:1659).

2.3.1.4.4 Trimipramine

Trimipramine has two interactions with significance two ratings based on the Tatro scale. The significance two interactions are the inhibition of guanethidine's hypotensive action (Fann *et al.,* 1971:111) and the potentiation of the pressor effects of directly-acting sympathomimetics whilst decreasing the pressor effect of indirectly-acting sympathomimetics (Ghose, 1980a:233).

2.3.1.5 Recommended daily dosages (RDDs)

Table 2.2 shows the recommended daily dosages of antidepressants for the treatment of children and adolescents. This table was composed using the Martindale (Reynolds, 2002), British National Formulary for Children (Martin, 2007), the electronic package inserts system (Malahyde Information Systems, 2009), the South African Medicines Formulary (SAMF) (Rossiter, 2012) and the Monthly Index of Medical Specialities (Snyman, 2012). RDDs were calculated using the weight-for-age percentiles growth charts of the Centre for Disease Control and Prevention (2009). The manner in which these dosages was calculated is described in Chapter 1 (refer to paragraph 1.4.7.2 and Annexure A).

2.3.2 NON-TRICYCLIC ANTIDEPRESSANTS

In this section the non-tricyclic antidepressants will be discussed under the following headings: definition, working mechanism, indications, drug interactions and recommended daily dosages (RDDs).

2.3.2.1 Definition

Rang *et al.* (2003:538) state that there are certain antidepressants which inhibit monoamine re-uptake that are chemically unrelated to TCAs, but have similar pharmacological properties, e.g. maprotiline. Both maprotiline and mianserin are classified under non-tricyclic antidepressants according to the MIMS (Snyman, 2012:13). Leonard (2003:174), however, classifies mianserin and mirtazapine as tetracyclic antidepressants based on the affinity that both agents show to 5-HT and H_1 receptors. For the purpose of this study, mianserin, mirtazapine and maprotiline will be classified as “non-tricyclic antidepressants”.

2.3.2.2 Working mechanism

Mianserin’s working mechanism relies on the blocking of certain receptors. It is classified as a second generation antidepressant which blocks α_1- and α_2-noradrenalin receptors, 5-HT_{1A}-, 5-HT_{2A}-, 5-HT_{3A}- and H_1-receptors (Katzung, 2004:484; Leonard, 2003:174; Papakostas *et al.*, 2010:121).

Mirtazapine is known as a noradrenalin and specific serotonin antidepressant which shows a higher affinity than mianserin for the α_2-noradrenalin and 5HT-receptors; mirtazapine works by the antagonism of α_2-noradrenalin receptors (Leonard, 2003:174, Rang *et al.*, 2003:541). Because of the selective blocking of noradrenalin uptake and subsequent similarities in dosing, mechanism of action and side effects maprotiline is grouped with the TCAs (Papakostas *et al.*, 2010:92; 22; Rang *et al.*, 2003:540).

2.3.2.3 Indications

All of the tetracyclic antidepressants are indicated for the treatment of depression, yet none are indicated for childhood or adolescent depression according to the MIMS (Rossiter *et al.*, 2010:488; Snyman, 2012). Other potential indications for the non-tricyclic antidepressants have been postulated in various publications, for example, according to Ikeguchi *et al.* (1995:320),

mianserin relieved psychosis induced by antiparkinsons' drugs. Mianserin may also be effective in the short term treatment of functional gastrointestinal disorders in patients with no psychopathology (Tanum *et al.*, 1996:324). Poyurovsky *et al.* (2003:123) published a study which showed that mianserin improved the results of selective neurocognitive tests in chronic schizophrenia patients who showed cognitive dysfunction.

Eberhard *et al.* (1988:33) documented maprotiline's effect in relieving physical discomfort and pain in patients diagnosed with idiopathic pain syndrome, whereas another study found maprotiline to be affective in the treatment of post-traumatic stress disorder (PTSD), especially in patients who showed tolerance toward SSRI treatment (Connor *et al.*, 1999:30). Maprotiline may also be a suitable substitute for patients receiving SSRI treatment experiencing sexual dysfunction (Gelenberg and McGahuey *et al.*, 2000:359).

According to Davidson *et al.* (2003:191) mirtazapine is increasingly being prescribed in the treatment of patients with post-traumatic stress syndrome (PTSD) either with SSRI treatment or as monotherapy. Mirtazapine may furthermore be effective as monotherapy or in conjunction with citalopram (Pallanti *et al.,* 2004:1399) in the pharmacotherapy of OCD (Koran *et al.,* 2005:520). Mirtazapine can be seen as a potential adjunctive treatment strategy for treatment of symptoms of schizophrenia (Abbasi *et al.*, 2010:105) and generalised anxiety disorder (Gambi *et al.,* 2005:486). Mirtazapine has shown promise in the treatment of acute antipsychotic-induced akathisia and may assist in improving current schizophrenic treatment practices (Poyurovsky *et al.,* 2006:1076). In addition, mirtazapine may be used for the treatment of chronic pain due to low weight, agitation, anxiety, insomnia, nausea and drug induced sexual dysfunction (Brannon *et al.,* 1999:384).

2.3.2.4 Drug-drug interactions

According to Tatro (2002) and Baxter (2008) there are no interactions which include the non-tricyclic antidepressants collectively. The interactions of each drug will be discussed individually in the following subsections.

2.3.2.4.1 Mianserin

No interactions were documented for mianserin according to Tatro's criteria. According to Baxter (2008) an interaction does occur between mianserin and carbamazepine, phenytoin (Richens *et al.*, 1983:296S) and phenobarbital (Nawishy *et al.,* 1981:871), which leads to a

decrease in mianserin levels (resulting in a decreased desired therapeutic effect). Three other interactions with mianserin were documented by Baxter (2008) and include:

- Increase in anticoagulant effects of warfarin that may lead to severe internal bleeding (Warwick, *et al.,* 1983:309).
- Rhabdomyolysis was developed with pravastatin (Takei *et al.*, 1999:539).

2.3.2.4.2 Maprotiline

Maprotiline has one significance interaction indicated with a significance rating of one, according to the Tatro significance scale, with cisapride. The interaction causes an increase in the risk of cardiac arrhythmias and *torsades de pointes* (Thomas *et al.,* 1996:77). Other drug interactions include those with antidiabetics, propranolol, fluvoxamine and risperidone (Baxter, 2008). The outcomes of these interactions include:

- An increase in maprotiline levels with fluvoxamine (Härtter *et al.,* 1993:305) or risperidone (Normann *et al.,* 2002:93) (which may lead to maprotiline toxicity and an increase in adverse effects).
- Hypoglycaemia may be induced with antidiabetic medication (Zogno *et al.*, 1994:406).
- Propranolol may lead to maprotiline toxicity (Tollefson *et al.*, 1984:148).

2.3.2.4.3 Mirtazapine

There are no significant interactions with mirtazapine based on the Tatro scale. Baxter (2008) however lists interactions with clonidine, carbamazepine, phenytoin, rifampicin, SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline) venlafaxine, cimetidine, levodopa, ketoconazole (all azole antifungals), protease inhibitors, erythromycin and nefazodone with mirtazapine. The effects of these interactions include:

- A decrease in mirtazapine levels with carbamazepine (Baxter, 2008:1208), phenytoin (Spaans *et al.*, 2002:428) and rifampin (Baxter, 2008:1209) (this leads to decreased therapeutic effects of mirtazapine).
- An increase in mirtazapine levels with cimetidine (Sitsen *et al.*, 2000: 391), paroxetine (Ruwe *et al.,* 2001:453), azole antifungals, protease inhibitors, erythromycin, nefazodone (Baxter, 2008:1209) and sertraline (Soutullo *et al.,* 1998:320) (this may lead to mirtazapine toxicity and increased adverse effects).
- Venlafaxine (Dimellis, 2002:167), fluoxetine (Benazzi, 1998a:495) and fluvoxamine

(Demers *et al.*, 2001:1218) cause serotonin syndrome when co-administered with mirtazapine.

- Hypertensive crisis in combination with clonidine (Abo-Zena *et al.,* 2000:477).
- An increase in the risk of psychosis with levodopa (Normann *et al.*, 1997:264).

2.3.2.5 Recommended daily dosages

Based on the guidelines advocated for the safe and correct use of mianserin, maprotiline and mirtazapine, assessed by reviewing the MIMS® (Snyman, 2012), electronic package inserts (MIS, 2009), the British National Formulary for Children (Martin, 2007) and Martindale (Reynolds, 2002), there are no recommended daily dosages for children and adolescents for mirtazapine, mianserin or maprotiline.

2.3.3 MONO-AMINE OXIDASE INHIBITORS (MAOIS)

The mono-amine oxidase inhibitors (MAOIs) will be discussed under the following headings: definition, working mechanism, indications, drug interactions and recommended daily dosages (RDDs).

2.3.3.1 Definition

The mono-amine oxidase enzymes consist of two different isoforms, namely isoform A (MAO-A) and B (MAO-B). MAO-A is primarily responsible for noradrenalin, serotonin and tyramine metabolism whereas MAO-B is primarily responsible for the metabolism of dopamine (Katzung, 2004:483).

The mono-amine oxidase inhibitors can be further sub-divided into selective and non-selective MAOIs; the selective MAOIs only inhibit either MAO-A or MOA-B, whereas the non-selective inhibits both MAO-A and MAO-B (Rang *et al.,* 2003:545). Non-selective MAOIs are also classified as irreversible, e.g. tranylcypromine, whereas selective MAOIs are classified as reversible, e.g. moclobemide (Rossiter, 2010:481).

2.3.3.2 Working mechanism

The MAOIs, as the name suggests, inhibit MAO-A and/or MAO-B enzymes. This inhibition leads to the increase in monoamines in the presynaptic stores, due to the decreased metabolism,

resulting in the increased release of amines helping in relieving depression (Rang *et al.,* 2003:545).

MAOIs, which are classified as “irreversible” have shown longer effects, but may easier lead to toxicity and increased adverse effects (Rang *et al.*, 2003:541).’

2.3.3.3 Indications

Moclobemide is primarily indicated for the treatment of major depression (Rossiter, 2010:487-488). Other studies have shown moclobemide is also indicated for social anxiety disorder (Versiani *et al.,* 1992:358; Schneier *et al.,* 1998:75; Rossiter, 2010:487-488) whereas moclobemide may be of benefit in smoking cessation. Due to the ability to increase MAO-A and B levels in the brain, these isoforms are lower in smokers than non-smokers (Fowler *et al.,* 2003:80). One open trial study has shown that moclobemide may be effective in the treatment of attention deficit hyperactivity disorder (ADHD) (Trott *et al.,* 1992:135). The authors of this trial, however, concluded that further studies were needed on this matter.

Tranylcypromine is primarily indicated for atypical depression or depression not responding to other therapies (Rossiter, 2010:487-488). Tranylcypromine is also indicated for phobic and panic disorders (Rossiter, 2010:487-488), and are generally reserved for patients who do not prefer other treatments, because of their serious side-effects (Marchesi, 2008:98). A study has shown that tranylcypromine may also prove useful in the treatment of nicotine addiction (Fowler *et al.,* 1996:14065).

According to Rossiter (2010:487-488) tranylcypromine and moclobemide are not indicated for children and adolescents because their safety has not yet been established.

2.3.3.4 Drug-drug interactions

There are 10 interactions with significance one ratings with the MAOIs according to the Tatro (2002) scale. Co-administration of the MAOI and TCA causes a severe interaction where hyperpyretic crisis and death are the outcomes (Ciocatto *et al.,* 1972:69). MAOIs exaggerate the effects of the anorexiants, which leads to ensuing cerebral haemorrhage, hypertensive crisis and reports of death (Lloyd *et al.,* 1965:168), whereas the MAOIs increase the hypertensive reactions with co-administration of levodopa (Hunter *et al.,* 1970:338).

L-tryptophan, the SSRIs and sibutramine interact with the MAOIs and cause serotonin syndrome which may be fatal (Alvine *et al.,* 1990:388; Gillman, 2005:437; Graber *et al.,* 1994:732). Dextromethorphan interacts with MAOIs and causes hyperpyrexia, abnormal muscle movement, hypotension, coma and death (Sovner *et al.*, 1988:1671). Concurrent administration of the sympathomimetic and MAOI-inhibiting agents may lead to hypertensive crises, high fever, hypertension and severe headaches (Davies *et al.,* 1978:172). Meperidine interacts with the MAOIs and causes rapid adverse reactions, such as agitation, seizures, diaphoresis and fever (Jounela *et al.,* 1973:1411), which in turn may progress to coma, apnoea and death (Goldberg *et al.,* 1964:456). The MAOIs cause an increase in selective $5HT_1$ receptor agonist serum concentrations, due to the inhibition of the mono-amine oxidase enzymes responsible for the sumatriptan metabolism, which in turn leads to increased risk of cardiac toxicity and possible serotonin syndrome.

There are three interactions with significance ratings of two with the MAOIs documented in Tatro (2002), with insulin, bupropion and the sulfonylureas. The sulfonylureas' hypoglycaemic actions are enhanced by the MAOIs' co-administration (Logie *et al.,* 1976:1031), whereas the MAOIs may lead to an increased risk of bupropion toxicity and may potentiate the hypoglycaemic response of insulin with delayed recovery in patients (Aleyassine *et al.*, 1972: 565). Other adverse effects resulting from drug interactions, according to Baxter (2008) worth noting include:

- Severe behavioural and neurological signs with tryptophan (Thomas *et al.,* 1984:282).
- Severe cases of serotonin syndrome with tramadol (Hernandez *et al.,* 1995:129).
- When two or more MAOIs are administered, or when one MAOI is replaced with another, fatal reactions, strokes and hypertensive crises have been reported (Mattes, 1998:382).

2.3.3.4.1 Moclobemide

Besides the interactions listed in paragraph 2.3.3.4, moclobemide also interact with omeprazole. Moclobemide's area under the curve (AUC) may be doubled when omeprazole is co-administered (Yu *et al.,* 2001: 270).

2.3.3.4.2 Tranylcypromine

Besides the interactions listed in paragraph 2.3.3.4, tranylcypromine has other relevant drug-drug interactions with buspirone and lithium. The interaction with buspirone causes a significant elevation in blood pressure (Baxter, 2008:1133), whereas tranylcypromine and the long-term use with lithium will lead to tardive dyskinesia (Stancer, 1979:727).

2.3.3.5 Recommended daily dosages

Based on the guidelines advocated for the safe and correct use of moclobemide and tranylcypromine, assessed by reviewing the MIMS® (Snyman, 2012), electronic package inserts (MIS, 2009), the British National Formulary for Children (Martin, 2007) and Martindale (Reynolds, 2002), there are no recommended daily dosages for children and adolescents for moclobemide and tranylcypromine.

2.3.4 SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS (SSRIS)

The selective serotonin re-uptake inhibitors (SSRIs) will be discussed under the following headings: definition, working mechanism, indications, drug interactions and recommended daily dosages (RDDs).

2.3.4.1 Definition

Most of the first-generation antidepressants have shown “irrelevant” pharmacological and adverse reactions, especially anticholinergic reactions (Katzung, 2004:483; Rang *et al.,* 2003:545). The SSRIs do not show these actions and effects and have become the antidepressant group which is most prescribed for the treatment of depression (Rang *et al.,* 2003:545). Agents included in this group of antidepressants includes fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine and sertraline (refer to Table 2.1).

2.3.4.2 Working mechanism

The SSRIs inhibit the re-uptake of serotonin which leads to an increase in secondary responses (Brunton *et al.,* 2009). One of these secondary responses is increased synaptic availability of serotonin; this in turn leads to an increase in postsynaptic 5-HT receptor types. In effect, it increases the levels of serotonin (Brunton *et al.,* 2009).

2.3.4.3 Indications

The SSRIs are primarily indicated for the treatment of depression in adults (Katzung, 2004:483). These agents are, however, beneficial for a number of other ailments. For example, fluoxetine is also indicated for the acute management of bulimia nervosa in adults (up to 16 weeks) (Goldstein *et al.,* 1995:664), as well as long term treatment in preventing bulimia nervosa relapse (Romano *et al.,* 2002:101). A recent study (Gowers *et al.,* 2010:22) investigated the possibility of SSRIs in child and adolescent treatment of eating disorders and found that although the drugs were tolerated well, more studies were needed to affirm the efficacy and safety in these age groups. A case study has shown that sertraline-induced enuresis in a prepubertal child resolved when sertraline was switched with fluoxetine (Maalouf *et al.,* 2010:161). Fluoxetine was established in the treatment of OCD in both adults (Pigott *et al.,* 1990:930; Chouinard, 2006:533) and children and adolescents (Coskun *et al.,* 2009:299; DeVane *et al.,* 1996:64; Geller *et al.,* 2001:777; Riddle *et al.,* 1990:46). Patients with elective mutism have shown that the disease may respond to fluoxetine treatment (Black *et al.,* 1994:1004). It is also used off-label for anxiety disorders (Birmaher *et al.*, 2003:521), certain personality disorders and general anxiety disorder (GAD) (Rossiter, 2010:485-486).

Paroxetine is indicated for the short and long term treatment of panic disorder in adults (Ballenger *et al.,* 1998:41; Pollack *et al.,* 2007:10), because of a faster onset of action when compared to drugs such as clomipramine (Lecrubier *et al.,* 1997:151). Paroxetine is well tolerated by children and adolescents with panic disorder (Masi *et al.,* 2001:155). Paroxetine is further indicated for OCD (Rossiter, 2010:485-486; Saxena *et al.,* 2007:486), and short term treatment (<11 weeks) of social anxiety disorder (SAD) (Stein *et al.,* 1998:712). Paroxetine further shows potential in the relieving of symptoms of GAD (Rocca *et al.,* 1997:449).

Citalopram and escitalopram are indicated for the treatment of OCD in both adults (Koponen *et al.,* 1997:346; Montgomery *et al.,* 2001:84) and children and adolescents (Alaghband-Rad *et al.,* 2009:133). Escitalopram has also been proven effective in the prevention of relapse with OCD patients (Fineberg *et al.,* 2007:438), panic disorder (Leinonen *et al.,* 2000:31; Wade *et al.,* 1997:551) and, in the use of depression which is resistant or non-responsive to fluoxetine or sertraline (Rossiter, 2010:486-487). Escitalopram is well tolerated by children for the treatment of GAD (Davidson *et al.,* 2004:239) and SAD (Kasper *et al.,* 2005:225). The safety and efficacy of escitalopram in these conditions have, however, not yet been established.

Fluvoxamine is a well-tolerated SSRI (Hudson *et al.,* 1998:1761). Fluvoxamine is indicated for

OCD in both children and adults (Apter *et al.,* 1994:347; Rossiter, 2010:486-487). Fluvoxamine is furthermore a potent anti-anxiety agent with a relatively rapid onset of action (Asnis *et al.,* 2001:11). Fluvoxamine has been shown effective in the treatment of certain child and adolescent mental disorders i.e social phobia, separation anxiety disorder and generalised anxiety disorder (Walkup *et al.,* 2001:1283). An open trial suggested fluvoxamine in the treatment of hypochondriasis, although further studies are needed to establish this treatment (Fallon *et al.,* 2003:302). Fluvoxamine has also shown to be effective in the treatment of bulimia nervosa (Ayuso-Gutierrez *et al.,* 1994:247), and for the acute treatment of binge-eating disorders (Hudson *et al.,* 1998:1761).

Sertraline is indicated for child, adolescent and adult OCD in combination with cognitive behaviour therapy (March *et al.,* 1998:1754; Rossiter, 2010:486-487) and panic disorder (Pohl *et al.,* 1998:1194; Rossiter, 2010:486-487). Sertraline may further be beneficial in the treatment of premenstrual dysphoric disorder (Yonkers *et al.,* 1997:987) and binge-eating disorder (Calandra *et al.,* 2012:183).

2.3.4.4 Drug-drug interactions

The SSRIs are inhibitors of the cytochrome P450-2D6 (CYP2D6) enzyme system. The CYP2D6 enzyme system is a specific enzyme family of the cytochrome P450 enzymes responsible for the metabolism of certain drugs (Bachmann, 2009:142). The co-administration of the SSRIs with drugs metabolised by this enzyme system subsequently leads to the increased plasma levels of these drugs and may lead to toxicity and increased adverse effects (Rossiter, 2010:484).

All SSRIs may potentially interact with the MAOIs and sumatriptan, causing significance one rated drug-drug interactions (Tatro, 2002). Both interactions may increase the risk of serotonin syndrome when co-administered with the SSRIs (FDA, 2009; Graber *et al.,* 1994:732; Shapiro *et al.,* 2007:268). Co-administration with St. John's Wort may lead to increased sedative-hypnotic effects (Gordon, 1998:951). Other relevant interactions of the SSRIs include an increased risk of bleeding with aspirin or NSAIDs (De Jong *et al.,* 2003: 593) (especially in the upper gastrointestinal tract).

2.3.4.4.1 Citalopram and escitalopram

Citalopram and escitalopram both have drug interactions with beta-blockers, clozapine and cyclosporine, resulting in drug-drug interactions with level two significance ratings (Tatro, 2002).

Both citalopram and escitalopram increase beta-receptor blockade (Hemeryck *et al.,* 2000:289), which in turn may cause severe cardiac and respiratory adverse effects. Both drugs administered concurrently with clozapine and perhexiline[1] may lead to the increase in serum levels of the latter agents (Borba *et al.,* 2000:301), resulting in toxicity and increased adverse effects of both drugs. The drugs also interact with irinotecan and omeprazole (Baxter, 2008) causing:

- Rhabdomyolysis (if co-administered with irinotecan) (Richards *et al.,* 2003: 1032).
- Escitalopram toxicity and adverse effects due to increased citalopram/escitalopram levels caused by the inhibition of the cytochrome-P450 enzyme system if co-administered with omeprazole (Baxter, 2008:973).

2.3.4.4.2 Fluoxetine

Fluoxetine interacts with the sympathomimetics and sibutramine causing an increase in the risk of developing serotonin syndrome (Barrett *et al.,* 1996:253; Gillman, 2005:437). Fluoxetine furthermore increases the sensitivity to sympathomimetic effects (Barrett *et al.,* 1996:253). These drug-drug interactions are classified as significance level one rating based on Tatro's scale.

There are seven drugs that interact with fluoxetine, causing significance two rated interactions based on Tatro's (2002) scale. For example, fluoxetine causes an increase in the serum levels of a number of drugs due to the CYP2D6-enzyme inhibition (Alfaro *et al.,* 2000:64) including clozapine, the TCAs, cyclosporine, carbamazepine and hydantoins (Byrne, 2003:14; Michalets, 1998:87). This inhibition of the CYP2D6-enzymes may lead to an increase in the risk of toxicity or adverse effects of any of the aforementioned drugs. Other interactions with level two significance ratings include the interactions with cyproheptadine and beta-blockers. Concomitant use of fluoxetine and beta-blockers will lead to excessive beta-receptor blockade (Hemeryck *et al.,* 2000:289), whereas the concurrent use of fluoxetine and cyproheptadine results in a decrease in fluoxetine effects (McDaniel, 2001:870).

Other important drug-drug interactions are with flecainide, mexiletine, phentermine, antihistamines with cardiotoxic effects, aripiprazole, the triptans (e.g. sumatriptan), perhexiline[1],

[1] Perhexiline and sertindole is not approved in South Africa, but was included for completeness of severe possible interactions

propafenone, sertindole[1], bupropion, lysergic acid diethylamide (LSD), nevirapine, antidiabetics, fluphenazine and pericyazine/trifluoperazine (Baxter, 2008). The effects of these interactions include:

- An increase in serum levels of certain drugs due to fluoxetine's CYP2D6-enzyme inhibitory effects (Alfaro *et al.,* 2000:64). These drugs include flecainide, mexiletine, phentermine, antihistamines with cardiotoxicity, aripiprazole, triptan, perhexiline[1], propafenone and sertindole[1] (which in turn may lead to toxicity and increased adverse effects).
- Psychosis, mania and seizures (co-administration of fluoxetine and bupropion) (Zubieta *et al.*, 1991:327).
- New onset or worsening of the LSD flashback syndrome (when a patient recovering from LSD addiction is administered fluoxetine) (Markel *et al.,* 1994:818).
- A decrease in fluoxetine serum levels, resulting in lowered effects (nevirapine) (DeSilva *et al.*, 2001:1284).
- Hypoglycaemia was documented with the combination of fluoxetine and any antidiabetic medication (Baxter, 2008:504).
- Fluphenazine caused a severe dystonic reaction with fluoxetine (Ketai, 1993:836).
- The concurrent administration of fluoxetine with pericyazine/trifluoperazine caused an increase in extrapyramidal symptoms (Coulter *et al.,* 1995:124).

2.3.4.4.3 Fluvoxamine

Fluvoxamine have drug-drug interactions with three drugs rated a significance level one based on the Tatro (2002) scale, with sibutramine, non-sedating antihistamines and sympatomimetics. Fluvoxamine causes an increase in the risk of developing serotonin syndrome with sibutramine (Gillman, 2005:437) and the sympathomimetics (Barrett *et al.,* 1996:253), whilst also increasing the sensitivity to the sympathomimetic effects (Barrett *et al.,* 1996:253). Fluvoxamine furthermore increases the serum concentrations of non-sedating antihistamines (especially astemizole and terfinadine), leading to cardiotoxicity (Byrne, 2003:14; Michalets, 1998:87).

Interactions with a significance rating of two occur between fluoxetine and cyclosporine, clozapine, the TCAs, tacrine and methadone, because of an increase in the serum levels of the latter agents (Tatro, 2002). Fluvoxamine may also increase serum concentrations of the phenotiazines (Alfaro *et al.,* 2000:64), nevirapine (De Maat *et al.,* 2003: 635), duloxetine (Baxter, 2008:1212), mexiletine (Kusumoto *et al.,* 2001:106), olanzapine (Weigmann *et al.,*

2001: 412), the proton-pump inhibitors (Yasui-Furukori *et al.,* 2004:493), pimozide (Baxter, 2008:761), sildenafil (Hesse *et al.,* 2005:592) and tizanidine (Gransfors *et al.,* 2004:337) (which may lead to toxicity and potentially life-threatening sinus bradycardia in the case of pimozide).

2.3.4.4.4 Paroxetine

According to the Tatro (2002) scale, paroxetine interacts with three drugs causing level one significance rating drug-drug interactions, and four leading to interactions with a significance rating level of two. The significance level one interactions include that of paroxetine with sympathomimetics, sibutramine and beta-blockers. Paroxetine, similar to fluoxetine and fluvoxamine, causes an increased risk for the development of serotonin syndrome if co-administered with sibutramine (Gillman, 2005:437) and the sympathomimetics (Barrett *et al.,* 1996:253) whilst increasing sensitivity in the sympathomimetic effects of the sympathomimetics (Barrett *et al.,* 1996:253). Paroxetine also leads to an excessive blockade of the beta-receptors when co-administered with beta-blockers (Hemeryck *et al.,* 2000:289).

The significance rating level two interactions occur with paroxetine and cyproheptadine, phenothiazines and TCAs. This interaction causes an increase in the serum levels of cyproheptadine, phenotiazines and TCAs (which in turn may lead to toxicity and increased adverse effects of these drugs) (Byrne, 2003:14; Michalets, 1998:87).

According to Baxter (2008), paroxetine furthermore increases the serum levels of aripiprazole (Baxter, 2008:715), duloxetine (Skinner *et al.,* 2003:176), flecanaide (Baxter, 2008:260), perhexiline[1] (Alderman *et al.,* 1997:602), and sertindole[1] (Baxter, 2008:769).

2.3.4.4.5 Sertraline

Sertraline interacts with the sympathomimetics and sibutramine (Tatro, 2002), leading to level one significance rating drug-drug interactions. Similar to fluoxetine, fluvoxamine and paroxetine, sertraline causes an increased risk for the development of serotonin syndrome if co-administered with sibutramine (Gillman, 2005:437) and the sympathomimetics (Barrett *et al.,* 1996:253) whilst increasing sensitivity in the sympathomimetic effects of the sympathomimetics (Barrett *et al.,* 1996:253).

The interactions with a level two significance rating, according to the Tatro (2002) scale, include interactions with beta-blockers and TCAs. Sertraline causes an excessive blockade in

combination with beta-blockers (Hemeryck *et al.,* 2000:289), whilst increasing the serum concentrations of the TCAs and phenotiazines (Byrne, 2003:14; Michalets, 1998:87) (which may lead to toxicity and increased adverse effects of these drugs). Other interactions documented by Baxter (2008) include:

- Experiences of new onset or worsening of the LSD flashback syndrome with LSD-addiction recovering patients (Markel *et al.,* 1994:819).
- Sertraline induced serotonin syndrome-like symptoms with the concurrent use of bupropion (Munhoz, 2004:221), dolasetron (Sorscher, 2002:191) or dihydroergotamine (Mathew *et al.,* 1996:235).
- A decrease in the efficacy of sertraline with rifampicin (Markowitz *et al.,* 2000:109) (requiring dosage increases or alternative treatment methods).

2.3.4.5 Recommended daily dosages

Table 2.2 shows the recommended daily dosages of antidepressants for the treatment of children and adolescents. This table was composed using the Martindale (2002), British National Formulary for Children (Martin, 2007), the electronic package inserts system (Malahyde Information Systems, 2009), the South African Medicines Formulary (SAMF) (Rossiter, 2010) and the Monthly Index of Medical Specialities (Snyman, 2012). RDDs were calculated using the weight-for-age percentiles growth charts of the Centre for Disease Control and Prevention (2009) (refer to paragraph 1.4.7.2).

2.3.5 SEROTONIN AND NORADRENALIN RE-UPTAKE INHIBITORS (SNRIS)

The serotonin and noradrenalin re-uptake inhibitors (SNRIs) will be discussed in the following section, under the following headings: definition, working mechanism, indications, drug interactions and recommended daily dosages (RDDs).

2.3.5.1 Definition

Similar to the TCAs (refer to paragraph 2.3.1.2) the SNRIs are all relatively potent re-uptake inhibitors of both serotonin and noradrenalin (Papakostas *et al.*, 2010:102). The SNRIs, however, show no resemblance to the chemical structure of the TCAs or SSRIs (Rossiter, 2010:490). The SNRIs venlafaxine and duloxetine will be discussed for the purpose of this study (refer to Table 2.1).

2.3.5.2 Working mechanism

Venlafaxine and duloxetine both have the same working mechanism. Venlafaxine is a phenylethylamine (Rossiter *et al.,* 2010:490) and a weak, nonselective inhibitor, which blocks the receptors responsible for the re-uptake of both serotonin and noradrenalin (Rang *et al.,* 2003:545). By blocking the receptors responsible for the re-uptake of these amines, it increases the concentrations of both serotonin and noradrenalin in the brain, thereby relieving depression. Duloxetine differs from venlafaxine in that it is a selective blocker of serotonin and noradrenalin in the brain (Rossiter *et al.,* 2010:490). According to Papakostas (2010:111) duloxetine is superior to venlafaxine due to its nonselectiveness.

2.3.5.3 Indications

The SNRIs are primarily indicated for the treatment of major depression (Rossiter *et al.,* 2010:490). Due to the dual action in their working mechanism the SNRIs have more significant benefits than the TCAs for the management of persistent pain from fibromyalgia (Arnold, 2007:73; Russell *et al.,* 2008:442). Venlafaxine is also indicated for the acute and long-term treatment for GAD (Gelenberg & Lydiard *et al.,* 2000:3088) and management of other panic disorders as SAD, PTSD and panic disorder (Katzman *et al.,* 2007:65; Pollack *et al.,* 2007:10). The safety and efficacy of the SNRIs in children and adolescents have, however, not yet been established.

A number of studies have shown duloxetine to be well tolerated, safe and effective for the management of persistent diabetic peripheral neuropathic pain in adults (Goldstein *et al.,* 2005:117; Raskin *et al.,* 2005:355), GAD (Koponen *et al.,* 2007:107; Rynn *et al.,* 2008:188), and as an alternative in potential treatment of stress urinary incontinence (Norton *et al.,* 2002:46).

2.3.5.4 Drug-drug interactions

There are two interactions documented to the SNRIs collectively (Baxter, 2008). These interactions are with cimetidine and warfarin. Cimetidine, a potent cytochrome-P450 enzyme system inhibitor, causes an increase in the serum levels of the SNRIs (Baxter, 2008:1211) (this, in turn, may lead to SNRI toxicity and increased adverse effects). The interaction of the SNRIs and warfarin increases bleeding tendencies in patients (Glueck *et al.,* 2006:1518).

2.3.5.4.1 Venlafaxine

Venlafaxine, according to Tatro (2002), has three interactions of significance one level ratings with the MAOIs, sibutramine and sumatriptan. Co-administration of these agents with venlafaxine leads to the development of serotonin syndrome (Weiner *et al.,* 1998:399; Gillman, 2005:437; FDA, 2009). Venlafaxine furthermore reacts with St. John's Wort, causing an increase in the sedative hypnotic effects of the latter agent. This interaction is classified as a level two significance interaction according to Tatro (2002). Other interactions according to Baxter (2008) include:

- Isolated cases of serotonin syndrome with the concurrent use of venlafaxine with amoxicillin/clavulanic acid (Connor, 2003:234), linezolid (Jones *et al.,* 2004:290), mirtazapine (Dimellis, 2002:167) and metoclopramide (Fisher *et al.,* 2002:70).
- The development of adverse antimuscarine effects in combination with the TCAs or fluoxetine (Benazzi, 1998b:181).
- The concurrent use of venlafaxine and aripiprazole (Cohen *et al.*, 2005:135) has led to adverse effects such as neuroleptic malignant syndrome and extrapyramidal symptoms.
- An increase in the levels of haloperidol, which may lead to haloperidol toxicity (Baxter, 2008:755).
- Some symptoms similar to serotonin syndrome were documented with venlafaxine in combination with lithium (Mekler *et al.*, 1997:272).

2.3.5.4.2 Duloxetine

Heavy alcohol intake may cause extensive liver damage to patients receiving duloxetine treatment (Baxter, 2008). An increase in duloxetine levels may also be caused in the concurrent administration with paroxetine (Skinner *et al.,* 2003:176), fluvoxamine, fluoxetine, ciprofloxacin, enoxacin and quinidine (Baxter, 2008:1212) (which also may lead to duloxetine toxicity and increased adverse effects). Duloxetine causes and increase in the AUC of the TCAs (Baxter, 2008:1240), leading to increased risk of TCA toxicity and adverse effects.

2.3.5.5 Recommended daily dosages

Based on the guidelines advocated for the safe and correct use of venlafaxine and duloxetine, assessed by reviewing the MIMS® (Snyman, 2012), electronic package inserts (MIS, 2009), the

British National Formulary for Children (Martin, 2007) and Martindale (Reynolds, 2002), there are no recommended daily dosages for the use of venlafaxine and duloxetine in children and adolescents.

2.3.6 NORADRENALIN AND/OR DOPAMINE RE-UPTAKE INHIBITORS

In subsequent paragraphs the noradrenalin and dopamine re-uptake inhibitors will be discussed under the following headings: definition, working mechanism, indications, drug interactions and recommended daily dosages (RDDs).

2.3.6.1 Definition

Bupropion and reboxetine inhibit the re-uptake of different amines which play a role in the aetiology of depression. Neither bupropion nor reboxetine, however, shows any resemblance to the chemical structures or working mechanisms of the TCAs, MAOIs or SSRIs (Katzung, 2004:483; Rang *et al.,* 2003: 540; Rossiter, 2010:491). These agents are not formally classified together, but were grouped together for the purpose of this study because of the similarities these drugs show in working mechanism (refer to Table 2.1).

2.3.6.2 Working mechanism

Bupropion is a chloropropiophenone and a dopamine re-uptake inhibitor (Rang *et al.,* 2003:540; Rossiter, 2010:491), whereas reboxetine is a selective and potent noradrenalin re-uptake inhibitor (Papakostas *et al.,* 2010:82). According to Rossiter *et al.* (2010:491), reboxetine shows no affinity for muscarinic receptors. By inhibiting the re-uptake of dopamine and noradrenalin, these agents cause a rise in the pre-synaptic amine levels, thereby relieving depression and other ailments.

2.3.6.3 Indications

Both bupropion and reboxetine are indicated for the treatment of depression in adults (Rossiter, 2010:491). Bupropion is furthermore used as an effective aid for smoking cessation, particularly in conjunction with nicotine patches (Jorenby *et al.,* 1999:690). According to Greenway *et al.* (2010:604) and Wadden *et al.* (2011:119), the slow release formulation of bupropion, combined with naltrexone and intensive behavioural modification, proved more effective for weight loss than behaviour modification alone. Bupropion furthermore showed an advantage in certain

aspects when compared to sertraline. This was with regard to bupropion inducing a higher cutback in the baseline body weight, a lower daytime somnolence and an enhancement in sexual performance (Calandra *et al.,* 2012:183). Bupropion may also be beneficial in the treatment of behavioural addictions (Kim *et al.,* 2012:1959) and adults diagnosed with ADHD (Wilens *et al.,* 2010:8).

Compared to escitalopram, reboxetine has a faster onset of action in the treatment of seasonal affective disorder, but have more side-effects (Pjrek *et al.,* 2008:795). Reboxetine may further be of benefit in the control of wakefulness in patients with narcolepsy because of its stimulation and anticataplectic effects (Larrosa *et al.,* 2001:283).

2.3.6.4 Drug-drug interactions

Each drug's interactions will be discussed separately in the subsequent/following section.

2.3.6.4.1 Bupropion

Bupropion interacts with carbamazepine, MAOIs and protease inhibitors, causing significance rating level two interactions (Tatro, 2002). This interaction causes an increase of bupropion levels as well as an increased risk of toxicity with carbamazepine (Ketter *et al.,* 1995:327), protease inhibitors (Hesse *et al.,* 2000:102) and MAOIs, which may also lead to a hypertensive crisis (Dwoskin *et al.,* 2006:196). Other important interactions include:

- Grand mal seizures or myocardial infarctions with the concurrent use of bupropion with methylphenidate (Ickowicz, 2002:790).
- A higher incidence of adverse effects like nausea, vomiting, excitement, restlessness and postural tremor when co-administered with antiparkinsonian drugs (Baxter, 2008:1206).
- Bradycardia and hypotension with metoprolol in combination with bupropion (McCollum *et al.,* 2004:230).
- Increased dextromethorphan levels with subsequent dextromethorphan toxicity (Kotlyar *et al.*, 2005:228).
- Psychosis, mania and seizures caused by bupropion in combination with the SSRIs (Zubieta *et al.*, 1991:327).

2.3.6.4.2 Reboxetine

Nefazodone, ketoconazole, potassium-depleting diuretics, ergot derivatives and lorazepam, all show important interactions with reboxetine (Baxter, 2008). The outcomes of these interactions are:

- Nefazodone and ketoconazole increase the reboxetine serum levels and may give way to reboxetine toxicity and adverse reactions (Baxter, 2008:1210).
- If reboxetine and potassium-depleting diuretics are co-administered, the possibility of hypokalaemia may rise (Baxter, 2008:1211).
- Ergot derivatives (Baxter, 2008:1211) and reboxetine concurrent use may result in increased blood pressure of patients.
- Mild to moderate drowsiness and an orthostatic increase in heart rate with lorazepam (Baxter, 2008:1211).

2.3.6.5 Recommended daily dosages

Based on the guidelines advocated for the safe and correct use of bupropion and reboxetine, assessed by reviewing the MIMS® (Snyman, 2012), electronic package inserts (MIS, 2009), the British National Formulary for Children (Martin, 2007) and Martindale (Reynolds, 2002) there are no recommended daily dosages for bupropion and reboxetine in children and adolescents.

2.3.7 MELATONERGIC SPECIFIC ANTIDEPRESSANTS

Agomelatine will be discussed under the following headings: definition, working mechanism, indications, drug interactions and recommended daily dosages (RDDs).

2.3.7.1 Definition

Agomelatine is a fairly new agent in the treatment of depression. It is a selective $5HT_{2C}$ antagonist and melatonergic agonist (Papakostas *et al.,* 2010:77).

2.3.7.2 Working mechanism

Agomelatine is a selective $5HT_{2C}$ antagonist, and potent agonist at melatonin receptors (Bourin *et al.,* 2003:132). Millan *et al.* (2003:964) have shown that the antagonistic properties of

agomelatine produced increased frontocortical dopaminergic and adrenergic activity and raised both dopamine and noradrenalin levels, thereby relieving depression.

2.3.7.3 Indications

Agomelatine is primarily indicated for the treatment of major depressive disorder in adults (Kasper *et al.,* 2009:124; Papakostas *et al.,* 2010:77). Agomelatine also shows promise as a drug of choice in the treatment of seasonal affective disorder (Pjerk *et al.,* 2007:578). In adolescents suffering from ADHD, especially those with sleeping disorders, agomelatine may help as a second line treatment (Niederhofer, 2012:531). Stein *et al.* (2008:564) show that although additional trials are required, agomelatine is tolerated well by patients with GAD.

2.3.7.4 Drug-drug interactions

According to McAllister-Williams *et al.* (2010:101) and Howland (2009:566), the SSRI fluvoxamine interacts with agomelatine, leading to a significant increase in agomelatine levels, and subsequent possible toxicity.

2.3.7.5 Recommended daily dosages

Based on the guidelines advocated for the safe and correct use of agomelatine, assessed by reviewing the MIMS® (Snyman, 2012), electronic package inserts (MIS, 2009), the British National Formulary for Children (Martin, 2007) and Martindale (Reynolds, 2002), there are no recommended daily dosages for children and adolescents for agomelatine.

2.3.8 LITHIUM

In this section lithium will be discussed under the following headings: definition, working mechanism, indications, drug interactions and recommended daily dosages (RDDs).

2.3.8.1 Definition

Although lithium is an element on the periodic table of the elements, it is still classified as an augmented drug in the treatment of depression and bipolar disorder (Rossiter, 2010: 469). It is administered through a variety of different lithium compounds, i.e. lithium carbonate and lithium citrate (Reynolds, 2002:292).

2.3.8.2 Working mechanism

A number of theories have been postulated regarding the working mechanism of lithium. For instance, lithium have been shown to cause depletion of membrane phosphatidylinositol (PI) (Rang *et al.,* 2003:548-549), and accumulation of intracellular inositol phosphate (Lenox *et al.,* 2000:8). This depletion of PI causes the inhibition of agonist-stimulated inositol triphosphate formation through numerous PI-linked receptors, leading to the block of many receptor mediated effects. In the early 1980s Ebstein *et al.* (1980:166) proposed that lithium reduced receptor-coupled stimulation of acetylcholine, and that increased the basal levels of cyclic adenosine monophosphate (cAMP) formation. According to Rang *et al.* (2003:548) it is believed that lithium's effects on these important secondary messengers are the reason for its selectivity to the brain and kidney.

2.3.8.3 Indications

Lithium is primarily indicated for the treatment of bipolar disorder, but can act as an augmentation drug in support of the treatment of depression, especially refractory depression (Rang *et al.,* 2003:548-549; Rossiter, 2010:469). According to Findling *et al.* (2011:204), lithium may also be beneficial in child and adolescent bipolar disorder.

2.3.8.4 Drug-drug interactions

According to Miller *et al.* (1987:1219), lithium interacts with haloperidol, causing severe alterations in consciousness, encephalopathy, extrapyramidal effects, fever and increased serum enzymes. This interaction is rated at a significance level of one based on Tatro's (2002) scale for interactions.

Lithium also interacts with the angiotensin-converting-enzyme (ACE) inhibitors, thiazide diuretics, non-steroid anti-inflammatory drugs (NSAIDs), carbamazepine, iodide salts and urinary alkalisers, causing level 2 significance effects (Tatro, 2002). ACE inhibitors, NSAIDs or thiazide diuretics co-administered with lithium cause the elevation of lithium serum levels (Egger *et al.,* 2003:776; Finely *et al.,* 1996:68; Wilting *et al.,* 2005:275), leading to lithium toxicity. Concomitant use of carbamazepine and lithium may develop adverse central nervous system effects including lethargy, muscular weakness, ataxia, tremor and hyper-reflexia (Ghose, 1980b:1122), whereas a synergistic reaction between lithium and iodide salts may produce hypothyroidism (Spaulding *et al.,* 1977:290). In combination with urinary alkalinisers, lithium

plasma levels may be decreased, which in turn could possibly decrease lithium effectiveness (Glassman *et al.,* 1987:241). Outcomes of other drug-drug interactions, according to Baxter (2008), are:

- Elevated lithium levels and lithium toxicity occurring with concurrent treatment with high doses of acyclovir (Sylvester *et al.,*1996:467), phenytoin (MacCallum, 1980:611), topiramate (Pinninti *et al.*, 2002:340), losartan (Blanche, 1997:501), and
- Serotonin syndrome-like symptoms have been documented with lithium and venlafaxine (Mekler *et al.*, 1997:272) or triptans (e.g. sumatriptan) (Gardner *et al.*, 1998:36).

2.3.8.5 Recommended daily dosages

The British National Formulary for Children (Martin, 2007) state that lithium's recommended daily dosage for children and adolescents, over 12 years, is dependant on the preparation. The RDD of lithium needs to achieve a serum-lithium concentration of 0.4–1 mmol/l, 12 hours after a dose on days 4–7 of treatment. This dosage must be continued weekly until the dosage has remained constant for 4 weeks, after which the dosage must be repeated three-monthly. Doses are initially separated throughout the day, but when serum-lithium concentration have stabilised, once daily administration is preferred. This is the dosage for the treatment of bipolar disorder, recurrent depression, aggressive or self-mutilating behaviour and mania.

2.3.9 OTHER ANTIDEPRESSANTS

A number of antidepressants show few similarities regarding chemical structure and/or working mechanism to any of the antidepressants, for example trazodone is the only "other" antidepressant classified based on the MIMS®-classification system for use in the South African context. This agent is discussed in the following section under the following headings: definition, working mechanism, indications, drug interactions and recommended daily dosages (RDDs).

2.3.9.1 Definition

Trazodone show some similarity to other antidepressants with regard to working mechanism, but none with regard to chemical structure (Leonard, 2003:178; Rang *et al.,* 2003: 540).

2.3.9.2 Working mechanism

Trazodone is a weak 5-hydroxytryptamine (5HT)-uptake inhibitor (Rang *et al.,* 2003:540) and a potent α_1-receptor antagonist (Leonard, 2003:178). By inhibiting the uptake of 5HT, it increases the levels of serotonin which in return relieves depression (Rang *et al.,* 2003: 540)

2.3.9.3 Indications

Trazodone is primarily indicated for the treatment of depression in adults (Rossiter, 2010:490), but shows potential in treatment of a number of other illnesses, for example in the treatment of alcohol post-withdrawal insomnia (Le Bon *et al.,* 2003:382).

2.3.9.4 Drug-drug interactions

Trazodone interacts with warfarin. The interaction between warfarin and trazodone causes a level two significance rating interaction according to Tatro's (2002) scale and may lead to a decrease of hypoprothrombinemic effects of warfarin and suboptimal anticoagulation with possible exacerbation of the disease being treated (Small *et al.,* 2000:736). Other important interactions of trazodone include that with nefazodone, the MAOIs, digoxin, the azole antifungals, and ritonavir (Baxter, 2008). The effects of these interactions include:

- Cases of serotonin syndrome with the concurrent use of trazodone and nefazodone/MAOIs (Baxter, 2008:1227) or ritonavir (DeSilva *et al.*, 2001:1284).
- Toxicity of digoxin (Rauch *et al.*, 1984:334) if co-administered.
- Increase in the serum levels of trazodone, leading to trazodone toxicity due to the concurrent administration with the azole antifungals (Zalma *et al.*, 2000:659).

2.3.9.5 Recommended daily dosages

Based on the guidelines advocated for the safe and correct use of trazodone, assessed by reviewing the MIMS® (Snyman, 2012), electronic package inserts (MIS, 2009), the British National Formulary for Children (Martin, 2007) and Martindale (Reynolds, 2002), there are no recommended daily dosages for children and adolescents for trazodone.

2.4 SECTION SUMMARY

The recommended daily dosages of all antidepressants which are indicated in the treatment of various ailments in children and adolescents are summarised in Table 2.2.

Table 2.2 Recommended daily dosages (RDDs) for antidepressants with indications in children and adolescents (mg/day)

Drug	Indication	Initial dose	0≤2 years	2≤6 years	6≤10 years	10≤13 years	13≤16 years	16≤18 years	Max(mg)	Reference
Amitriptyline	Depression	30-75	-	-	-	-	-	150 - 200	200	Martin (2007)
		-	-	-	-	-	30 - 75 (oral) 80 - 120 (IV/IM)	30 - 75 (oral) 80 - 120 (IV/IM)	200	Reynolds (2002)
	Nocturnal enuresis	-	-	-	10 – 20	25 - 50	25 - 50	25 - 50	200	Reynolds (2002)
					-	25 – 50[e]	25 - 50	25 - 50	25-50	Rossiter (2012)
					10 – 20	25 – 50[e]	25 - 50	50 - 100	200	MIS (2009)
					-	25 – 50[e]	25 - 50	25 - 50	200	Snyman (2012)
	Neuropathic pain	10[f] 0.2 - 0.5mg/kg	-	2.4 - 4.6* 2.2 - 4.6**	3.8 - 7.2* 3.6 - 7.6**	5.6 - 10.4* 5.8 - 10.6** 10 - 25	10 – 25[f]	10 – 25[f]	1 mg/kg or 75 mg[f]	Martin (2007)
Clomipramine	Obsessive compulsive disorder	25 ≥ maximum	-	48[a] - 69* 45[a] - 69** -	57 - 108* 54 - 114** -	84 - 156* 87 - 159** -	120 - 200* 123 - 200** -	162 - 200* 147 - 200** -	3 mg/kg or 200 mg	Reynolds (2002); Rossiter (2012); Snyman (2012)
		25	-	25	25 – 50[f]	25 - 50	25 - 50	25 - 50	250	MIS (2009)
Imipramine	Nocturnal enuresis	-	-	-	25 – 50[c]	25 - 50	50 – 75[e]	50 - 75	-	Martin (2007)
		-	-	-	25[b]	25 - 50	50 – 75[e]	50 - 75	-	Reynolds (2002)
		-	-	20 - 30[a]	25 – 50[d]	25 – 75[f]	25 - 75	25 - 75	-	Snyman (2012)
		-	-	10 - 25[a]	25 – 50[d]	25 – 75[f]	25 - 75	25 - 75	-	Rossiter (2012)
	Attention deficit hyperactivity disorder	-	-	-	20 - 60	40 - 60	40 - 60	40 - 60	-	Martin (2007)
	Child behavioural disorders	-	-	-	25	50[f]	50	50	-	Snyman (2012)
	Depression	-	-	-	-	-	25 - 50	25 - 50	100	Reynolds (2002)
Trimipramine	Depression	50 ≥ maximum	-	-	-	-	50-100	50-100	100	Reynolds (2002)

Table 2.2 Recommended daily dosages (RDDs) for antidepressants with indications in children and adolescents (mg/day) (continued)

Drug	Indication	Initial dose	0≤2 years	2≤6 years	6≤10 years	10≤13 years	13≤16 years	16≤18 years	Max (mg)	Reference
Citalopram	Major Depression	10 or 8[d]	-	-	-	10 – 20[c] 8 – 16[cg]	10 – 20 8 – 16[g]	10 – 20 8 – 16[g]	60 48[g]	Martin (2007)
Fluoxetine	Major Depression	10	-	-	10 – 20[c]	10 - 20[c]	20-Oct	10 – 20	20	Martin (2007)
	*Depression	5 – 10	-	-	5 – 20[a]	5 – 20[a]	5 – 20	5 – 20	20	Rossiter (2010)
	OCD	2 – 5 5 – 10[c]	-	-	2 – 20[a]	5 – 20[c]	5 – 20	5 – 20	30 40 – 60[#]	
Fluvoxamine	OCD	25	-	-	25 – 200[b]	50 – 200	25 – 200	25 – 200	200	Martin (2007) Reynolds (2002)
Sertraline	OCD	25 50[c]	-	-	25 – 200	25 – 200 50 – 200[c]	50 – 200	50 – 200	200	Martin (2007) Reynolds (2002)
		50	-	-	-	-	50 – 200	50 – 200	200	Snyman (2012)
		50	-	-	-	-	50 – 200	50 – 200	200	Rossiter (2010)
	Major Depression	50	-	-	-	50 – 200[c]	50 – 200	50 – 200	200	Martin (2007)

[a] Children over 5 years
[b] Children 6-7 years
[c] Children over 8 years
[d] Children over 9 years
[e] Children over 11 years
[f] Children over 12 years
[g] Route of administration is mg/drops
Areas were denoted as '-' when none of the references clearly stated a dosage for the age group
* For boys calculated using the 25th and 75th percentile on the average weight-for-age percentiles for boys 2-20 years (Centre for Disease Control and Prevention 2000), rounded to the nearest decimal (refer to Annexure A)
** For girls calculated using the 25th and 75th percentile on the average weight-for-age percentiles for girls 2-20 years (Centre for Disease Control and Prevention 2000), rounded to the nearest decimal (refer to Annexure B).
IV/IM – Intravenous/intramuscular
MIS - Malahyde Information Systems (2009) (refer to references)

2.5 FACTORS INFLUENCING ANTIDEPRESSANT PRESCRIBING IN CHILDREN AND ADOLESCENTS

Several studies have been conducted to establish the factors influencing prescribing patterns in adults, *inter alia* Dekker *et al.* (2007:663) and Bauer *et al.* (2008:71). Most of the identified factors may also influence prescribing in children and adolescents, such as gender, drug history and prescriber factors. The following paragraphs contain a discussion on some of these factors.

2.5.1 COUNTRY OF ORIGIN

Zito *et al.* (2008:3) found prominent differences in psychotropic medication prescribing patterns in children and adolescents between the United States of America (USA) and Western Europe. Based on their study, the annual prevalence of psychotropic medication prescribing in youth in the USA (6.7%) was significantly greater than the annual prevalence of countries such as the Netherlands (2.9%) and Germany (2.0%). The reason for these differences falls on dissimilarities in medicine prescribing policies and regulations of each country (refer also to paragraph 2.5.2). According to Zito and colleagues the regulatory differences, especially regarding higher schedule medicines such as amphetamines, and government cost restrictions in the European countries, reduce the prescribing of antidepressants. Other factors related to influencing prescribing of antidepressant include:

- Drug classification system difference (there exists a difference in the classification between the USA and Europe regarding the allowed indications for antidepressants).
- Co-medication patterns (in the USA, prescribers are two to three times more likely to prescribe combined-medication treatment to a patient than in European countries).
- Access to physician specialties (in the USA paediatricians are more likely to prescribe the stimulants to youth compared to general practitioners in European countries prescribing the stimulants) (Zito *et al.,* 2008:4).

2.5.2 GOVERNMENTAL REGULATORY RESTRICTIONS AND POLICIES

According to Haw *et al.* (2011:84), physicians tend to adhere to national guidelines when prescribing antidepressants to children and adolescents. Several major governmental bodies in the world publish guidelines and warnings regarding medicinal control and safety, including the United States Food and Drug Administration (FDA), the European Medicines Agency (EMEA)

and the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK). The guidelines and statement made by these governing bodies with regard to antidepressant prescribing to children and adolescents will be discussed in subsequent paragraphs, together with those issued by the South African Medicines Control Council (MCC).

2.5.2.1 United States of America (USA)

The FDA issued a black box warning on the prescription of SSRIs in 2003. The issue of this warning has resulted in the change of SSRI prescribing in the USA. For example, Olfson *et al.* (2008:98) compared pre-warning prescription rates to those after the warning had been issued and found a 36.0% per year increase in prescriptions before the warning, followed by a 9.6% decrease of antidepressant prescriptions per year to children and adolescents between the ages of 6 and 17 years after the warning had been issued. Hassanin *et al.* (2010:18) conducted a study of prescribing rates in Hawaii after the black box warning and found a decrease in SSRI prescribing of 35% in children aged 0–12 years over a period of 3 years, 3.1% in children and adolescents from 13–15 years and a 19.4% decrease in adolescents aged 14–19 years. A study by Cox *et al.* (2008:1059), evaluating trends in chronic medication in children and adolescents, also established that the expanding FDA warnings against SSRI safety had a major effect in the decrease of antidepressant prescribing, especially in the new user rate rather than patient whom already received treatment (Parkinson *et al.*, 2012:18). In addition to the black box warning the FDA furthermore increased the age from 18 years up to 24 years of age after conducting further placebo controlled studies and found that the risk of suicidal thoughts and behaviour also increased in patients up to the age of 24 years (FDA, 2007).

2.5.2.2 Europe

In 2005 the European Union (EU) issued a press release regarding the use of paroxetine in children and adolescents stating that the risks of the drug outweigh the benefits thereof. In January 2007 the EU published and enforced legislation to further studies regarding paediatric research in medication dosages. Auby (2008:38) concluded that these legislations were a major breakthrough in the European drug regulatory history. Auby further stated that these legislations opened a new portal to which children could have access to medicines.

2.5.2.3 United Kingdom (UK)

The Medicines and Healthcare products Regulatory Agency (MHRA) — an executive agency of

the Department of Health in the UK, responsible for ensuring that medicines and medical services work, and are acceptably safe (MHRA, 2012), regard the use of SSRIs in children and adolescents of 18 years and younger, as not safe (MHRA, 2003).

2.5.2.4 South Africa

The Medicines Control Council (MCC) of South Africa is defined as: *"a statutory body that regulates the performance of clinical trials and registration of medicines and medical devices for use in specific diseases"* (South African Department of Health, 2012). The purpose of this Council is to ensure that all clinical trials of non-registered and new indications of registered medicines, comply with the necessary requirements for safety, quality and efficacy.

Antidepressants in South Africa are all classified as schedule 5 medicines, resulting in strict measures and regulations with regard to the manufacturing, handling and dispensing of antidepressants as stipulated in the Medicines and Related Substances Control Act (101/1965). The MCC, together with the Department of Health, has issued an amendment to this Act providing guidelines with regard to the control and prescription of medicine in general. Guidelines specifically pertaining to the prescribing of schedule 5 medicines such as antidepressants include that schedule 5 medicines:

- "*may not be repeated for longer than six months, afterwards only if the authorised prescriber has indicated that the medication must be repeated again,*
- *used for its antidepressant/tranquilising or its analgesic properties, it shall not be prescribed for longer than six months unless the initial prescriber respectively consults with a psychiatrist or another medical practitioner,*
- *In an emergency a pharmacist may sell any Schedule 5 substance in a quantity not greater than that required for continuous use for a period of 48 hours, on the verbal instructions of a medical practitioner, dentist, veterinarian, practitioner, nurse or other person registered under the Health Professions Act, 1974, who is known to such pharmacist, but the prescriber who has given such verbal instructions shall within 72 hours after giving such instructions furnish to such pharmacist a written prescription confirming the instructions,*
- *No person shall manufacture, use or supply any Schedule 5 substance for other than medicinal purposes, unless he or she has been issued by the Director-General with a permit for such manufacture, use or supply upon the prescribed conditions,*
- *Any person may possess a Schedule 5 if he or she is in possession of a prescription*

issued by an authorised prescriber."

2.5.3 MEDIA COVERAGE

A systematic review by Hernandez *et al.* (2011:7) on the influence of negative articles or comments published by media found that media coverage overshadowed published scientific evidence regarding the use of SSRI in children and adolescents. Another study by Hernandez *et al.* (2012:8) found that prescribing patterns of SSRIs in children and adolescents in some European countries decreased after negative media coverage of the safety of these drugs in treatment of paediatric mental illness.

2.5.4 FINANCIAL FACTORS AND REIMBURSEMENT POLICIES

There are several financial factors which may play a significant role in the prescribing of antidepressants in children and adolescents, such as family income, insurance and reimbursement policies. For example, a study by Wu *et al.* (2001:191) showed that children who received antidepressant therapy were more likely to come from a family with a higher average annual income. These families were also more likely to have private insurance allowing better health care. Poluzzi *et al.* (2004:827) found that the prevalence of antidepressant prescription increased fourfold when these medicines received full reimbursement. Poluzzi and co-workers furthermore concluded that the abolishment of reimbursement policies could explain the increase in frequency of sporadic SSRI together with the perception of the safe drug profile of SSRIs.

2.5.5 PATIENT-RELATED FACTORS

Some factors which may influence prescribing patterns stem from the patient's background and educational factors. These factors will be discussed in the following section.

2.5.5.1 Race and cultural beliefs regarding the role of medication for emotional and behavioural treatment

Kirby *et al.* (2009:356) showed that prescribing differed between racial groups in the USA, in that antidepressant use in adolescents by the age of 17 years, increased steadily up to 6% in white non-Hispanics, compared with a more gradual increase, peaking at 2% in Hispanics. Compared with non-Hispanic black adolescents there was a minimal increase in usage, peaking

at 1.2% (five times less than white non-Hispanic adolescents) (Kirby *et al.*, 2009:356). These findings were also confirmed by Pratt *et al.* (2011:1), showing that 14% of non-Hispanic white adolescents use antidepressants compared to 4% of non-Hispanic blacks and 3% of Hispanics. Similar prescribing patterns were also demonstrated by Olfson *et al.* (2009:854) in adults from Hispanic and non-Hispanic origin.

A number of reasons have been hypothesised for the difference in racial antidepressant prescription rates. According to Kirby *et al.* (2009:357) the difference between antidepressant prescribing among racial groups may be ascribed to the different extents of behavioural characteristics and child mental health. According to Diala *et al.* (2000:462) the difference may be ascribed to racial or ethnic variation in mental health care access and availability, the trust of mental health services where some racial groups are more open to mental treatment, educational factors (especially if one racial group is more educated than another), and the acceptability of treatments.

2.5.5.2 Parental education

Children and adolescents from families where the parents have a higher education level are more inclined towards higher antidepressant use in comparison to families where the parents have a lower or no education (Wu *et al.,* 2001:191). Parents who have a higher level of education also tend to adhere much sooner to warnings issued by governing policies than parents who are less educated (Parkinson *et al.,* 2012:18).

2.5.5.3 Gender

Prescribing rates of antidepressants differ between male and female children and adolescents. According to Burger *et al.* (2009:6), Cox *et al.* (2008:1059), Mancini *et al.* (2006: 499) and Wu *et al.* (2001:193), female patients younger than 18 years received a larger number of prescriptions for antidepressants than their male counterparts, with the prevalence peaking at ages 15–19 years. In younger ages, however, antidepressant prescribing is higher in males than in females (Wu *et al.,* 2001:194), especially in those 15 years and younger (Shireman *et al.,* 2002:1446).

Kairuz *et al.* (2003:380-381) furthermore observed that female adolescents and young adults received more prescriptions for antidepressants than their male counterparts, whereas males received more antidepressants per prescription. One reason for the higher antidepressant prescribing prevalence among female patients may be that females tend to ask their physicians

for help more often than male patients do (Dekker *et al.,* 2007:663). According to Kessler *et al.* (2005:265), female patients may also show a higher tendency to develop depressive or anxiety symptoms than their male counterparts.

2.5.5.4 Age

Several studies have shown that antidepressant prescribing prevalence increases with age. For example, Mancini *et al.* (2006:497) found that the prevalence of antidepressant prescribing in male and female adolescents at 13 years of age was less than 5%, increasing to 7.5% for male adolescents at 17 years of age and more than 20% for females aged 17 years. Hsia *et al.* (2009:214) showed similar age-dependent prevalence rates in children and adolescents aged 0-2 years of age, escalating gradually from 0.2% to 2.2% in children aged 10–12 years, to 20.2% in adolescents aged 16–18 years. According to Leslie *et al.* (2000:472) the higher utilisation rates among older children may be ascribed to a higher number of mental health visits (ranging from 1 visit per year for children between the ages of one and three years of age up to 4–5 visits per year in children 12–17 years of age).

2.5.6 PRESCRIBER-RELATED FACTORS

Some factors which may influence prescribing patterns of antidepressants are dependent on the prescriber. A summary of these factors follows in the subsequent sections.

2.5.6.1 Better screening methods and diagnostic classification systems

Cox *et al.* (2008:1059) suggest that a factor which may contribute to the rise in antidepressant prescribing is the better recognition of depression screening in children and adolescents. Zito *et al.* (2008:26) list differences in diagnosis classification system factors which may influence the selection of the appropriate antidepressants, giving an example of the USA and Western European countries using different drug diagnostic classification systems. In the USA the International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) is used *vs.* the International Classification of Diseases, Tenth Revision (ICD-10) system, mainly used in Western Europe. South Africa also uses the ICD-10 code system.

2.5.6.2 Speciality of prescriber

Hassanin *et al.* (2010:18) found significant differences in prescribing patterns between

psychiatrists and non-psychiatrists in a study evaluating prescribing patterns after the press-release of the FDA black box warning against SSRI prescribing. This study showed that psychiatrists' fluoxetine prescription numbers increased gradually (from 8.5% in 2002 to 20.0% in 2005) after the warning had been issued, whilst the non-psychiatrists' prescriptions decreased (from 19.6% in 2002 to 14.6% in 2005). Hassanin *et al.* (2010:18) also showed a constant increase for long-acting paroxetine prescriptions by non-psychiatrists (0% in 2002 to 6.5% in 2005) compared with prescriptions by psychiatrists which decreased from 1.6% in 2002 to 0.9% in 2005. This study suggested that psychiatrists were adhering to the warning to a better extend than non-psychiatric prescribers.

2.5.6.3 Prescriber's age and gender

Bauer (2008:71) established that the age and gender of the prescriber were also important factors in determining prescribing patterns. According to the author, in some countries, the prescriber's age influenced SSRI prescription but not SNRI prescription, and that female physicians tended to prescribe SNRIs more often than male physicians.

2.5.6.4 Drug-related factors

Several studies have established that dosage form, drug safety, drug history and outcome play an important role in the prescribing of antidepressants. Bauer *et al.* (2008:70) found that past experience and treatment outcome of antidepressant use in the patient were the main factors influencing antidepressant prescribing in adults. Zimmerman *(*2004:1287) further states that a prior positive or negative result from treatment history is a factor in prescribing antidepressants in children and adolescents. With regard to drug safety, Zimmerman *et al.* (2004:1288) state that "*the most common factors include the avoidance of side effects, the presence of co-morbid psychiatric disorders, and the presence of specific clinical symptoms*". Olfson *et al.* (1998:315) state that the safety and more favourable adverse drug profile of newer antidepressants, like the SSRIs, may be a significant factor in the prescribing patterns of antidepressants.

In contrast to general prescribing guidelines, with regard to dosage form in child and adolescent prescribing, Star *et al.* (2011:311) found in a study comparing different prescribing patterns with regard to dosage forms of NSAIDs that capsules were more prescribed than liquid dosage forms. The compliance of medication in children is affected by a variety of factors including taste, formulation, appearance and ease of administration (Palanisamy *et al.,* 2012:17).

2.5.6.5 Chronic illnesses

Walters *et al.* (2008:238) found that there is a strong association between antidepressant prescribing and other chronic illnesses, especially epilepsy, asthma and chronic obstructive pulmonary disease (COPD). This may be due to a significant link between chronic illnesses and depressive disorders. In support of these findings, Chapman *et al.* (2005:6) demonstrated that all depressive ailments play a significant part in the aetiology, course and outcomes associated with any chronic disease.

2.5.7 PREVIOUS STUDIES

Table 2.3 shows studies conducted in South Africa regarding the prescribing patterns of antidepressants in children and adolescents.

Table 2.3 Previous studies regarding antidepressant prescribing in South Africa

Author and Year	Total number of patients	Measurements	Main Findings
Kairuz *et al.* 2003	98	• Prescribing frequency of SSRIs and TCAs • Patient gender • Doses of antidepressants • Duration of antidepressant treatment • Antidepressant cost	• TCAs were more prescribed than SSRIs • The average number of antidepressants per patient was higher for males, even though more female patients received antidepressants than male patients • Amitriptyline documented a low calculated average PDD, whilst SSRIs were prescribed in quantities sufficient for a month's antidepressant treatment • Duration of treatment was short, with 70.4% of patients receiving only one antidepressant prescription
Burger *et al.* 2009	1 013	• Prescribing frequency of the antidepressants • Prescribed daily dosages of antidepressants	• The mean number of antidepressant prescriptions per patient per year was 2.88 ±3.04 • In patients aged 9 < 15 years, antidepressant use was 1.4 times more common in males than females, compared with a 1.75 female: male ratio in those aged 16–19 years • The most commonly prescribed pharmacological groups of antidepressants were the SSRIs and the TCAs • Antidepressants were prescribed to this study population that are not recommended for use and the PDDs were higher than recommended
Truter *et al.* 2006	4327 (278 children and adolescents)	• Age and sex distribution of patients receiving tricyclic antidepressants • Prescribing frequency of tricyclic antidepressants • Distribution and ages of patients receiving tricyclic antidepressants • Average PDDs of single-component tricyclic antidepressant drugs • Percentage distribution of the average PDDs of single-component tricyclic antidepressant drugs • Prescribing of other antidepressants	• That the prescribing patterns of TCAs changed from 1996 to 2002/2003 • The dosages in which TCAs were prescribed were low and decreased in 2002/2003. • Younger patients were being prescribed TCAs more in recent years

Table 2.3 Previous studies regarding antidepressant prescribing in South Africa (continued)

Author and Year	Total number of patients	Measurements	Main Findings
Van der Westhuizen 2009	44 915 (patients from 2004-2006)	• Prevalence of antidepressant prescribing according to age • Prevalence of antidepressant prescribing according to gender • Prevalence of antidepressant prescribing according to active ingredient • Prevalence of antidepressant prescribing with regard to generic and innovator prescribing • The cost of antidepressant medication focusing on age, • The cost of antidepressant medication focusing on gender • The cost of antidepressant medication focusing on generic substitution • The cost of antidepressant medication focusing on the active ingredient prescribed	• Antidepressant prescriptions accounted for 5.66%, 5.05% and 4.51% of all prescriptions claimed during 2004, 2005 and 2006, respectively • Prescriptions of antidepressants to female patients represented 42.26% (n = 44 915) compared to 17.86% prescribed to male patients. • The most common prescribed antidepressant for 2004 was fluoxetine while amitriptyline was the drug of choice during 2005 and 2006 • 6.4% of all patients receiving antidepressants in 2006 were ≤20 years of age
Moch, 2009	-	• Reviewing antidepressants with regard to mechanism of action, side-effects and safety of antidepressants • Reviewing the combined therapy treatment of antidepressants	• The author compared the different antidepressants, formulated frequently asked questions regarding antidepressants and answered them. • These include the time of action of antidepressants, the safety thereof in pregnancy and adolescence, different side effects, the probability of addiction and the steps a pharmacist can take in the treatment of the patient.
Joubert (2004)	3978364 central nervous system items prescribed (study focused on items)	• Analysis of usage patterns of certain central nervous system drugs (antidepressants) • Analysis of costs of certain central nervous system drugs (antidepressants)	• Antidepressants comprised 33.97% of central nervous system items • Antidepressants comprised 45.53% of all costs associated with the central nervous system drugs prescribed • Amitriptyline was highest prescribed antidepressant • All antidepressants, except clomipramine, were prescribed with a generic subsitution rate of more than 50%

Table 2.3 Previous studies regarding antidepressant prescribing in South Africa (continued)

Author and Year	Total number of patients	Measurements	Main Findings
Moosa *et al.*., (2012)	62	• Describe HIV positive patient's responses to treatment with either an antidepressant or psychotherapy	• Found that both pharmacotherapy and psychotherapy may be equally effective for depression in HIV –positive patients

2.6 CHAPTER SUMMARY

This chapter consists of a literature review, discussing the antidepressant medication group and each drug's indications for children and adolescents, interactions which may influence prescribing patterns, mechanism of action, factors influencing prescribing patterns of antidepressants and previous studies conducted in South Africa. Hereby the objectives of the literature review were met.

CHAPTER 3
RESULTS AND DISCUSSION

3.1 INTRODUCTION

This chapter contains the general findings of the study and is presented in the form of two manuscripts, which will be submitted for consideration of publication, followed by extensive results found in this study.

Manuscript one, entitled “Potential drug-drug interactions among South African youth receiving antidepressants” will be submitted to the journal “*Pharmacoepidemiology and Drug Safety*”. The author’s guidelines for this journal are included in Annexure C.

Manuscript two, entitled “Antidepressant prescribing patterns to children and adolescents in South African private health sector: variations in age, gender and dosage prescribed” will be submitted to the “*Journal of clinical pharmacy and therapeutics*”. The author’s guidelines for this journal are available in Annexure D.

MANUSCRIPT 1

Potential drug-drug interactions among South African youth receiving antidepressants

Running head: Potential drug-drug interactions

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Keywords:
Antidepressants, children, adolescents, South Africa, medicine claims data, cross-sectional analysis

Key points:

- Approximately 2.5% of the study population was exposed to at least one potentially life-threatening drug-drug interaction
- Methylphenidate was indicated in the majority of both levels one and two drug-drug interactions
- The highest prevalence of potential interactions occurred in patients taking imipramine

Funding:
This work was funded by 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: 2067 words

Prior posts and presentations

Parts of this discussion was presented at the 3's Company Academic conference, Cape Town, South Africa, October 2013.

Abstract

Assessment of potential drug-drug interactions among South African children and adolescents receiving antidepressants

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Purpose: To determine and evaluate the prevalence and significance of potential drug-drug interactions (DDIs) among South African private health children and adolescents aged ≤18 years.

Methods: This retrospective cross-sectional analysis was performed using nationally representative medicine claims data for a 1-year period (1 Jan. to 31 Dec. 2010). DDIs were determined, using agreement between 2 commonly used DDI Compendia: Tatro 2012 and Stockley's Drug Interactions. DDIs that may result in a severity rating of 1 or 2 interactions based on Tatro's scale were counted as prescriptions for an antidepressant in a potentially interacting combination dispensed during the study period.

Results: Potential significance levels 1 and 2 DDIs were observed on 284 (2.4%) of 11 743 prescriptions dispensed during the study period (average number of prescriptions per patient per year: 3.3 ± 3.2, median 2). Overall, the highest prevalence of potential interactions occurred in patients taking imipramine (32.0%, n = 3611), amitriptyline (17.3%, n = 3611) and fluoxetine (16.9%, n = 3611). The drug pairs prescribed most were imipramine with methylphenidate [accounting for 43 (15.1%) of DDIs] and valproic acid [accounting for 38 (13.4%), followed by methylphenidate in combination with fluoxetine and sertraline [both accounting for 32 (11.3%) of DDIs, respectively]. The number of DDIs increased with age, with the highest number of cases in adolescents aged 10-16 years (58.1%, n = 284).

Conclusions: Methylphenidate was indicated in the majority of potential drug-drug interactions. The reasons and ramifications of these prescribing patterns should be evaluated to guard patient's safety.

INTRODUCTION

Child and adolescent populations worldwide experience increases in the prescribing of antidepressants[1,2]. The indication for antidepressant therapy in the child and adolescent population is more extensive than depression alone. Antidepressants are also indicated in other conditions for children and adolescents, such as obsessive compulsive disorder, child behaviour disorders and nocturnal enuresis[3]. With an increase in antidepressant prescribing and the number of indications, an increase in probability of drug-drug interactions may follow. The outcomes of these interactions may be of a severe nature and result in possible hospitalization or even death[4].

The prevalence and nature of drug-drug interactions among South African children and adolescents on antidepressant are not known. The present study contributes to bridging the knowledge gap by aiming to determine and evaluate the prevalence and significance of potential drug-drug interactions (DDIs) among South African private healthcare children and adolescents aged ≤18 years.

This study set out to determine to what extent a portion of the South African private health child and adolescent population was exposed to a prescription containing at least one potentially serious drug-drug interaction. This study will focus, specifically, on prescriptions containing a potential drug-drug interaction with ≥1 antidepressant.

METHODS:

Data source and study population

A retrospective cross-sectional analysis was performed on nationally representative medicine claims data for a total of 1 220 289 patients (661 007 females and 559 282 males), submitted for reimbursement between January 2010 and 31 December 2010. Data were obtained from a South African Pharmaceutical Benefit Management (PBM) company. The PBM currently provides real-time electronic pharmaceutical claims processing services to approximately 39 medical schemes in South Africa, or more than 1.6 million medical scheme beneficiaries, representing ~24% of the total medical aid

scheme industry across South Africa.

During the study period we selected all patients with a paid claim for a prescription containing one or more antidepressants. Antidepressants were identified using the Monthly Index of Medical specialties (MIMS®) classification system, a general reference guide to medicine used in the South African health system[3]. We queried field data for patient demographic information (patients' member number and dependant code, gender and date of birth), and pertinent prescription information (such as drug trade name, strength and date of treatment). The variables 'birth date' and 'treatment date' were used to calculate the age of patients on the date of treatment.

Patients were divided into 6 age groups based on Needleman's[5] classification for child development ranging from infancy (>0, ≤2 years), preschool (>2, ≤6 years), middle childhood (>6, ≤10 years), early adolescence (>10, ≤13 years), middle adolescence (>13, ≤16 years) up to late adolescence (>16, ≤18 years). The flow diagram of selection of eligible patients for analysis is shown in Figure 1.

<< Insert Figure 1 here >>

A total of 8 515 428 prescriptions containing 20 527 777 items were analysed. Children and adolescents ≤ 18 years represented 21.1% (257 484 cases) of the documented cases. Girls under the age of 18 years represented 19.0% (n = 661 007) of all female patients on the database, compared to 23.5% (n = 559 282) represented by boys. These children and adolescents received 11 743 prescriptions during the study period (average number of prescriptions per patient per year: 3.3 ± 3.2, median 2), containing 12 272 items (an average of 3.3 items per patient per year).

Identification of potential drug-drug interactions (DDIs)

DDIs were determined using agreement between two commonly used DDI Compendia, namely Tatro 2002[4] and Stockley's Drug Interactions[6]. DDIs were divided into 5 levels of significance using a measure of severity and documentation based on Tatro's interaction classification[4], level 1 interaction being a severe interaction with suspected

documentation compared to a level 5 interaction being minor with possible or unlikely proof of documentation. Interactions with severity ratings of 1 and 2 may lead to hospitalisation or in some cases death[4]. DDIs that may result in a severity rating of 1 or 2 were counted as a prescription dispensed during the study period for an antidepressant in a potentially interacting combination with either another medication or antidepressant.

The study was conducted with the approval of the Research Ethics Committee of North-West University (Potchefstroom campus), and the board of directors of the PBM. Data were analysed anonymously.

Statistical analysis

Variables were characterised descriptively, such as proportions/ratios and confidence intervals for categorical variables, and means, standard deviations and interquartile ranges for continuous variables. Cramer's V statistics was used to test for practical significance of this association. Statistical significance was considered with a two-sided probability ($P < 0.05$).

Statistical analyses were performed using SAS/STATS Software, version 9.3 (SAS Institute Inc., Cary, NC, 2002-2010).

RESULTS

General prescribing patterns

A total of 3 611 (1.4%, n = 257 484) (male: female ratio 1) was classified as patients receiving antidepressants in the study population. The total number of female patients receiving antidepressants on the dataset accounted for 1.5% (n = 125 705), whereas the total number of male patients encompassed 1.3% (n = 131 579). The number of patients increased gradually from those 0≤6 years of age for both genders after which the number of male patients receiving antidepressant peaked and stabilised from the age group middle childhood (>6, ≤10 years) onwards. Female patients stabilised from

6≤13 years of age and increased up until late adolescence (16≤18 years) (Table 1).

<< Insert Table 1 here >>

Identification of potential drug-drug interactions

Potential significance levels one and two DDIs were observed on 284 (2.4%) (n = 11 743) prescriptions (Table 1). The age group accounting for the largest number of prescriptions containing potential level one and two interactions DDIs (84 cases, 29.6%) peaked with the age group 13-16 years of age, followed by the age group 10–13 years of age which accounted for 28.5% (81 cases) of prescriptions containing potential DDIs. Overall, the highest prevalence of potential interactions occurred in patients taking imipramine (32.0%, 91 cases), amitriptyline (17.3%, 49 cases) and fluoxetine (16.9%, 48 cases). These prescriptions containing potential DDIs peaked within the age group 10–13 years for both imipramine and fluoxetine, peaking between 6–10 years for amitriptyline. The drug pairs prescribed most were imipramine with methylphenidate [accounting for 43 (15.1%) of DDIs] and valproic acid [accounting for 38 (13.4%)], followed by methylphenidate in combination with fluoxetine and sertraline [both accounting for 32 (11.3%) of DDIs, respectively]. The highest prevalence of drug-pairing between two or more antidepressants occurred between amitriptyline and sertraline, accounting for 10.2% (29 cases) of DDIs. The number of DDI cases increased with age, with the highest number of cases in adolescents aged 10-16 years (58.1%, n = 284).

<< Insert Table 2 here >>

Of all the DDIs documented, 31% of all cases (88 cases) were classified as level one interactions, whilst 69% (196 cases) of the DDIs were classified as level two. The TCAs accounted for 182 (64.1%) cases of possible DDIs. A total of 140 cases (49.3%, n = 284) were documented as monotherapeutic prescriptions whilst 42 cases (14.8%, n = 284) were prescribed concurrently with SSRIs (Table 1).

Possible significance level 1 interactions could be grouped into four drug-pairings based on pharmacological class. The groups included selective serotonin re-uptake inhibitors

(SSRIs) with centrally-acting sympathomimetic agents (methylphenidate and atomoxetine), SSRIs with antihistamines (cetirizine), tricyclic antidepressants (TCAs) with clonidine and lithium with haloperidol representing 86% (76 cases), 1% (1 case), 6% (5 cases) and 7% (6 cases) of the level one interactions, respectively.

The possible level 2 interactions were composed by the prescribing of either TCAs or SSRIs with other medication as monotherapy or in combination therapy. The 196 cases of level two interactions were composed of interactions between TCAs with proton pump inhibitors (ranitidine and cimetidine) (3.6%), centrally-acting sympathomimetics (33.2%) or anticonvulsants (32.1%) and SSRIs with anticonvulsants (4.6%) or beta-blockers (propranolol) (5.1%). Combination therapy of SSRIs and TCAs accounted for 21.4% of potential level two interactions in the study population.

DISCUSSION:

The present study investigated the prevalence of severe and potential life-threatening drug-drug interactions in the concurrent prescribing of antidepressants in children and adolescents.

Of the patients exposed to possible drug-drug interactions, a third were exposed to possible level one significance interactions. Almost 86% of these interactions were prescriptions containing SSRIs with the centrally-acting sympathomimetics, methylphenidate and atomoxetine. The potential outcome of the interaction included an increased sensitivity to the sympathomimetic effect and possible serotonin syndrome, which in severe cases might be life-threatening, and was characterised by a high fever, seizures, irregular heartbeat and unconsciousness[7]. A further 14% of the level one interactions were linked to the drug pairing of amitriptyline and clonidine, fluvoxamine with cetirizine and lithium with haloperidol. The outcomes of these interactions, respectively, entailed possible impairment of blood-pressure control and possible life-threatening elevated blood pressure levels[8], possible cardiotoxicity due to elevated cetirizine levels[9] and severe alterations in consciousness, encephalopathy, extrapyramidal effects, fever and increased serum enzymes[10].

Nearly two-thirds of the possible level two interactions were due to two drug-drug interacting groups namely the TCAs with central acting sympathomimetics and the pairing of valproic acid and carbamazepine. The outcome of a TCA-anticonvulsant interaction might lead to increased TCA levels[11], resulting in increased adverse reactions and possible TCA toxicity in patients. The possible effect of the concurrent prescribing of sympathomimetics and TCAs might result in a decreased pressor effect of the sympathomimetic agents[12] and severe blood pressure levels which might lead to hospitalisation. The rest of the level two interactions were documented between antidepressants and either propranolol or histamine H_2-antagonists (cimetidine and ranitidine). The outcomes of these interactions were excessive β-receptor blocking[13] and increased TCA levels, respectively. A fifth of the possible level two interactions were due to combined prescribing of TCAs with SSRIs. This interaction might lead to increased TCA levels due to the inhibiting effect of SSRIs on the CYP2D6 enzyme system[14], resulting in increased TCA pharmacological and adverse effects and in extreme cases toxicity.

Almost half of the documented potential DDIs (Table 2) occurred with tricyclic antidepressant (TCAs) prescribing. This may be ascribed to TCAs being indicated in the treatment of children from as young as 2 years, for ailments other than depression, such as nocturnal enuresis[15], neuropathic pain and ADHD[16]. Amitriptyline, imipramine and fluoxetine represented almost two-thirds of the potential drug interactions in the study population. Fluoxetine's high prevalence of potential interactions may be ascribed due to fluoxetine being the only antidepressant indicated in the treatment of obsessive compulsive disorder (OCD), which affects 1 in 200 children and adolescents ≥6 years worldwide[17].

The strengths of the current study include the use of a large, nationally representative pharmaceutical claims data set with a large number of patients at baseline, thereby increasing the power for subgroup analyses. Data quality was ascertained by several automated validation processes that were applied in-house by the PBM, such as data integrity validation and eligibility services, utilisation management services, clinical management services and pricing management, along with real-time benefit management.

This study had some limitations. Due to the lack of clinical/diagnostic data it was not possible to determine the reason for the co-prescribing of these agents. The data were subject to the accuracy of the claimed data as processed by service providers, which opened the possibility of faulty/inaccurate claims. Another limitation was the lack of information with regard to the number of prescriptions per age group per gender. The true extent of these interactions could not be determined for the total South African child and adolescent population since data only accounted for the private sector of South Africa. However, the identification of these interactions presented an opportunity to rationalise health services to deliver coordinated care to adolescents and children.

CONCLUSION

The study concluded that methylphenidate was indicated in the majority of both level one and two drug-drug interactions. The safety of all antidepressants in children and adolescents needs to be explored and verified. Future studies should determine the full extent of the exposure of children and adolescents to these interactions and the ramification of these interactions in society. The resources and procedures prescribers have to prescribe the correct antidepressant with fewer, if any, drug-drug interactions to ensure patient safety, should also be investigated.

ACKNOWLEDGMENTS

The authors wish to thank the medicine claims database that provided the data for the study. We are also grateful to the North-West University for funding this study.

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Table 1 Frequency of potential drug-drug interactions between antidepressants and other medications per age group

Antidepressant	Age Groups (years)					
	>0; ≤2	>2; ≤6	>6; ≤10	>10; ≤13	>13; ≤16	>16; ≤18
TCAs						
Amitriptyline & Clonidine*	-	1	-	-	-	4
Amitriptyline & Valproic Acid	-	-	2	1	5	11
Amitriptyline & Methylphenidate	-	-	8	3	6	-
Amitriptyline & Atomoxetine	-	-	-	1	-	-
Amitriptyline & Ranitidine	-	-	-	-	1	-
Amitriptyline & Cimetidine	-	-	-	-	-	3
Amitriptyline & Carbamazepine	-	-	-	-	2	1
Imipramine & Valproic Acid	-	-	5	15	18	-
Imipramine & Methylphenidate	-	-	19	18	6	-
Imipramine & Atomoxetine	-	-	2	1	1	-
Imipramine & Cimetidine	-	-	-	-	1	2
Imipramine & Carbamazepine	-	-	-	3	-	-
SSRIs						
Citalopram & Propranolol	-	-	-	-	-	1
Escitalopram & Propranolol	-	-	-	-	-	5
Fluoxetine & Methylphenidate*	-	-	2	19	9	2
Fluoxetine & Atomoxetine*	-	-	1	4	-	-
Fluoxetine & Carmbamazepine	-	-	-	4	3	2
Fluoxetine & Propranolol	-	-	-	-	-	2
Fluvoxamine & Cetirizine*	-	-	1	-	-	-
Paroxetine & Methylphenidate*	-	-	-	2	-	-
Paroxetine & Atomoxetine*	-	-	-	1	2	-
Sertraline & Methylphenidate*	-	-	-	2	20	10
Sertraline & Atomoxetine*	-	-	1	-	-	1
Sertraline & Propranolol	-	-	-	-	-	2
Other						
Lithium & Haloperidol*	-	-	-	1	5	-
Total	0	1	41	75	79	46

* - indicates level 1 interactions

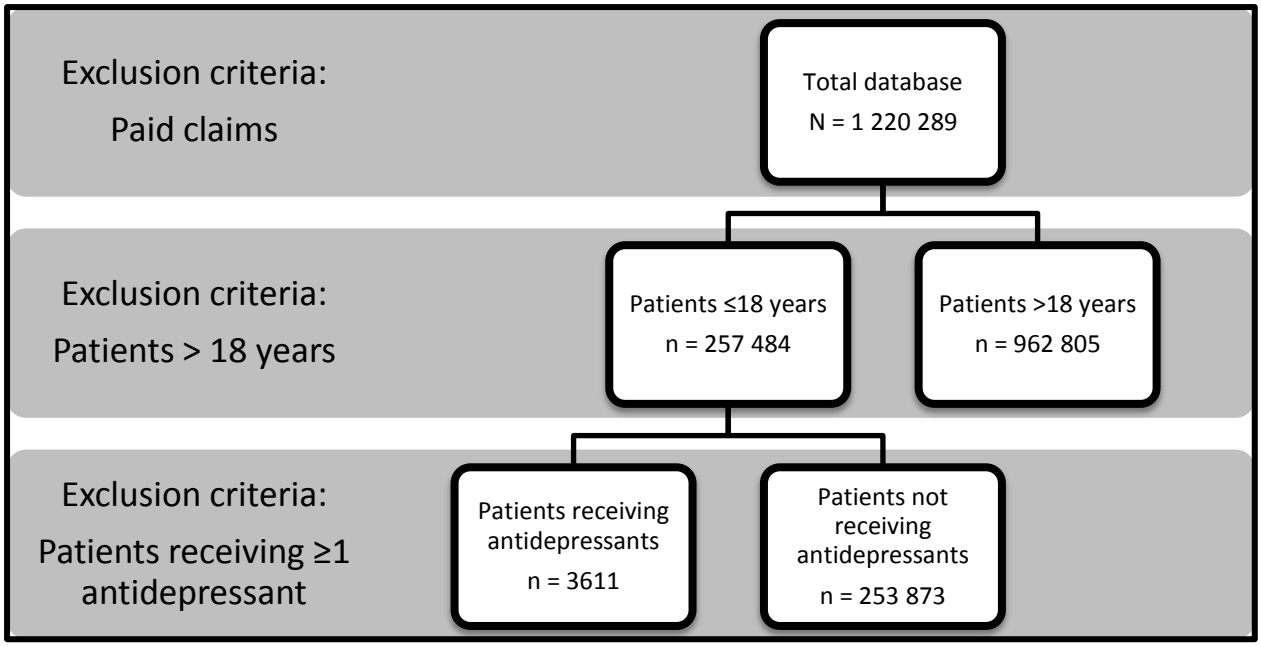
‘-' - indicates no cases were documented in the datasets

Table 2 Drug interactions between antidepressants per age groups

Antidepressant combination	Age Groups (years)					
	>0; ≤2	>2; ≤6	>6; ≤10	>10; ≤13	>13; ≤16	>16; ≤18
Amitriptyline & Fluoxetine	-	-	-	4	1	1
Amitriptyline & Sertraline	-	-	20	-	-	9
Imipramine & Fluoxetine	-	-	-	1	1	1
Imipramine & Fluvoxamine	-	-	-	1	-	-
Imipramine & Sertraline	-	-	-	-	3	-
Total	0	0	20	6	5	11

‘-' - indicates no cases were documented in the datasets

Figure 1 Process of establishing study population



MANUSCRIPT 2

Antidepressant prescribing patterns to children and adolescents in the South African private health sector: focus on variations in age, gender and dosage prescribed

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Abstract

Purpose: To establish prescribing patterns in a sub-population of children and adolescents in the private health sector of South Africa, with emphasis on age, gender and dosages prescribed.

Methods: A retrospective cross-sectional analysis was performed on nationally representative medicine claims data for medications dispensed between January 2010 and 31 December 2010, obtained from a South African Pharmaceutical Benefit Management (PBM) company. The study population consisted of children and adolescents receiving ≥1 antidepressant during the study period. Recommended daily dosages were compared to prescribed daily dosages for six different age groups and according to gender.

Results: The selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antridepressants (TCAs) were the most prescribed antidepressants in both gender groups. Girls received more SSRIs than boys (male: female ratio 0.9). TCAs were more prescribed to boys than girls (male: female ratio 1.2). The DU95% for antidepressant medicine items was achieved with general practitioners, psychiatrists, paediatricians, neurologists and urologists. Approximately 25% of antidepressants were inappropriately prescribed.

Conclusions: There were significant differences with regard to the different age groups, gender, type of prescriber and appropriateness *vs*. inappropriate antidepressant prescribing. 25% of all items prescribed were deemed unsafe in the prescribing in children and adolescents. There were a number of items prescribed to children younger than 6 years old, which is considered unsafe.

Keywords: Antidepressant, children, adolescents, prescribing patterns, South Africa, dosage, gender, age.

Introduction

Antidepressants are increasingly being prescribed to children and adolescents in populations worldwide [1], either as monotherapy or psychotropic polypharmacy [2]. Approximately 11% of Americans aged 12 years and over, take antidepressant medication of which 3.7% are aged between 12 and 17 years [3]. South Africa is no exception to these observed prescribing patterns, as illustrated by recent reports indicating prevalence rates increasing from 3.8% in 1996 to 8.7% in 2002/2003 [4]. Another study found that 6.4% of all patients who received antidepressants in 2006 were aged ≤19 years [5].

Although antidepressants are primarily prescribed for the treatment of depression, it may also be prescribed in the treatment of other ailments, such as obsessive compulsive disorder, child behaviour disorders and nocturnal enuresis [6]. The prescription of antidepressants in a child and adolescent population is dependent on a number of different factors such as age [7], gender [8-9], speciality of the prescriber [10] and drug history [11].

This study's conclusions will assist in the understanding of the influence of the aforementioned factors in the prescribing patterns of antidepressants to children and adolescents. This study specifically focused on the comparison of recommended daily dosages *vs*. prescribed daily dosages. We furthermore investigated antidepressant prescribing patterns with regard to type of prescriber, type of antidepressant prescribed (appropriate or inappropriate), gender and in patients ≤18 years.

Methods

Data collection

A retrospective cross-sectional analysis was performed on nationally representative medicine claims data for medications dispensed between January 2010 and 31 December 2010, obtained from a South African Pharmaceutical Benefit Management (PBM) company. The PBM currently provides real-time electronic pharmaceutical claims processing services to approximately 39 medical schemes in South Africa, or more than 1.6 million medical scheme beneficiaries, representing ~24% of the total medical aid scheme industry across South Africa. All patients with a paid claim during the study period for a prescription containing one or more antidepressants were selected.

The study population was selected by dividing patients on the database based on age, into adults (patients above 18 years) and children and adolescents (≤ 18 years). All children and adolescents receiving ≥1 antidepressant during the study period were then selected for analysis. The study population was further divided into 6 age groups based on Needleman's classification for child development [12] ranging from infancy (>0, ≤2 years), preschool (>2, ≤6 years), middle childhood (>6, ≤10 years), early adolescence (>10, ≤13 years), middle adolescence (>13, ≤16 years) up to late adolescence (>16, ≤18 years). Figure 1 shows the flow diagram of selection of eligible patients for analysis.

<<Insert Figure 1 here>>

A total of 1 220 289 patients (661 007 females and 559 282 males) submitted prescriptions for 2010. A total of 8 515 428 prescriptions containing 20 527 777 items were analysed. Children and adolescents ≤ 18 years represented 21.1% (257 484 cases) of the documented cases. Girls under the age of 18 years represented 19.0% (n = 661 007) of all female patients on the database compared to 23.5% (n = 559 282) of all males, represented by their male counterparts. The study population was narrowed down to 3611 children and adolescents receiving 11 743 prescriptions during the study period.

Classification of antidepressants

Antidepressants were identified using the Monthly Index of Medical specialties (MIMS®) classification system, a general reference guide to medicine used in the South African health system [6].

Recommended daily dosage determination

Recommended daily dosages (RDDs) for antidepressants, classified as safe for prescribing of children and adolescents, were determined by cross-referencing a number of drug prescribing compendia. These references include the Martindale [13], British National Formulary for Children [14], the electronic package inserts system (Malahyde Information Systems) [15], the South African Medicines Formulary (SAMF) [16] and the Monthly Index of Medical Specialities [6]. The RDDs of antidepressants in children are subject to the diagnoses and in some cases the weight and height of the child. This information lacks in the data obtained and therefore some RDDs were established by utilising the 25th and 75th percentile on the average weight-for-age percentiles found on the Centre for Disease Control and Prevention's growth charts [17] for both genders. For the purpose of this study the RDDs were documented by using the lowest allowed dosage documented according to the references up to the highest dosage deemed safe. All identified RDDs for the TCAs are stipulated in Table 2; the RDDs for SSRI's are in Table 3.

<<Insert Table 1 here>>

<<Insert Table 2 here>>

Prescribed daily dosage determination

The prescribed daily dosage for antidepressants was determined by multiplying the number of tablets prescribed by their strength (mg), and dividing the total by the number of days covered by the prescription. Weighted averages and standard deviations were calculated by active ingredient.

Identification of potential inappropriate drugs prescribed

A small number of antidepressants are indicated for use in children and adolescents. The identification of inappropriate antidepressant prescribing in children and adolescents was established through the comparison of drugs prescribed against drug prescribing compendia [6;13-16]. This includes cases where antidepressants that are contra-indicated and those of which the safety has not been established in child and adolescent treatments were prescribed.

DU95%

DU90% is a "*simple, inexpensive and flexible method to determine the quality of a drug*" or a group of drugs prescribed in routine health care [18]. Bergman *et al.* [18] further state that the number of products together with prescription guideline adherence in the DU90% may serve as general qualitative indicators. Based on this principle, in the present study, the antidepressants and different prescribers that form part of the DU95% (i.e. 95% of antidepressants prescribed according to active ingredient and according to the type of prescriber) were determined.

Statistical analysis

Variables were characterised using two sets of descriptive variables. Demographic variables were queried, including encrypted patient member numbers and dependent codes, age of patient and date of birth to determine differences in patterns with regard to age and gender. Prescription-related information queried included trade name, strength and date of treatment to determine the speciality of the prescriber and PDDs of antidepressants in children and adolescents. Statistical analyses were performed using SAS/STATS Software, version 9.3 (SAS Institute Inc., Cary, NC, 2002-2010).

Ethical Considerations

The study was conducted with the approval of the Research Ethics Committee of North-West University (Potchefstroom campus), and the board of directors of the PBM. Data were analysed anonymously.

Results

Study population

The study population consisted of 3611 patients (male-to-female ratio 1). The mean age of girls was 13.7 (SD = 3.9) years, *vs.* 12.3 (SD = 3.8) years for boys (d = 0.4). Demographic characteristics of the study population are stipulated in Table 3.

General prescribing patterns

The average number of prescriptions claimed per patient increased with age, from an average of 1.0 (SD = 0.28) among those below the age of 2 years, to average 3.4 (SD = 3.21) among those 16 to 18 years of age. The DU95% for antidepressant items prescribed (n = 12 272) was achieved with the selective serotonin re-uptake inhibitors (SSRIs) (54.8%), tricyclic antidepressants (TCAs) (37.1%) and the serotonin and noradrenalin re-uptake inhibitors (SNRIs) (3.3%). The top five antidepressants prescribed were imipramine (21.8%), citalopram (15.3%), escitalopram (14.7%), amitriptyline (14.0%) and fluoxetine (13.1%, n = 12 272).

Prescribing patterns by gender

The SSRIs and the TCAs were the most prescribed antidepressants in both gender groups. Girls received more SSRIs than boys. Overall, 3 541 items classified as SSRIs were claimed for girls compared to the 3 188 items for boys (male: female ratio 0.9). The TCA ratio differed slightly from the SSRIs comparing male patients *vs.* female patient giving a ratio of 1.2 (male cases = 2 515, female cases = 2 037) suggesting that TCAs were more prescribed to boys than girls. The overall ratio of male *vs*. female patients receiving antidepressants was 1.7, with the lowest ratio being 0.1 (trazodone) and the highest ratio with lithium (5.8). For both populations, citalopram, escitalopram and fluoxetine were the top 3 prescribed SSRIs with 29.3%, 28.5% and 22.5% (n = 3 541) in the female population correspondingly and 26.1%, 24.8% and 25.6%, respectively, in the male population (n = 3188).

Prescribing patterns with regard to age

The number of children receiving antidepressants peaked differently with regard to age groups, for boys and girls. Antidepressant drug prescribing rose gradually from birth and peaked at middle childhood for boys, whereas antidepressant use in girls increased from birth up to 6 years of age where it reached a plateau and increased again from age 13 and onward.

Type of prescriber

The DU95% for antidepressant items (n = 12 272) was achieved with general practitioners, psychiatrists, paediatricians, neurologists and urologists, representing 51.7%, 27.7% 10.8% , 3.4% and 1.8% (n = 12 272), respectively. Rheumatologists were responsible for a further 1.2% (n = 12 272) of claims. The number of items prescribed according to prescriber speciality, for each age group is documented in Table 5. The number of items prescribed increased gradually from birth up to 18 years of age for general practitioners and psychiatrists. General practitioners prescribing ranged from 9 items for the infancy age group up to 2 428 items for the late adolescence group, whereas the psychiatrists' scope of prescribing was from 0 items for age group 1, increasing to 1 378 items at age group 6. The number of items prescribed by urologists and pediatricians rose gradually and peaked at age group 3, after which it declined down to 18 years of age. The number of items prescribed by rheumatologists increased gradually in patients up to ≤10 years of age, but increased rapidly up to late adolescence.

Recommended daily dosages vs. prescribed daily dosages

Of all the antidepressants prescribed approximately 25% (n = 12 272) were classified as inappropriate, including the third most prescribed antidepressant, escitalopram. The top three inappropriate antidepressants prescribed were escitalopram, venlafaxine and bupropion, representing 59.5%, 8.6% and 7.7% of the total inappropriately prescribed antidepressants (n = 3031), respectively. The appropriate prescribed antidepressants' PDDs per age groups are stipulated in Table 4. All antidepressants prescribed in 2010 from birth up to 6 years of age were identified as inappropriate. Middle childhood (>6, ≤10 years) dosages had only two antidepressant PDDs not falling in the dosage range namely citalopram (which is not indicated for that age group) and clomipramine (having a lower than recommended dosage). Except for the PDD of trimipramine in early adolescents, and a higher than recommended PDD (25.5 mg) for fluoxetine in the late adolescent age group, most of the PDDs prescribed were deemed safe for patients 10 years and older.

<<Insert Table 4 here>>

Discussion

In this cross-sectional retrospective study of the prescribing patterns of antidepressants in private healthcare of South African children and adolescents receiving antidepressants, the different prescribing patterns were identified with regard to age, gender, type of prescriber and the level of inappropriate antidepressant prescribing.

The ratio of girls to boys (male: female 1) with regard to prescribing rates of antidepressants correlated with studies conducted in countries in Western Europe but the prescription peaks were different with regard to age groups. There was a slightly higher prevalence overall toward female patients receiving antidepressants in the study population which concurred with rates of three western European countries (Denmark, Germany and the Netherlands), but not the US [18].

The number of children receiving antidepressants peaked differently with regard to age groups, for boys and girls. Antidepressant drug prescribing rose gradually from birth and peaked at middle childhood for boys. This may be attributed to antidepressants being indicated for other ailments such as nocturnal enuresis, which affects boys aged 6-11 years three times more than girls of the same age [18], and ADHD, which boys are 2.1 times more likely to develop than girls [19]. Antidepressant use in girls increased from birth up to 6 years of age where it reached a plateau and increased again from age 13 and onward. This increase in antidepressant prescribing from puberty (≥13 years) up to late adolescence may be ascribed to the change of sex hormone levels and the fluctuations thereof, increasing the vulnerability of the brain to depression. The result of these hormonal levels and fluctuations may result in potently and lastingly affecting the mood and behaviour of female patients [20]. These findings are supported by another study stating that female patients are twice as likely to develop mood disorders especially between 12–15 years of age [21]. An increase in possible mood and behaviour disorders may lead to increased antidepressant prescribing in female patients, since antidepressants

are indicated for child behaviour disorders and depression from age 12 and older [6;13].

The top 2 antidepressants prescribed by general practitioners were imipramine and amitriptyline, both of which are indicated in children and adolescents from as young as 2 years of age for nocturnal enuresis [6, 16] and neuropathic pain [14], respectively. Escitalopram and sertraline were the top 2 antidepressants prescribed by the psychiatrists on the dataset in 2010. Almost 90% of the escitalopram prescribed by psychiatrists were for patients aged 13–18 years, in spite of escitalopram not being indicated for the use in children and adolescents (Table 1). Escitalopram has, however, recently shown to be well tolerated in the treatment of adolescent depression [22]. In accordance we found that imipramine was mostly prescribed by pediatricians and urologists, with a peak in prescriptions for patients aged 6≤10 years. The prescribing of imipramine decreased from 10 years onward. Imipramine is indicated for nocturnal enuresis [18] from the age of 2 years onward. Several studies in Taiwan, Turkey and South Africa have shown that nocturnal enuresis decreases with age [23-25]. Rheumatologists prescribe certain antidepressants in patients with fibromyalgia due to the antidepressants' analgesic effect [26]. According to an analysis by the Boston children's Hospital, there is an increase in the diagnosis of fibromyalgia in patients aged 11–15 years [27]; antidepressants have been shown effective in the treatment of fibromyalgic pain and other chronic pain management [28].

Due to the lack of clinical and diagnostic data, the indication for specific prescribing could not be determined. A quarter of all items prescribed were deemed inappropriate, including bupropion, venlafaxine and trazodone. This trend of inappropriate antidepressant prescribing is a well-documented trend found in other populations worldwide [29-30]. Some antidepressants prescribed under the age of 6 years were also deemed as inappropriate prescribing, although the antidepressant safety was established but not for the respective age group. The prescribing of antidepressants to very young children is not a new occurrence, as it was documented, and regarded as "off-label" prescribing, in another study which found a total of 125 items were prescribed to children 5 years and younger in South Africa [31]. The higher than recommended PDD (25.5 mg) for fluoxetine in the late adolescent age group did not exceed the maximum daily dosage, and can therefore be deemed as safe.

Strengths

The strengths of the current study include the use of a large, nationally representative pharmaceutical claims data set with a large number of patients at baseline, thereby increasing the power for subgroup analyses. Data quality was ascertained by several automated validation processes that were applied in-house by the PBM, such as data integrity validation and eligibility services, utilisation management services, clinical management services and pricing management along with real-time benefit management.

Limitations

There were a number of limitations in this study. The lack of clinical and diagnostic data made it difficult to determine whether the inappropriate prescribing was intentional or accidental. The claims processed were

subject to the accuracy of the claim as processed by the service provider. The exact RDDs could not be determined for each patient since the patients' weights and heights were not present in the dataset. The lack of a proper dosage system with regard to children and adolescents made it difficult to compare the PDDs and the RDDs. This study only represents ≈ 24% of the private health children and adolescents and the results can therefore not be generalised for the total child and adolescent population.

Conclusions

This study showed that in spite of the safety of these medications in children and adolescents, 25% of the study population received at least 1 antidepressant which was not indicated for the study population. It also showed a difference in prescribing patterns with regard to gender, age and the type of prescriber. This study further concluded that there exists a trend of antidepressant prescribing to young children, which is considered unsafe. Future studies should look into the safety and efficacy of all antidepressants in children and adolescents especially with regard to the dosage of antidepressants. Future studies should look into the full extent of inappropriate drug prescribing in children and adolescents. Future studies should also revise the indications of antidepressants in various child and adolescents ailments.

Acknowledgements

The authors wish to thank the medicine claims database that provided the data for the study. We are also grateful to the North-West University for funding this study.

Conflict of interest statement

None of the authors have any conflicts to declare.

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Fig. 1 Process for study population selection

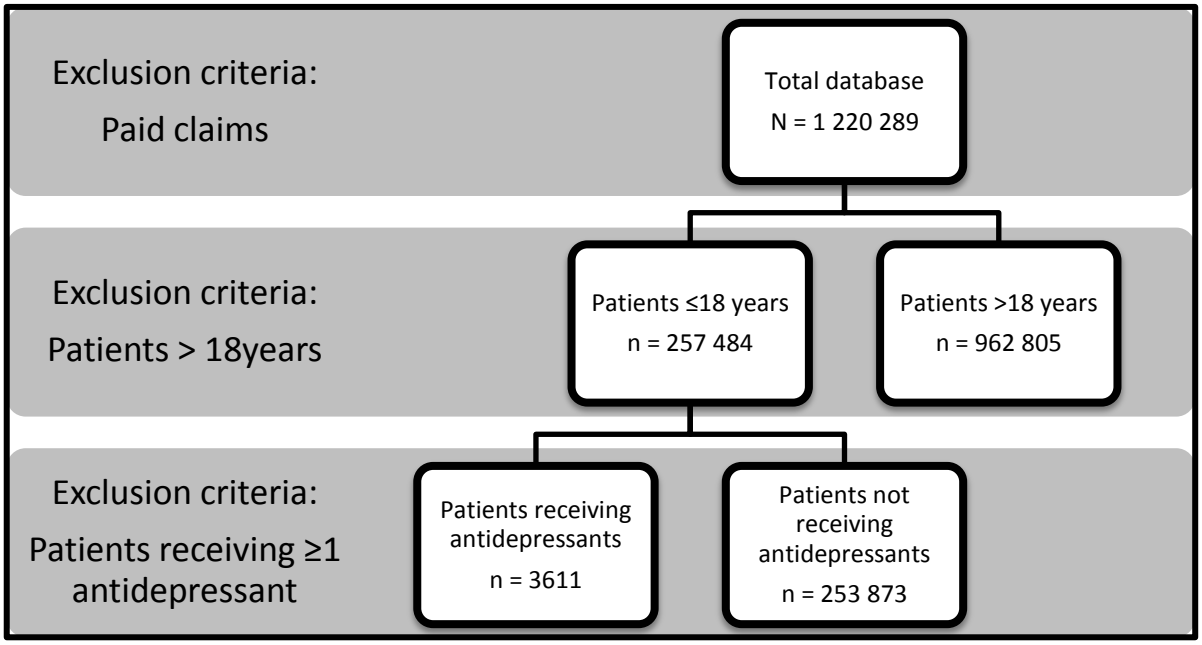


Table 1 Recommended daily dosages (RDDs) for tricyclic antidepressants with indications in children and adolescents (mg/day)

Drug	Indication	Initial dose	0≤2 years	2≤6 years	6≤10 years	10≤13 years	13≤16 years	16≤18 years	Max (mg)	Reference
Amitriptyline	Depression	30-75	-	-	-	-	-	150 - 200	200	Martin (2007) [14]
		-	-	-	-	-	30 - 75 (oral) 80 - 120 (IV/IM)	30 - 75 (oral) 80 - 120 (IV/IM)	200	Reynolds (2002) [15]
	Nocturnal enuresis	-	-	-	10 – 20	25 - 50	25 - 50	25 - 50	200	Reynolds (2002) [15]
					-	25 – 50[e]	25 - 50	25 - 50	25-50	Rossiter (2012) [16]
					10 – 20	25 – 50[e]	25 - 50	50 - 100	200	MIS (2009) [13]
					-	25 – 50[e]	25 - 50	25 - 50	200	Snyman (2012) [6]
	Neuropathic pain	10[f]	-	2.4 - 4.6*	3.8 - 7.2*	5.6 - 10.4*	10 – 25[f]	10 – 25[f]	1 mg/kg or 75 mg[f]	Martin (2007) [14]
		0.2 - 0.5mg/kg		2.2 - 4.6**	3.6 - 7.6**	5.8 - 10.6**				
		-		-	-	10 - 25				
Clomipramine	Obsessive compulsive disorder	25 increase to max	-	48[a] - 69*	57 - 108*	84 - 156*	120 - 200*	162 - 200*	3 mg/kg or 200 mg	Reynolds (2002) [15]
				45[a] - 69**	54 - 114**	87 - 159**	123 - 200**	147 - 200**		Rossiter (2012) [16]
										Snyman (2012) [6]
		25	-	25	25 – 50[f]	25 - 50	25 - 50	25 - 50	250	MIS (2009) [13]
Imipramine	Nocturnal enuresis	-	-	-	25 – 50[c]	25 - 50	50 – 75[e]	50 - 75	-	Martin (2007) [14]
		-	-	-	25[b]	25 - 50	50 – 75[e]	50 - 75	-	Reynolds (2002) [15]
		-	-	20 - 30[a]	25 – 50[d]	25 – 75[f]	25 - 75	25 - 75	-	Snyman (2012) [6]
		-	-	10 - 25[a]	25 – 50[d]	25 – 75[f]	25 - 75	25 - 75	-	Rossiter (2012) [16]
	ADHD	-	-	-	20 - 60	40 - 60	40 - 60	40 - 60	-	Martin (2007) [14]
	Behavioural disorders	-	-	-	25	50[f]	50	50	-	Snyman (2012) [6]
	Depression	-	-	-	-	-	25 - 50	25 - 50	100	Reynolds (2002) [15]
Trimipramine	Depression	50 ≥ max	-	-	-	-	50-100	50-100	100	Reynolds (2002) [15]

[a] Children over 5 years
[b] Children 6-7 years
[c] Children over 8 years
[d] Children over 9 years
[e] Children over 11 years
[f] Children over 12 years
[g] Route of administration is mg/drops
Areas were denoted as '-' when none of the references clearly stated a dosage for the age group
* For boys calculated using the 25th and 75th percentile on the average weight-for-age percentiles for boys 2-20 years (Centre for Disease Control and Prevention 2000), rounded to the nearest decimal.
** For girls calculated using the 25th and 75th percentile on the average weight-for-age percentiles for girls 2-20 years (Centre for Disease Control and Prevention 2000), rounded to the nearest decimal.
IV/IM – Intravenous/intramuscular
MIS - Malahyde Information Systems (2009) (refer to references)

Table 2 Recommended daily dosages (RDDs) for selective serotonin re-uptake inhibitors with indications in children and adolescents (mg/day)

Drug	Indication	Initial dose	0≤2 years	2≤6 years	6≤10 years	10≤13 years	13≤16 years	16≤18 years	Max (mg)	Reference
Citalopram	Major Depression	10 or 8[d]	-	-	-	10 – 20[c]	10 – 20	10 – 20	60	Martin (2007) [14]
						8 – 16[cg]	8 – 16[g]	8 – 16[g]	48[g]	
Fluoxetine	Major Depression	10	-	-	10 – 20[c]	10 - 20[c]	20-Oct	10 – 20	20	Martin (2007) [14]
	*Depression	5 – 10	-	-	5 – 20[a]	5 – 20[a]	5 – 20	5 – 20	20	Rossiter (2010) [16]
	OCD	2 – 5	-	-	2 – 20[a]	5 – 20[c]	5 – 20	5 – 20	30	
		5 – 10[c]							40 – 60	
Fluvoxamine	OCD	25	-	-	25 – 200[b]	50 – 200	25 – 200	25 – 200	200	Martin (2007) [14]
										Reynolds (2002) [15]
Sertraline	OCD	25	-	-	25 – 200	25 – 200	50 – 200	50 – 200	200	Martin (2007) [14]
		50[c]				50 – 200[c]				Reynolds (2002) [15]
		50	-	-	-	-	50 – 200	50 – 200	200	Snyman (2012) [6]
		50	-	-	-	-	50 – 200	50 – 200	200	Rossiter (2010) [16]
	Major Depression	50	-	-	-	50 – 200[c]	50 – 200	50 – 200	200	Martin (2007) [14]

[a] Children over 5 years
[b] Children 6-7 years
[c] Children over 8 years
[d] Children over 9 years
[e] Children over 11 years
[f] Children over 12 years
[g] Route of administration is mg/drops
Areas were denoted as '-' when none of the references clearly stated a dosage for the age group
* For boys calculated using the 25th and 75th percentile on the average weight-for-age percentiles for boys 2-20 years (Centre for Disease Control and Prevention 2000), rounded to the nearest decimal.
** For girls calculated using the 25th and 75th percentile on the average weight-for-age percentiles for girls 2-20 years (Centre for Disease Control and Prevention 2000), rounded to the nearest decimal.
IV/IM – Intravenous/intramuscular
MIS - Malahyde Information Systems (2009) (refer to references)

Table 3 Demographic characteristics of the study population

Study population	Number of patients	Total number of items dispensed
Characteristic	n (%)	n (%)
Gender		
Males	1 761(48.8)	6 146 (50.1)
Mean age male (years)	12.3 ± 3.8	
Females	1 850 (51.2)	6 126 (49.1)
Mean age female (years)	13.7 ± 3.9	
Age Groups		
>0, ≤2 years	8 (0.2)	9 (0.1)
>2, ≤6 years	212 (5.9)	367 (3.0)
>6, ≤10 years	671 (18.6)	1 904 (15.5)
>10, ≤13 years	663 (18.4)	2 495 (20.3)
>13, ≤16 years	917 (25.4)	3 237 (26.4)
>16, ≤18 years	1 140 (31.6)	4 260 (34.7)

Table 4 PDDs determined for appropriate antidepressants per age group

Age Group	>0, ≤2 years		>2, ≤6 years		>6, ≤10 years		>10, ≤13 years		>13, ≤16 years		>16, ≤18 years	
Antidepressant	n	PDD (mg) ±SD	n	PDD (mg) ±SD	n	PDD(mg) ±SD	n	PDD (mg) ±SD	n	PDD (mg) ±SD	n	PDD (mg) ±SD
Amitriptyline	6	15 ±7.8	37	15.8 ±6.5	276	18.9 ±7.9	365	19.8 ±10.3	502	27.7 ±14.1	536	34.2 ±19.9
Citalopram	1	20 ±0	4	22.5 ±12.6	164	17 ±2.9	365	18.7 ±3.6	560	20 ±1.2	783	24.5 ±1.4
Clomipramine	-	-	-	-	13	15.4 ±6.7	27	32.2 ±11.9	13	27.3 ±9.3	70	60.1 ±45.7
Fluoxetine	-	-	5	26 ±12.9	213	14 ±2.6	319	16.6 ±1.3	407	20.5 ±2.6	670	25.5 ±4.8
Fluvoxamine	-	-	-	-	21	89.9 ±5.8	64	111.4 ±9.9	53	114 ±10.6	60	108.4 ±6.7
Imipramine	1	10 ±0	293	19.9 ±7.5	962	22.5 ±7.9	778	26.8 ±9	480	30 ±10	161	45.2 ±4.2
Sertraline	-	-	1	50 ±0	101	48.7 ±13	206	61.7 ±6.1	341	68.4 ±12.3	382	65.5 ±14.5
Trimipramine	-	-	-	-	-	-	1	41.7 ±0	-	-	-	-

Areas denoted as '-'stipulate no clear dosage as per reference guide, or no data was received for that particular field

Table 5 Medicine items prescribed by type of prescriber and age group

Type of prescriber	Age Group (%)					
	0≤2 years (n = 9)	2≤6 years (n = 367)	6≤10 years (n = 1904)	10≤13 years (n = 2495)	13≤16 years (n = 3237)	16≤18 years (n = 4260)
Dentist	-	2 (0.5%)	6 (0.3%)	15 (0.6%)	9 (0.3%)	23 (0.5%)
Dermatologists	-	-	-	3 (0.1%)	7 (0.2%)	48 (1.1%)
General practitioners	9 (100%)	236 (64.3%)	842 (44.2%)	1116 (44.7%)	1719 (53.1%)	2428 (57.0%)
Hospital	-	3 (0.8%)	21 (1.1%)	30 (1.2%)	31 (1.0%)	23 (0.5%)
Neurologists	-	1 (0.3%)	84 (4.4%)	71 (2.8%)	153 (4.7%)	105 (2.5%)
Obstetrics	-	3 (0.8%)	7 (0.4%)	8 (0.3%)	30 (0.9%)	12 (0.3%)
Otorhinolaryngologist	-	-	-	12 (0.5%)	4 (0.1%)	19 (0.4%)
Other	-	2 (0.5%)	10 (0.5%)	9 (0.4%)	23 (0.7%)	11 (0.3%)
Pediatrician	-	74 (20.2%)	479 (25.2%)	461 (18.5%)	217 (6.7%)	100 (2.3%)
Psychiatrists	-	28 (7.6%)	317 (16.6%)	683 (27.4%)	989 (30.6%)	1378 (32.3%)
Rheumatologists	-	2 (0.5%)	10 (0.5%)	13 (0.5%)	44 (1.4%)	84 (2.0%)
Surgeons	-	1 (0.3%)	4 (0.2%)	5 (0.2%)	3 (0.1%)	19 (0.4%)
Urologists	-	15 (4.1%)	124 (6.5%)	69 (2.8%)	8 (0.2%)	10 (0.2%)
Total	9	367	1904	2495	3237	4260

ADDITIONAL RESULTS

This paragraph contains additional results not included in the aforementioned manuscripts.

3.4 GENERAL PRESCRIBING PATTERNS OF CHILDREN AND ADOLESCENTS RECEIVING ANTIDEPRESSANTS IN 2010 WITH REGARD TO PROVINCE

According to the South African census undertaken in 2011, a total of 51 770 560 people are permanent residents in South Africa (Statistics South Africa, 2011). To evaluate the geographic distribution of prescribing patterns, paid claims for patients receiving antidepressants were stratified based on postal codes for providers. Figure 3.1 portrays the distribution of processed claims according to the provinces of South Africa.

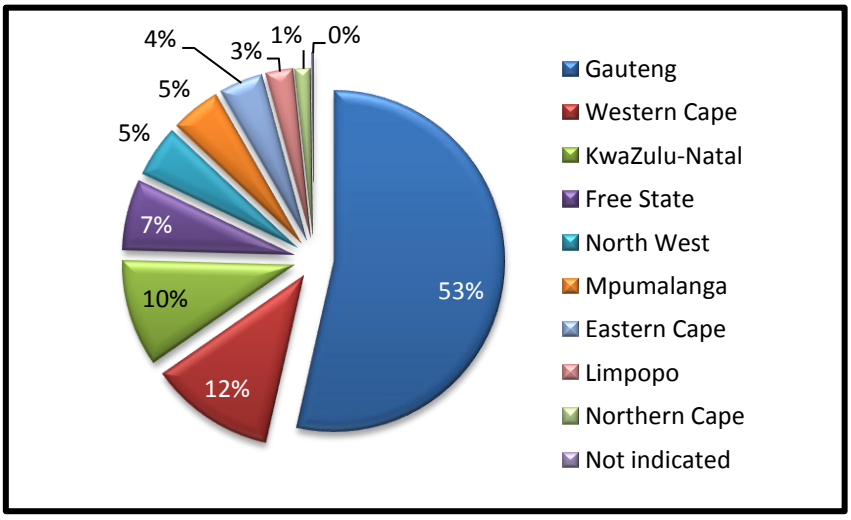


Figure 3.1 Antidepressant prescribing to children and adolescents in South African provinces

Based on Figure 3.1, more than 50% (n = 12 272) of antidepressants prescribed in South Africa for 2010 were in the Gauteng province. Claims in the Western Cape Province and KwaZulu-Natal accounted for approximately 12% and 10% (n = 12 272) of all processed claims for antidepressants in children and adolescents, respectively. According to the 2011 census, the three most populous provinces in South Africa were Gauteng, KwaZulu-Natal and the Western Cape, housing a total of 23.7%, 19.8% and 11.2% of the population. This might explain the prevalence of the number of antidepressants per province in the country. The South African Police Service (SAPS, 2013) furthermore released statistics showing the Gauteng province experiencing almost 7 times the number of trio crimes (three most frequent crimes) for 2010-

2011, compared to the Western Cape, and double the number of trio crimes when compared to the Kwazulu-Natal province. This might be additive to the explanation of the high antidepressant prescribing in Gauteng, since antidepressants being indicated for ailments such as general anxiety disorder (Davidson *et al.,* 2004:239) and panic disorder (Barlow *et al.,* 2000:2533). One limitation in the geographical data was that the geographical distribution of the study population is influenced by the distribution of the medical aid members included in the database, and should not be seen as a general prescribing pattern.

3.5 CHAPTER SUMMARY

This chapter contained the results and was documented in the form of two manuscripts. Chapter 4 will discuss the strengths, limitation, recommendations and the conclusions derived.

CHAPTER 4
CONCLUSION AND RECOMMENDATIONS

4.1 INTRODUCTION

In this chapter the conclusions based on the specific objectives stated in Chapter 1 will be stipulated, the limitations of the study will be listed and recommendations will be made for future studies.

The general objective of this study was to review and analyse aspects of antidepressant prescribing in children and adolescents, in a section of the private health care sector of South Africa. To obtain the general objective, a number of specific objectives were formulated, divided into a literature review and an empirical study and provided the conclusions derived for these specific objectives.

4.2 LITERATURE REVIEW

The specific objectives of this study's literature review were to

- Review antidepressants as a pharmacological treatment class in children and adolescents from the literature;
- Identify possible drug-drug interactions and consequences in children and adolescents;
- Establish factors influencing antidepressant medicine usage patterns in children and adolescents; and
- Determine the recommended daily dosages in by cross-referencing various dosage compendia.

4.2.1 Review antidepressants as a pharmacological treatment class in children and adolescents

The antidepressants were identified and classified using the MIMS® classification system (Table 2.1). Each antidepressant was discussed according to pharmacological class under the following headings: definition, working mechanism, indications, drug-drug interactions and recommended daily dosages in children and adolescents (Section 2.3 and Table 2.2). This

review concluded that only certain antidepressants (amitriptyline, clomipramine, imipramine, trimipramine, citalopram, fluoxetine, fluvoxamine, sertraline) were indicated in the treatment of child and adolescent ailments. This review also concluded that, apart from depression, antidepressants were indicated for a number of other ailments, as well such as neuropathic pain, attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD) and nocturnal enuresis.

4.2.2 Identify possible drug-drug interactions and consequences in children and adolescents

After cross-referencing two interaction compendia, Tatro's drug interactions and Stockley's drug interactions, a number of interactions were identified, together with documented individual reports of a severe nature. Each antidepressant's possible interactions and consequences were listed under the heading "drug-drug interactions" for each respective pharmacological class (Section 2.3). This objective concluded that there were potential drug-drug interactions with antidepressants accompanied by severe consequences.

4.2.3 Establish factors influencing antidepressant medicine usage patterns in children and adolescents

This objective concluded that a number of factors influenced the prescribing of antidepressants in children and adolescents. These factors were identified and listed as country of origin, governmental restrictions and policies, media coverage, financial factors and reimbursement policies, patient-related and prescriber-related factors (Section 2.5). Factors such as age and gender were discussed under the heading "patient related factors" (Paragraph 2.5.5) and found that a number of studies had shown differences with regard to gender and age in the prescribing of antidepressants in children and adolescents. Prescriber speciality was discussed under prescriber-related factors (Paragraph 2.5.6) and noted psychiatric doctors' adherence to regulations published by governing bodies was lower than that of non-psychiatric doctors.

4.2.4 Determine the recommended daily dosages by cross-referencing various dosage compendia

The recommended daily dosages (RDDs) were determined by cross-referencing a number of dosage compendia. These references included the Martindale (2002), British National Formulary for Children (Martin, 2007), the electronic package inserts system (Malahyde

Information Systems, 2009), the South African Medicines Formulary (SAMF) (Rossiter, 2012) and the Monthly Index of Medical Specialities (Snyman, 2012). Some RDDs were calculated using the weight-for-age percentiles growth charts of the Centre for Disease Control and Prevention (2009) (refer to paragraph 1.4.7.2). A table was compiled with all the known RDDs for children and adolescents with regard to antidepressant prescribing (Table 2.2). It was shown that antidepressants were not solely indicated for depression, and that dosages varied by age. This objective established the specific recommended dosage for child and adolescent therapy according to the different age groups.

4.3 EMPIRICAL STUDY OBJECTIVES

The objectives of the empirical phase of the study are as follows:

- To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to age and gender, using medicine claims data.
- To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to type of prescriber, using medicine claims data.
- To establish the prescribed daily dosages of antidepressants prescribed to children and adolescents in South Africa, using medicine claims data.
- To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to geographical area, using medicine claims data.
- To determine the number of potential drug-drug interactions in children and adolescents receiving antidepressant therapy, using medicine claims data.

4.3.1 To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to age and gender, using medicine claims data

The ratio of girls-to-boys with regard to prescribing rates of antidepressants was 1. This correlated with studies conducted in countries in Western Europe. There was a slightly higher prevalence overall toward female patients receiving antidepressants in the study population which concurred with rates of three western European countries (Denmark, Germany and the Netherlands), but not the USA. The SSRIs and the TCAs were the most prescribed antidepressants in both gender groups. The male-to-female ratio for the SSRIs was 0.9, compared to the male-to-female ratio for TCAs being 1.2. (n = 3 611).

When comparing prescribing patterns with regard to age groups, the number of children

receiving antidepressants peaked according to both genders. For boys, antidepressant drug prescribing increased and peaked in middle childhood. Antidepressant use in girls also increased from birth up to 6 years of age, where it reached a plateau and increased again from age 13 years and onward.

4.3.2 To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to type of prescriber, using medicine claims data

The number of prescriptions increased gradually from birth up to 18 years of age for both general practitioners and psychiatrists. The top two antidepressants prescribed by general practitioners were imipramine and amitriptyline, whereas escitalopram and sertraline were mostly prescribed by psychiatrists. Imipramine was the most prescribed by both pediatricians and urologists, with a peak in imipramine prescriptions for both specialities in patients aged 6≤10 years of age. The prescribing of antidepressants by rheumatologists (155 cases) may be ascribed to the analgesic effect of certain antidepressants.

4.3.3 To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to prescribed daily dosages, using medicine claims data

A quarter of all items prescribed in children and adolescents were deemed inappropriate, including bupropion, venlafaxine and trazodone. Some antidepressants prescribed under the age of 6 years were also deemed as inappropriate prescribing, although the antidepressant safety was established but not for the respective age groups. The higher than recommended prescribed daily dosages (PDD) (25.5 mg) for fluoxetine in the late adolescent age group did not exceed the maximum daily dosage, and could therefore be deemed as safe.

4.3.4 To establish the prescribing patterns of antidepressants in children and adolescents in South Africa, with regard to geographical data, using medicine claims data

More than 50% of antidepressants prescribed in South Africa for 2010 were in the Gauteng province. Claims in the Western Cape Province and KwaZulu-Natal accounted for approximately 12% and 10% of all processed claims for antidepressants in children and adolescents, respectively.

4.3.5 To determine the number of potential drug-drug interactions in children and adolescents receiving antidepressant therapy, using medicine claims data

A third of patients from our study population were exposed to possible level one significance interactions. Almost 86% of these interactions were prescriptions containing SSRIs with the central-acting sympathomimetics, methylphenidate and atomoxetine with a potential outcome of increased sensitivity to the sympathomimetic effect and possible serotonin syndrome. Nearly two-thirds of the possible level two interactions were due to two drug-drug interacting groups, namely the TCAs with central acting sympathomimetics and the pairing of valproic acid and carbamazepine. The outcome of a TCA-anticonvulsant interaction might lead to increased TCA levels, resulting in increased adverse reactions and possible TCA toxicity in patients. The possible effect of the concurrent prescribing of sympathomimetics and TCAs might result in a decreased pressor effect of the sympathomimetic agents and severe blood pressure levels which might lead to hospitalisation. A fifth of the possible level two interactions were due to combined prescribing of TCAs with SSRIs. This interaction may lead to increased TCA levels due to the inhibiting effect of SSRIs on the CYP2D6 enzyme system, resulting in increased TCA pharmacological and adverse effects and in extreme cases toxicity. Almost half of the documented potential DDIs (Table 2) occurred with tricyclic antidepressant (TCAs) prescribing. Amitriptyline, imipramine and fluoxetine represented almost two-thirds of the potential drug interactions in the study population. This objective documented that there was a percentage of child and adolescent patient population which was exposed to at least 1 prescription containing potentially life-threatening drug-drug interactions.

These prescribing factors documented with regard to prescribing patterns of certain factors (Paragraph 4.2.1) and potential drug-drug interactions (Paragraph 4.2.2) ensured that the specific objectives of the empirical study were met, and contributed to the achievement of the general objective stated in paragraph 1.3.1.

4.4 LIMITATIONS

This study had a number of limitations. The lack of clinical and diagnostic data made it difficult to determine whether prescribers intentionally or accidentally prescribed certain antidepressants in combination with other medications, in spite of the possible drug-drug interactions or inappropriateness of the antidepressant. The claims processed were liable to the accuracy of the claim as processed by the service provider. The exact recommended daily dosages (RDDs) could not be determined for each patient since the patients' weight and height were not present

on the dataset. The lack of a proper dosage system with regard to children and adolescents made it difficult to compare the PDDs and the RDDs thoroughly. This study only represents ≈ 24% of the private health children and adolescents and the results can therefore not be generalised for the total child and adolescent population. The geographical distribution of the study population was influenced by the distribution of the medical aid members included in the database, and should not be seen as a general prescribing pattern. For the purpose of this study dosages were not included.

4.5 STRENGTHS

The strengths of the current study include the use of a large, nationally representative pharmaceutical claims data set with a large number of patients at baseline, thereby increasing the power for subgroup analyses. Data quality was ascertained by several automated validation processes that were applied in-house by the PBM, such as data integrity validation and eligibility services, utilisation management services, clinical management services and pricing management along with real-time benefit management. The strength of the empirical investigation phase of the study centres mainly on the use of the medicine claims database employed during the empirical investigation phase of the study. Andrade *et al.* (2012:166) stated that these types of database were known resources for drug utilisation reviews, pharmacoepidemiological, health economics studies, and other types of health services research.

4.6 RECOMMENDATIONS

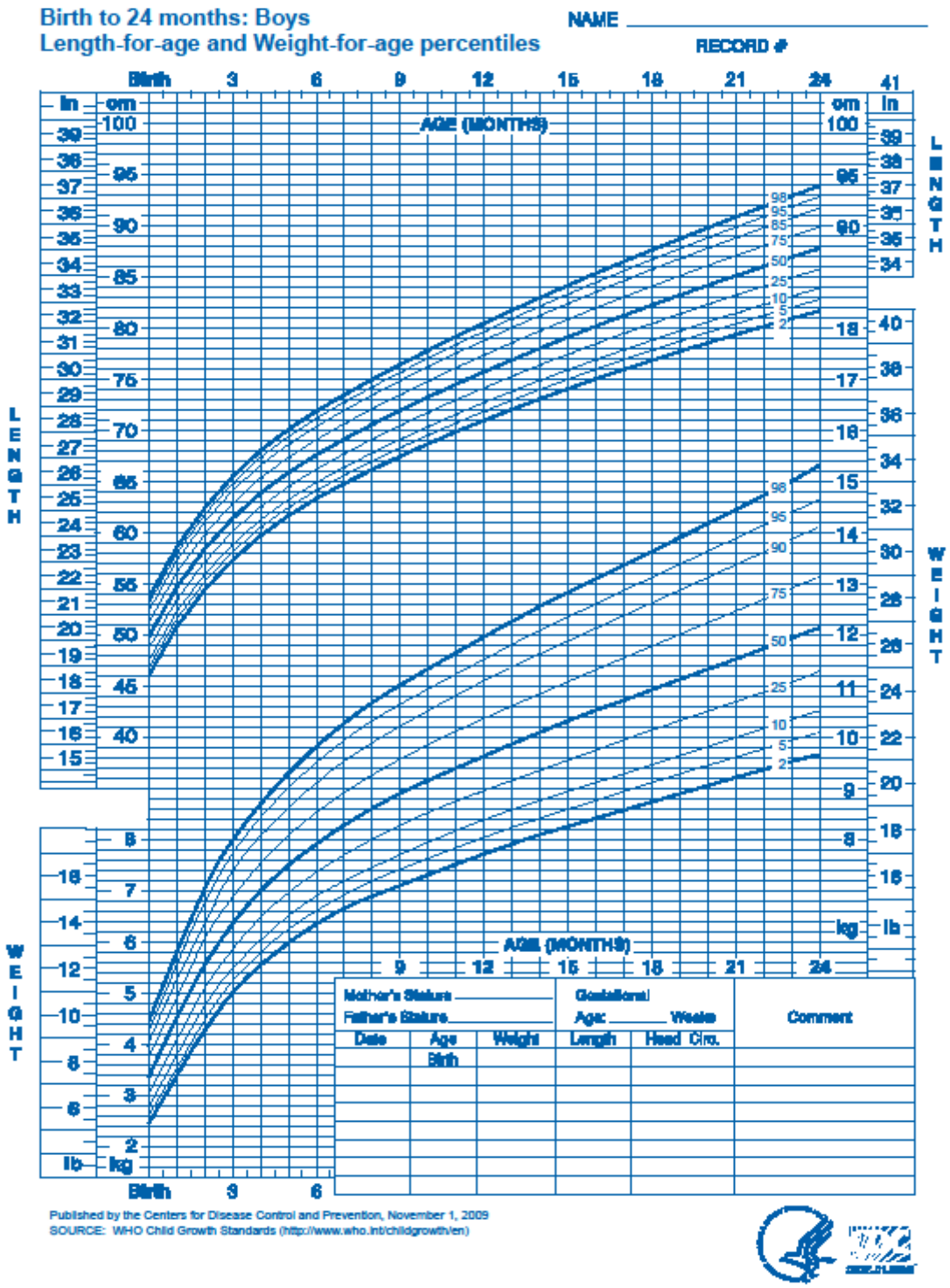
This study recommends that future studies be conducted to ensure the safety of all antidepressants in child and adolescent prescribing. Future studies should further look into the indications of antidepressants by reviewing new clinical data. Future studies should determine the full extent of the exposure of children and adolescents to these interactions and the ramification of these interactions in society. Future studies could also investigate the resources and procedures prescribers should have to prescribe the correct antidepressant with fewer, if any, drug-drug interactions to ensure patient safety.

4.7 CHAPTER SUMMARY

With regard to these conclusions it can be stated that different prescribing patterns for children and adolescents receiving antidepressants in a section of the private health sector in South

Africa, were identified and that the general research objective for this study was met.

ANNEXURE A:
CDC GROWTH CHART (BOYS)



Example of RDD calculation by utilising the CDC Growth charts:

For a minimum and maximum dosage of a specific age group, the respective weights of those patients were required. Minimum weight was derived by using the 25th age-to-weight percentile of the lowest age in a specific age group, whereas the 75th age-to-weight percentile of the highest age in the same age group represented the maximum dose of that age group.

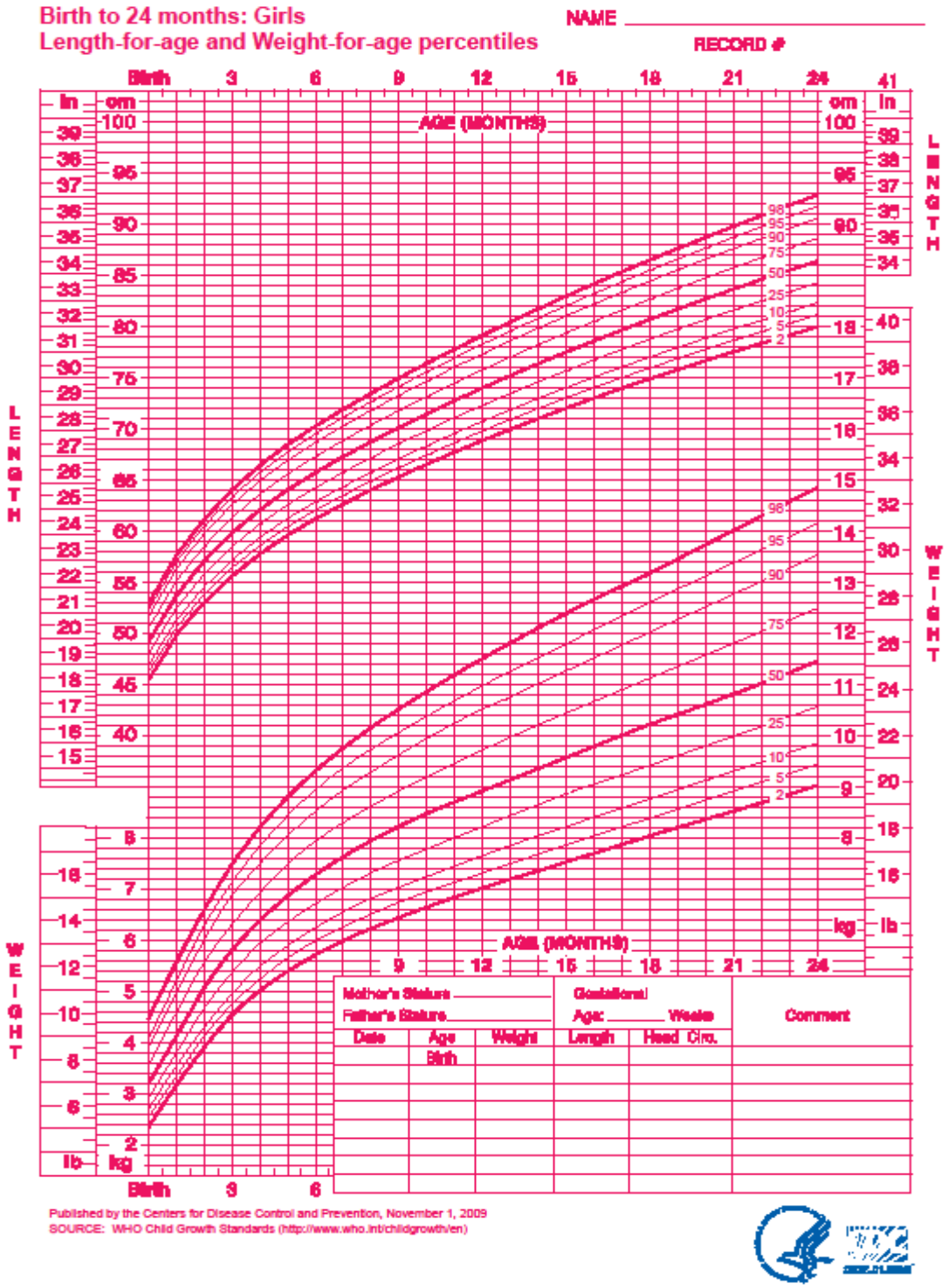
Example:

If amitriptyline was indicated for neuropathic pain in boys aged 2-6 months in a dosage of 0.2mg/kg, the RDDs were determined, with the CDC growth chart for boys, by measuring the 25th age-to-weight percentile of the boys' weight at 2 years as the minimum dosage, and the 75th age-to-weight percentile of the boys' weight at 6 years of age as the maximum dosage.

Minimum weight for boys at 2 months: 5.2 kg
Maximum weight for boys at 6 months: 23 kg
Thus, for male patients aged 2-6 months of age, a dosage between 1.04 mg-4.6 mg of amitriptyline would be deemed as appropriate.

The same process was followed for female patients, using the CDC growth chart for girls (Annexure B).

ANNEXURE B:
CDC GROWTH CHART (GIRLS)



ANNEXURE C:
Author Guidelines - Pharmacoepidemiology and Drug Safety

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.

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.

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.

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/studies Database.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

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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 un-submitted back to you.

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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

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: .

Use Index Medicus abbreviations for journal names. For correct abbreviations visit ftp://ftp.ncbi.nih.gov/pubmed/J_Medline.txt.
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:

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

Supporting Information

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

6. DECLARATION

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Submission of a manuscript will be held to imply that it contains original unpublished work

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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 these 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.

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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.)

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In accordance with the trials registration policy of the International Committee of Medical Journal Editors (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/).

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) as a guideline for the reporting of observational studies and CONSORT (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.

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ANNEXURE D:
Author Guidelines - Journal of Clinical Pharmacy and Therapeutics

Original research papers

The number of printed pages per article including figures, tables and references should not exceed 8-10 printed pages (one printed page accounts to approx. 650 words or 4300 characters, plain text without spaces; figures and tables have to be counted extra as half a page each).

Editorials (without abstract)

Letter to the Editor

A commentary or a case report or otherwise a brief communication on a specific topic should have no more than 600 words main text (excepting the reference list) and contain no more than one table or one figure. The letter should not contain an abstract and should not be subdivided into sections.

Review articles

Review articles on various topics are welcome. Both invited and unsolicited submissions are published. The submitted review will be peer-reviewed as other submissions. A word limit is no specified for reviews. The Journal welcomes “full-sized” reviews of up to 4,000 words (main text) as well as “condensed” reviews or “occasional updates” of around 1,000 words.

Reporting Clinical Trials

The Editors believe that it is important to foster a comprehensive, publicly available database of clinical trials. In compliance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), EJCP therefore requires that authors must register clinical trials before the first subject is enrolled. This policy goes into effect on June 1, 2007. Trials that were under way before that date and not registered and that are submitted to EJCP no later than June 1, 2008 will not be forced under the new

guideline. For EJCP, clinical trial is defined as any research project that prospectively assigns human subjects to a pharmacological intervention or concurrent comparison or control groups to study the cause-and-effect relationship between this intervention and a health outcome. The ICMJE policies on registration of clinical trials can be found at: http://www.icmje.org/clin_trialup.htm.

EJCP does not advocate one particular registry. Appropriate registries (such as www.clinicaltrials.gov) must be (1) accessible to the public at no charge, (2) open to all prospective registrants, and (3) managed by a not-for-profit organization. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable. An acceptable registry must include at minimum the data elements available at the ICMJE website listed above. The title page of a manuscript describing the results of a clinical trial must contain the name of the clinical trial registry and registration number of the trial. Any report of a clinical trial not containing such information will be returned to the corresponding author without review. Reports of randomized, controlled trials should follow the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement. See for the current CONSORT guidelines and checklist

http://www.consort-statement.org/statement/revisedstatement.htm.

Contributions that are part of a Special Issue must include the following footnote on the title page: "This article is published as part of the Special Issue on [title of the Special Issue]"

Manuscript submission

Manuscript Submission

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

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Authors should submit their manuscripts online. Electronic submission substantially reduces the editorial processing and reviewing times and shortens overall publication times. Please follow the hyperlink “Submit online” on the right and upload all of your manuscript files following the instructions given on the screen.

Contributions of Authors statement

It is required to specify the contribution/responsibility of each author in the work in a statement at the end of the manuscript. State the contribution detailed, with relevance to the international guidelines of co-authorship by ICMJE and for each author separately.

The statement should be placed after the Acknowledgments and before the reference list.

ICMJE guidelines

Title Page

The title page should include:

- The name(s) of the author(s)
- A concise and informative title
- The affiliation(s) and address(es) of the author(s)
- The e-mail address, telephone and fax numbers of the corresponding author

Abstract

Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

- Purpose (stating the main purposes and research question)
- Methods
- Results
- Conclusions

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

Text

Text Formatting

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Manuscripts with mathematical content can also be submitted in LaTeX.

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section before the reference list. The names of funding organizations should be written in full.

Specific remarks

Introduction

- This section can be brief and should state the relevant background for and the main purposes of the study reported. Avoid review type introductions.

Terminology

- Generic names of drugs and pesticides are preferred; if trade names are used, the generic name should be given at first mention. The proprietary name, chemical composition, and manufacturer should be stated in full in Materials and Methods. If a generic name has not been created or otherwise is not available, the chemical name should be given. Use of an industry code name alone is not sufficient.

SI units

- Please always use internationally accepted signs and symbols for units, SI units.

Statistics

- Sample size consideration must be given for any clinical study and power calculations are needed for negative results of pivotal variables. This can be done post-hoc if insufficient information was available a priori. Bioequivalence/bioavailability and drug-drug interaction studies should include tests/reference ratios and the respective 90% or 95% confidence intervals.

Analytical methods

- Any method used to quantify drug or metabolite concentrations in body fluids should be characterised at least by the following information:
    - Range of quantification (defined by an acceptable accuracy/precision and not by a factor above baseline noise),
    - accuracy and precision over the entire range of quantification,

    - recovery (if applicable) and stability information for the period of measurement.
- This information is needed either in the manuscript or must be available in a reference the author provides. Normally the methods should be described in such a detailed way that other researchers will be able to repeat it.

References

Citation

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ASSOCIATED PRESENTATIONS

The following conference presentations relevant to the study were produced during candidature during the 3's company conference in Cape Town 2013:

Assessment of potential drug-drug interactions among South African children and adolescents receiving antidepressants

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Purpose: To determine and evaluate the prevalence and significance of potential drug-drug interactions (DDIs) among South African private healthsector children and adolescents aged ≤18 years.

Methods: A retrospective cross-sectional analysis was performed on nationally representative medicine claims data for a 1-year period (1 Jan. to 31 Dec. 2010), obtained from a South African Pharmaceutical Benefit Management (PBM) company. DDIs were determined using agreement between 4 commonly used DDI Compendia: Tatro 2012, MIMS, Martindale and Stockley's Drug Interactions. DDIs that my result in a severity rating of 1 or 2 interactions based on Tatro's scale were counted when a prescription was dispensed during the study period for an antidepressant in a potentially interacting combination. Interactions with severity ratings of 1 and 2 may lead to hospitalization.

Results: A total of 11 743 antidepressants were dispensed during the study period. Potential significant level 1 and 2 DDIs were observed on 284 (2.4%) of these. Overall, the highest prevalence of potential interactions occurred in patients taking imipramine (32.0%, 91 cases), amitriptyline (17.3%, 49 cases) and fluoxetine (16.9%, 48 cases). The drug pairs prescribed most were imipramine with methylphenidate [accounting for 43 (15.1%) of DDIs] and valproic acid [accounting for 38 (13.4%), followed by methylphendidate with fluoxetine and sertraline [both accounting for 32 (11.3%) of DDIs]. The number of cases showed a gradual increase with age whilst peaking for imipramine between 6-10 years with methylphenidate and 13-16 years of age with valproic acid respectively. The highest incidence of antidepressant drug-pairing took place between amitriptyline and sertraline, accounting for 10.2% (29 cases) of the potential interactions.

Conclusions: At least 2.4% of the child and adolescent population in the South African private healthcare sector were exposed to ≥1 potential drug-drug interaction of clinical importance

during 2010. The potential reasons and ramifications of these prescribing patterns should be evaluated to guard patient's safety.

The Academy of Pharmaceutical Sciences of the Pharmaceutical Society of South Africa

hereby commends

Jaycee van Rooyen

As the winner of the
Young Scientist award for
2013

Chairman

Secretary