Assessment of potentially inappropriate medicine prescribing for elderly patients in the South African private health sector

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It all starts here ™

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PREFACE

This study was presented in article format. The chapters in this dissertation are outlined as follows:

- Chapter 1 provides the background and justification for the study, followed by the research methodology and ethical considerations.
- Chapter 2 is the literature review, focusing on prescribing for elderly patients and the factors that influence prescribing for this group of patients. It further focuses on the available screening tools and criteria available to assess appropriateness of prescribing for elderly patients and a summary of the studies available that identified inappropriate prescribing in elderly patients.
- Chapter 3 consists of the results and discussion of the dissertation presented in the form of two manuscripts. The manuscripts were submitted for publication in the following journals:
    - South African medical journal (manuscript one)
    - International journal of pharmacy practice (manuscript two)
- Chapter 4 is the conclusion, recommendations and the limitations for the study.
- The annexures and references form the last part of the dissertation.

The co-authors mentioned in the manuscripts were the supervisor and co-supervisor during the study period and the manuscripts that formed part of the dissertation were done upon their approval. The contributions of each author are subsequently outlined.

AUTHORS' CONTRIBUTIONS (MANUSCRIPT ONE)

The contribution of each author for manuscript one entitled "Inappropriate medicine prescribing in older South Africans: A cross-sectional analysis of medicine claims data" is provided below:

Author	Role in the study
Ms JA van Heerden	Literature review Planning and designing the manuscript Data analysis Interpretation of results Writing of manuscript
Dr JR Burger (Supervisor)	Supervision of concept of manuscript Planning and designing the manuscript Data and statistical analysis Supervision on writing of manuscript Reviewing the manuscript for final approval
Prof JJ Gerber (Co-supervisor)	Reviewing manuscript for final approval

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

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

..... **.....**

Dr JR Burger **Prof JJ Gerber**

AUTHORS' CONTRIBUTIONS (MANUSCRIPT TWO)

The contribution of each author for manuscript two entitled "Detecting potentially serious drug-drug interactions among South African elderly private health sector patients using the Matanović/Vlahović-Palčevski drug-drug interaction protocol" is provided below:

Author	Role in the study
Ms JA van Heerden	Literature review Planning and designing the manuscript Data analysis Interpretation of results Writing of the manuscript
Dr JR Burger (Supervisor)	Supervision of concept of manuscript Planning and designing the manuscript Data and statistical analysis Supervision on writing of manuscript Reviewing the manuscript for final approval
Prof JJ Gerber (Co-supervisor)	Reviewing manuscript for final approval
Prof V Vlahović-Palčevski (co-author)	Reviewing manuscript for final approval

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

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

..... **.....**

Dr JR Burger **Prof JJ Gerber**

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ABSTRACT

The aim of this study was to investigate the medicine prescribing patterns for elderly patients in the private health sector of South Africa utilising different screening tools for potentially inappropriate prescribing.

The study consisted of a literature review and an empirical investigation. The literature review entailed an overview of the concept and prevalence of potentially inappropriate prescribing (PIP), factors influencing prescribing for the elderly and a comparison of different screening tools for PIP in elderly patients. The empirical investigation followed a quantitative, descriptive, cross-sectional design to study inappropriate prescribing for elderly patients' ≥65 years using medicine claims data from a one-year period (1 January – 31 December 2013). PIP was assessed by applying the 2012-Beers criteria list for potentially inappropriate medicine items (PIMs) and the Mimica Matanović and Vlahović-Palčevski comprehensive protocol for potentially clinically important drug-drug interactions (DDIs).

Variables were characterised using 95% confidence intervals, descriptive statistics such as proportions/ratios for categorical variables, and means and standard deviations for continuous variables. Independent two-sample *t*-tests were used to assess the statistical significance of mean differences between men and women, whereas one-way between-group analysis of variance (ANOVA) with post-hoc comparisons using the Tukey HSD test was conducted to determine significant differences between the means of two or more independent groups. The Chi-square test was done to determine the association between categorical variables. Practical significance was assessed using Cohen's *d*-value (for mean differences between groups), and Cramér's *V* statistic (for associations between categorical variables). Statistical analyses were performed using SAS Software, version 9.3. Medicine claims data for 103 420 patients, mean age 74.1 ± 6.7 years, 57.1% female, were included in the analyses.

Only 102 of the 143 2012-Beers criteria list items were available in South Africa at the time of the study. Application of the criteria list identified 562 852 PIMs in 71 206 patients (68.9%). The most common PIMs were: oestrogen (12.4%), meloxicam (7.3%), amitriptyline and combinations thereof (6.5%), diclofenac (6.4%), ibuprofen (6.1%), alprazolam (5.3%), meprobamate and combinations thereof (5.0%), insulin (3.3%), amiodarone (3.1%) and doxazosin (2.6%). There were statistically significantly more PIMs prescribed to women than to men (1.9:1; $P<0.0001$), although this difference was not practically significant (Cramér's $V = 0.0559$). General practitioners were the group that prescribed the highest number of PIMs.

Only 65 of the 70 Mimica Matanović and Vlahović-Palčevski comprehensive protocol for potentially clinically important drug-drug interactions were available in South Africa at the time of

the study. Application of the protocol identified a total of 331 655 (7.8%) DDIs among 912,712 prescriptions. Women experienced proportionally more DDIs than men (62.6% *vs.* 37.4%) ($P < 0.0001$, Cramér's $V = 0.0491$). A mean 0.36 ± 0.7 (95% CI, 0.36-0.37) DDIs were encountered per prescription. There was no practically significant difference between sexes ($P < 0.0001$, Cohen's d-value = 0.05) or age groups ($F(3, 235\ 869) = 112.38$, $P < 0.0001$; Cohen's d-value < 0.05) with regard to the mean number of DDIs per prescription. The most common DDIs were between several drugs acting on the central nervous system (30.6%), antihypertensives and nonsteroidal anti-inflammatory drugs (23.5%), diuretics and nonsteroidal anti-inflammatory drugs (8.3%), angiotensin-converting enzyme inhibitors and potassium supplements (4.9%), and nonsteroidal anti-inflammatory drugs/aspirin and corticosteroids (4.8%).

Inappropriate medicine item prescribing and drug-drug interactions were common among the patients in the study population. Female patients received more PIMs and had a higher prevalence of potentially serious DDIs than their male counterparts. The prevalence of PIMs was the highest among patients between the ages of 72 and 78 years, whereas the prevalence of potentially serious DDIs was the highest in patients older than 78 years. Drug groups of concern included sedative hypnotics, antihypertensives, antidepressants and NSAIDs. The Beers criteria list and the Mimica Matanović and Vlahović-Palčevski drug-drug interaction list were useful to determine inappropriate prescribing patterns; however, there is a clear need for custom-made screening instruments for determining potentially inappropriate prescribing in South African elderly patients.

Key words: potentially inappropriate prescribing; potentially inappropriate medicine items; older/elderly people; Beers criteria list; pharmaceutical claims data; potentially clinically important drug-drug interactions; Mimica Matanović and Vlahović-Palčevski drug-drug interaction list.

OPSOMMING

Die doel met hierdie studie was om ondersoek in te stel na die medisynevoorskryfpatrone vir bejaardes in die private gesondheidsektor in Suid-Afrika deur gebruik te maak van verskillende meetinstrumente vir moontlike ongewensde voorskrywing.

Die studie het bestaan uit ’n literatuuroorsig en ’n empiriese ondersoek. Die literatuuroorsig het ’n oorsig van die konsep en voorkoms van moontlike ongewensde voorskrywing (MOV), faktore wat voorskrywing vir bejaardes beïnvloed en ’n vergelyking van verskillende meetinstrumente vir moontlike ongewensde voorskrywing vir bejaarde pasiënte, behels. Die empiriese ondersoek het ’n kwantitatiewe, beskrywende, deursnee-ontwerp gevolg om ongewensde voorskrywing vir bejaarde pasiënte ≥ 65 jaar te ondersoek met gebruik van medisyne-eisedata vir ’n eenjaar periode (1 Januarie – 31 Desember 2013). Moontlike ongewensde voorskrywing is bepaal deur toepassing van die 2012 Beers-kriterialys vir moontlike ongewensde medisyne-items (MOM’e) en die Mimica Matanović en Vlahović-Palčevski omvattende protokol vir moontlike kliniesbelangrike geneesmiddel-geneesmiddel interaksies (GGI’s).

Veranderlikes is uitgedruk in terme van 95% vertrouensintervalle, beskrywende statistiek soos proporsies/verhoudings vir kategoriese veranderlikes, en gemiddeldes en standaardafwykings vir kontinue veranderlikes. Onafhanklike tweesteekproef-*t*-toetse is gebruik om die statistiese betekenisvolheid van die verskil in gemiddeldes tussen mans en vrouens te bepaal, terwyl eenrigtingvariansieanalise (ANOVA) met post-hoc vergelykings uitgevoer is met behulp van die Tukey-HSD-toets, om betekenisvolle verskille tussen die gemiddeldes van twee of meer onafhanklike groepe te bepaal. Die chi-kwadraattoets is uitgevoer om die verwantskap tussen kategoriese veranderlikes te bepaal. Praktiese betekenisvolheid is bepaal deur van Cohen se *d*-waarde (vir verskille in gemiddeldes tussen groepe) en Cramér se *V*-statistiek (vir verwantskappe tussen kategoriese veranderlikes), gebruik te maak. Statistiese ontleding is met SAS sagteware, weergawe 9.3, uitgevoer. Medisyne-eisedata vir 103 420 pasiënte, gemiddelde ouderdom 74.1 ± 6.7 jaar, 57.1 % vroulik, is in die ontledings ingesluit.

Slegs 102 van die 143 2012-Beers kriterialys items was in Suid-Afrika beskikbaar ten tye van die studie. Toepassing van die Beers-kriterialys het 562 852 MOMs in 71 206 pasiënte (68.9%) geïdentifiseer. Die algemeenste MOM’e was: estrogeen (12.4%), meloksikam (7.3%), amitriptilien en kombinasies daarvan (6.5%), diklofenak (6.4%), ibuprofeen (6.1%), alprasolaam (5.3%), meprobamaat en kombinasies daarvan (5.0%), insulien (3.3%), amiodaroon (3.1%) en doksasosien (2.6%). Statisties was daar betekenisvol meer MOM’e aan vrouens as mans voorgeskryf (1.9:1; $P < 0.0001$). Hierdie verskil was egter nie prakties betekenisvol nie (Cramér se $V = 0.0559$). Algemene praktisyns was die groep wat die meeste MOM’e voorgeskryf het.

Slegs 65 van die 70 van die Mimica Matanović en Vlahović-Palčevski omvattende protokol vir moontlike klinies-belangrike geneesmiddel-geneesmiddel interaksies was in Suid-Afrika beskikbaar ten tye van die studie. Toepassing van die protokol het ’n totaal van 331 655 (7.8%) GGI’s uit 912 712 voorgeskrifte, uitgewys. Meer GGIs het by vrouens in verhouding tot mans voorgekom (62.6% *vs.* 37.4%) ($P < 0.0001$, Cramér se $V = 0.0491$). ’n Gemiddelde 0.36 ± 0.7 (95% CI, 0.36-0.37) GGI’s per voorskrif is gevind. Daar was geen praktiese betekenisvolle verskil tussen geslagte ($P < 0.0001$, Cohen se *d*-waarde = 0.05) of ouderdomsgroepe ($F(3, 235\,869) = 112.38$, $P < 0.0001$; Cohen se *d*-waarde < 0.05) met betrekking tot die gemiddelde GGI’s per voorskrif, nie. Die algemeenste GGI’s was dié tussen meerdere middels werksaam op die sentrale senuweestelsel (30.6%), antihipertensiewe- en nie-steroïd anti-inflammatoriese middels (23.5%), diuretika en nie-steroïd anti-inflammatoriese middels (8.3%), angiotensien-omsettingsensieminhibeerders en kaliumaanvullings (4.9%) en nie-steroïd anti-inflammatoriese middels/aspirien en kortikosteroïede (4.8%).

Die voorskryf van ongewensde medisyne-items en geneesmiddel-geneesmiddel interaksies was algemeen onder pasiënte in die studiepopulasie. Vroulike pasiënte het meer MOM’e in verhouding tot mans ontvang, en het ‘n hoër voorkoms van moontlike klinies-belangrike GGI’s gehad. Die voorkoms van MOM’e was die hoogste onder pasiënte tussen die ouderdomme van 72 en 78 jaar, terwyl die voorkoms van moontlike klinies-belangrike GGI’s die hoogste was by pasiënte ouer as 78 jaar. Geneesmiddelklasse van belang het die volgende ingesluit: sedatiewe hipnotika, antihipertensiewe middels, antidepressante en nie-steroïd anti-inflammatoriese middels. Die Beers-kriterialys en die Mimica Matanović en Vlahović-Palčevski geneesmiddel-geneesmiddel interaksielys was nuttig om ongewensde voorskryfpatrone te bepaal, maar daar bestaan ’n duidelike behoefte aan pasgemaakte meetinstrumente vir die bepaling van moontlike ongewensde voorskrywing in bejaarde Suid-Afrikaanse pasiënte.

Trefwoorde: moontlike ongewensde voorskrywing; moontlike ongewensde medisyne-items; ouer/bejaarde persone; Beers-kriterialys; medisyne-eisedata; moontlike klinies-belangrike geneesmiddel-geneesmiddel interaksies; Mimica Matanović en Vlahović-Palčevski geneesmiddel-geneesmiddel interaksielys.

LIST OF ACRONYMS AND ABBREVIATIONS

A

ACE	Angiotensin-converting enzyme
ACOVE QIs	Assessing Care of Vulnerable Elders Quality Indicators
ADEs	Adverse drug events
ADRs	Adverse drug reactions
ANOVA	Analysis of variance
ARMOR	A tool to evaluate polypharmacy in elderly persons

B

BPH	Benign prostatic hypertrophy

C

CD	Considering diagnosis
CDL	Chronic Disease List
cGMP	Cyclic guanosine monophosphate
CHF	Chronic heart failure
CI	Confidence interval
CNS	Central nervous system
COX	Cyclooxygenase
CPRD	Clinical Practice Research Data link
CrCl	Creatinine clearance
CVS	Cardiovascular system
CYP	Cytochrome P450

D

DDIs	Drug-drug interactions
DRPs	Digoxin-reduction products
DUR	Drug utilisation review

E

E2	Estradiol
EVIDEM	Evidence-based Interventions in Dementia

LIST OF ACRONYMS AND ABBREVIATIONS CONTINUED

F

FDA	Food and Drug Administration, United States of America
FORTA	Fit for the Aged

G

GEM	Geriatric evaluation and management
GFR	Glomerular filtration rate
GI	Gastro-intestinal
GLM	General linear model

H

HbA1c	Glycated haemoglobin test
HMG-Co A	Hydroxymethylglutaryl-coenzyme A
HREC	Health Research Ethics Committee
HRT	Hormone replacement therapy

I

ICD-10	10th revision of the International Classification of Diseases
ID	Independent diagnosis
INR	International normalized ratio
IP(s)	Inappropriate prescription(s)
IPET	Improving Prescribing in the Elderly Tool

K

KPC	Kaiser Permanente Colorado

L

LHRH	Luteinizing hormone-releasing hormone

M

MAI	Medication Appropriateness Index
MAO	Mono-amine oxidase
MAOI(s)	Mono-amine oxidase inhibitor(s)
MIMS®	Monthly Index of Medicine Specialities
MUSA	Medicine Usage in South Africa

LIST OF ACRONYMS AND ABBREVIATIONS CONTINUED

N

NAPA	N-acetyl-procainamide
NAPPI®	National Approved Product Pricing Index
NCQA	National Committee for Quality Assurance
NORGEP	Norwegian General Practice
NSAID(s)	Non-steroidal anti-inflammatory drug(s)
NWU	North-West University

P

PASA	Population Association of South Africa
PBM	Pharmaceutical benefit management company
PDD	Prescribed daily dose
PIDP(s)	Potentially inappropriate drug prescriptions
PIM(s)	Potentially inappropriate medicine(s)
PIP(s)	Potentially inappropriate prescriptions
PMB	Prescribed Minimum Benefits
PMDRP	Pharmacist's Management of Drug-Related Problems
PPIs	Proton pump inhibitors
PPO	Potentially prescribing omission
PT	Prothrombin time

R

RA	Rheumatoid arthritis
RDUR	Retrospective drug utilisation review

S

SAMS	South African Menopause Society
SANHANES	South African National Health and Nutrition Examination survey
SAS®	Statistical Analysis System
SASH	South African Stress and Health
SD	Standard deviation
SSRIs	Selective serotonin-reuptake inhibitors
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Persons' Prescriptions

LIST OF ACRONYMS AND ABBREVIATIONS CONTINUED

T

TCAs	Tricyclic antidepressants
TIMER	Tool to Improve Medications in the Elderly via Review

U

UK	United Kingdom
US	United States
USA	United States of America

W

WHO	World Health Organization

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CHAPTER 1: INTRODUCTION

1.1 Background and justification

In 2013 the United Nations (2013:3) estimated that the total elderly population worldwide will increase from 841 million in 2013 to over 2 billion by 2050, whereas Mimica Matanović and Vlahović-Palčevski (2012:1123) anticipates that around 30% of the population in first world countries will be at the age of 65 years or older in 2050. Based on calculations by the International Labour Organization (2009), the percentage of citizens aged 65 years and older in less developed countries is also expected to rise from 5.8% to 15% over the next 40 years. Similar ageing trends are also visible in developing countries such as South Africa. For instance in 2000, the average percentage older adults in South Africa were at 5.7%, the second highest proportion of elderly people on the African continent at the time (Joubert & Bradshaw, 2006:206-207). The Profile of Older Persons in South Africa report, based on the three population censuses of 1996, 2001 and 2011 and released by Statistics South Africa at the Population Association of South Africa (PASA) conference in 2014, showed that the proportion of the South African community 60 years of age and older increased from 7.1% in 1996 to 8.0% in 2011, leading to an accruement from 2.8 million to 4.1 million people (Statistics South Africa, 2014:iv). At the same time, the number of persons older than 65 years in the medical scheme environment increased from approximately 6% in 1996 (Harrison, 2003:291) to 6.5% in 2011 and 7.1% in 2013, respectively (Council for Medical Schemes, 2013:147).

The population aging process can be associated with increased disease, disability and frailty due to a decrease in physiological, physical, mental and cognitive functional capabilities (Kaur *et al*., 2009:1015). Old age are therefore often characterised by an increased prevalence of chronic conditions (Shah *et al*., 2011:251) and co-morbidities (Maio *et al.,* 2010:219-220). Longevity is also associated with conditions such as Alzheimer's disease, musculoskeletal problems (osteoarthritis, rheumatoid arthritis and osteoporosis) and cardiovascular conditions (Buvinić *et al.,* 2006:201). Higher disease prevalence in turn leads to increased drug utilisation. For example, according to Shelton *et al*. (2000:438), the average number of drugs consumed by an elderly patient is three for community-dwelling persons and eight for nursing-home patients. In South Africa, chronic medication use among the elderly (60-64 years old) are reported to be 38% of national use, with elderly female patients (43.9%) using more chronic medication than elderly male patients (37.8%) (Statistics South Africa, 2014:70). It was reported that in 2000, chronic diseases of lifestyle were responsible for approximately 84% of mortalities in the older population. Ischemic heart disease (17.2% in males and 16.0% in females, respectively) and stroke (12.2% in males and 17.7% in females, respectively) were the two leading causes of death in both male and female patients; these two diseases were responsible for approximately

33% of deaths in older adults (Joubert & Bradshaw, 2006:210-211). Other chronic conditions responsible for death in elderly patients include hypertensive heart disease (4.2% in males and 9.8% in females, respectively) and chronic obstructive pulmonary disease (8.0% in males and 4.4% in females, respectively) (Joubert & Bradshaw, 2006:211).

The largest proportion of prescription and non-prescription medicines is consumed by elderly women (Mimica Matanović & Vlahović-Palčevski, 2012:1123). Physicians tend to recommend and prescribe psychotherapeutic drugs more readily to women than to men with the same complaint, which indicates that overprescribing is more prevalent in females than in males. Female patients tend to visit physicians frequently, which may also be the cause of increased medicine use in women (Verbrugge, 1982:428-429). According to Kaufman *et al*. (2002:342), women in the United States of America aged 65 and above had the highest percentage of medicine usage with 94% taking a minimum of one, 57% taking five or more and 12% taking 10 or more medicine items representing 19, 12 and 1.4 million elderly women respectively. Prescription drug use is also the most prevalent in this group, with rates of 81% and 23%, respectively, for a minimum of one and a minimum of five drugs. Male patients in this age group also have an increased prevalence of drug use but not as significant as that of women (Kaufman *et al.*, 2002:342). Increased drug utilisation, in turn, is linked to a higher probability of medication errors and possible drug-related problems (Maio *et al.*, 2010:219-220; Shah *et al*., 2011:251).

Inappropriate medicine prescribing in older adults is a well-known issue. Appropriate or rational prescribing bases the choice of medicine on the safety, efficacy and convenience thereof when compared to other items for a specific patient and it considers the cost of treatment when the above norm for choice have been satisfied (Shah *et al*., 2011:248). Inappropriate prescribing can be described as the use of medicine items that introduces an increased probability of adverse effects when there is proof of a similar or more efficient lower-risk substitute treatment for the same medical condition (Page *et al*., 2010:75). Shah *et al.* (2011:251) define inappropriate prescribing as the prescribing of medicine outside the accepted medical standards.

According to Aparasu and Mort (2000:338), inappropriate or inadequate prescribing is a significant risk factor contributing to medicine-related illness in older patients. For instance, a review (Aparasu & Mort, 2000:341) based in the United States indicated that almost 40% of individuals residing in old-age homes received inappropriate prescriptions and almost half as much was seen in elderly patients residing in the community. A similar Australian-based study found that almost 20% of patients 70 years and older had a minimum of one inappropriate prescription in a 6-month period (NPS Medicinewise, 2013:1). The items most frequently inappropriately prescribed were identical in these studies and consisted of long-acting

benzodiazepines, amitriptyline, amiodarone, oxybutynin and doxepin, and dextro-propoxyphene (NPS Medicinewise, 2013:1). Drug-drug interactions also develop more often in the aged and it was found that approximately 24% of older adults are prescribed medicines that have the potential to interact (Shelton *et al*., 2000:438).

The high prevalence of inappropriate prescribing is linked to an escalation in adverse drug reactions, morbidity and mortality (Maio *et al.*, 2010:219-220; Shah *et al.,* 2011:248-249), and excessive utilisation of healthcare resources e.g. increase in outpatient visits, hospital admission and higher health care system expenditure (Maio *et al.*, 2010:219-220; Page *et al.,* 2010:75). For instance, in the United States of America (USA), even though only 13% of the population is elderly patients, it represents the biggest per capita consumption of prescription medicine. Most of the medicine items used by the elderly are taken over long periods of time to manage chronic conditions, however, medicine items may also be used over the short-term to prevent, alleviate and treat acute conditions (Shah *et al.,* 2011:251). Other unfavourable results may include therapeutic failure and worsening of the condition in the case of underuse of the medicine and adverse drug events in the case of overuse of medicine items. In some instances the adverse event is not identified as such and is managed as a new medical condition, which increases the patient's possibility for medicine-related complications (Maio *et al*., 2010:219-220; Oates, 2006:124; Shelton *et al*., 2000:438). Medicine non-adherence is also common among elderly patients (Shelton *et al*., 2000:438). The financial burden of treatment may also lead to medication non-adherence (Shelton *et al*., 2000:438).

An increase in the elderly population therefore puts greater pressure on the national health services, economic growth and productivity. In South Africa the population growth in older adults are more rapid than in the younger cohorts under the age of 60 years (Joubert & Bradshaw, 2006:207). As the South African community grows older, there will be a shift in their health needs (Joubert & Bradshaw, 2006:205). There is also an increase in the number of patients who need health and related care, which will lead to more pressure on the current healthcare system (Joubert & Bradshaw, 2006:205).

Medicines should not be withheld from patients just because they are elderly; instead both the benefits and the risks should be identified for each individual patient (Shelton *et al.,* 2000:438). Prescribing in elderly patients should not be generalised as each patient has a different health status (Maio *et al*., 2010:219-220). Healthcare workers should consider whether a new complication is due to an adverse event of the current treatment and action should be taken only once this has been determined. New drugs should not be initiated without consideration of alternative approaches (Shelton *et al*., 2000:438).

Several tools and criteria to improve rational medicine use in elderly patients are available.

These tools or criteria can be grouped into implicit tools, explicit tools and tools based on a combination of implicit and explicit tools. Explicit tools are fixed specifications and do not consider individual characteristics of the patient or the suitability of the medicine regimen whereas implicit tools are based on clinical knowledge and takes into consideration the characteristics of the specific patient involved and the complete medication regimen. The combination of implicit and explicit tools uses the advantages of each approach (Kaufmann *et al*., 2014:1-2). The appropriate use of medications in elderly patients should be emphasised more, since more medications are prescribed to elderly patients (Shelton *et al*., 2000:439). The main aim of all of these tools and criteria is to ensure appropriate medicine prescribing and to monitor adverse drug events in the elderly population worldwide.

The Beers criteria are the most frequently, generally accepted explicit criteria used for the evaluation of potentially inappropriate medicine prescribing (Page *et al.,* 2010:80). The Beers criteria have been adopted by several health plans and pharmacy benefit managers to assist with the pointing out of older adults with and increased potential of experiencing adverse drug effects linked to possible inappropriate prescribing and are easy to use (Page *et al.,* 2010:80, 84). The Mimica Matanović and Vlahović-Palčevski comprehensive protocol (Mimica Matanović & Vlahović-Palčevski, 2012:1134-1135) developed in 2008 consist of, *inter alia,* a list of 70 potentially clinically important drug-drug interactions. Lists of medicines included in the Beers criteria and Mimica Matanović and Vlahović-Palčevski comprehensive drug-drug interaction protocol are provided in Annexure A, Tables A.1 to A.3, respectively.

Based on the foregoing discussion, the research questions for the study included:

- What does appropriate prescribing based on pharmacodynamic and pharmacokinetic principles for the elderly entail and which factors influence these prescribing principles?
- What measures exist that can be used to assess appropriate prescribing for the elderly?
- What is the extent of inappropriate prescribing for the elderly in the South African private health sector?

1.2 Study aim and objectives

The general aim of the study was to investigate the medicine prescribing patterns for elderly patients in the private health sector of South Africa utilising different screening tools for identifying potentially inappropriate prescriptions.

This study consisted of a literature review and an empirical investigation, each with its own objectives.

1.2.1 Literature review

The following objectives pertain to the literature review:

- To determine what appropriate prescribing for the elderly entails.
- To determine the factors influencing prescribing for the elderly and to determine which unique factors of elderly patients influence the medication prescribed to them.
- To determine the prevalence and criteria for the measurement of inappropriate prescribing for elderly patients by analysing previous studies.
- To compare different tools or criteria available to ensure appropriate medicine prescribing for elderly patients with regard to items listed in the different tools or criteria.

1.2.2 Empirical investigation

The following objectives pertain to the empirical investigation:

- To determine the appropriateness of prescribing in patients 65 years and older on the database to be used in this study by application of Beers criteria stratified by age, gender and prescriber.
- To determine the prevalence of potentially serious drug-drug interactions (DDIs) in patients 65 years and older on the database by application of the Mimica Matanović and Vlahović-Palčevski comprehensive drug-drug interaction list stratified by age and gender.

1.3 Research methodology

A two-dimensional research procedure consisting of a literature review and an empirical investigation was followed.

1.3.1 Literature review

Books, websites and articles were used for the literature review. Databases used during the literature search include Google Scholar, EBSCOhost, Scopus, ProQuest, Science Direct, Nexus and ISI Web of Knowledge. Keywords used include medicine claims data; prevalence; criteria for appropriate prescribing in elderly patients; screening tools for appropriate prescribing in elderly patients; appropriate prescribing; inappropriate prescribing; elder; elderly; aged; old; aging; geriatric; geriatrics; gerontology; gerontological; gerontology; drug utilisation; medicine(s) review. Relevant articles identified during the Boolean search were reviewed by a standard

narrative review to determine the prevalence and criteria for the measurement of inappropriate prescribing for elderly patients.

1.3.2 Empirical investigation

1.3.2.1 Study design

The study followed a quantitative, descriptive, cross-sectional design.

A quantitative study focuses on a few concepts and uses analytical procedures and formal equipment to gather information. Information is collected in a controlled environment emphasising objectivity in the gathering and analysis of information. Quantitative studies also incorporate logistic, deductive reasoning (Brink *et al.,* 2012:11).

A descriptive study aims to describe the characteristics of the group that is being investigated and attempts simple data description based on the estimation of a characteristic in the study population (Katzenellenbogen, 2012:62). Descriptive studies also aim to answer specific question(s) (Aldous *et al.,* 2011:12) and do not test any hypotheses, but rather only uncover problems that exist (Aldous *et al.,* 2011:24).

A cross-sectional study examines data at one point in time. The data are gathered at a specific point in time with different participants (Brink *et al.,* 2012:115). Subjects included in cross-sectional studies can be recruited prospectively and are not all seen on the same day (Aldous *et al.,* 2011:25).

1.3.2.2 Setting and/or data source

This study focused only on the private health sector of South Africa, which comprises approximately 16% of the total health sector in the country (Statistics South Africa, 2014). Medicine claims data from a well-known South African pharmaceutical benefit management company (PBM) was used. The PBM used had approximately 22 years of service excellence and approximately 1.6 million South Africans were benefiting from their services. The company provided services to 35 medical schemes and five capitation provider clients, administered by 15 different healthcare administrators. The PBM was at the time linked up to most of South Africa's pharmacies and 98% of all dispensing medical practitioners and it processed over 300 000 real-time and 30 000 prescribers' transactions on a daily basis. More than 16% of the patients in the private sector benefited from the services of the PBM used. Data elements (fields) in the database needed for this study include:

- Date of birth;

- Date of dispensing of the prescription;
- Gender;
- Anonymous member identification;
- Anonymous member dependant identification;
- Medicine prescribed (NAPPI-code and extension);
- Prescriber type;
- Quantity dispensed;
- Days' supply; and
- ICD-10 code for chronic disease list conditions

1.3.2.3 Reliability and validity of the data source

The use of reimbursement data on submitted claims for research purposes has increased over the past few years. These databases are more representative and complete for groups who are usually excluded from clinical trials. These groups include old people, youngsters, less fortunate people and those in old-age homes (Schneeweiss & Avorn, 2005:323). Some of the advantages of using claims data include that it is anonymous, both in terms of the supplier and the patient, plentiful data are available and it is relatively inexpensive to access (Ferver *et al.,* 2009:11).

A checklist from Hall *et al*. (2012:2) can also be applied to ascertain the validity and reliability of database research. (See Table A.4, Annexure A for the checklist).

The PBM that provided the data has certain validation processes in place to ensure validity and reliability of the data. Ways in which the PBM ensures validity and reliability of their data include gate-keeping services; eligibility services; utilisation management services; clinical management services and pricing management; fully integrated pre-authorisation services including exception management; management of medicines for the Chronic Disease List (CDL), Prescribed Minimum Benefits (PMB) and other conditions; medicine management in capitation environments; on-line medicine expenditure reporting; and supplementary services, which include network management, development and implementation of reference price lists, formulary management, and price and product file management.

The study was conducted from the viewpoint that all data obtained are correct and accurate. However, ways to reduce error and thereby improve the validity and reliability of the study incorporated included:

- Only including paid claims for prescribed items (all non-paid and non-medicine claims were excluded);
- Random checks for outliers; and
- Limit bias (relatively low risk for bias as there are no financial funding supplied and no other companies involved).

1.3.2.4 Target population and study population

The target population for this study was all elderly patients 65 years or older in the private health sector of South Africa who are active members of any medical aid scheme. The profiles of these patients had to be similar to those of other patients belonging to medical schemes administrated by the PBM used.

The study population included all elderly subjects (both male and female) above the age of 65 years on the claims database. No sampling was done. Prescribing patterns for a one-year period (1 January to 31 December 2013) were evaluated. The study population for 2013 consisted of 103 420 individual patients. The inclusion and exclusion criteria applied in this study are presented in Table 1.1.

Table 1.1: Inclusion and exclusion criteria for the study

Inclusion criteria	Exclusion criteria
Age: All subjects aged 65 years and older with a paid claim(s) for any medicine item during the study period. **Gender:** Both male and female patients. **The date the prescription was filled:** Prescriptions claimed during the period 1 January to 31 December 2013.	**Age:** All subjects aged younger than age 65 years and all patients whose age was not available. **Gender:** All patients whose gender was not available. **The date the prescription was filled:** All prescriptions claimed before 1 January 2013 and after 31 December 2013. All non-medicine items.

1.3.2.5 Data analysis

A retrospective drug utilisation review (RDUR) study was performed using medicine claims data from a South African PBM. In 1977, the World Health Organization (WHO) defined drug utilisation review (DUR) as the “marketing, distribution, prescription, and use of drugs in a

society, with special emphasis on the resulting medical, social and economic consequences" (WHO, 2003). According to Wettermark *et al*. (2008:159), drug utilisation research can be described as "an eclectic collection of descriptive and analytical methods for quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes". For a retrospective DUR, the treatment is evaluated after the prescription has been dispensed, focusing on the prevention of the recurrence of the problem. For this study, the problem under investigation can be quantified, measured and expressed numerically. The prescribing patterns for elderly patients were observed and the occurrence then described. No intervention with regard to treatment was made.

A DUR study usually includes six steps of which three was used in this study. The steps used were:

- Determining optimal medicine use;
- Determining actual medicine use; and
- Evaluating the prescribed medicine (actual use) based on the optimal use (Truter, 2008:100-101).

The correct classification of the medicine items used in this study was very important as it enabled fast and accurate analysis of the data. Different classification systems are available, all of which classify medicines according to their therapeutic and pharmacologic action. For this study only the National Approved Product Pricing Index (NAPPI®) and Monthly Index of Medicine Specialities (MIMS®) classification were used (Snyman, 2015).

The criteria used in the RDUR include the Beers criteria list and the Mimica Matanović and Vlahović-Palčevski drug-drug interaction list. (See Table A.1 to A.3 in Annexure A for medicines listed in the Beers criteria and the Mimica Matanović and Vlahović-Palčevski drug-drug interaction list. A comprehensive discussion of the Beers criteria and the Mimica Matanović and Vlahović-Palčevski comprehensive drug-drug interaction list are found under sections 2.4.1 and 2.4.2, respectively). Items available in South Africa and listed in the Beers criteria and the Mimica Matanović and Vlahović-Palčevski comprehensive drug-drug interaction list were used to evaluate inappropriate prescribing patterns for elderly patients.

1.3.2.6 Data analysis plan

Data analysis was done according to the specific objectives for the empirical investigation. Measurements included in the data analysis plan are described in Table 1.2.

Table 1.2: Measurements included in the data analysis plan

Variables	Description
Age	Age was calculated by determining the age of the patient on the treatment date. Patients were divided into six age groups of approximately the same size (based on descriptive statistics) to determine which age group is prescribed the most potentially inappropriately medicines: age ≤ 68 years 68 < age ≤ 72 years 72 < age ≤ 78 years 78 < age years
Gender	Only patients whose gender was known were included in the study. Gender groups used were male and female.
Number of medicine items	Medicine items refer to any product prescribed or issued to the patient that is recorded on the database.
Number of prescriptions	Number of prescriptions refers to the total number of records that were claimed. The prescription may contain more than one medicine item. For the analysis of the potential DDIs, all prescriptions received in one month and of which the days overlapped, was counted as one prescription.
Prescriber type	The prescriber type refers to general practitioners or specialists.
Criteria and screening tools	Criteria in this study refer to the Beers criteria (refer to Tables A.1 and A.2, Annexure A). Drug-drug interaction list refers to the Mimica Matanović and Vlahović-Palčevski drug-drug interaction list (refer to Table A.3, Annexure A).
Prescribed daily dose (PDD)	The PDD is defined as "the average dose prescribed according to a representative sample of prescriptions" (World Health Organization, 2003). The PDD provides the recommended everyday quantity of medicine that is actually ordered by the prescriber.

1.3.2.7 Statistical analysis

The Statistical Analysis System® SAS 9.3® (SAS Institute Inc., 2012) was used to analyse the data in consultation with the statistical consultation services of the North-West University (NWU).

The study variables in Table 1.2 were analysed using both descriptive and inferential statistics. The paragraphs below provide a brief summary of the test statistics employed to address the objectives of the empirical investigation.

1.3.2.7.1 Frequency

Frequency refers to the number of times that a result occurs and is obtained by counting the occurrence of scores or values represented in the data (Brink *et al*., 2012:180).

1.3.2.7.2 Ratio

Ratios are statistics that demonstrate the comparative frequency of one set of frequencies in relation to another and are useful for the distribution of illness or symptoms, or in categories of participants requiring or benefiting from treatment (Brink *et al*., 2012:183).

1.3.2.7.3 The 95% confidence interval

The confidence interval provides the range of values where it can be stated with 95% confidence that the true average of the population is included in the calculated values (Pietersen & Maree, 2013:202).

1.3.2.7.4 Average (arithmetic mean)

The mean is the arithmetic midpoint of all the values in a distribution obtained by adding all the values up and dividing the total by the total number of values (Brink *et al*., 2012:185). The following formula was used to calculate the average:

$$\bar{X} = \frac{1}{n}\sum_{i=1}^{n} X_i$$

Where

X_i= the i^{th} observation

n = the number of observations.

1.3.2.7.5 Standard deviation

The standard deviation demonstrates how scores vary from the average of the distribution and is defined as “the square root of the variance”. The larger the standard deviation, the more spread out the scores are about the mean in a distribution (Brink *et al*., 2012:180). The following formula was used to calculate the average:

$$Standard\ deviation = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(X_i - \bar{X})^2}$$

Where

X_i = the i^{th} observation

$\bar{X}$ = arithmetic mean

n = number of observations.

1.3.2.7.6 Two sample *t*-test

The student's *t*-test is a parametric statistic that is applied when one wants to compare the means of groups to decide if the differences between the means are meaningful or only by chance (Brink *et al.*, 2012:191). The two-sample *t*-test for unpaired data is defined as:

$$t = \frac{\bar{\gamma}_1 - \bar{\gamma}_2}{\sqrt{\frac{S_1^2}{N_1} + \frac{S_2^2}{N_2}}}$$

Where

N_1 and N_2 = the sample sizes

$\bar{\gamma}_1$ and $\bar{\gamma}_2$= the sample means

s_1^2 and s_2^2 = the sample variances (Pagano & Gauvreau, 2000:221).

1.3.2.7.7 Chi-square test

The chi-square test is a non-parametric statistic that is used to compare groups on a categorical variable (Joubert, 2012:147). The chi-square test "compares the observed frequencies in each of the categories in the contingency table (represented by O) with the expected frequencies (denoted by E)", and is applied when one wants to decide if the difference between the observed and expected counts (O-E) is too large to be attributed to chance alone. The chi-square test can be calculated as follows:

$$\mathcal{X}^2 = \frac{\sum(O - E)^2}{E}$$

Where

O = observed counts

E = expected counts.

The degrees of freedom can be calculated as follows:

(r-1)(c-1)

Where

r = number of rows in the contingency table

c = number of columns in the contingency table (Pagano & Gauvreau, 2000:345).

From these calculated values, the *p*-value should be looked up in the applicable table and the *p*-value can be identified, which will be used to identify whether the difference between the observed and the expected counts is significant or merely by chance alone.

1.3.2.7.8 Cohen's *d*-value

The effect size indicates the magnitude or size of an effect. Effect sizes can be calculated in a number of different cases of which the most important are for the difference between two means or the relationship between variables. Cohen's *d*-value is used to express the mean difference between two groups in standard deviation units. Interpretation of the *d*-value suggests a small effect at 0.2, a medium effect at 0.5 and a large effect at 0.8 (Pietersen & Maree, 2013:211). Cohen's *d*-value can be calculated by subtracting one mean ($\bar{x}$) from the other, divided by the pooled, or average, of the two groups' standard deviations (SD):

$$d = \frac{\bar{x}_1 - \bar{x}_2}{SD_{pooled}}$$

Where the pooled standard deviation can be calculated as follows:

$$SD_{pooled} = \sqrt{(SD^2_{group\ 1} + SD^2_{group\ 2})/2}$$

1.3.2.7.9 Cramér's *V*

Contingency tables larger than the 2 x 2 table use Cramér's *V* to measure the effect size. The effect size ranges between 0 and 1 (Abbott & McKinney, 2013:98). Cramér's *V* coefficient is another measure to assess dependence of two variables. The degree of the dependence, however, does not change when the values of the observations change relative to one another. Cramér's *V* is easily calculated by dividing the chi-square statistic by the product of the sample size (n) multiplied by the smaller of either the number of categories for a row (r) or a column (c) minus 1 and then taking the square root of the quotient. Coefficients range from 0 to 1, with 0 indicating no association and 1 indicating a perfect association. Generally, a coefficient of > 0.80 indicates a strong association, a coefficient 0.30-0.80 indicates a weak to fairly strong association and a coefficient of < 0.30 indicates a weak to negligible association (Kraska-Miller, 2013:70).

1.3.2.7.10 Analysis of variance (ANOVA)

Analysis of variances is a way in which the researcher can compare two means. ANOVA is an extension of the *t*-test, where the F statistic or ratio is calculated. The larger the F value, the

greater the difference between the groups compared with the variation within the groups (Brink *et al.,* 2012:191).

1.4 Ethical considerations

Goodwill permission to conduct the study was obtained from the Board of Directors of the PBM via a formal contract between the PBM and Medicine Usage in South Africa (MUSA). The study was approved by the Health Research Ethics Committee (HREC) of the Faculty of Health Sciences of the North-West University (NWU-00179-14-S1).

There was no need for informed consent by individual patient, medical aid or prescriber as they could be not identified. Membership of medical schemes is mostly voluntary. By registering as beneficiary of a medical scheme, patients grant permission (written) to the scheme to disclose, collate and process any patient's personal information collected during the use of any of the products, services, facilities, tools or utilities offered by medical schemes. All patients are informed that all data (e.g. patient, prescriber, etc.) will be kept strictly confidential, and depersonalised if shared with a third party. Thus all data are anonymised on the level of the medical scheme before the PBM obtains the data.

For this study, the benefits outweighed the risks. This was a low-risk study since retrospective depersonalised medicine claims data were used.

1.5 Chapter summary

In this chapter it was indicated that the elderly population is on the increase worldwide. The elderly suffer from more conditions requiring treatment with medicine items. Inappropriate prescribing is therefore more likely to occur. Several criteria exist to assess potentially inappropriate prescribing in elderly patients. The research questions, aim and objectives were given and the chapter also included a brief discussion of the purpose of this study. A brief summary of the study design was given and the potential advantages of this study were explained.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter contains the background information gathered during the literature review. The specific objectives of the literature review were:

- To determine what appropriate prescribing for the elderly entails.
- To determine the factors influencing prescribing for the elderly and to determine which unique factors of elderly patients influence the medication prescribed to them.
- To determine the prevalence and criteria for the measurement of inappropriate prescribing for elderly patients by analysing previous studies.
- To compare different tools or criteria available to ensure appropriate medicine prescribing for elderly patients with regard to items listed in the different tools or criteria.

This chapter has been arranged under these headings and answers to these objectives.

2.2 Prescribing for the elderly

The World Health Organization (WHO, 2014) states that although the majority of first world countries accept persons aged 65 years and older as 'old persons', there is no concurred standard numerical criterion. The United Nations agrees that the people reaching 60 years and older refer to the 'older population' (United Nations, 2013:3). According to The Old Persons Act (Act 13 of 2006) of South Africa, people may be classified as 'old' or 'elderly' when males and females reaches the ages of 65 years or older and 60 years or older, respectively.

The number and proportion of elderly and very old people are increasing rapidly (Waite, 2004:3). The term 'ageing population' is used to refer to this occurrence where the percentage of elderly people in the specific community is becoming more when compared to younger people (Joubert & Bradshaw, 2006:204). 'Ageing' can be defined as a progressive physiological process that is associated with degeneration and loss or reduction of functions of the organ systems (Garner, 2013:25).

Prescribing of medicine is regarded as the most common form of therapeutic intervention; the consistent quality within prescribing is therefore essential for all patients (Garner, 2013:19). The elderly, however, suffer from more diseases requiring drug therapy (refer to paragraph 1.1). The complexity of treatment combinations used to treat older adults increases with age and the elderly also usually have multiple prescribers (Malone *et al*., 2004:143). Careful planning and

knowledge of the aging process and the drugs prescribed are therefore essential in prescribing for elderly patients as they have an increased probability to develop medicine-related complications (Garner, 2013:19; Malone *et al.,* 2004:143; Shelton *et al.,* 2000:439).

The prescribing of medicine can usually be classified as 'rational' or 'appropriate' *vs.* 'irrational' or 'inappropriate'. Other synonym pairs include appropriateness/inappropriateness, appropriate or inappropriate prescribing, appropriate or inappropriate prescriptions, appropriate or inappropriate medicine prescribing, rational or irrational drug or medicine use, rational or irrational medicine prescribing or rational or irrational prescriptions (Gallagher *et al*., 2007:113; Kaur *et al.,* 2009:1015; Maio *et al.*, 2010:219; Mimica Matanović & Vlahović-Palčevski, 2012:1123; Page *et al.,* 2010:75; Rancourt *et al.*, 2004:2, Shah *et al*., 2011:248).

Rational or appropriate prescribing bases the selection of medicine items on the efficacy, safety and convenience when compared to other medicine items for use in an individual patient and considers the cost-effectiveness of that specific treatment (Shah *et al*., 2011:248). Rational prescribing refers to prescribing where there is maximum benefit and minimum harm to the patient, whereas irrational prescribing is usually a result of unsuccessful efforts in the clinical practice and development of medicine items (Lipworth *et al*., 2011:1). Some of the most important values that determine the appropriateness of prescribing include patient demand, the rationale behind the prescribing of the item(s) and quality of prescribing; the reason behind appropriateness anticipates reviewing the detail and conditions in all three of these areas (Spinewine *et al*., 2007:173). According to Parsons *et al.* (2012:144), medicine items may be seen as appropriate when there is distinct, evidence-based proof that the item is well tolerated by most of the patients and that the treatment is cost-effective. The aim of appropriate prescribing should be to increase the use of treatment with available evidence on the effectiveness and to exclude medicine that is not needed, has questionable evidence and is a duplication of items that are already being taken. Providers should use their knowledge based on experience and personal clinical reasoning in the decision-making process regarding prescribing (Page *et al*., 2010:84).

According to Rancourt *et al.* (2004:2) and Maio *et al.* (2010:219), potentially inappropriate prescriptions can be seen as prescriptions where the patient will have a higher risk for negative outcomes than potential benefit from the treatment. Inappropriate prescribing can be defined as the prescribing of an item with a higher risk profile for the patient to develop adverse events when a more cost-effective alternative with the same or even better outcome is available for the same condition (Gallagher *et al*., 2007:113; Kaur *et al.,* 2009:1015; Mimica Matanović & Vlahović-Palčevski, 2012:1123; Page *et al.,* 2010:75). Inappropriate prescribing can also refer to "a range of suboptimal prescribing practices" (Parsons *et al.,* 2012:144). Inappropriate prescribing is associated with negative outcomes, which include drugs with no obvious reason

for being included in the treatment plan based on available proof, drugs with an increased potential to lead to adverse events, are not cost-effective, may lead to hospitalisation, and increased resource utilisation (Gallagher *et al.,* 2011:1176; Parsons *et al.,* 2012:144). According to Gallagher *et al*. (2007:113), inappropriate prescribing also includes the use of medicine items at increased doses and extended time periods than normal, the use of items with known drug-drug and drug-disease interactions and the utilisation of items which are regarded as not suitable for use in elderly patients due to age-related reasons.

Medicine appropriateness can be measured by means of evaluating the outcome and process measures. Outcome measures would evaluate the effect of the medicine on the patient. Outcome measures could, for example, assess the drugs prescribed to the elderly who might be susceptible to falls (O'Connor *et al.*, 2012:439). Long-acting benzodiazepines, for example, are associated with a higher potential of falls in elderly patients and therefore this group of medicine items would be regarded as inappropriate for use in this age group. Process measures clearly predict the outcome measures. Explicit and implicit criteria can be used to evaluate the prescribing appropriateness (O'Connor *et al.*, 2012:439). According to O'Connor *et al.* (2012:439) prescribing appropriateness should "encompass the domains of misprescribing, overprescribing and underprescribing".

Kuijpers *et al*. (2007:131) and O'Connor *et al.* (2012:439) define underprescribing as the lack or the omission of an item that has a clear indication for the treatment of that specific condition and for which there is no clinical reason for excluding the treatment. In contrast, overprescribing, polypharmacy or duplicative prescribing refers to the prescription of medication for which no clear indication exists (O'Connor *et al.*, 2012:439), or the use of more than one, similar item for the same condition and may also include the excess use of medicine items or the prescribing of unnecessary drugs (Gallagher *et al*., 2007:114; Hajjar *et al.,* 2005:1518).

Polypharmacy may be associated with inappropriate prescribing and other medicine-related problems such as drugs that are being used without indication, adverse drug reactions and interactions, sub-therapeutic dosages, over dosage and non-compliance (O'Mahony *et al.*, 2012:423). All these drug-related problems can be classified as inappropriate prescribing. Polypharmacy generates prescribing cascades where additional medication is prescribed to relieve symptoms of unrecognised disadvantageous effects. The effects experienced by the patient are then exacerbated rather than improved since there is reluctance among some prescribers to stop certain medication even when there is clear evidence to indicate that the patient might not live long enough to experience the favourable effect of the medicine (O'Mahony *et al.*, 2012:423). Polypharmacy may be avoided in elderly patients by using simple medication treatment plans, having evidence-based proof of the effectiveness of the treatment and to pay more attention to any adverse effects that may occur (Garner, 2013:19). Methods of

simplifying the dosing regimens include the use of long-acting or slow-release items that can be taken once daily and to avoid items that can interact with one another when taken concurrently (Garner, 2013:20-21).

Deprescribing can be defined as the process of stopping medicines with the aim of minimising polypharmacy and improving patient outcomes (Scott *et al.,* 2015:827). Deprescribing of medicine should be encouraged as there is a need to discontinue medicines that no longer have a positive benefit-to-harm ratio (The Traux Group, 2014). A deprescribing protocol was proposed by Scott *et al.* (2015:827) which includes the following five steps: (1) identify all the medicines that is part of the current treatment and the indication of each item in that specific patient; (2) determine the probability of medicine-related harm that may come to the patient by considering the vigorousness of deprescribing; (3) evaluate the overall benefit: harm profile for individual items in that specific patient (current and future benefit and harm should be considered); (4) items with the lowest benefit: harm profile that would have the lowest possible impact on the patient with regards to withdrawal and rebound, should be discontinued first; (5) start with the execution of medicine discontinuation and evaluate the patient on a regular basis for onset of any negative effects that the discontinuation might have. Obstacles to deprescribing include underappreciation of the magnitude of polypharmacy-related harm where the symptoms in the elderly are not recognised as side effects, increased intensity in care and focusing on the wrong medicine items (The Traux Group, 2014).

Tatro (2004:xii) defines a drug-drug interaction as a “pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two drugs when given separately”. Drug interactions may also refer to a significant change in the effect of one medicine item when another medicine items is administered concurrently (Goldberg *et al*., 1996:447; Hanlon & Schmader, 2005:61). System factors for adverse drug reactions include illegible orders, incomplete patient information, inadequate medical knowledge, failure to monitor drug concentration. Risk factors for adverse drug reactions include the age and the sex of the patient, the number of medicine items as part of the treatment regimen, comorbidities and medical services (Evans *et al.,* 2005:1161). Drug interactions can be divided into pharmacodynamic or pharmacokinetic interactions. In pharmacokinetic drug-drug interactions, the absorption, distribution, metabolism and excretion of one medicine item is altered by the presence of another medicine item with the most prevalent interactions being those that include the inhibition of cytochrome P450 metabolism in the liver whereas in pharmacodynamic drug-drug interactions, the response of a medicine item is changed in the presence of another medicine item. Drugs usually involved in pharmacodynamic interactions include those with a narrow therapeutic index and those involved in the inhibition of metabolism in the liver (Hanlon & Schmader, 2005:61). According to Mimica Matanović and Vlahović-

Palčevski (2012:1123) the use of items with the potential to cause serious interactions may also be classified as inappropriate prescribing as it poses a risk for medicine-related morbidity and mortality. The majority of older adults receive two or more chronic medicines and evidence indicates that there is a higher risk in experiencing adverse effects when the patient presents with three or more comorbidities (Page *et al.,* 2010:77).

The term 'misprescribing' refers to the prescribing of medication that has a higher potential to cause adverse events. These adverse events include inaccurate dosing, frequency, route of administration, and duration of the treatment and may be more likely to lead to serious drug-drug or drug-disease interactions. Misprescribing should be prevented by considering safer, equally efficacious alternatives (O'Connor *et al.*, 2012:438-439).

Off-label prescribing is particularly common in the elderly population since this group is poorly represented in clinical trials assessing the premarketing efficacy and safety of items (Herrera *et al*., 2010:S106). Jackson *et al*. (2012:427) defines off-label prescribing as the "practice of prescribing drugs either for unregistered therapeutic indications and age groups or using unregistered doses or methods of administration".

2.3 Factors influencing prescribing for the elderly

Factors contributing to the inappropriate prescribing of medicine may include advanced age, polypharmacy and multiple comorbidities. Concerns surrounding impairment, social and emotional infrastructure and financial position may have an impact on inappropriate prescribing (Page *et al.,* 2010:76).

Patients receiving inappropriate medication have an increased potential to experience medicine-related morbidity and mortality and it is therefore important that inappropriate medications for older adults should be recognized, their patterns understood and future prescribing patterns improved (Aparasu & Mort, 2000:38).

According to O'Mahony *et al.* (2012:424), the optimization of pharmacotherapy in the elderly is complex and demanding. Aspects that must be considered include accurate drug indication, avoidance of drug contraindications, minimisation of interactions (drug-drug and drug-disease interactions), minimisation of overprescribing and the related increased potential of medicine-related issues, switching to palliative pharmacotherapy where appropriate, and getting the best value for money (O'Mahony *et al.*, 2012:424). Improved pharmacotherapy in the elderly may lead to people living longer, healthier and more independent lives. Suboptimal pharmacotherapy may lead to increases in morbidity and mortality, failure of disease prevention and an increase in health care cost (O'Mahony *et al.*, 2012:424-425).

2.3.1 Factors innate to the elderly that influence prescribing

The aging process can be defined as a progressive, universal decline in physiological and biological processes (Garner, 2013:19; Gupta *et al*., 1996:184; Yogita & Priti, 2013:636). Age-related changes in pharmacokinetics and pharmacodynamics may contribute to medicine items being categorized as inappropriate for use in the elderly (Page *et al*., 2010:76). Both the pharmacokinetic and pharmacodynamic actions of medicine absorption, distribution, metabolism and excretion are altered by the aging process and therefore the clinical status of individual patients should be taken into consideration with the effects associated with old age. Elderly patients have a significant decrease in reserve potential of most organs, which leads to a decrease in the safety margin between the beneficial and harmful doses of some medicine items (Gupta *et al.,* 1996:184).

2.3.1.1 Physiological changes associated with aging

Aging is associated with time-related decrease of functional components, disturbances of some of the regulatory processes (Mangoni & Jackson, 2003:6) and anatomical and physiological changes. The cardiac, renal and gastro-intestinal systems are affected the most with old age (Mangoni & Jackson, 2003:7). As a person ages, there is a rise in total body fat proportion, a reduction in total body water volume and a reduction in muscle mass. About 25% of the ability of the organs to function optimally is lost at age 60 years, with a decrease in organ volume and weight (Hutchinson & O'Brien, 2007:4-5). The decrease in functionality affects the doses of medication that can be tolerated by each patient. Medicine must be prescribed with the potential changes in absorption, distribution, metabolism and excretion taken into consideration (Hutchinson & O'Brien, 2007:4-5).

Table 2.1 (adapted from Hämmerlein *et al.*, 1998:51) indicates some of the most significant age-related changes in the physiology associated with aging.

Table 2.1: Age-related changes in physiology of elderly people

System	Effect
Changes in body composition • Body fat • Lean body mass • Total body water	 Elevated Reduced Reduced
Alterations in the cardiovascular system • Resting heart rate • Stroke volume • Cardiac output	 Reduced Slightly reduced Slightly reduced
Central nervous system	

System	Effect
• Blood supply to the brain	Diminished
Reflex responses • Baroreceptor reflex activity	 Diminished
Renin-angiotensin-aldosterone system • Plasma renin • Urine aldosterone • Sympathetic innervation to juxtaglomerular cells	 Diminished Diminished Diminished

Any new item prescribed to an elderly patient must be evaluated in the context of the alterations in the pharmacokinetics and pharmacodynamics of the geriatric patient (Gallagher *et al*., 2007:114).

2.3.1.1.1 Pharmacokinetic changes

Pharmacokinetics describes the effect that the body has on medication once it is ingested and includes the absorption, metabolism, distribution and elimination of medicine (Garner, 2013:19). Several pharmacokinetic changes are associated with old age. Pharmacokinetic knowledge supplies the clinician with a specific basis for the appropriate dose of a specific drug and also includes how the dose should be adjusted due to physiological changes like aging (Belloto, 2007:37). Table 2.2 (adapted from Hämmerlein *et al.,* 1998:50) provides a summary of age-related alterations in pharmacokinetics.

Table 2.2: Age-related alterations in pharmacokinetics of elderly patients

Pharmacokinetic property	Effect of aging
Absorption • Secretory capacity • Gastrointestinal blood flow	 Elevated Reduced /Diminished
Distribution • Plasma albumin • Protein affinity • α1–acid glycoprotein	 Diminished Diminished Elevated
Metabolism • Liver size • Hepatic blood flow	 Reduced Reduced
Renal function • Glomerular filtration rate • Renal plasma flow • Filtration fraction	 Reduced Reduced Elevated

Physiologic and illness-related alterations in the organs and enzyme systems alter the pharmacokinetics of a product in elderly patients. With an increase in age, there is a decline in the renal drug elimination and along with that there is a decrease in the creatinine clearance, which is a typical consequence in older patients. Old age is also linked to a lower tempo of elimination, particularly those items eliminated by the cytochrome P450 enzyme system. The strength of the skin and the changes in muscle and fat associated with old age furthermore lead to altered transdermal absorption of drugs (Belloto, 2007:37). The volume of distribution of drugs is also altered by the difference in distribution of water and fat soluble drugs. Knowledge of these alterations is helpful in understanding dosage recommendations and adjusting doses (Belloto, 2007:37-38).

- **Absorption of drugs**

Elderly patients have decreased saliva production which may decrease the rate of absorption of orally administrated drugs (Garner, 2013:19). Old age is also associated with reduced gastro-intestinal emptying due to decreases in both blood flow and gastro-intestinal motility (Garner, 2013:19). Medicines such as calcium channel blockers, proton-pump inhibitors (PPIs) and beta-blockers may also lead to a decrease in stomach emptying (Garner, 2013:19). Acidic medicine items are poorly absorbed because they elevate alkaline stomach secretions. Enteric coated tablets dissolved in alkaline liquid can dissolve quicker, whereas iron and calcium tablets may not be absorbed as readily (Kee & Hayes, 2003:165-166). The absorption of medicine is further affected by a decrease in blood flow and slowed intestinal transit time (Hutchinson & O'Brien, 2007:5).

- **Distribution of drugs**

The availability of medicine at the target site is affected by the distribution of the medicine (Garner, 2013:19). As old age is linked to a reduction in the total bodily water volume, water soluble medicine items are prone to have a smaller volume of distribution and tend to become more concentrated in the body, resulting in higher drug levels in the elderly (Belloto, 2007:40). Drugs in this category include aminoglycosides, cimetidine, ethanol and theophylline (Belloto, 2007:40). In contrast, as there is an elevation in total body fat, lipid soluble medicines tend to have higher volumes of distribution, which causes a decrease in the desired effect (Garner, 2013:19; Hämmerlein *et al*., 1998:51; Kee & Hayes, 2003:166; Mangoni & Jackson, 2003:8). Drugs bind to albumin and alpha$_1$-acid glycoprotein, depending on both the level of the drug and the level of the protein. Aging is associated with a general decrease in albumin levels whereas the levels of the alpha$_1$-acid glycoprotein remain unchanged. The loss of protein-binding sites for drugs leads to an elevation in the circulation of unbound drug molecules and an elevation in the probability of adverse reactions. The loss of protein binding of drugs is generally not age-

related but rather pathological, since drug disposition is altered more by disease states such as congestive heart failure and a decrease in renal function (Belloto, 2007:39).

- **Metabolism and elimination of drugs**

Loss of protein-binding sites, which increases the amount of free circulating drug, causes a decline in first-pass metabolism, and results in a prolonged half-life of the drug due to a decrease in liver and kidney function, contributes to adverse reactions in older adults (Kee & Hayes, 2003:167).

Drug metabolism may also be affected by genetics, smoking, diet, gender, comorbid conditions and concomitant medicine items. These factors influence drug metabolism in all patients, not just the elderly. The cytochrome P450 enzyme system which is primarily part of the phase I hepatic metabolism pathway may be affected by numerous medication items. The most vital isoenzymes accountable for drug metabolism include CYP3A4, CYP2D6, CYP1A2 and the CYP2C subfamily (Murphy, 2001:475).

Aging is associated with a decrease in size (20-30%) and blood flow (20-40%) to the liver (Herrlinger & Klotz, 2001:900-901). As liver mass and blood flow reduces with age, first-pass metabolism decreases (Garner, 2013:19; Mangoni & Jackson, 2003:8), which in turn leads to a remarkable elevation in the bioavailability of drugs metabolised by the liver. Pro-drugs such as the angiotensin-converting enzyme (ACE) inhibitors which need to be activated in the liver might be converted slower or at reduced rates (Mangoni & Jackson, 2003:8). A reduction in cytochrome P450 activity might also affect metabolism in the liver (Mangoni & Jackson, 2003:9); however, according to Herrlinger and Klotz (2001:901) and Kinirons and Crome (1997:304), the total microsomal cytochrome P450 activity does not decrease significantly with advanced age.

The limited oxygen supply may contribute to the decrease in the first-pass metabolism of the liver (Belloto, 2007:40). Some of the physiological changes involve pseudocapillarization of the sinusoidal endothelium of the liver (Belloto, 2007:41). Drug clearance by hepatic metabolism is affected more in older male adults than in females. Both the liver and the kidneys play a crucial part in the drug clearance process in the body. The probability of medicine toxicity is elevated by the decrease in liver enzyme functions, which leads to a reduction in the ability of the liver to metabolise and detoxify drugs (Kee & Hayes, 2003:166). Drug metabolism that takes place in the liver (biotransformation) can occur either in phase I (hydroxylation, de-alkylation or reduction) or in phase II (conjugation, acetylation or methylation). Hepatic microsomal enzymes are responsible for phase I oxidation reaction (Herrlinger & Klotz, 2001:899). The hepatic microsomal oxidation may be impaired by the aging process or other factors such as liver disease or drugs that can reduce oxidation capability, which in turn leads to the reduction of

drug clearance by the liver. Phase II of the biotransformation process involves the conjugation or attachment of the drug to an inactive state. Phase II is usually well preserved during old age, liver disease or drug interactions so that the drug is inactivated and excreted in urine (Kee & Hayes, 2003:166). Drugs that undergo phase II enzymatic biotransformation are therefore the drugs of choice for elderly patients (Murphy, 2001:475). Drug metabolism, by either phase I or II, must be taken into consideration when choosing a medicine item for use in the elderly patient (Kee & Hayes, 2003:166).

Blood flow plays a crucial part in the metabolism of certain medicine items by the liver. Blood flow to the liver decreases significantly with an increase in age and this metabolism is influenced negatively in the presence of chronic heart failure (CHF). Medicine items that are particularly reliant on hepatic metabolism may have increased toxic concentrations in patients where there is a decrease in hepatic clearance. Changes in hepatic blood flow may also affect the rate of hepatic clearance which in turn may lead to alterations in the intrinsic activity of certain hepatic enzymes. This activity has been found in phase I enzymatic pathway (Murphy, 2001:474).

A reduction of renal function, especially glomerular filtration rate, is associated with old age (Mangoni & Jackson, 2003:9). In patients older than 65 years, nephron function might be reduced by 35% and blood flow to the kidneys might be reduced by 40% in patients older than 70 years (Kee & Hayes, 2003:167). The decline in renal function is the main reason why the dose of medication for the elderly patient should be adjusted (Belloto, 2007:41). Clearance of water-soluble medicines is affected, especially items with a narrow therapeutic index. Accumulation of these medicines might lead to serious adverse effects and even toxicity (Mangoni & Jackson, 2003:9). A decrease in hepatic blood flow also affects clearance of medicines that depends on the liver for elimination. A decrease in cytochrome P450 might also affect the elimination of medicine (Mangoni & Jackson, 2003:9). The majority of medicine items are eliminated via the kidneys and therefore there is an association between the glomerular filtration rate (GFR) and the renal clearance of the medicine item (Belloto, 2007:41). Urinary excretion of drugs can involve glomerular filtration, active tubular secretion, passive tubular resorption or all three processes. For drugs that are neither excreted not resorbed, there will be a strong correlation between the GFR and the clearance of the drug (Belloto, 2007:42).

2.3.1.1.2 Pharmacodynamic changes

Pharmacodynamics describes the association between drug concentration at the site of action and the resulting effect (Garner, 2013:20).

Not much is known about the pharmacodynamic changes associated with aging (Hämmerlein *et al.,* 1998:53; Garner, 2013:20). According to Drenth-van Maanen *et al.* (2009:688), the most

crucial pharmacodynamic modification is changed receptor function, mainly due to a reduced number of receptors. Pharmacodynamic responses depend on the number of receptors and their affinity, signal transduction mechanisms, cellular responses and homeostatic regulation (Hämmerlein *et al.*, 1998:53). Insufficient affinity to receptor sites throughout the body in the elderly alters the pharmacodynamic response. Elderly patients may be more or less sensitive to drug action due to age-related alterations in the central nervous system, the number of drug receptors and the affinity of receptors to drugs (Kee & Hayes, 2003:167). Other changes in the pharmacodynamic parameters include changes in the sensitivity of target tissue to drugs. Older people tend to react more sensitively to certain drugs than less sensitively to others when compared to younger adults (Novotný, 2006:85). Changes in organ functions are important factors to consider in drug dosing and in some cases the dose needs to be lowered. According to Garner (2013:20), the central nervous system (CNS) and cardiovascular system (CVS) is especially affected with age and it is not uncommon to see confusion, drowsiness and postural hypotension in older adults, which can lead to a higher probability of falls and fractures (Garner, 2013:20). Orthostatic hypotension could be the result of the compensatory response to physiologic changes that decreases when a drug with vasodilator properties is administered and the sympathetic feedback does not occur quickly. In younger adults, the sympathetic response of vasoconstriction works to prevent the severe hypotensive effect (Kee & Hayes, 2003:167).

Table 2.3 (Hämmerlein *et al.,* 1998:53) indicates some of the most important age-related alterations in receptors and physiological responsiveness.

Table 2.3: Age-related changes in receptors and physiological responsiveness

Receptor	Tissue	Physiological change	Receptor density
Muscarinic	Brain	Reduced memory	Reduced
Parathyroid hormone	Kidney	Reduced activity of vitamin D	Reduced
β-adrenergic	Heart	Rate and contractility	Slightly reduced
α_1-adrenergic	Liver	Unchanged in glycogenolysis	Reduced
Opioid	Brain	Anorexia; hypodipsia	Reduced

2.3.2 External factors influencing prescribing for the elderly

Non-adherence refers to patients not taking their medicines as prescribed. These patients are in control of their behaviour and decision-making on whether or not to take the medicine regimen as prescribed (Hershberger & Tindall, 2007:19). Medication non-adherence in the general population is about 50% and ranges from 26 to 60% among elderly patients (Hershberger & Tindall, 2007:19). Non-adherence rates in clinical trials are reported to range from 22 to 57%

(Hershberger & Tindall, 2007:19). Based on these statistics, it is reasonable to assume that about 50% of older adults with chronic illnesses are non-adherent in some way.

Factors contributing to non-adherence can be categorised into four groups: (1) those that pertain to the patient, (2) those that pertain to the medication, (3) those that pertain to relationships with health care providers, and (4) those that pertain to weaknesses in the health care system (Hershberger & Tindall, 2007:21). The cost of treatment also plays a crucial role in medicine adherence. Patients prefer to use high-cost items to get the therapeutic benefit, even though lower-cost items will be equally effective (Eaddy *et al*., 2012:45). Of the 66 studies included in the literature review by Eaddy *et al*. (2012:47, 50), 56 (85%) indicated that as the patient cost sharing increased, it had a negative effect on the adherence. Elderly patients with a reduced quality of life and limited income also have poor health outcomes since they cannot afford the prescribed treatment. Other factors contributing to medication non-adherence is polypharmacy, cognitive issues and adverse drug reactions (Hershberger & Tindall, 2007:20).

The factors pertaining to the patient may include interpersonal factors (physician-patient relationship), the patient involvement in the decision-making process, and the patient's attitude, beliefs, group norms and cultural variations (which may include marital status, level of income, age and gender) (Martin *et al.,* 2005:191-194). Most elderly patients have impaired vision, hearing, ambulation or other functional abilities that may impede adherence (Martin *et al.,* 2005:191-194). Illiteracy and the health beliefs of the patient about the illness or the prescribed medicine may also contribute to non-adherence (Martin *et al.,* 2005:191-194).

Factors pertaining to medicine prescribed may include the regimen being too complex, failure of the health care professional to explain the benefits of taking the medicine as well as the side effects, failure to adjust the medication regimen to suite the way of living of the specific patient, failure to review the cost-effectiveness of the treatment, and failure between health care professionals and the patient to develop a good therapeutic or helping relationship (Hershberger & Tindall, 2007:21-22). The complexity of the regimen is one of the most important and controllable factors in medication non-adherence. As the number of drugs and the dosing intervals increase, the likelihood of non-adherence also increases. This is due to the fact that the demand on the older patient is too great (Martin *et al*., 2005:190). Non-adherence also tends to increase with more troublesome side-effects, especially when the medication is used to treat an asymptomatic condition such as hypertension (Hershberger & Tindall, 2007:23).

Health care professionals should talk about possible obstacles to adherence with the patient and assist them to overcome such barriers, for example by prescribing a less costly medication when possible. Prescribers must also ensure that they speak and write clearly when giving

instructions to the patient to eliminate any patient misunderstanding (Hershberger & Tindall, 2007:23-24).

Healthcare system factors include the increase in polypharmacy or unnecessary drug interactions due to inadequate communication between professionals on the healthcare team. Some patients decide not to fill their prescriptions due to the cost of the item(s) prescribed. Packaging of the medication may also contribute to non-adherence. Screw-top containers, child-resistant closures of prescription vials, and blister or foil packs are too difficult to be opened by the frail and elderly patients (Hershberger & Tindall, 2007:24).

Underprescribing is considered an important part of inappropriate prescribing and could also be a result of well recognised obstacles to rational prescribing in elderly patients with comorbid diseases (Kuijpers *et al*., 2007:131-132; Lipworth *et al*., 2011:1). Some of these barriers include prescribing habit, lack of motivation, time, resources and organisational support. Some of the doctors who manage chronic conditions in the elderly are often not specialised in prescribing for the elderly and might not realise the importance of treating the specific condition. Lack of knowledge and unfamiliarity with treatment guidelines for elderly patients might also contribute to underprescribing for the elderly patient. Poor management of chronic conditions contributes to poor patient adherence (Lipworth *et al*., 2011:1). Strategies to improve prescribing to elderly patients include feedback to the clinicians about their prescribing practices to enhance clinical leadership and to find ways to disseminate unbiased information to clinicians (Lipworth *et al*., 2011:2).

All age-related alterations in both the pharmacokinetics and pharmacodynamics should be considered when prescribing new medicine items for the elderly patient. Alterations in the physiology and body composition should also be evaluated in context of new items prescribed (Gallagher *et al*., 2007:114). Older patients have contributing factors such as co-morbidities, the natural ageing process and an increase in frailty that present special challenges in prescribing (Garner, 2013:19; Shelton *et al.,* 2000:439).

Poor economic and clinical outcomes contribute to problems with drug prescribing. Clinical outcomes are measured by means of morbidity and mortality, and the economic values are measured by means of the cost of medical care, pharmaceutical services and the cost associated with the productivity related to disease (Gupta *et al*., 1996:184).

2.4 Significance of inappropriate prescribing

2.4.1 Economic outcomes

Non-essential and unnecessary drugs (those for which there are no rationale for their use or those that have a rationale but are inefficient or duplicated) are sometimes taken by older patients. These items are not clinically indicated and increase to the quantity, complexity and cost of an elderly patient's medicine treatment regimen (Hajjar *et al.,* 2005:1518). Previous documentation shows that the high prevalence of inappropriate prescribing is related to a higher morbidity and mortality, treatment cost and a decrease in quality of life (Shah *et al*., 2011:248-249). The burden of taking 10 drugs is associated with high cost and unpredictability of the effect of the individual items; in some instances, the risk outweighs the benefit (Wehling, 2009:561). Polypharmacy may lead to an increase in the probability of adverse drug reactions, drug-drug interactions, drug-disease interactions and health care cost and it decreases patient compliance (Hamdy & Moore, 1995:534; Kaur *et al*., 2009:1015).

2.4.2 Clinical outcomes

Items that are not clinically indicated may reduce adherence and may be potentially harmful (Hajjar *et al.,* 2005:1518). The suboptimal use of medicine may lead to disadvantageous patient outcomes which have to be improved by guidance, assessment and changes in the drug use (Kaur *et al*., 2009:1015). Negative patient outcomes include adverse drug reactions, drug interactions, related morbidity and hospitalisation (O'Connor *et al.*, 2012:437).

2.4.3 Humanitarian outcomes

The prescribing of potentially inappropriate medicines in elderly patients affects their quality of life. Some of the effects that the use of potentially inappropriate medicines has on quality of life include low hand grip strength, dizziness, muscle weakness, coordination and balance disorders, and dehydration. The use of benzodiazepines has been linked with reduced performance in elderly patients. A decrease in quality of life also means that there will be an increase in health care (Jensen *et al*., 2014:574-576).

2.5 Assessment of inappropriate prescribing in the elderly

Several tools and criteria exist to evaluate the appropriateness of drugs prescribed for geriatric patients (Gallagher *et al*., 2011:1176). These criteria can be explicit, implicit or a combination of both. Table 2.4 summarises the difference between explicit and implicit measures for evaluating the appropriateness of prescribing in geriatric patients.

Table 2.4: Implicit and explicit measures for assessing prescribing appropriateness (adapted from Parsons *et al*., 2012:145)

Implicit measures*	Explicit measures*
Based on judgement. Very patient specific. Access to large number of clinical data needed. Well trained clinician evaluators needed.	Based on specific criteria that were developed from evidence-based suggestions, published reviews, expert opinions and consensus methods. Limited degree of clinical judgement needed. Beers criteria are considered as the gold standard.

*Lists of explicit, implicit and mixed approach criteria are available in Table 2.5, 2.6 and 2.7 respectively.

Explicit criteria are applied as fixed specifications and do not consider individual characteristics on the individual patient. Implicit criteria are based on clinical knowledge, does not have the consensus-based structure, which complicates the process of getting justifiable and dependable measures of appropriateness. On the other hand, limitations of the implicit criteria includes poor inter-rater reliability as these techniques depend on the users understanding and prescribing beliefs and the fact that not all users will pinpoint the same issues and solutions in the same way (Shelton *et al*., 2000:441). The combination of the implicit and explicit criteria is specific for the individual patient, it is supportive and provides a structured technique with the option for the reviewer to apply clinical knowledge when required (Shelton *et al*., 2000:439).

An internet search was done to identify all relevant articles containing information about the different criteria and screening tools for assessing the prevalence of appropriateness of prescribing in elderly patients. Table 2.5 gives a description of the papers identified in the Boolean search.

According to the literature, Lindblad's criteria, Screening tool of Older Persons' Prescriptions (STOPP) Tool to Alert doctors to Right Treatment (START), Improving Prescribing in the Elderly Tool (IPET) and the Geriatric Medication Algorithm are easy to use (Mimica Matanović & Vlahović-Palčevski, 2012:1125-1126; Shelton *et al*., 2000:442; Yogita & Priti, 2013:639), the Assessing Care of Vulnerable Elders (ACOVE) criteria are complicated to apply (Wenger *et al.,* 2007:S251) and the Beers criteria are the most extensively used (Chang & Chan, 2010:949).

Polypharmacy, including underprescribing, is addressed in the ACOVE criteria, STOPP/START criteria, assessment of underutilization of medicine, ARMOR, and prescribing optimisations method for improving prescribing in the elderly (Drenth-van Maanen *et al.,* 2009:689; Haque, 2009:27; Wenger *et al.,* 2007:S247; Yogita & Priti, 2013:638). Criteria that suggest therapeutic alternatives include Austrian criteria, Laroche criteria, McLeod's criteria, the PRISCUS list and the Europe 7 PIMs list (Chang & Chan, 2010:949-950; Holt *et al.,* 2010:543; Mann *et al.,* 2012:160; Renom-Guiteras *et al.,* 2015:861), while Lindblad's criteria and National Committee

for Quality Assurance (NCQA) involves drug-disease interactions (Albert *et al.,* 2010:409; Mimica Matanović & Vlahović-Palčevski, 2012:1125).

Drug-drug interactions (DDIs) are addressed in Malone's list (Malone *et al.,* 2004:65), while the Norwegian General Practice (NORGEP) criteria can be used for cases where no clinical information is needed (Dimitrow *et al.,* 2011:1527). Rancourt's criteria do not take clinical information into consideration (Rancourt *et al*., 2004:6).

Overall medicine usage is evaluated in the Winit-Watjana criteria (Winit-Watjana *et al.,* 2008:49) and the prescribing indicators tool, the Zhan criteria focus on drugs to avoid (Dimitrow *et al.,* 2011:1527; Yogita & Priti, 2013:639), while the Maio criteria and Terrell Computerized Decision Support System determines the prevalence of potentially inappropriate medicines (PIMs) (Maio *et al.,* 2010:225-226; Terrell *et al.,* 2009:1392).

The Beers criteria list, Maio criteria, Tool to Improve Medications in the Elderly via Review (TIMER) and the Medication Management Outcomes Monitor need to be updated on a regular basis (Drenth-van Maanen *et al.,* 2009:689; Lee *et al.,* 2009:5-7; Maio *et al.,* 2010:226; National Guideline Clearinghouse, 2012). The Matsumura alert system focuses on overprescribing and is a web-based system (Matsumura *et al.,* 2009:556).

Adverse drug reactions (ADRs) are taken into consideration in the American Medical Directors Association's Top 10 particular dangerous drug interactions list (American Medical Directors Association, 2011).

The quality of prescribing is better assessed applying the Fit for the Aged (FORTA) criteria and Oborne's prescribing indicators (Frohnhofen *et al.,* 2011:1417; Oborne *et al.,* 1997:96), while Phadke's criteria and Cantrill's indicators can be useful when evaluating the prescription as a whole (Cantrill *et al.,* 1998:130; Yogita & Priti, 2013:640).

The Medicine Appropriateness Index, Lipton's criteria and Pharmacist's Management of Drug-Related Problems (PMDRP) are time consuming tools (Drenth-van Maanen *et al.,* 2009:689; Shelton *et al.,* 2000:442-443). Owen's steps for medicine-related problems as well as Barenholtz-Levy and Brown's model can be used to identify patients with medicine-related problems (Barenholtz-Levy, 2003:985; Brown *et al.,* 1998:696; Owens *et al.,* 1994:47).

Table 2.5: List of available explicit tools to assess inappropriate prescribing

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
American Medical Directors Association – Top 10 particularly dangerous drug interactions (United States of America)	Identification of the 10 most dangerous interactions for patients in long-term care in America.	Increase surveillance and prompt identification of symptoms of adverse drug reactions (American Medical Directors Association, 2011).		Group of experts got together to develop an approach to manage medicine in nursing homes. 3 lists emerged from the first round. Medicines that were present on all 3 lists were included (American Medical Directors Association, 2011).	No indication that the method has been validated.
Assessing Care of Vulnerable Elders Quality Indicators (ACOVE QIs) (United States of America)	Measures the quality of care given to frail, elderly patients.	Can detect underprescribing (Drenth-van Maanen *et al.*, 2009:689). Can be applied to evaluate the overall quality of care and pinpoint areas that need to be improved (Wenger *et al*., 2007:S247). Includes geriatric conditions such as dementia and falls. Indicators can be applied to patients with progressed dementia and poor outcome (Spinewine *et al*., 2007:175; Yogita & Priti, 2013:636).	All the processes involved in the ACOVE indicators cannot be performed by a single physician. Individual quality indicators or selected groups can be applied to a single physician, but this would need attention to an appropriate sample big enough to demonstrate significant measures of the quality of care that was given (Wenger *et al*., 2007:S251).	Indicators were developed using systematic reviews of publications, expert opinion, and guidance from expert groups and stakeholders. Includes 68 indicators that refer to medication. Indicators relate to treatment, avoidance, observing, training and documentation (Spinewine *et al*., 2007:175; Yogita & Priti, 2013:636).	There is no indication that the method is validated.

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Austrian Criteria (Austria)	Identification of drugs to avoid due to unfavourable benefit-risk profiles and/or ambiguous efficacy.	Suggests alternative treatment options. Includes information with regard to pharmacological and pharmacokinetic properties of all medicine items identified as potentially inappropriate (Mann *et al*., 2012:160).	Validity still needs to be proven (Mann *et al*., 2012:160).	Based on a two-round Delphi process with 8 experts. 73 medications to avoid in older patients due to unfavourable benefit/risk profile and/or unproven effectiveness (Mann *et al.*, 2012:160).	Method not validated (Mann *et al*., 2012:160).
Beers Criteria (United States of America)	Identification of medicines or classes of medicine that should be generally avoided in older people.	Revised regularly (original criteria designed in 1991, revised in 1997, 2003 and 2012). Reduce the prescribing of potentially inappropriate medication to elderly patients (Drenth-van Maanen *et al*., 2009:689). Most widely cited explicit criteria (Chang & Chan, 2010:949).	Transferability across different healthcare settings is limited (Basger *et al*., 2008:788). Most of the medicine items listed is not available outside of the USA. Several drugs (amiodarone, doxazosin and naproxen) in the Beers criteria have debateable appropriateness in different expert groups (Chang & Chan, 2010:949). Criteria are not organized according to a specific system (Hamilton *et al*., 2011:1014).	Applicable to persons aged ≥ 65 years of age. Three-round survey based on the Delphi method. 68 criteria statements are categorised as having high or low seriousness: 48 criteria outlining potentially inappropriate medicine items and 20 diseases or conditions with medicine items to avoid in these conditions (Dimitrow *et al*., 2011:1524).	Developed by expert consensus panel so further validations studies are needed to establish the potential to decrease the prevalence of adverse drug reactions and to improve health outcomes (Chang & Chan, 2010:955).

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Beers-Liste (Germany)	Identification of medicine or classes of medicine that should be avoided in general in older people – adapted for the German market.	Can optimise pharmacotherapy of geriatric patients in Germany (Schwalbe *et al*., 2007:244).	Only applicable to patients in Germany (Schwalbe *et al*., 2007:244).	Beers list adapted for the German population by expert panel consensus (Schwalbe *et al*., 2007:244).	Unknown
Europe (7)-PIM list (Europe)	To develop a list of potentially inappropriate medicine items for the elderly to be used to examine and compare prescribing patterns across European countries and for clinical practice (Renom-Guiteras *et al*., 2015:861).	Contains proposals for dose adjustments and alternative treatment options. Permits identification and comparison of PIM prescribing patterns for the elderly across European countries. Is useful as a guideline in clinical practice (Renom-Guiteras *et al*., 2015:861).	Cannot be used to replace the decision-making process of individualised prescribing for elderly patients. No systematic review was done on the relevant literature identified (Renom-Guiteras *et al*., 2015:861).	Preliminary list developed based on the German PRISCUS list and other lists from the USA, Canada and France. Consensus reached over 282 medicine classes from 34 therapeutic groups categorized as potentially inappropriate for older adults. Some of these PIMs are limited to a specific dose or time of use (Renom-Guiteras *et al*., 2015:861).	Further research is required to explore the feasibility, appropriateness and clinical benefits of the list (Renom-Guiteras *et al*., 2015:861).
Fit for the aged (FORTA) Criteria (Germany)	Grade medicines into groups concerning their evidence for use in the older adults.	The quality of alterations in drug treatment in a geriatric ward is described in a plausible way (Frohnhofen *et al*., 2011:1417).	Provides basic uncontrolled data. Uncontrolled pilot study (Frohnhofen *et al*., 2011:1417).	Drugs are graded as positive, intermediate and negative (Frohnhofen *et al*., 2011:1417).	Study not validated and should be performed in a controlled environment where the quality of treatment with or without the use of FORTA can be compared (Frohnhofen *et al*., 2011:1417).

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Improving Prescribing in the Elderly Tool (IPET) (Canada)	Represent potentially inappropriate prescribing – shortened version of the McLeod Criteria.	Has been validated in a prospective study (O'Mahony & Gallagher, 2008:139). User-friendly as it has fewer criteria than the McLeod Criteria (Yogita & Priti, 2013:639).	The criteria are not organised in any particular order or structure. Not used frequently outside Canada (O'Mahony & Gallagher, 2008:139).	Applicable to persons aged ≥ 70 years. 14 inappropriate practices in prescribing — 10 drug-disease interactions, 2 inappropriate medication classes and 2 criteria with regard to guidance for duration of treatment (Dimitrow *et al*., 2011:1524).	Not validated; however, McLeod criteria were applied in IPET and items of the McLeod criteria were validated (Dimitrow *et al*., 2011:1524).
Kaiser Permanente Colorado (KPC) Criteria (United States of America)	Identification of potentially inappropriate medicine use in elderly and suggestion of alternative therapies.	Associated with better satisfaction than the control model it was compared to on 5 of the 6 items in high-risk patients (Johnson *et al*., 1998:2621).	Outcomes for low-risk patients are inconsistent (Johnson *et al.*, 1998:2621).	Model was applied to patients receiving pharmaceutical services and was allocated to risk groups as per patterns of prescription medicine use (Johnson *et al*., 1998:2621).	
Laroche Criteria (France)	Identification of drugs that should be avoided in elderly individuals – designed for the French health system.	Lists all generic medications that are used in France. Suggests alternative medicines for use in elderly patients (Chang & Chan, 2010:950). Indicates drugs with controversial effectiveness as potentially inappropriate. Categorises drugs with disadvantageous benefit/risk ratio and	Underutilisation of medicine items is not addressed. Needs to be addressed and confirmed in clinical studies (Mimica Matanović & Vlahović-Palčevski, 2012:1125-1126). Does not suggest any alternatives to the potentially inappropriate medications.	Applicable to persons aged ≥ 75 years. Two-round mail survey based on the Delphi method with 15 experts (Dimitrow *et al*., 2011:1524). 34 criteria for inappropriateness: 25 criteria with disadvantageous benefit/risk ratio, 1 with controversial efficacy and 7 with a disadvantageous	Method not validated (Mimica Matanović & Vlahović-Palčevski, 2012:1125-1126).

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Laroche Criteria (France) *continued*		controversial effectiveness (Mimica Matanović & Vlahović-Palčevski, 2012:1127).	Not usable in other pharmacoepidemiological studies outside France (Laroche *et al*., 2007:726).	benefit/risk ratio and controversial efficacy. 29 criteria independent of disease or condition and 5 linked to disease or condition (Mimica Matanović & Vlahović-Palčevski, 2012:1125-1126).	
Lechevallier Criteria (France)	Identification of inappropriate prescriptions – a French adaption of the Beers Criteria.	Indicates that certain features of pharmacotherapy for the elderly can be improved (Lechevallier-Michel, 2005:818).	Lack of data on co-morbidity. May underestimate the extent of potentially inappropriate prescribing. Lack of consensus on several of the items included in the Beers criteria (Lechevallier-Michel, 2005:818).	List was derived from the Beers criteria by a panel of French experts (Lechevallier-Michel, 2005:813).	Further research is needed (Lechevallier-Michel, 2005:818).
Lindblad's list of clinically important drug-disease interactions (United States of America)	Identification of clinically significant drug-disease interactions.	Straightforward and easy to use. Presents new criteria not outlined by Beers or McLeod's lists (Mimica Matanović & Vlahović-Palčevski, 2012:1125).	Medicine items to be avoided despite a disease or condition are excluded (Mimica Matanović & Vlahović-Palčevski, 2012:1125).	Based on the Delphi method. Includes 28 drug-disease interactions involving 14 diseases or conditions (Mimica Matanović & Vlahović-Palčevski, 2012:1125).	List was validated (Lindblad *et al*., 2006:1139).
Maio Criteria (Italy)	Identification of potentially inappropriate medicine – Italian adaptation of the Beers Criteria.	Dynamic tool to alert general practitioners to improve prescribing for older adults.	Unable to determine from the data source whether patients are actually taking the medicine that is given to them.	Applicable to persons aged ≥ 65 years (Dimitrow *et al*., 2011:1527). Nominal group technique was used with 9 experts.	Validated by nominal group technique (Dimitrow *et al*., 2011:1525).

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Maio Criteria (Italy) *continued*		May be used to estimate the prevalence of potentially inappropriate prescribing in outpatient setting. May be used as guideline to develop country-specific potentially inappropriate prescribing lists in Europe (Maio *et al*., 2010:225-226).	Inadequate link between potentially inappropriate prescribing and the effect on patient outcome. Generalizability to other countries is unknown and will need further investigation. Regular updates required (Maio *et al*., 2010:226). Developed for prescription database that encompasses only reimbursement data, therefore non-reimbursed items were not included in the list (Dimitrow *et al*., 2011:1527).	23 inappropriate medications were identified and classified into 3 categories: 17 medications always to be avoided, 3 rarely appropriate and 3 with some indication but often misused (Maio *et al*., 2010:219).	Further validation needed.
Malone's List of Drug-Drug Interactions (United States of America)	Identification of potential harmful drug-drug interactions.	Makes pharmacists aware of drug-drug interactions to prevent patients from receiving these interacting medicines (Malone *et al*., 2004:65).		Modified Delphi consensus-building process with 5 experts. 25 clinically important interactions identified (Malone *et al*., 2004:65).	
Matsumura alert system for inappropriate prescriptions (Japan)	Assist physicians in prescribing medicine appropriately.	Alerts for overprescribing and contraindications for liver disease, renal disease and diabetes (Matsumura *et al.*, 2009:556).	System is web-based (Matsumura *et al*., 2009:556).	Developed alert system to evaluate renal function and to evaluate doses of medicine according to patients' renal function (Matsumura *et al*., 2009:556).	

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
McLeod Criteria (Canada)	Identification of inappropriate prescribing practices to avoid in elderly, and includes mean clinical significance ratings to a maximum of 4 points.	Contain suggestions for alternative medications (Chang & Chan, 2010:949). Has the ability to decrease the prevalence of potentially inappropriate medicines (Chang & Chan, 2010:954).	Not organised based on physiological systems. No studies available to show the capability to decrease the prevalence and negative effect of adverse drug reactions (Chang & Chan, 2010:954).	Applicable to persons aged ≥ 65 years. Two-round mail survey based on the Delphi method with 32 experts. 38 inappropriate, high risk practices in prescribing categorised into 4 classes with guidelines for substitute therapy: 18 practices including medicine items normally contraindicated 16 involving drug-disease interactions and 4 involving drug-drug interactions (Dimitrow *et al*., 2011:1524).	Developed by expert consensus panel so further validation tests are required to establish the capability to decrease the prevalence of adverse drug reactions and to improve health outcomes (Chang & Chan, 2010:955).
NCQA Criteria – high risk medications and potentially harmful drug-disease interactions in the elderly (United States of America)	Forms part of the Health Plan Employer Data and Information Set to assess the standard of care in the ambulatory setting	Includes drug-disease interactions and laboratory monitoring requirements for certain medicine items (Albert *et al*., 2010:409).	Does not include any information on medicine adherence, and generalizability of findings is limited (Albert *et al*., 2010:414-415).	Geriatric medicine issues reviewed by medication management technical subgroup. Some actions of the subgroup involves to identify, prioritise and define crucial areas for development; develop selected measures; and make suggestions to Geriatric Measurement Advisory Panel (Albert *et al*., 2010:408).	Validity is still unclear (Albert *et al*., 2010:408).

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Norwegian General Practice (NORGEP) Criteria (Norway)	Identification of medicine and medicine dosages that should be avoided in geriatric patients in general practice.	Easily applicable to medicine lists with no clinical data (Dimitrow *et al*., 2011:1527). Lists single inappropriate medicines and combinations that were not addressed by previous tools (Mimica Matanović & Vlahović-Palčevski, 2012:1126).	Does not include any statement for drug-disease interactions. Does not suggest any alternative medications (Chang & Chan, 2010:951). Aimed at patients in the general practice so further studies are required to evaluate the application of this tool. (Mimica Matanović & Vlahović-Palčevski, 2012:1126).	Applicable to persons aged ≥ 70 years in general practice. Three-round mail survey based on the Delphi method with 47 experts. 36 criteria for pharmacologically inappropriate prescribing in general practice: 21 criteria for single medicine items and dosages, and 15 criteria for medicine combinations to be avoided (Dimitrow *et al*., 2011:1525).	List is validated (Ragnstad *et al*., 2009:156).
Phadke's criteria (India)	Determines whether the prescription is rational, semi-rational or irrational.	Assesses prescription as a whole and decides whether it is rational, semi-rational or irrational (Yogita & Priti, 2013:640). Not very time consuming (Shah *et al*., 2011:252).	A single medicine item cannot be categorised as appropriate or inappropriate (Shah *et al*., 2011:252).	Based on a 30-point scale: 20 points for main drugs and 10 points for complementary drugs. If more than one medication is needed for a specific condition, the points allocated are subdivided accordingly. Negative points are assigned for irrational drugs, unnecessary drugs, hazardous drugs or unnecessary injection (Yogita & Priti, 2013:640).	

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Prescribing indicators tool (Australia)	Developing a list of prescribing measures for geriatric patients based on medications that were most frequently prescribed to Australians and to pinpoint the medical conditions for which Australians visits a medical practitioner most frequently (Basger *et al*., 2008:777).	Focus on the use of medicine items in everyday medical conditions. Easier to make medication interventions as the indicators are based on medications commonly used in Australia (Basger *et al*., 2008:788). Asks about the presence of any interactions, addresses under-dosing. Includes explicit criteria for treatments that are not indicated. States that unneeded duplication should be avoided. Has a warning of ineffective treatment (Dimitrow *et al*., 2011:1527).	No expert consensus process involved. Evidence to support application of treatment guideline in frail elderly patients with co-morbidities is often inadequate, which may restrict the practicality of the model (Basger *et al*., 2008:790).	Applicable to patients over the age of 65 years in Australia (Basger *et al*., 2008:777). 45 explicit and 3 implicit prescribing indicators: 18 concerning medicine items to avoid in certain disease states or conditions, 19 recommending treatment in certain disease states or conditions, 4 concerning medication monitoring, 3 for specific drug interactions, 1 asking about smoking status of the changes in medication in the last 90 days, 1 asking about the patient and 1 concerning the vaccination status of the patient (Dimitrow *et al*., 2011:1526).	List must be evaluated and validated for applicability (Basger *et al*., 2008:788).
Rancourt Criteria (Canada)	Identify potentially inappropriate prescriptions.	The generic name and the Anatomical Therapeutic Chemical classification code for each medicine item available in Canada are listed (Chang & Chan, 2010:950).	May not be appropriate for certain individual patients. Do not consider any clinical information (Rancourt *et al*., 2004:6).	Cross-sectional chart review. List of explicit criteria developed based on literature review and Delphi method with 4 local experts.	Validated by local experts (Rancourt *et al*., 2004:5).

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Rancourt Criteria (Canada) *continued*				A total of 111 explicit criteria included to evaluate quality of prescribing (Rancourt *et al*., 2004:2-3).	
Screening Tool of Older Persons Prescriptions (STOPP) (Ireland)	Focus on common issues related to frequently prescribed drugs.	Includes explicit criteria for treatment not for which there is no clear indication (Drenth-van Maanen *et al*., 2009:689). Criteria grouped into physiological system-based divisions (Chang & Chan, 2010:950). Easily applicable. Medicine group duplication and drug-drug interactions are seen as potentially inappropriate. Can pinpoint individuals with the possibility to suffer adverse drug reactions due to potentially inappropriate prescribing (Mimica Matanović & Vlahović-Palčevski, 2012:1126). Validated, reliable and comprehensive (Gallagher *et al*., 2008:72). Good inter-rater reliability and includes both American and European medication (Page *et al*., 2010:84).	Does not address drugs with questionable efficacy (Mimica Matanović & Vlahović-Palčevski, 2012:1126). Designed to be used with the START criteria (Hamilton *et al*., 2011:1018).	Applicable to persons aged ≥ 65 years. Two-round mail survey based on the Delphi method with 18 experts. 65 criteria focus on issues linked to frequently prescribed drugs grouped according to physiological systems: 42 criteria for avoidance of medicine in specific medical conditions, 4 for certain drug combinations to avoid, 12 on period of treatment, 2 concerning dosages, 3 to avoid prescribing without an indication and 2 regarding the need for supplementary treatment (Dimitrow *et al*., 2011:1525).	Developed by expert consensus panel so further validations studies are required to determine the capability to decrease the prevalence of adverse drug reactions and to improve health outcomes (Chang & Chan, 2010:955).

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Screening Tool to Alert doctors to the Right Treatment (START) (Ireland)	Prescribing indicators to identify prescribing omissions in older adults.	Can detect prescribing omissions (Drenth-van Maanen *et al*., 2009:689). Effective in detecting under-treatment (Drenth-van Maanen *et al*., 2009:689; Mimica Matanović & Vlahović-Palčevski, 2012:1126). Criteria are validated, reliable and comprehensive (Gallagher *et al*., 2008:72).	Does not address any other issues of polypharmacy such as lack of adherence, overtreatment, adverse drug reactions, interactions and incorrect dose and administration regimens (Drenth-van Maanen *et al*., 2009:689). Aimed at patients in general practice (Mimica Matanović & Vlahović-Palčevski, 2012:1126).	Applicable to persons aged ≥ 65 years. Two-round mail survey based on the Delphi-method with 18 experts. 22 evidence-based explicit prescribing indicators for general conditions in elderly (Dimitrow *et al*., 2011:1525).	Validated by consensus panel. Further validation is required (Dimitrow *et al*., 2011:1525).
Terrell Computerized Decision Support System to reduce potentially inappropriate prescribing (United States of America)	Serves as an alert system when using one of nine high-use potentially inappropriate medications.	Prescribing of potentially inappropriate medicine items for older adults in the emergency unit is reduced significantly. Receive an actual time response from practitioners indicating why they do not follow the recommendations made by the decision support system (Terrell *et al*., 2009:1392).	Only a single small-scale study at one site with a few medical practitioners and residents who had access to a good information technology infrastructure was included. Generalizability of the findings may not be possible in other healthcare settings and other providers (Terrell *et al*., 2009:1392-1393).	All older adults visiting the emergency department were included in the study. Two sensitivity analyses were conducted for provider and patient features, resident medical practitioners and the patients who received care (Terrell *et al*., 2009:1390).	Not yet validated (Terrell *et al*., 2009:1393).

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
The PRISCUS list (Germany)	Identification of potentially inappropriate medicine and classes of medicine for use in German healthcare.	Suggests therapeutic alternatives (Holt *et al*., 2010:543). Easily applied. Includes main concerns and preventative measures. Includes medicine items that were not listed in other tools and addresses drugs with questionable efficacy (Mimica Matanović & Vlahović-Palčevski, 2012:1126).	Does not provide concrete suggestions for safe monitoring where prescribing of potentially inappropriate medication cannot be avoided. Have to be updated regularly (Holt *et al*., 2010:543). Primarily aimed at the German elderly population (Mimica Matanović & Vlahović-Palčevski, 2012:1126).	Applied to older (≥ 65 years) German adults. Two rounds based on the Delphi method. 83 drugs in 18 drug classes seen as potentially inappropriate in older adults (Holt *et al*., 2010:543).	Method still needs to be validated (Holt *et al*., 2010:543).
Winit-Watjana Criteria (Thailand)	Identification of high-risk drugs for older people.	Medications or medication classes are grouped as medicine items that should be avoided, are rarely appropriate, have some indication and are unclassified (Chang & Chan, 2010:951). Recommendations in prescribing and monitoring drug use in older adults. Useful to assess overall medication use for individual patients and to improve the overall care for the elderly (Winit-Watjana *et al*., 2008:49).	Most (70%) of the statements involve unclassified drugs and therefore the usefulness of grouping is limited (Chang & Chan, 2010:951). Further studies need to be performed to evaluate the implementation and application of the criteria (Winit-Watjana *et al*., 2008:49).	Applied to older Thai adults. Three rounds based on the Delphi method. Classification of 77 statements into 3 categories: 33 high-risk medications with possible negative effects, 32 high-risk items with drug-disease interactions and 12 high-risk items with drug-drug interactions (Chang & Chan, 2010:950-951).	Method not validated (Winit-Watjana *et al*., 2008:49).

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Zhan Criteria (United States of America)	Recognition of potentially inappropriate medicine.	Focus on medicine items that should be avoided in the elderly (Yogita & Priti, 2013:639).	Does not consider dosages, interactions or drug combinations (Yogita & Priti, 2013:639).	Applicable to the general ambulatory community aged ≥ 65 years. Two-round survey based on the Delphi method with 7 experts. Classification of 33 medicine items: 11 items that should always be avoided, 8 items that are rarely appropriate and 14 items that have some usefulness in older adults (Dimitrow *et al*., 2011:1524).	Validated by Delphi consensus panel (Dimitrow *et al*., 2011:1524). Further validation needed.

Table 2.6: List of available implicit tools to assess inappropriate prescribing

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Assessment of Underutilisation of Medication (United States of America)	Measures the proportion of patients with a minimum of one drug omission detected by the tool (Yogita & Priti, 2013:638).	Can detect underprescribing (Yogita & Priti, 2013:638).	Health professionals are needed to match the prescribed medication to the list of chronic medical disorders and to determine whether omission of a certain medication is required (Yogita & Priti, 2013:638).	Applicable to persons aged ≥ 65 years of age. Necessary treatment in chronic conditions is evaluated. Ratings are given to each illness: A = no exclusion; B = marginal exclusion; and C = exclusion (Dimitrow *et al*., 2011:1526).	Validity was demonstrated in a small scale case study in one facility (Dimitrow *et al*., 2011:1526).
Barenholtz Levy self-administered medication-risk questionnaire (United States of America)	Self-administered questionnaire for older adults to pinpoint those at higher risk of potentially experiencing a drug-related issues.	Acceptable and feasible for self-administration. Pinpoints patients with a higher chance for drug-related issues. Streamlines efforts to provide medication reviews (Barenholtz Levy, 2003:985).	The drug regimen reviews were based on the judgement of only one pharmacist and further studies need to be done on the modification of the questionnaire (Barenholtz Levy, 2003:985).	Patients aged 65 years and older and taking a minimum of two medicine items on a regular basis were included. Patients were excluded if they were unable to complete the questionnaire on their own, were unable to communicate with the investigating pharmacist, or had no caregiver to assist them (Barenholtz Levy, 2003:983).	Questionnaire was validated (Barenholtz Levy, 2003:985).

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Cantrill indicators of appropriateness of long-term prescribing (United Kingdom)	Provide indicators of prescribing appropriateness to assess the entire medicine regimen of patients on long-term treatment.	Currently the only means available to evaluate a patient's medicine regimen in its totality (Cantrill *et al*., 1998:130).	Does not link prescription to diagnosis. Rely on the level of documentation of the prescriber (Cantrill *et al*., 1998:134).	Nominal group was used to identify potential indicators of appropriateness of prescribing. Two-round Delphi method done with 200 experts to find 13 indicators suitable for application (Cantrill *et al*., 1998:130).	Have face and content validity according to a selected group of general practitioners and community pharmacists. Further validity assessment is required (Cantrill *et al*., 1998:135).
Lipton's tool to assess the appropriateness of physicians' geriatric drug prescribing (United States of America)	Evaluates each drug in the patient's regimen and categorises potential drug-therapy problems.	Asks about the presence of any interactions, addresses under-dosing and states that the prescribed medicine item must have a clear indication. Mentions that unnecessary duplication should be avoided (Dimitrow *et al*., 2011:1527). Inter-rater reliability is demonstrated. Patients can be tracked over time by means of the scoring system (Shelton *et al*., 2000:443). Reviewer is allowed to apply implicit judgement (Shelton *et al*., 2000:446).	Studies the prevalence of drug-therapy problems and therefore the criteria must be expanded upon and updated regularly (Dimitrow *et al*., 2011:1527). Does not deal with adverse drug reactions, drug-disease interactions, duration or cost of treatment. Time consuming. Scoring system is not weighted. Only one study assessed the tool's validity and reliability (Shelton *et al*., 2000:443).	Applicable to person's ≥ 65 years. 6 explicit medicine-therapy issues categories with definitions and examples. Requires implicit judgement. Explicit categories include: allergy, dosage, schedule, appropriateness, drug-drug interaction and unneeded therapeutic duplication (Dimitrow *et al*., 2011:1525).	Content validity was established during 5 review panel meetings (Dimitrow *et al*., 2011:1525). Further validation is required.

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Medication Appropriateness Index (MAI) (United States of America)	Assesses medicine appropriateness in relation to 10 criteria for each item prescribed.	Queries the presence of any interactions and whether dose is correct, and includes drug cost. Prescribed items must have a clear indication. Mentions that unnecessary duplication should be avoided. States that medicine use must be effective for the specific condition (Dimitrow *et al*., 2011:1527). Useful in identifying adverse drug reactions, drug-drug interactions and overtreatment (Drenth-van Maanen *et al*., 2009:689). Valid and reliable. Inter-rater and intra-rater reliability is demonstrated. Scoring system is weighted. Assessment provides a total score that can be tracked (Shelton *et al*., 2000:443). Gives an organized analysis and is adjustable enough to account for inter-patient variability (Shelton *et al*., 2000:447).	Does not detect under treatment. Very time consuming (Drenth-van Maanen *et al*., 2009:689; Shelton *et al*., 2000:443). Generalizability is controversial and more validation in various situations and populations is required (Shelton *et al*., 2000:447).	Developed for persons ≥ 65 years, but its use is not restricted to older adults. 10 academic healthcare professionals judged MAI items to be definitely or moderately important. Independent validation of suitability of MAI items is provided. 10 criteria are structured as questions to evaluate the appropriateness of each prescribed item with guidelines for use and operational definitions for each criterion. The 10 criteria include: indication, effectiveness, dosage, correct directions, drug-drug interactions, drug-disease interactions, practical directions, costs, duplication and duration (Dimitrow *et al*., 2011:1525).	Independent validation of the suitability of the items has been done (Dimitrow *et al*., 2011:1525).

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Owen's steps to achieve optimal pharmacotherapy (USA)	Consists of 5 questions to determine whether the medicine is still appropriate for the specific patient.	Pinpoints patients with a higher probability to be discharged to an old age home, die or suffer high hospitalisation cost for the institution (Owens *et al*., 1994:47).		Short 7-item screen with questions regarding cognitive potential, physical strength, nourishment, number of medicine items used and hospitalisation	
Pharmacist's Management of Drug-Related Problems (PMDRP) (Canada)	Facilitates learning and improve the provision of pharmaceutical care by pharmacists.	Supports guidance through care process. Asks explicit questions and requires implicit decision-making. Can be individualised to practitioner and setting (Shelton *et al*., 2000:442).	Time consuming and can be long and cumbersome to the practitioner (Shelton *et al*., 2000:442).	Identifying and resolving medicine-related issues with drug regimen and numerous patient-specific factors (Shelton *et al*., 2000:442).	Consensus panel improves content validity but there is limited information regarding validation of the drug utilisation (Shelton *et al*., 2000:443).

Table 2.7: List of available tools with a mixed approach to assess inappropriate prescribing

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
A Tool to Evaluate Polypharmacy in Elderly Persons (ARMOR) (United States of America)	Stepwise approach for the assessment of the geriatric patient (Haque, 2009:27).	Reduces polypharmacy, cost of care and hospitalisation. Considers the complete patient profile (both clinical profile and functional status). Emphasises the quality of life as key factor in decision-making - use of certain drug items is weighed against its effect on primary biological functions. Useful in monitoring and optimising outpatient prescribing patterns.		An interdisciplinary team-based approach was used to develop the tool (Haque, 2009:27).	
Brown Model for Improving Medication Use in Home Health Care Patients (United States of America)	Recognition of potential medication problems occurring in patients receiving home healthcare.	Useful to recognise and resolve medicine-related issues in home healthcare settings (Brown *et al*., 1998:696).	Not yet evaluated (Brown *et al*., 1998:696).	Review panel compiled a list of possible issues linked to the most commonly utilised groups of medicines (Brown *et al.,* 1998:696).	Not validated.
Geriatric Medication Algorithm (United States of America)	Developed to train medical practitioners on how to decrease inappropriate prescribing and improve physician prescribing older adults.	Simple and quick to use. Structures the review for medications known to be problematic in elderly patients and the dosage for patients with renal and hepatic impairment (Shelton *et al*., 2000:442).	Algorithm is very general and open. An implicit type of review that permits greater variability in results (Shelton *et al*., 2000:442).	Tool that measures indication, risks, dose, interactions, complexity and compliance (Shelton *et al*., 2000:442).	Consensus validity, but limited information regarding drug utilisation validity (Shelton *et al*., 2000:443).

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Indicators for Quality use of Medicines (Australia)	Monitoring facets of care in Australian hospitals.	Allow consistent but practical monitoring of care aspects (New South Wales Therapeutic Advisory Group, 2007).	Improvement of supplementary indicators will need to continue (New South Wales Therapeutic Advisory Group, 2007).	52 indicators were selected by consultation with relevant experts from a variety of clinical disciplines (New South Wales Therapeutic Advisory Group, 2007).	Validated for use in adults, but not in children (New South Wales Therapeutic Advisory Group, 2007).
Medication Management Outcomes Monitor (United States of America)	Focuses on decreasing inappropriate prescribing, reducing polypharmacy, avoiding adverse events and maintaining functional status of older adults.	Reduces the risk of medicine mismanagement (National Guideline Clearinghouse, 2012).	Must be updated annually. Focuses only on long-term care facilities (National Guideline Clearinghouse, 2012).	Experts examined the available research and wrote the guideline. Was reviewed internally and externally (National Guideline Clearinghouse, 2012).	Validated by internal and external peer review (National Guideline Clearinghouse, 2012).
Oborne's Prescribing Indicators (United Kingdom)	Recognition of prescribing indicators based on medicine charts.	Allow recognition of sectors of substandard prescribing and offer potential for applying measures to better prescribing practises (Oborne *et al*., 1997:96).	Assessment of prescribing is restricted by the quality of documentation (Oborne *et al*., 1997:96).	A consensus list of medicines was compiled and indicators were subject to review by an expert group (Oborne *et al*., 1997:92).	Only some of the indicators are validated (Oborne *et al.,* 1997:96).
Prescribing Optimisations Method for improving prescribing in elderly patients (Netherlands)	Assists medical practitioners to correct polypharmacy prescribing in geriatric patients.	Deals with familiar problems associated with polypharmacy, like under-treatment, non-adherence, over-treatment, adverse drug reaction, unfavourable interactions and incorrect dose and administration regimens (Drenth-van Maanen *et al*., 2009:697).	Patient is not included in the investigation and thus the model only tests the theory which means that the level of evidence was not significant (Drenth-van Maanen *et al*., 2009:697).	Based on 6 open questions to assist medical practitioners to ensure that their patients are getting the best possible treatment (Drenth-van Maanen *et al*., 2009:689).	Further investigation is required (Drenth-van Maanen *et al*., 2009:699).

Tool/criteria (Country)	Aim	Advantages	Disadvantages	Description	Sensitivity and specificity
Tool to Improve Medications in the Elderly via Review (TIMER) (United States of America)	To assist dispensing staff with the recognition of any medicine associated issues during patient medication analysis.	Gives a structured way to review patients' profiles and medications. Useful to recognise medicine-related issues that the pharmacist would otherwise not have considered (Lee *et a*l., 2009:5-7).	Require training to use. Must be updated regularly (Lee *et al*., 2009:5-7).	Used 4 regional experts and identified 4 sections: Cost-effective medicine choice, adherence, medication safety and achieving other objectives (Lee *et al*., 2009:5-7).	Content validity was established by experts who practice geriatrics or family medicine (Lee *et al*., 2009:6).

There is a clear necessity for a straightforward, affordable, time-efficient assessment tool which can be used as a guideline in the prescribing practice to strive to decrease the percentage of inappropriate prescriptions (Shah *et al*., 2011:248-249) and improve pharmacotherapy in the elderly (Shelton *et al*., 2000:439). Characteristics of such a tool should include sensitivity, specificity, generally experienced ADRs and having good inter-rater reliability. The application of such an assessment tool must convert into favourable clinical results (Shah *et al*., 2011:248-249). It should also be affordable, convenient and aimed at helping the prescriber in the selection of medicine items for the elderly patient with the general aim of decreasing irrational and inappropriate prescribing, ultimately leading to better health outcomes (Kaur *et al*., 2009:1015).

In this study, the Beers criteria and the Mimica Matanović and Vlahović-Palčevski comprehensive drug-drug interaction list were used to determine inappropriate prescribing in geriatric patients. The Beers criteria are the most favourable and accepted explicit criteria applied for the assessment of potentially inappropriate medicine prescribing. The Beers criteria have been adopted by several medical schemes and pharmacy benefit managers to help recognise and pinpoint older patients at risk of adverse drug effects linked to possible inappropriate prescribing (Page *et al.,* 2010:80). It is also easy to use (Page *et al.,* 2010:84). The Mimica Matanović and Vlahović-Palčevski-comprehensive protocol (Mimica Matanović & Vlahović-Palčevski, 2012), developed in 2008, consist of, *inter alia,* a list of 70 potentially clinically important drug-drug interactions. They are subsequently discussed in greater detail.

2.5.1 Beers criteria

The Beers criteria are one of the most generally applied consensus criteria for drug use in older adults (Fick *et al.,* 2003:2716-2717; Ryan *et al.,* 2009:937; Shah *et al*., 2011:251). The Beers criteria consist of a list of explicit criteria for potentially inappropriate medicine items used in older adults (Shah *et al*., 2011:249) that categorise the formulation as appropriate or inappropriate (Shah *et al*., 2011:249, 252). During the past 20 years, these criteria have been used to study the prescribing patterns within communities, to train medical practitioners, and to assess health outcomes, cost and utilisation data to reduce drug-related issues in the elderly (Fick *et al.,* 2003:2716-2717). The criteria are based on an expert consensus panel that was developed using a modified Delphi method that requires regular updates to take into consideration any new drugs available on the market and to remove drugs that are no longer available (Fick *et al.,* 2003:2716-2717).

The first version of the criteria was published by Beers and colleagues in 1991 (Barry *et al*., 2006:618; Childress *et al.*, 2012:25-26). The team included 12 clinicians with expertise in geriatrics who together created a list that can be used as a quick reference to determine which

medicine should be avoided in elderly patients (Childress *et al.*, 2012:25-26). The criteria were developed to identify the prevalence of inappropriate prescribing in nursing home residents (Barry *et al*., 2006:618; Dimitrow *et al*., 2011:1524). Content credibility of the criteria was based on the Delphi method, using a two-round written review, with 13 nationally and internationally acknowledged specialists from the USA and Canada. Thirty medicine items that should be avoided in nursing home residents despite the diagnosis, dosage and frequency of medicine usage were identified (Dimitrow *et al*., 2011:1524; Page *et al*., 2010:77). Most of the items listed in the 1991 version became obsolete.

Due to an increased awareness of items responsible for drug-drug interactions and drug-disease interactions, the 1991 version of the criteria was reviewed in 1997 (Barry *et al*., 2006:618). Beers and colleagues gathered again to identify inappropriate medicine use in ambulatory patients (Fick *et al.,* 2003:2716-2717). The main objective of the 1997 version was to evaluate the standard of prescribing in all elderly patients, despite the extent of frailty and place of residence (Van der Hooft *et al*., 2005:4; Page *et al*., 2010:77). The target population was all patients 65 years and older (Dimitrow *et al*., 2011:1524). Content validity consisted of a two-round survey using the Delphi method with six nationally recognised experts (Dimitrow *et al*., 2011:1524). In the 1997 version, inappropriate drugs were classified into three groups: 1) medicine items that should normally be avoided in the elderly, 2) medicine items that exceed a maximum recommended daily dose, frequency or duration of treatment that vary from those normally accepted as appropriate in older adults, and 3) medicine items to be avoided in combination with a specific co-morbidity (Van der Hooft *et al*., 2005:4; Page *et al*., 2010:77). Items responsible for drug-drug interactions and drug-disease interactions were also included and this version could be applied to all elderly patients (Barry *et al*., 2006:618).

Another update to the Beers criteria was done in 2003 to include new medicine items and information available, to allocate and re-assess the relative severity rating for each item listed and to pinpoint additional disorders and contributing factors that was not considered in the 1997 criteria. A total of 15 drugs or drug classes were removed or adjusted from the 1997 version (Van der Hooft *et al*., 2005:4; Page *et al*., 2010:77). Content validity consisted of a three-round survey based on the Delphi method with 12 nationally and internationally recognised experts from the United States. A total of 68 criteria statements were categorised as having a high severity (52 items) or low severity (16 items), with 48 criteria describing the potentially inappropriate medicine items and 20 criteria describing diseases or conditions with medicine items to be avoided (Chang & Chan, 2010:949; Dimitrow *et al*., 2011:1524).

The latest update of the Beers criteria was conducted in 2012 by the American Geriatrics Society and an interdisciplinary panel which consisted of 11 specialists in geriatric care and pharmacotherapy by applying a modified Delphi method (Fick *et al.,* 2003:2716-2717). The

2012 version of the Beers criteria consists of 53 drugs or drug classes that are separated into three groups: 1) potentially inappropriate drugs and drug classes to avoid in older patients, regardless of the diagnosis (34 medicine items), 2) potentially inappropriate drugs and drug classes to avoid in the elderly with specific conditions and disorders that the listed medicine items can worsen (19 medicine items), and 3) drugs that should be used with caution in the elderly (14 medication items). Uses of the 2012 Beers criteria include close observation of medicine use and applying interventions to reduce adverse drug events and improve patient outcomes (Fick *et al.,* 2003:2716-2717; Yogita & Priti, 2013:639).

Regular updates of the Beers criteria are required for them to stay up to date and useful to clinicians, health care administrators and researchers. The Beers criteria list also do not identify problems such as underuse of medicine items or drug interactions in elderly patients (Fick *et al.,* 2003:2716-2717; Fick *et al.,* 2012:617), they do not address all types of potentially inappropriate medications, and they do not comprehensively address the need of a specific patient getting sedative and hospice care, in whom symptom control is often more significant than avoiding the use of the potentially inappropriate medicine (Yogita & Priti, 2013:639).

Table A.1 to A.2 in Annexure A contain the medicines listed in the Beers criteria.

2.5.2 Mimica Matanović and Vlahović-Palčevski comprehensive drug-drug interaction list

This list of clinically important drug-drug interactions in geriatric patients was developed by adjusting the Malone's and Hanlon's lists for drug interactions and including four new drug interactions. North American and European tools were combined to make a new, combined tool generally applicable to older adults (Mimica Matanović & Vlahović-Palčevski, 2012:1124).

In 2004, Malone and colleagues developed a list of 25 drug-drug interactions with the highest clinical significance by applying the Delphi method (Malone *et al*., 2004:142). All items included in the list involved medicine items with a narrow therapeutic index and were generally pharmacokinetic in origin. Hanlon and Schmader (2005:61) studied possible drug interactions in older adults and added on to Malone's list with seven clinically important pharmacokinetic drug-drug interactions involving anti-arrhythmic drugs, 12 involving anti-epileptics and 15 involving other medicine items. Nine clinically important pharmacodynamic drug-drug interactions were also added, like the use of ACE inhibitors with potassium-sparing diuretics or with potassium supplements (Mimica Matanović & Vlahović-Palčevski, 2012:1133).

For the Mimica Matanović and Vlahović-Palčevski comprehensive drug-drug interaction list, items that are rarely prescribed and items withdrawn from the market were excluded. Overall, 17 of the drug interactions listed in Malone's list were included in the Mimica Matanović and

Vlahović-Palčevski interaction list. Several additions were also made. Common combinations used by elderly patients that were included in the Mimica Matanović and Vlahović-Palčevski list are levodopa-monoamine oxidase inhibitors, potassium-potassium sparing diuretics, HMG Co-A reductase inhibitors-gemfibrozil and cytochrome P450 (CYP) 3A4-metabolized HMG Co-A reductase inhibitors-macrolide antibiotics. The recently developed protocol also includes four other potentially significant interactions of medicine items normally prescribed to geriatric patients which may possibly lead to serious adverse events. These interactions include the combination of amiodarone with CYP3A4-metabolized HMG Co-A reductase inhibitors, i.e. simvastatin or atorvastatin; combination of selective serotonin reuptake inhibitors with either tramadol or metoclopramide; and the combination of clopidogrel with proton pump inhibitors (PPIs). One of the pharmacodynamic interactions included by Hanlon and Schmader was the potential interaction between corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) where there is a higher probability for peptic ulcer disease. The Mimica Matanović and Vlahović-Palčevski interaction list also include the potential interaction between aspirin and corticosteroids which can result in a higher chance of peptic ulcers, and the interaction between two antiplatelet agents, leading to a higher chance of bleeding. A total of 70 potentially clinically significant drug-drug interactions are included in the new protocol (Mimica Matanović & Vlahović-Palčevski, 2012:1135).

Table 2.8 contains the potential serious drug-drug interactions that are listed in the Mimica Matanović and Vlahović-Palčevski comprehensive drug-drug interaction list. Table 2.9 contains the description of the Tatro (2004) significance rating.

Table 2.8: Potentially serious drug-drug interactions (adapted from Mimica Matanović & Vlahović-Palčevski, 2012:1134-1135; Tatro, 2004)

Drug interaction	Effect	Tatro significance rating	Mechanism	Effect
Clinical significant pharmacokinetic drug-drug interactions				
Anti-arrhythmic				
Disopyramide – Cimetidine	Increased concentration of disopyramide	4	Cimetidine may increase the absorption of disopyramide.	Plasma concentrations of disopyramide may be increased, leading to increased pharmacological and adverse effects.
Disopyramide – Macrolides (except Azithromycin)	Increased concentration of disopyramide	4	Inhibition of disopyramide metabolism by macrolide antibiotic is suspected.	Increased plasma levels of disopyramide may occur. Arrhythmias, increased QT intervals and hypoglycaemia have been reported.
Procainamide – Amiodarone	Increased concentration of procainamide	2	Unknown	Procainamide serum concentrations may be increased by amiodarone.
Procainamide – Trimethoprim	Increased concentration of procainamide	2	Competition for renal tubular cationic secretion between procainamide and trimethoprim may be responsible.	Increased procainamide and N-acetyl-procainamide (NAPA) serum levels may produce an elevation in the pharmacologic effect of procainamide.
Quinidine – Cimetidine	Increased concentration of quinidine	2	It is unclear if this interaction is due to increased quinidine absorption, decreased quinidine metabolism or a combination of the two.	An elevation in the pharmacologic and toxicological effects of quinidine may occur secondary to increased quinine concentrations. The quinine concentrations appear to return to pre-treatment values approximately 48 hours after cimetidine is discontinued.

Drug interaction	Effect	Tatro significance rating	Mechanism	Effect
Quinidine- Fluvoxamine	Increased concentration of quinidine	4	Inhibition of quinidine metabolism (CYP3A4) is suspected.	Quinine levels may be increased, leading to an increase in both the therapeutic and adverse effects.
Anti-epileptics				
Carbamazepine – Danazol	Increased concentration of Carbamazepine	2	Danazol inhibition of carbamazepine metabolism	Serum carbamazepine levels may be increased, resulting in an increase in the pharmacological and harmful effects.
Carbamazepine – Diltiazem	Increased concentration of Carbamazepine	2	Diltiazem inhibition of the metabolic degradation of carbamazepine is proposed but not established.	Serum concentrations of carbamazepine may be increased and carbamazepine toxicity may result.
Carbamazepine – Macrolides	Increased concentration of Carbamazepine	1	Inhibition of carbamazepine hepatic metabolism (CYP3A4) results in reduced carbamazepine clearance.	Carbamazepine concentrations and toxicity may be increased.
Carbamazepine – Verapamil	Increased concentration of Carbamazepine	2	Verapamil appears to decrease the hepatic metabolism of carbamazepine.	Serum carbamazepine concentration may be higher, resulting in a higher probability for pharmacologic and harmful effects.
Phenytoin – Amiodarone	Increased concentration of Phenytoin	2	Possible reduction in phenytoin metabolism and an increase in amiodarone metabolism.	Higher serum phenytoin levels with symptoms of toxicity. Phenytoin may reduce amiodarone serum concentrations.
Phenytoin – Cimetidine	Increased concentration of Phenytoin	2	Cimetidine inhibits the hepatic microsomal enzyme metabolism of phenytoin.	Serum phenytoin concentrations may be elevated, leading to an increase in pharmacologic effects.
Phenytoin – Fluoxetine	Increased concentration of Phenytoin	2	Inhibition of phenytoin metabolism by fluoxetine	Serum phenytoin concentrations may be higher, leading to an increase in the pharmacologic

Drug interaction	Effect	Tatro significance rating	Mechanism	Effect
				and harmful effects.
Phenytoin – Isoniazid	Increased concentration of Phenytoin	2	Isoniazid inhibits the hepatic microsomal enzyme metabolism of phenytoin.	Serum phenytoin concentrations may be higher, leading to an increase in the pharmacologic and toxic effects of phenytoin. In normal therapeutic doses, phenytoin toxicity is most significant in patients who are slow acetylators of isoniazid.
Phenytoin – Omeprazole	Increased concentration of Phenytoin	4	Omeprazole seems to obstruct the oxidative hepatic metabolism of phenytoin.	Serum phenytoin concentrations may be elevated, resulting in an elevation in pharmacologic and harmful effects.
Quinidine – Phenytoin	Decreased concentration of Quinidine	2	Appears to be due to phenytoin stimulation of the hepatic microsomal enzyme system resulting in an increase in quinine metabolism.	A reduction in the therapeutic effect of quinidine may occur.
Theophylline – Phenytoin	Reduced concentration of Theophylline	2	It appears that phenytoin metabolism is enhanced by theophylline and likewise theophylline metabolism is increased by phenytoin.	Decrease or loss of pharmacological effects of theophylline or phenytoin.
Warfarin - Phenytoin	Decreased in PT INR	2	Phenytoin increases prothrombin time (PT) when added to the regimen of patients taking warfarin. Phenytoin may initially dislodge Warfarin from protein binding sites followed by enzyme induction increasing metabolism	Elevated phenytoin serum concentrations with possible toxicity. Elevated prothrombin times and higher risk of bleeding.

Drug interaction	Effect	Tatro significance rating	Mechanism	Effect
Digoxin – Clarithromycin	Higher concentration of Digoxin	1	In some (10%) of patients, digoxin is metabolized by GI bacteria to digoxin reduction products (DRPs). Macrolide antibiotics may change this likelihood by changing GI flora, allowing for more digoxin to be absorbed. Clarithromycin may also inhibit renal tubular P-glycoprotein excretion of digoxin.	The co-administration of macrolide antibiotics and digoxin may lead to elevated serum levels of digoxin in about 10% of patients. Toxicity may occur.
Digoxin – Amiodarone	Increased concentration of Digoxin	1	Unknown	Serum digoxin concentrations may be elevated, resulting in an elevation in the pharmacologic and harmful effects.
Digoxin – Quinidine	Increased concentration of Digoxin	1	Reduced renal and biliary clearance and volume of distribution of digoxin	Higher serum digoxin concentrations with possible toxicity
Digoxin – Propafenone	Increased concentration of digoxin	1	Unknown, however decreased digoxin volume of distribution and renal and non-renal clearance appear to be involved.	Serum digoxin levels may be elevated, leading to toxicity.
Digoxin – Verapamil	Increased concentration of Digoxin	1	Verapamil increases plasma digoxin concentrations and decreases digoxin elimination. Total body digoxin clearance is reduced.	Digoxin effects may be enhanced leading to increased digoxin levels and toxicity could occur.
Lithium – ACE inhibitors	Increased concentration of Lithium	2	ACE inhibitors may reduce lithium excretion via the kidneys by increasing its reabsorption.	Plasma lithium concentrations may be raised, leading to an elevation in the pharmacologic and toxic effects of lithium like ataxia, confusion and delirium.

Drug interaction	Effect	Tatro significance rating	Mechanism	Effect
Lithium – Diuretics	Increased concentration of Lithium	4	Unknown	Increased plasma lithium concentrations with a higher chance that toxicity may occur.
Lithium – NSAIDs	Increased concentration of Lithium	2	NSAID interference with renal prostaglandin production may reduce renal elimination of lithium.	Serum lithium levels may be increased, resulting in an elevation in the pharmacologic and toxic effects of lithium.
Procainamide – Cimetidine	Increased concentration of Procainamide	2	Probably reduced procainamide renal clearance	Increased serum procainamide concentrations may occur.
Salicylates – Probenecid	Increased concentration of Salicylates	2	Unknown. Probably due to changes in the renal filtration of uric acid	Co-administration of probenecid and aspirin may inhibit uricosuric action of either drug alone.
Theophylline – Cimetidine	Increased concentration of Theophylline	2	Inhibition of the hepatic metabolism of theophylline	Elevated theophylline levels which may lead to toxicity.
Theophylline – Erythromycin, Azithromycin	Increased concentration of Theophylline	2	Certain macrolides inhibit the metabolism of theophylline. Theophylline decreases the bioavailability and enhances the renal clearance of oral erythromycin.	Increased theophylline serum levels with toxicity may occur. Decreased erythromycin levels have been reported.
Warfarin – Amiodarone	Increased concentration of Warfarin	1	Amiodarone inhibits the metabolism (CYP1A2 and CYP2C9) of the R- and S-enantiomers of Warfarin.	Hypoprothrombinemic effect of oral anticoagulants is increased by concomitant amiodarone therapy.
Warfarin – Macrolides	Increased concentration of Warfarin	1	The total body clearance of Warfarin is reduced.	The anticoagulant effect of oral anticoagulants may be increased. Haemorrhage has occurred.
Warfarin – Quinolones	Increased concentration of Warfarin	4	Unknown	Increased anticoagulant effect of Warfarin

Drug interaction	Effect	Tatro significance rating	Mechanism	Effect
Warfarin – Sulfamethoxazole	Increased concentration of Warfarin	1	Unclear, however trimethoprim/sulfamethoxazole seems to obstruct hepatic metabolism of S-Warfarin.	The anticoagulant effect of Warfarin may be elevated, leading to haemorrhage.
Drug-drug interactions selected by Malone *et al*. as having the greatest clinical importance				
Benzodiazepines – Azole antifungal agents		2	Decreased oxidative metabolism (CYP3A4) of certain benzodiazepines and first-pass metabolism of triazolam.	Elevated and extended serum levels. CNS depression, and psychomotor impairment with some benzodiazepines, which may possibly continue for a few days after the azole treatment has been completed or stopped.
Cyclosporine – Rifampin		1	The metabolism of cyclosporine is thought to be markedly enhanced because of hepatic enzyme induction by rifampin. Cyclosporine bioavailability is decreased because of inhibition of intestinal cytochrome P450 enzymes.	The immunosuppressive effects of Cyclosporine may be reduced. This appears to take place within 2 days of starting the rifampin and may persist for 1 to 3 weeks after their discontinuation.
Ergot alkaloids – Macrolide antibiotics (except Azithromycin)		1	Unknown. A possible hypothesis is that macrolide antibiotics hamper with the hepatic metabolism of ergotamine.	Concomitant use of these items may lead to acute ergotism manifested as peripheral ischemia.
MAO inhibitors – Sympathomimetics (dopamine, ephedrine, phenylephrine, pseudoephedrine)		1	Inhibition of MAO leads to a build-up of norepinephrine, resulting in a higher pressor response at the receptors.	Co-administration of these items may lead to severe headache, hypertension, high fever and hypertensive emergency. Direct-acting sympathomimetic drugs appear to interact minimally.

Drug interaction	Effect	Tatro significance rating	Mechanism	Effect
Meperidine – MAO inhibitors		1	Unknown	Concurrent administration could lead to negative effects including agitation, seizures, diaphoresis and fever, which may advance to coma, apnoea, and death. Effects even possible several weeks after withdrawal of MAO inhibitors.
Methotrexate – Trimethoprim		1	Methotrexate and trimethoprim are folate antagonists and may have a synergistic effect on folate metabolism.	Trimethoprim may increase the risk of Methotrexate-induced bone marrow suppression and megaloblasticanemia.
Nitrates – Sildenafil		1	Sildenafil enhances the hypotensive effects of by inhibiting phosphodiesterase type 5, which is responsible for degradation of cyclic guanosine monophosphate (cGMP) in the *corpus cavernosum*. Elevated cGMP causes smooth muscle relaxation in the *corpus cavernosum*, which allows inflow of blood.	Severe hypotension may occur.
SSRIs – MAO inhibitors		1	Potential quick, immoderate build-up of serotonin.	Serotonin syndrome may occur.
Theophylline – Fluvoxamine		2	Fluvoxamine obstructs the hepatic metabolism (CYP1A2) of theophylline.	Increased theophylline serum concentrations with possible toxicity.
Theophylline – Quinolones		2	Obstruction of the hepatic metabolism of theophylline.	Elevated theophylline levels and toxicity may occur.

Drug interaction	Effect	Tatro significance rating	Mechanism	Effect
Thiopurines – Allopurinol		1	Obstruction of xanthine oxidase by Allopurinol reduces the rate at which mercaptopurine is converted to inactive 6-thiouric acid. Allopurinol inhibits the first-pass metabolism of oral mercaptopurine.	Increases in pharmacologic and toxic effects of orally administered thiopurines have occurred with co-administration of allopurinol
Warfarin – Fibric acid derivatives		1	Coagulation factor synthesis may be affected.	Hypoprothrombinemic effects of oral anticoagulants are elevated by fibric acid. Previous cases of bleeding and death have occurred. No effect on the Warfarin plasma levels.
Warfarin – NSAIDs		2	Gastric irritation and decreased platelet function.	Anticoagulant activity may be increased by NSAIDs, increasing the risk of bleeding.
Warfarin – Cimetidine		1	Stereo-selective obstruction of the hepatic metabolism of the less potent (R)-warfarin enantiomer.	Elevated effect of warfarin with possible haemorrhage.
Warfarin – Thyroid hormones		1	A possible proposal is that thyroid hormone administration may cause a quicker disappearance of Vitamin K dependent clotting factors but this has not been clearly established.	The simultaneous administration of thyroid hormones and anticoagulants leads to an increased anticoagulant action by anticoagulants.
Warfarin – Barbiturates		1	Enhanced metabolic clearance of anticoagulants, possible due to induction of hepatic microsomal enzymes.	Barbiturates reduce the effects of anticoagulants.
Other clinically important drug-drug interactions (pharmacokinetic and pharmacodynamic)				
Atorvastatin/simvastatin – Amiodarone		Unknown	Unknown	Unknown

Drug interaction	Effect	Tatro significance rating	Mechanism	Effect
Potassium – potassium-sparing diuretics		1	A reduction in the elimination of the potassium ion	Potassium-sparing diuretics will increase potassium retention and can result in severe hyperkalaemia.
Clopidogrel – PPIs		Unknown	Unknown	Unknown
Levodopa – MAO inhibitors		1	Inhibited peripheral metabolism of levodopa-derived dopamine with increased levels at dopamine receptors	Simultaneous administration of levodopa and MAO inhibitors may lead to hypertensive reactions.
SSRIs – Metoclopramide		4	Unknown	Serotonin syndrome may occur. Symptoms include irritability, increased muscle tone, shivering, myoclonus and altered consciousness.
SSRIs – Tramadol		4	The serotonergic effects of these agents may be additive.	Serotonin syndrome may occur.
HMG Co-A reductase inhibitors - Gemfibrozil		1	Unknown	Serious myopathy or rhabdomyolysis may occur.
Atorvastatin – Macrolide antibiotics		1	Inhibition of metabolism (CYP3A4) is suspected.	Serious myopathy or rhabdomyolysis may occur due to an increase in HMG Co-A reductase inhibitor levels.
Simvastatin – Macrolide antibiotics		1	Inhibition of metabolism (CYP3A4) is suspected.	Serious myopathy or rhabdomyolysis may occur due to an increase in HMG Co-A reductase inhibitor levels.

Drug interaction	Effect	Tatro significance rating	Mechanism	Effect
Clinically significant pharmacodynamic drug-drug interactions				
ACE inhibitors – Potassium-sparing diuretics	Increased Potassium level	1	Unknown	Simultaneous administration of ACE inhibitors and potassium-sparing diuretics may lead to increased serum potassium concentrations in specific high-risk (like renal impaired) patients.
ACE inhibitors – Potassium supplements	Increased Potassium concentration	4	ACE inhibitors reduce aldosterone secretion, possibly leading to potassium retention.	ACE inhibitors plus potassium supplementation may increase serum potassium in certain patients, possibly leading to severe hyperkalaemia.
Anticholinergic – Anticholinergic	Increased anticholinergic effect			
Antihypertensive – NSAIDs	Decreased antihypertensive effect			
CNS agents (diazepam) – CNS agents (codeine)	Increased CNS effect			
Diuretics – NSAIDs	Decreased diuretic effect	3	Possible inhibitions of prostaglandins responsible for maintaining renal hemodynamics.	Effects of the loop diuretics may be decreased.
NSAIDs, Aspirin – Corticosteroids	Increased risk for peptic ulcer	2	Corticosteroids probably stimulate liver metabolism of salicylates and may also increase renal elimination.	Corticosteroids will decrease serum salicylate levels and may reduce salicylate effectiveness. Discontinuation of corticosteroids may elevate salicylate levels.
Verapamil – Beta blocker	Decreased heart rate	1	May be synergistic or additive effects. Verapamil may obstruct oxidative metabolism of specific beta-blockers.	Effects of both drugs may be elevated.

Drug interaction	Effect	Tatro significance rating	Mechanism	Effect
Warfarin – Antiplatelet agents	Increased chance of bleeding			
Antiplatelet agent – Antiplatelet agent	Increased chance of bleeding			

ACE – Angiotensin-converting enzyme; cGMP – cyclic guanosine monophosphate; CNS – central nervous system; DRPs – Digoxin reduction products; GI – Gastro-intestinal; HMG CoA – Hydroxymethylglutaryl-coenzyme A; INR – International normalised ratio; MAO – Monoamine oxidase; MAOI – Monoamine oxidase inhibitors; NAPA – N-acetyl-procainamide; NSAIDs – Nonsteroidal anti-inflammatory drugs; PPIs – proton pump inhibitors; PT – Prothrombin time; SSRIs – selective serotonin-reuptake inhibitors.

Rifampin = Rifampicin (South Africa); Meperidine = Pethidine (South Africa); Phenobarbital = Phenobarbitone (South Africa).

Table 2.9: Description of the Tatro significance rating (Tatro, 2004)

Significance rating	Severity	Documentation
1	Major*	Suspected or more
2	Moderate**	Suspected or more
3	Minor***	Suspected or more
4	Major/moderate	Possible
5	Minor	Possible
	Any	Unlikely

*Major refers to effects that are potentially life-threatening or capable of causing permanent damage. ** Moderate refers to effects that may cause deterioration in a patient's clinical status. ***Minor refers to effects that are usually mild and where additional treatment is usually not required.

2.6 Prevalence of inappropriate prescribing for elderly patients

Of the total US population, 12.6% are aged 65 years or older and account for 33.6% of reported adverse drug reactions (Kaur *et al*., 2009:1015). In the Netherlands, 17% of all patients receiving long term treatment receive five or more medicine items and almost 50% of these individuals are over the age of 70 years (Drenth-van Maanen *et al*., 2009:688). Older adults take three to four times more drugs than the rest of the population. The most prevalent conditions for which medicine items are prescribed include diabetes mellitus, hypertension and cardiovascular conditions (Drenth-van Maanen *et al*., 2009:688).

Table 2.10 gives a summary of all the papers identified for the prevalence of inappropriate prescribing in elderly patients during the Boolean search. Each paper is described according to country or location (alphabetically ordered), setting, method and inception year, criteria or screening tool used, sample size, inappropriate prescribing measured prevalence, noteworthy findings and the author and year.

Table 2.10: Description of papers and samples identified in the Boolean search

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
Australia	Medical, surgical and rehabilitation wards of a public teaching hospital in Adelaide, South Australia	Treatment plans for 100 patients aged 65 years and older were prospectively studied to calculate the prevalence of pre-admission PIM use.	STOPP criteria	100 patients	STOPP criteria - identified 138 PIMs in 60% of the patients.	Main outcome was to measure pre-admission prevalence of PIMs. Most commonly prescribed PIM was opiates given to patients with a history of falls (12.3%), followed by benzodiazepines in fallers (10.1%) and proton pump inhibitors for peptic ulcer disease at optimal doses for extended periods (9.4%).	Wahab *et al*. (2012)
Brazil	Internal medicine department of a teaching hospital	The researcher evaluated each patient on a daily basis and all medicine items before and during hospitalization was documented and investigated. September 2002 to May 2004	Naranjo algorithm was used to determine the chance for adverse reactions.	186 elderly patients	115 patients (61.8%) presented at least one ADR. A total of 199 ADRs were identified at a mean of 1.7 per patient.	The ADRs appeared during hospitalisation in 46.2% of patients but did not cause hospitalisation in 17.2% of patients.	Passarelli *et al*. (2005)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
Canada	400-bed acute care hospital	In-patient charts were examined for potentially inappropriate medicines.	McLeod list	361 consecutive patients: 185 from a clinical teaching unit and 176 from a geriatric assessment unit	42 of the 361 patients (12.5%) had 45 potentially inappropriate prescriptions representing 14 different potential drug-disease interactions.	This study was used to establish the IPET screening tool.	Naugler *et al.* (2000)
Canada	Licenced nursing homes	Database of a drug benefit plan was used to identify individuals to whom drugs were dispensed between April 1997 and March 1999.	Beers criteria	19911 patients	Before nursing home admission – 25.4% of the patients received IPs. During the follow-up period – 20.8% of the patients received IPs. Of the 14854 patients who did not receive an IP before admission to long-term care, 11.7% received an IP during the follow-up period. Of the 5057 patients who were prescribed an IP before nursing home admission, 52.5% did not receive any inappropriate agents during the follow-up period.	72% of the sample was female.	Dhalla *et al.* (2002)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
Canada	Long-term care facility patients in the Quebec city area	A cross-sectional chart review of long-term care patients between April 1995 and December 1996	Rancourt criteria	2633 individuals	54.7% of the population under study had one or more potentially inappropriate prescriptions (PIPs). Most frequent group of PIPs was drug-drug interactions (33.9%), potentially inappropriate duration (23.6%), potentially inappropriate medication (14.7%) and potentially inappropriate dosage (9.6%).	94% of the patients had one or more prescribed medications. 48% of the total population had 5 or more medications. The proportion of patients receiving any type of PIP decreased with age.	Rancourt *et al.* (2004)
China	Nursing home residents	Cross-sectional study. Medical charts and medicine administration data were collected.	PIM use was evaluated by applying the STOPP criteria and drug-drug interactions (DDIs) were identified by applying the pre-set criteria of two compendia, Drug-Reax and Lexi-Interact.	114 patients for the STOPP criteria and 111 patients for the DDIs	STOPP criteria – 46.5% of patients used one or more PIMs on a regular basis. The prevalence of DDI's was 37.8% among the patients who consumed at least two separate medicine items.	Further studies are needed to assess the end result of pharmacist-led interventions for older patients in local old age homes.	Lao *et al.* (2013)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
Czech Republic, Denmark, Finland, Iceland, Italy, Netherlands, Norway and United Kingdom	Patients in home care	Retrospective, cross-sectional study of elderly patients in home care between September 2001 and January 2002.	Beers and McLeod criteria	2 707 patients	19.8% of patients used at least one inappropriate medicine.	Inappropriate medicine use was between 9.8 and 10.9%. Significant differences were recorded between Eastern and Western Europe.	Fialová *et al.* (2005)
England and Wales	Medical inpatients in 19 hospitals in England and Wales	Prescription and personal information were collected from medical inpatients records.	WHO prescribing indicators	1686 patients	Benzodiazepines were prescribed for 22% of the patients, but were appropriate for only about one third.	The prescribing indicators are sensitive to inappropriate prescribing and cover a wide range of therapeutic areas.	Oborne *et al.* (1997)
England	Elderly patients diagnosed with dementia residing in six residential care homes	Retrospective analysis using medication data collected for older people with dementia who participated in the prospective, longitudinal EVIDEM – end of life study.	STOPP criteria	Time point 1 – 119 patients. Time point 2 (approximately 16 weeks later) – 110 patients	At the time point 1, 68 PIMs were identified. 55 residents (46.2%) were prescribed one or more PIMs, 11 (9.2%) were prescribed two or more PIMs and 2 (1.7%) were prescribed 3 PIMs. At time point 2, 57 PIMs were identified.45 residents (40.9%) were prescribed one or more PIMs, 10 (9.1%) were	13 of the 31 STOPP criteria were used. Long-term antipsychotics were the most commonly encountered PIMs, followed by proton-pump inhibitors (PPIs) at the maximal therapeutic dosage for more than 8 weeks, non-steroidal anti-inflammatory drugs (NSAIDS) for more than 3 months and tricyclic antidepressants	Parsons *et al.* (2012)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
					prescribed two or more PIMs, but only 1 patient (0.9%) was prescribed 3 PIMs.	(TCAs) in patients with dementia.	Parsons *et al*. (2012) *continued*
England	Specialist health and ageing unit of an acute hospital trust	Retrospective, non-randomised study in which participants were patients aged 65 years and older admitted to the hospital during June and July 2011. Data were collected by applying the STOPP criteria to electronic admission and discharge medication lists.	STOPP criteria	195 patients	STOPP criteria – admission PIM prevalence was 26.7%, 52 patients with 74 PIMs. Discharge PIM prevalence was 22.6%, 44 patients with 51 PIMs.	A total of 66 (34%) patients were prescribed more than 10 medicine items. Most frequently encountered PIMs on admission were central nervous system and psychotropic drugs, urogenital drugs and cardiovascular agents. Most frequently encountered discharge PIMs were medicine items with a negative effect on patients at risk of falls, CNS and psychotropic drugs, urogenital drugs and cardiovascular agents	Onatade *et al.* (2013)
Finland	Home-dwelling elderly patients	Cross-sectional mail survey from November 1998 to March 1999.	Beers criteria	3 219 patients	12.5% were taking at least 1 inappropriate drug, 1.3% was taking at least 2 inappropriate drugs and 0.2% was taking at least 3 inappropriate drugs.		Pitkala *et al.* (2002)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
Finland	Non-institutionalized people aged 65 years and older	Register-based, cross-sectional, national study, 2007	Beers criteria, 2003	841 509 patients	123 545 (14.7%) received PIMs according to the Beers criteria.	Temazepam (4.4%) was most popular, followed by amitriptyline (2.0%) and diazepam (1.8%).	Leikola *et al.* (2011)
France	Study population was recruited from the electoral rolls of three French towns.	Data was collected by face-to-face interviews using standardised questionnaires. March 1999 to March 2001	Beers criteria adapted for the French population	9294 subjects	About 40% of participants used at least one PIM. 23.4% used cerebral vasodilators, 9.2% long-acting benzodiazepines and 6.4% medicines with anticholinergic properties. Excluding cerebral vasodilators from the list, the frequency of PIMs were 21.7%.	The use of PIMs was significantly more common among female patients, elderly subjects and poorly educated participants. Women and participants with a low socio-economic status were more likely not to receive the best possible pharmacotherapy.	Lechevallier-Michel *et al.* (2005)
France	Acute geriatric unit of a university hospital	Systematic and prospective medicine surveillance study from May 1997 to January 1999	Beers criteria (1997) adjusted to French practice	2018 patients	66% of patients received at least one IP on admission.	460 ADRs were grouped into definite or possible, and involved 385 patients. In 201 patients, ADRs were the reason for admission. ADR prevalence was 20.4% among the 1 331 patients using inappropriate medicine.	Laroche *et al.* (2006).

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
France	All elderly patients (75 years and older) registered on the French National Insurance Healthcare database	Cross-sectional study using participants from the French National Insurance Healthcare System database, March 2007 to February 2008.	French PIM list	35 259 patients	18 864 (53.5%) of patients received at least one PIM.	66.1% (23 296) of patients were women. 45.9% of men and 57.4% of women received at least one PIM and. Of the population, 38.3% received at least one PIM with an adverse benefit-risk profile, 19.5% received at least one PIM with questionable efficacy, and 10.4% received at least one medicine item with both an adverse benefit-risk ratio and questionable efficacy.	Bongue *et al*. (2011)
Germany	Geriatric ward of hospital	Medication of patients was assessed on admission and at discharge.	FORTA assessment system	46 patients	Use of FORTA resulted in a reduced number of prescribed medicine items. Under-treatment decreased from 65 to 39% and over-treatment from 65 to 20%. The number of drug interactions decreased from 79 to 54.	Uncontrolled pilot study which indicates that FORTA criteria can be used in day-to-day clinical care.	Frohnhofen *et al.* (2011)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
India	Tertiary care hospital	Patients aged 60 years and older from medical sections of a tertiary hospital were included. 2012.	Beers criteria and STOPP criteria	540 patients	Beers criteria – prevalence of PIMs was 24.6%. STOPP criteria – prevalence of PIMs were 13.3%.	PIMs as per the Beers criteria accounted for 11 adverse drug reactions (ADRs) and 6 ADRs for the STOPP criteria. Sensitivity and specificity were assessed by using 2x2 contingency tables. Sensitivity and specificity of Beers criteria in detecting PIMs were 0.65 and 0.53 respectively. The researcher can use the Beers criteria to determine PIMs when the diagnosis or condition is unknown and use the STOPP criteria when the diagnosis or condition is known.	Vishwas *et al.* (2012)
Ireland	Urban-based university hospital	Prospective, consecutive observational cohort study carried out over a 4-month period	Beers criteria and IPET	350 subjects	Beers criteria (independent diagnosis - ID) 148 PIMs affecting 121 patients; Beers criteria (considering diagnosis - CD) 69 PIMs affecting 60 patients;	Beers criteria used ID and CD; IPET tool has been validated.	Barry *et al*. (2006)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
					Beers combined – 34%; IPET 112 PIMs affecting 78 patients – 22%		Barry *et al*. (2006) *continued*
Ireland	Teaching hospital	Data on active medical related issues and prescribed drugs were collected from patients admitted from the community with acute illness. Omitted items were investigated to determine if a valid reason for the omission was present.	START criteria	600 patients	A total of 3234 medications were prescribed to 600 patients. Using the START criteria, one or more appropriate drugs were omitted for 347 (57.8%) patients where no contra-indication were present.	There was a noteworthy probability of omission of appropriate drugs in the age group 85 years and older.	Barry *et al.* (2007)
Ireland	University teaching hospital	Studied 715 back-to-back elderly patients admitted with acute illness over a 4-month period in 2007. Admitted through the emergency unit after referral by general practitioner or self-referral	STOPP and Beers	715 consecutive acute admissions	STOPP - 35% (336 PIMs affecting 247 patients); Beers - 25% (226 PIMs affecting 177 patients of whom 43 presented with an associated adverse drug events)	STOPP contributed to 11.5% of all admissions and the Beers criteria to 6%	Gallagher & O'Mahony (2008)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
Ireland	Three general practices in one region	Case records of patients were studied. Current patient diagnosis and medicine items prescribed were evaluated and the Beers criteria and the STOPP/START criteria were applied.	Beers criteria and STOPP/START criteria	1329 patients	A total of 6684 medicine items were prescribed. Beers criteria – identified 286 PIMs in 243 (18.3%) participants. STOPP criteria – identified 346 PIMs in 284 (21.4%) patients. START criteria –330 PPOs were identified in 302 (22.7%) patients.	An important association was identified between the number of medicine items prescribed and the occurrence of inappropriate prescribing (IP). The number of PIMs identified was significantly lower using Beers criteria than STOPP.	Ryan *et al.* (2009)
Ireland	Hospital	Data was collected prospectively on 600 consecutive unselected patients.	STOPP criteria Beers criteria	600 patients	STOPP criteria - 610 PIMs were identified in 337 patients (56.2% of all patients); Beers criteria – 235 PIMs were identified in 173 patients (28.8% of all patients).	A total of 329 adverse drug events (ADEs) were identified in 158 of the 600 patients (26.3%) of which 183 (55.6%) have been judged as clinically significant by an expert panel. From these findings it seems that the STOPP criteria are more effective to identify PIMs that may lead to ADEs than the Beers criteria and are thus more clinically applicable.	Hamilton *et al*. (2011)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
Ireland	Community pharmacy	Three pharmacists applied the STOPP/START criteria to patient treatment lists, with information regarding dose, frequency and duration of treatment. Each pharmacist identified PIMs and PPOs and consensus was reached when two pharmacists identified the same item. 2012.	STOPP/START criteria	250 patients	No percentages indicated	Pharmacists with access to patients' clinical records identified significant fewer PIMs than pharmacists without. Most commonly identified PIMs were benzodiazepines, proton pump inhibitors and duplicate drug classes. PPOs were identified more often when clinical information was considered.	Ryan *et al.* (2013)
Italy	Hospitalized older adults	Prescriptions of patients admitted to the geriatric and internal medicine wards from 1995 to 1997 were reviewed.	Beers criteria (1997)	5 734 patients	837 (14.6%) of the patients received one or more medications classified as inappropriate.		Onder *et al.* (2003)
Italy	Long-term nursing home residents	All participants underwent a standardised all-inclusive assessment. All data on medical prescriptions were documented.	Italian version of the InterResident Assessment Instrument Minimum Data Set for nursing home care	1716 patients	48% had at least one potentially inappropriate drug prescription (PIDP) and almost 18% had two or more PIDPs.	Compared to the residents without PIDPs, those with two or more PIDPs at baseline had an increased chance for hospitalisation.	Ruggiero *et al.* (2010)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
Netherlands	General practice research database	Population-based cohort study 1997-2001	Beers criteria	120218 patients over a 6 year period	Beer criteria 1997 - 9.3%; Beer criteria 2002 - 14.3%	20% of ambulatory elderly patients received a minimum of one inappropriate drug prescription per year. Applied the complete Beers criteria and assesses the effect of the updated criteria compared with the previously used 1997 criteria.	Van der Hooft *et al*. (2005)
Norway	General practice	Retrospective study of prescription database for a 12-month period	NORGEP	85 836 patients	15 790 (18.4%) of the participants received one or more potentially harmful prescriptions. Of these, 74.5% received 1, 19.6% received 2, 4.6% received 3 and 1.2% received 4 or more inappropriate prescriptions during the one-year period.	The female gender represented 66% of the total number of participants.	Brekke *et al.* (2008)
Portugal	Hospital based	Cross-sectional study. Medication analysis was done in elderly patients at their admission in a medicine ward. Descriptive analysis was done. 2013	Beers criteria and STOPP/START criteria	100 patients	A total of 770 items were prescribed for the participants. Beers criteria - 87 (11.3%) were PIMs taken by 58 patients.	Only disease independent part of the Beers criteria was used for prescription analysis. Benzodiazepines were the most frequently prescribed PIMs	Moraes *et al*. (2013)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
					34% of patients were taking at least one PIM and 24% of patients were taking more than one PIM. STOPP criteria – 79 (10.26%) were PIMs. PIMs were taken by 74 patients.	according to the Beers and STOPP.	Moraes *et al.* (2013) *continued*
South Africa	Provincial government chronic prescription pharmacy which dispenses medicine to primary health care facilities and old age homes	Cross-sectional survey of prescription records during June 2002.	Beers criteria (modified)	6410 prescriptions	1926 (30%) of the prescriptions included at least one IP.	Of the total number of prescriptions, 1623 (25.3%) were for men and 3716 (58.0%) were for women. In 1071 (16.7%) the gender of the patient was unknown.	Chetty & Gray (2004)
Spain	Geriatric department of hospital	Prospective study of patients hospitalised during September to October 2012. Diagnosis and pre-admission medication were recorded.	STOPP criteria and Beers criteria	112 patients	STOPP criteria – identified 114 PIMs affecting 63 patients (56.25%). Beers criteria – identified 82 PIMs affecting 47 patients (41.96%).	According to STOPP the most commonly prescribed PIM was benzodiazepines in fallers and proton pump inhibitors. According to the Beers criteria the most commonly prescribed PIM was short to intermediate acting benzodiazepines.	Azana Fernandez & Davila Barboza (2013)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
Switzerland, Spain, Belgium, Italy, Czech Republic and Ireland	Six university teaching hospitals	Prospective data were collected from 900 consecutive elderly patients admitted to six university teaching hospitals. 2011	STOPP criteria	900 patients- 150 patients per centre	STOPP criteria – 51.3%		Gallagher *et al.* (2011)
Taiwan	Ambulatory care visits by patients aged 65 years and older	Patients 65 years and older were identified on the National Health Insurance claims database, 2001-2004	Beers criteria, 2003	176 661 994 patients	19.1% of patients received prescriptions for PIMs	There was a decline in the frequency of PIMs over the study period, but 62.5% of patients were exposed to PIMs in 2004.	Lai *et al*. (2009)
Taiwan	General hospital	All patients discharged from the hospital from January to December 2009 were randomly sampled for study. Each medical record was then carefully reviewed by trained medical practitioner.	STOPP and START criteria	520 patients	STOPP criteria – 36.2% of the study participants had a minimum of at least one PIM. 218 patients (41.9%) had a minimum of one potentially prescribing omission (PPO).	Most common PIMs were: benzodiazepines, neuroleptics, first generation antihistamines, and calcium channel blockers with chronic constipation.	Liu *et al*. (2012)
United Kingdom	Computerized patient records of 201 UK general practices	Analysis of routine, anonymised, computerized patient records. 1996-2005	Modified Beers criteria	In 2005, 218 567 patients were registered.	1996 – 32.2% 2005 – 28.3%	57% of patients registered in 2005 were female and 13% were 85 years of age or older.	Carey *et al.* (2008)
United Kingdom	Clinical Practice Research Data link (CPRD) was	Retrospective, cross-sectional study, 2007	STOPP criteria	1 019 491 patients	Overall prevalence of PIMs was 29%.	PIMs were slightly more prevalent in female patients than in male patients but the difference was not	Bradley *et al.* (2014)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
	used to identify all patients older than 70 years of age.					significant. Of the patients aged 70-74, 37.4% were prescribed PIMs compared to 16% of patients older than 85 years. Almost 15% of the population were prescribed at least 1 PIM, 7.6% were prescribed 2 PIMs and 6.8% were prescribed 3 or more PIMs	Bradley *et al*. (2014) *continued*
United States of America	Nursing home residents	Prospective, cohort study where the appropriateness of medication prescriptions was assessed using the criteria.1992.	Beers criteria	1106 patients	40% of the residents received at least one IP, and 10% received 2 or more IPs.7% of all prescriptions was inappropriate. Patients experienced a total of 131 adverse drug effects. Only 9.2% of the adverse drug effects were attributed to the drugs listed in the Beers criteria.	Physicians prescribed a greater number of inappropriate medications to female residents.	Beers *et al.* (1992)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
United States of America	Resident outpatient clinic	Medication items of patients using 3 or more items were compared pre- and post-algorithm using the paired t-test.	Geriatric medication algorithm	41 patients	Pre-algorithm the mean number of medicine items was 5.8 per patient.15 drugs were discontinued, 7 were substituted for a less harmful one and 5 were added. Post-algorithm the mean number of medicine items was 5.6 per patient.	Pilot study that demonstrates that the algorithm assists physicians to decrease inappropriate prescribing.	Newton *et al.* (1994)
United States of America	Homebound, older people	Cross-sectional study of the pharmacy profiles of patients	Beers criteria	21 93 patients	Of the total 11 689, 1 152 (9.9%) prescriptions were inappropriate.871 (39.7%) had at least one IP and 230 (10.4%) had two or more.		Golden *et al.* (1999)
United States of America	Veterans Affairs Medical Centres	Cross-sectional secondary analysis	MAI	397 patients	Of the 27 960 ratings (10 criteria items, 2 796 drugs), 2 207 (7.9%) were rated as inappropriate.	78% of the drugs and almost 92% of the patients had one or more MAI problems.	Hanlon *et al.* (2004)
United States of America	Hospital	The study used data as part of the Geriatric Evaluation and Management (GEM) Drug Study. Cross-sectional study consisting of a random subsample	MAI	384 patients	Overall, almost 44% of the participants had a minimum of one unnecessary medicine item at discharge.	The largest part of the veterans included in the study were men aged 65-74. These men had comorbidities and almost 40% of them took 9 or more medicine items.	Hajjar *et al.* (2005)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
						No clear indication for treatment (32.8%) was the most prevalent reason for unnecessary medicine use, followed by lack of efficacy (18.5%) and therapeutic duplication (7.6%).	Hajjar *et al.* (2005) *continued*
United States of America	Hospital patients	Retrospective database review for at least one quarter of 2004.	Beers criteria	226 690 patients	68 550 (30.2%) of elderly patients received one inappropriate item while 43 906 (19.4%) received two or more inappropriate items.	50.4% of the senior patients in the study received no inappropriate medications.	Bonk *et al.* (2006)
United States of America	Hospital	Retrospective review of patients. March 2000 to August 2001.	Beers criteria	389 patients	107 (27.5%) of the patients were prescribed a total of 116 items listed in the Beers criteria.124 (31.9%) of the	68.9% of the participants in the study were women.	Page & Ruscin (2006)
United States of America	Community-dwelling elderly patients	Retrospective cohort study using administrative database, January 2000 to June 2000.	Beers criteria	16 877 patients	6 875 (40.7%) of the patients filled at least one PIM prescription and 2 326 (13.8%) filled more than one.	61% of the sample was females. Drug-related problems among those with at least one PIM were 14.3% compared to those with no PIMs at 4.7%.	Fick *et al*. (2008)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
United States of America	384 hospitals	Retrospective cohort study. September 2002 to June 2005	Modified Beers criteria	493971 patients	49% of patients received a minimum of one PIM while 6% received 3 or more PIMs.	For the high-severity PIMs, the internists and hospitalists had similar prescribing rates at 33%, cardiologists had a higher rate of 48% and geriatricians had the lowest rate of 24%. At 7 hospitals PIMs were never prescribed.	Rothberg *et al.* (2008)
United States of America	Medicine claims data	Examination of medicine claims data from 2003-2005	Beers criteria and NCQA list	7 459 patients	53.3% of patients had prescription for items listed in the Beers criteria and 38.8% were prescribed an item listed in the NCQA list.	Patients taking one or more potentially inappropriate medicine were 1.8-1.9 times more likely to be admitted to hospital.	Albert *et al.* (2010)
United States of America	Residents of nursing homes	Retrospective analysis of claims files. 2003	2003 Beers criteria	7 594 patients	The prevalence of PIM use over a one-year period was 42.1%.	The largest part of the participants was women (76.5%), white (89.7%) and widowed (58.8%).	Dedhiya *et al.* (2010)
United States of America	Medicare beneficiaries aged 65 years and older hospitalized for acute myocardial infarction	Observational study, 2007-2008	The High Risk Medications in Elderly Adults quality indicator were used to identify PIMs	124 051 patients	9 607 (7.7%) of the outpatients were already using PIMs on admission, and the discharge rate increased to 8.6%.	PIM use was higher from the long-term perspective, with 6-month period prevalence rates of 22.6% before admission and 24.6% after discharge.	Lund *et al.* (2015)

Country/ Location	Setting	Method/ Inception year	Criteria/ Screening tool	Sample size (n)	IP* Measured Prevalence (%)	Other noteworthy findings	Author and year
						A noteworthy increase in PIM use was seen in a real-life setting but further research is required to develop an approach to minimize PIM use in the inpatient setting that is cost-effective and suitable for widespread implementation.	Lund *et al.* (2015) *continued*

ADEs – adverse drug events; ADR – adverse drug reaction; CD – considering diagnosis; CNS – central nervous system; CPRD – Clinical Practice Research Data link; DDIs – drug-drug interactions; EIVDEM – Evidence-based Interventions in Dementia; FORTA – Fit for the Aged; GEM – Geriatric Evaluation and Management; ID – independent diagnosis; IPET – Improving Prescribing in the Elderly Tool; IPs – Inappropriate prescriptions; MAI – Medication Appropriateness Index; NCQA – National Committee for Quality Assurance; NORGEP – Norwegian General Practice; NSAIDs – nonsteroidal anti-inflammatory drugs; PIDP – potentially inappropriate drug prescription; PIM –potentially inappropriate medicine; PIPs – potentially inappropriate prescriptions; PPOs – potentially prescribing omissions; START – Screening Tool to Alert doctors to Right Treatment; STOPP – Screening Tool of Older Persons' Prescriptions; TCAs – tricyclic antidepressants; WHO – World Health Organization

Table 2.10 indicates that the Beers criteria were the most popular criteria, used in 25 of the 44 studies identified. In studies outside the USA, the Beers criteria were amended to suite the specific drugs available in that country. The prevalence of inappropriate prescribing when using the Beers criteria varied from 9.3% to 66%. The number of patients in the studies listed in Table 2.10 ranged from 100 to 493 971. Several studies using the Beers criteria indicated that the prevalence of potentially inappropriate prescribing varied from 12% to 40% globally in a diversity of settings including medical centres, retirement facilities and the community (Maio *et al.*, 2010:220).

The STOPP/START criteria were also frequently used, with most of these studies using only the STOPP criteria. Other criteria used were the FORTA criteria, WHO prescribing indicators, geriatric medication algorithm, McLeod criteria, Rancourt criteria, InterResident Assessment Instrument Minimum Data Set for nursing home care, non-specific criteria, Medicine Appropriateness Index, NORGEP criteria, and the French potentially inappropriate medication list.

2.7 Chapter summary

This chapter provided an overview of inappropriate prescribing in elderly patients. Topics addressed were factors influencing prescribing for the elderly; pharmacokinetic and pharmacodynamic changes in the elderly; appropriate prescribing for elderly patients; prevalence of inappropriate prescribing for elderly patients; determining of the appropriateness of prescriptions; and significance of inappropriate prescribing. The chapter concluded with the comparison of the different tools and criteria available and the tools and criteria to be applied in this study. Hereby the specific objectives of the literature review have been answered.

Chapter 3 will focus on the results of the study.

CHAPTER 3: RESULTS AND DISCUSSION

3.1 Introduction

The results and the discussion of the empirical investigation are presented in article format in this chapter. Two manuscripts address the main objectives of the empirical investigation.

Manuscript one addresses the objective of determining the appropriateness of prescribing in patients 65 years and older on the database by application of the Beers criteria stratified by age, gender, and prescriber. The manuscript was submitted to the South African medical journal (see Annexure D). It conformed to the guidelines for authors (see Annexure B) per requirements of the specific journal.

Manuscript two addresses the objective of determining the prevalence of potentially serious drug-drug interactions in patients 65 years and older on the database by application of the Mimica Matanović and Vlahović-Palčevski-comprehensive drug-drug interaction list, stratified by age and gender. The manuscript was submitted to the International journal of pharmacy practice (see Annexure D). The manuscript conformed to the guidelines for authors (see Annexure C) per requirements of the specific journal.

3.2 Manuscript one

Inappropriate medicine prescribing in the South African elderly: a cross-sectional analysis of medicine claims data

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Compliance with Ethical Standards

No sources of funding were used to assist with the preparation of this manuscript. The study was conducted with the approval of the Health Research Ethics Committee (HREC) of the North-West University (Potchefstroom campus) (NWU-00179-14-S1) and the board of directors of the PBM. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Abstract

Background: Prescribing for elderly patients is a well-known problem and inappropriate items are prescribed frequently. Several tools and criteria are available to promote the rational prescribing in the elderly.

Objectives: To determine the prevalence of potentially inappropriate prescriptions (PIP) in elderly South African patients.

Method: A retrospective drug utilisation review was conducted using medicine claims data of a one-year period. Patients 65 years and older with at least one paid claim for any medicine item during this period were included. Prevalence of PIP was identified by applying the 2012-Beers criteria list.

Results: A total of 103 420 patients, mean age 74.0 ± 6.7 years, 57.1 % female, were included in the analysis. The number of PIPs identified was 562 852 in 71 206 patients (68.9 %). The most common medicines inappropriately prescribed were: oestrogen (12.4 %), meloxicam (7.3 %), amitriptyline and combinations thereof (6.5 %), diclofenac (6.4 %), ibuprofen (6.1 %), alprazolam (5.3 %), meprobamate and combinations thereof (5.0 %), insulin (3.3 %), amiodarone (3.1 %) and doxazosin (2.6 %). PIP was statistically significantly more in women than in men (1.9:1; $P<0.0001$), although this difference was not of practical significance (Cramér's $V = 0.0559$).

Conclusion: Medicine use among elderly patients must be appropriate and evaluated regularly. The occurrence of PIPs according to explicit criteria was found to be common in elderly patients registered on the database. Monitoring of PIPs may increase the quality of prescribing; however, explicit criteria cannot substitute clinical judgement based on the individual patient.

Keywords:

Potentially inappropriate prescribing; older/elderly people; Beers criteria list; pharmaceutical claims data

1 Background

Altered pharmacokinetics and pharmacodynamics in elderly patients may contribute to drugs being classified as inappropriate for use in older adults. [1] With the number of elderly and very old people increasing rapidly, [2] inappropriate medicine prescribing in the elderly population is becoming a well-recognised problem. [3] Developing countries such as South Africa are not exempt from the effects of an aging population. For instance, the pensioner ratio in South Africa increased from 5.9% in 2001 to 7.3 % in 2014 [4] with approximately half of elderly patients in the private health sector of South Africa suffering from more than one chronic disease, with some being diagnosed with up to eleven conditions. [5] There is an increase in the complexity of medication regimens used to treat elderly patients and they usually have multiple prescribers. Careful planning and knowledge on the aging process and the drugs prescribed is essential in prescribing for elderly patients as they are at higher risk for developing drug-related problems. [6]

Several tools and criteria to improve rational medicine use in elderly patients are available and can be grouped into implicit and explicit tools, and tools based on a combination of these two. The Beers criteria list is one of the most frequently applied and adopted explicit screening tools to assess PIP and has been adopted by numerous medical aid groups and administrators to pinpoint older patients with an increased probability of experiencing negative outcomes related to PIP, and it has shown to be a useful tool for assessing PIP in large populations. [1]

A review of US-based studies [7] indicated that almost 40 % of people living in aged-care facilities received inappropriate prescriptions and almost half as much was seen in community-dwelling people 65 years and older. A similar Australian-based study found that almost 20 % of patients aged 70 years or older had at least one inappropriate prescription in a 6-months' period. [7] Similar to these, an earlier study conducted in South Africa to identify potentially inappropriate medicine items prescribed to elderly patients showed that 30 % (N = 6,410) of prescriptions included at least one potentially inappropriate item. [8] A common finding is that elderly female patients are more likely to be prescribed potentially inappropriate medication. [8] Some of the most common potentially inappropriate medicine items prescribed are those acting on the cardiovascular system, psychotropic agents, and neuroleptic agents, especially those for neuropathic pain. Specific medicine items include amitriptyline, benzodiazepines, doxazosin, proton-pump inhibitors, non-steroidal anti-inflammatory agents (NSAIDs), digoxin, antihistamines and oestrogen.

Our study focused only on the private health sector of SA, which comprises approximately 16% of the country's total health sector. In December 2014, the total number of medical aid beneficiaries was 8.81 million, which consisted of more female (52.5%) than male (47.5%) beneficiaries. [4] Although the private sector serves almost a quarter of the SA population, data on the utilisation of medicine items in the private sector are difficult to access as most of the medical aid administrators regard such data as proprietary. The general objective of the study was to investigate medicine prescribing patterns for older patients in the private health sector of SA utilising the 2012-Beers criteria list [10] for potentially inappropriate prescriptions.

2 Method

2.1 Design and Data source

A cross-sectional analysis was conducted using a database obtained from a well-known South African pharmaceutical benefit management company (PBM). At the time, the PBM used had approximately 22 years of service excellence and more than 1.6 million South Africans were benefiting from their services. The company provided services to 35 medical aid schemes and five capitation provider clients administered by 15 different healthcare administrators. At the time of writing, the PBM was linked up to all South Africa's pharmacies and 98 % of all dispensing doctors.

The database for the period 1 January - 31 December 2013 contained pharmaceutical claims information for a total of 8 776 279 patients. A total of 103 420 patients on the database were aged ≥65 years (44 343 men, 59 077 women), representing 2.5% of all people aged ≥60 years with medical aid coverage across SA during 2013. [11] We queried data fields for patient demographic information (sex and date of birth), and pertinent prescription information (drug trade name, strength, how many days' supply, quantity and treatment date). Date of birth and treatment date were used to calculate the age of patients on the day of treatment.

2.2 Assessment of potentially inappropriate prescribing

The 2012-Beers criteria list [10] was used to identify PIPs of medicine items among older patients by counting the number of drugs on the Beers criteria list per prescription. Some drugs listed in the 2012-Beers criteria are marketed under different names in SA. For example, mepiridine is known as pethidine, scopolamine as hyoscine and phenobarbital as phenobarbitone. Any item listed in the 2012-Beers criteria that was not available in SA at the time of the study was excluded.

2.3 Data analysis

Statistical analysis

Variables were characterised using 95% confidence intervals (CIs), descriptive statistics such as proportions/ratios for categorical variables, and means and standard deviations (SDs) for continuous variables. An independent two-sample *t*-test (assuming unequal variances) was used to assess the statistical significance of the age difference between men and women. The χ^2test was performed to determine the association between the prevalence of the Beers criteria list items and gender or age group. Because statistical significance tests yielded small *p*-values (indicating significance), in most tests we focused our interpretation on effect sizes, which are independent of units and sample size. Cohen's *d*-value was used to evaluate mean differences between groups (with significance defined as a level of at least 0.8), and Cramér's *V* statistic (defined as a level of at least 0.5) was used for associations between categorical variables. Statistical analyses were performed using SAS software, version 9.3 (SAS, USA).

3 Results

3.1 Study population characteristics

A total of 103 420 patients aged ≥65 years (male/female ratio1:1.3) were included in the study. Their characteristics are shown in Table 1. There was no difference in the mean age of female and male patients ($p<0.001$; Cohen's $d=0.10$).

A total of 1 544 268 prescriptions were claimed for older patients, at an average of 14.9 (SD 9.5) per patient (95% CI 14.87-14.99). Women received more prescriptions than

men (58.6%v. 41%), but there was no difference between the sexes in terms of the average number of prescriptions claimed per patient (p<0.001; Cohen's d=0.09). A total number of 4 231 014 drugs were prescribed, of which 2 494 560 (59.0%) were prescribed to women. A mean of 2.7 drugs (SD 2.1) (95% CI 2.73-2.74) were claimed per prescription (median 2 drugs), with no difference in the average number of drugs per prescription between the sexes (p<0.001; Cohen's d=0.02).

3.2 Potentially inappropriate prescribing as determined by the 2012-Beers criteria

A total of 102 of the 143 2012-Beers criteria items (71.3%) were available in SA at the time of the study and therefore utilised to identify PIPs. Application of these criteria to the claims data identified 562 852 potentially inappropriate medicine items (13.0%) prescribed to a total of 71 206 patients (68.9%). The majority of these patients (37.2%) received one potentially inappropriate item, 26.1% received two and 16.2% received three. A further 10.7% (n=7 646) received five or more potentially inappropriate items.

As shown in Table 2, significantly more women (72.3%) received potentially inappropriate drugs than men (64.3%) (p<0.001). However, this difference in prevalence was not practically significant (Cramér's V=0.06). There was also no difference between the sexes in terms of the average number of potentially inappropriate items prescribed per patient (p<0.001; Cohen's d=0.16). PIPs decreased overall with an increase in age. However, the differences between the age groups in terms of the prevalence of prescribing of inappropriate medicine items were also not practically significant (p<0.001; Cramér's V=0.04).

The most frequently potentially inappropriately prescribed item was oestrogen (oral and patch formulations) (Table 3), prescribed in 69 894 of the patients (12.4%), followed by meloxicam (n=41 030, 7.3%), amitriptyline and combinations thereof (n=36 509, 6.5%), diclofenac (n=36 062, 6.4%), ibuprofen (n=34 162, 6.1%), alprazolam (n=29 896, 5.3%), meprobamate and combinations thereof (n=27 894, 5.0%), sliding-scale insulin (n=18 715, 3.3%), amiodarone (n=17 433, 3.1%) and doxazosin (n=14 816, 2.6%). The χ^2analysis showed that for oestrogen (oral and patch formulations), women received significantly more prescriptions than men (p<0.001); this association was moderate (Cramér's V=0.27). It also indicated that for both sliding-scale insulin (p<0.001; Cramér's V=0.11) and doxazosin (p<0.001; Cramér's V=0.13) men received significantly more prescriptions than women. The association for both of these items were small. For the other items forming part of the top 10 most frequently prescribed items (i.e. meloxicam, amitriptyline, diclofenac, ibuprofen, alprazolam, meprobamate and amiodarone), there was no significant difference between the sexes (Table 3).

General practitioners prescribed the largest number of inappropriate medicine items to the older population (70.7%), followed by the specialist group (15.7%), pharmacists (9.0%) and 'other', which included psychiatrists, radiologists, oncologists and surgical medical professionals (4.7%). Table 4 sets out the 10 most frequently inappropriately prescribed items according to each of these groups. The number of potentially inappropriately prescribed items per prescriber group differed significantly (p<0.001). This association, however, was weak (Cramér's V=0.09). Of the 102 items listed in the 2012-Beers criteria that were available in SA at the time of the study, a total of 84 were prescribed and identified in the study. Of these 84 items, 71 were prescribed most frequently by general practitioners, followed by pharmacists with 7 items, specialists with 3 items and psychiatric professionals with 3 items (under prescriber group 'other').

4 Discussion

Older patients often have multiple diseases requiring multiple drugs.[3] Polypharmacy increases the potential for the prescribing of potentially inappropriate medications.[3] The prevalence of PIPs in this particular study (13.0%) was found to be lower than that in international studies (ranging from 20% to 40%) [7,8] and that found by Chetty and Gray [9] in SA public sector primary healthcare facilities and old-age homes in 2004. However, similar to our study, the screening tool used by Chetty and Gray was adjusted based on the availability of data collected and the list of drugs obtainable in SA. In our study, only 102 of the 143 2012-Beers criteria items were available in SA at the time of the study. These results underscore the importance of adapting the Beers criteria list or developing a country-specific list to fit the needs of a prescribing measure in older adults in the SA health sector.

The rate of inappropriate prescribing is generally higher in women than in men, [9] in accordance with a higher prescription claim rate per female patient. Similarly, in our study women tended to receive more inappropriate medicine items than men; however, we found no difference between the sexes in terms of the average number of prescriptions per patient or the average number of items prescribed per patient, which could have influenced this association. Further studies are therefore needed in the SA private health sector to clarify the dynamics of sex differences in interactions between healthcare providers and patients resulting in women being prescribed more medication.

Studies assessing inappropriate prescribing report that the most common potentially inappropriate medicine items include amitriptyline, benzodiazepines, doxazosin, proton-pump inhibitors, NSAIDs, digoxin, antihistamines and oestrogen. In agreement with these studies, the most frequent potentially inappropriate medicine items prescribed for our population included oestrogen (oral and patch formulations), followed by non-steroidal anti-inflammatory drugs, meprobamate and/or combinations thereof, amitriptyline and/or combinations, alprazolam, sliding-scale insulin, amiodarone and doxazosin. The prescribing of oestrogen (oral and patch formulations) among patients in our population was significantly higher in women than in men, whereas for both sliding-scale insulin and doxazosin, men received significantly more prescriptions than women. Oestrogen is essentially used as hormone replacement therapy (HRT) in women with oestrogen deficiency and to ameliorate hot flushes and atrophic changes in the urogenital tract. It is also indicated for preventing bone loss and the development of osteoporosis, and may reduce the risk of coronary artery disease, memory loss and Alzheimer's disease. [12] In men, oestrogen is used for the treatment of low oestradiol (E2) levels from congenital aromatase deficiency. E2 can furthermore be used to relieve hot flushes in men treated with luteinising hormone-releasing hormone. [12,13] According to the position statement by the South African Menopause Society,[14] HRT can be prescribed for long-term use, and need not be routinely stopped within 5 years or by age 65 years, provided the patient has no untoward complications and continues to be monitored appropriately. However, since the prescription data analysed in this study contained no clinical indicators, it was not possible to determine whether medicines were prescribed without appropriate indications or whether existing clinical conditions may have provided reasons for, or against, the choices exercised.

The longevity of older adults is furthermore associated with musculoskeletal disorders that include osteoarthritis, rheumatoid arthritis (RA) and osteoporosis. According to Usenbo *et al*., [15] the prevalence of RA in SA for adults aged ≥65 years is relatively low at 2.5% in urban settings and 0.07% in rural settings; however, that for osteoarthritis is 55.1% in urban settings and ranges from 29.5% to 82.4% in rural settings. NSAIDs are effective in

controlling pain and stiffness and are often prescribed on a long-term basis for patients with RA. Meloxicam, a cyclo-oxygenase (COX) inhibitor with antipyretic, anti-inflammatory and analgesic activity, has been approved by the US Food and Drug Administration for use in osteoarthritis. Diclofenac is a COX-2 selective inhibitor that is effective for pain relief and the prevention and alleviation of fever, and to reduce inflammation. It is also useful to treat RA, osteoarthritis and ankylosing spondylitis. Ibuprofen is useful in the treatment of RA and osteoarthritis, and may also be used to alleviate moderate pain. It is therefore not surprising that a significant proportion (19.8%) of patients in our study population received NSAIDs, in particular meloxicam, diclofenac and ibuprofen.

Approximately 1 in 15 patients (male/female ratio 1:3) in our study population received amitriptyline or combinations thereof. A further 5% of patients received alprazolam. According to the South African Stress and Health (SASH) study [16] the lifetime disorders most frequently encountered by South Africans are anxiety disorder (15.8%), drug use disorders (13.3%) and mood disturbances (9.8%). Antidepressant medication such as amitriptyline is mainly used for the treatment of depression; however, its off-label use includes indications such as insomnia, panic disorders, alcohol dependence, pain management, and agitation in patients with dementia.[17] Benzodiazepines are essentially used to treat acute anxiety conditions and as hypnotics, [12] and are frequently prescribed for older persons, in particular females.

A substantial number of meprobamate-containing items were prescribed for older patients in our study population. Analgesics, in general, are one of the most frequently prescribed drug groups, particularly to women. Earlier studies conducted in SA indicated that the second and third most frequently prescribed analgesics were combinations of drugs of which meprobamate formed part of the combination.[18] Women in these studies received analgesics containing meprobamate nearly five times more often than men, whereas in our study, women were about three times more likely to receive analgesics containing meprobamate.

Men received significantly more prescriptions than women for both sliding-scale insulin and doxazosin. Insulin is indicated for the treatment of type 1 diabetes mellitus and as supplement in type 2 diabetes. According to the South African National Health and Nutrition Examination Survey (SANHANES-1), ~19% of older patients (≥65 years) in the country had a diagnosis of diabetes in 2012.[19] At a national level, mean glycosylated haemoglobin ((HbA_{1c}) levels increased significantly with age, reaching their highest value in the group 55 - 64 years of age. Among men in particular, the increase in mean HbA_{1c}values was associated with a significantly higher age-related prevalence of impaired glucose homeostasis (HbA_{1c}>6.1% and <6.5%) and diabetes (HbA_{1c}>6.5%), with the highest prevalence in the groups aged ≥65 years and 55 - 64 years (19.7% and 20.9%, respectively).

Benign prostatic hypertrophy (BPH) can be classified as a common urological condition that increases with age. BPH affects 40% of men in their 50s, with an increase in prevalence to 80% of men in their 70s. Medical therapy generally includes alpha-blockers such as doxazosin.[12] It is therefore conceivable that the men in our study population received more prescriptions for doxazosin than their female counterparts.

Similar to the trend that has been observed in other studies, the potentially inappropriate items in our study were prescribed most frequently by general practitioners. It is not clear why we observed this trend; however, as noted by Chetty and Gray, [9] the Beers criteria are limited in both sensitivity and specificity, as these criteria do not take into account the individualisation of medicine regimens by prescribers to suit individual patients' needs.

Other factors to consider when interpreting our findings include the use of only one PBM's data, so only members of the medical aid schemes administered by the selected PBM were represented in the study. The database furthermore only included claims for medicine items and not for other medical devices and interventions. Patients may also have gone in and out of eligibility, which could have led to subjects and data being missed with subsequent under-reporting of PIPs.

5 Conclusion

Our study showed that PIPs according to explicit criteria were common in older patients registered on the database. In this study, women were more likely to be exposed to PIPs than their male counterparts. Although it is important to remember that the use of explicit criteria cannot substitute for clinical judgement based on the individual patient, there is a need for a prescribing measure for older adults in the SA health sector that can be used to encourage value-driven healthcare.

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Table 1. Patient characteristics

Demographics	Total study population	Female	Male
Patients, *N* (%)	103420	59077 (57.1)	44343 (42.9)
Age (yr), mean (SD) (95% CI)	74.0 (6.7) (73.9-74.0)	74.3 (6.9) (74.2-74.3)	73.6 (6.5) (73.5-73.6)
Age group (yr), *n* (%)			
65 ≥ age ≤ 68	23 027 (22.3)	12 615 (12.2)	10 412 (10.1)
68 < age ≤ 72	25 066 (24.2)	13 981 (13.5)	11 085 (10.7)
72 < age ≤ 78	28 604 (27.7)	16 277 (15.7)	12 327 (11.9)
age > 78	26 723 (25.8)	16 204 (15.7)	10 519 (10.2)
Prescriptions, *n* (%)	1544268	905582 (58.6)	638686 (41.4)
Prescriptions per patient, mean (SD) (95% CI)	14.9(9.5) (14.87-14.99)	15.3 (9.6) (15.25-15.41)	14.4 (9.4) (14.32-14.49)
Drugs prescribed, *N* (%)	4231014	2494560 (59.0)	1736454 (41.0)
Drugs per prescription, mean (SD) (95% CI)	2.74 (2.07) (2.73-2.74)	2.76 (2.08) (2.75-2.76)	2.72 (2.05) (2.71-2.72)

Table 2. Prevalence of potentially inappropriate drugs prescribed for the study population

	Total study population	Female	Male	*P*-value	Effect size
Total number of potentially inappropriate drugs, *n* (%)	562852	371958 (66.1)	190894 (33.9)	<0.001	0.06*
Average number of potentially inappropriate drugs per patient, mean (SD) (95% CI):					
Gender	2.41 (1.62) (2.40 - 2.43)	2.52 (1.69) (2.51 - 2.54)	2.25 (1.52) (2.23 - 2.27)	<0.001	0.16†
Age group (yr.)				<0.001	
65 ≥ age ≤ 68 (*n*=16124)	2.52 (1.74) (2.50 - 2.55)	2.64 (1.80) (2.61 - 2.68)	2.36 (1.63) (2.32 - 2.40)		0.16†
68 < age ≤ 72 (*n*=17290)	2.45 (1.65) (2.42 - 2.47)	2.57 (1.72) (2.54 - 2.61)	2.26 (1.52) (2.23 - 2.30)		0.18†
72 < age ≤ 78 (*n*=19526)	2.41 (1.61) (2.38 - 2.43)	2.53 (1.68) (2.50 - 2.57)	2.21 (1.47) (2.18 - 2.25)		0.19†
age > 78 (*n*=18266)	2.29 (1.51) (2.26 - 2.31)	2.36 (1.55) (2.34 - 2.39)	2.15 (1.43) (2.12 - 2.19)		0.14†

*Cramér's *V* statistic.

†Cohen's *d*-value

Table 3. Prevalence of potentially inappropriate drug items identified in the study

Potentially inappropriate drug item	Total study population (*N*)	Female *n* (%)	Male *n* (%)	*p*-value	Effect size*
Alprazolam	29896	21523 (72.0)	8373 (28.0)	< 0.001	0.03
Amiodarone	17433	7579 (43.5)	9854 (56.5)	< 0.001	0.09
Amitriptyline and combinations thereof	36509	27039 (74.1)	9470 (25.9)	<0.001	0.04
Aripiprazole	208	132 (63.5)	76 (36.5)	0.424	0.00
Aspirin and combinations thereof	5447	2818 (51.7)	2629 (48.3)	<0.001	0.03
Belladonna	2	2 (100.0)	-	0.311	0.55†
Brompheniramine	21	11 (52.4)	10 (47.6)	0.185	0.00
Chlordiazepoxide and combinations thereof	3926	2957 (75.3)	969 (24.7)	<0.001	0.02
Chlorpheniramine	12668	7369 (58.2)	5299 (41.8)	<0.001	0.03
Chlorpromazine	365	166 (45.5)	199 (54.5)	<0.001	0.01
Clemastine	1	-	1 (100.0)	0.163	0.34†
Clomipramine	496	367 (74.0)	129 (26.0)	<0.001	0.01
Clonazepam	5372	3663 (68.2)	1709 (31.8)	0.001	0.00
Clonidine	70	70 (100.0)	-	<0.001	0.01
Clozapine	297	203 (68.4)	94 (31.6)	0.409	0.00
Cyproheptadine	289	168 (58.1)	121 (41.9)	0.004	0.00
Dexchlorpheniramine	5605	3444 (61.5)	2161 (38.5)	<0.001	0.01
Diazepam	4395	2778 (63.2)	1617 (36.8)	<0.001	0.01
Diclofenac	36062	19546 (54.2)	16516 (45.8)	<0.001	0.07
Dicyclomine and combinations thereof	880	536 (60.9)	344 (39.1)	0.001	0.00
Diphenhydramine and combinations thereof	11171	6177 (55.3)	4994 (44.7)	<0.001	0.03
Digoxin	11761	5567 (47.3)	6194 (52.7)	<0.001	0.06
Dipyridamole and combinations thereof	1866	891 (47.8)	975 (52.2)	<0.001	0.02
Disopyramide	179	112 (62.6)	67 (37.4)	0.321	0.00
Doxazosin	14816	4235 (28.6)	10581 (71.4)	<0.001	0.13
Doxylamine and combinations thereof	8977	5746 (64.0)	3231 (36.0)	<0.001	0.01
Ergot	866	603 (69.6)	263 (30.4)	0.027	0.00
Oestrogen and combinations thereof	69894	69845 (99.9)	49 (0.1)	<0.001	0.27
Flecainide	1761	899 (51.0)	862 (49.0)	<0.001	0.02
Fluphenazine	39	22 (56.4)	17 (43.6)	0.202	0.00
Flurazepam	125	76 (60.8)	49 (39.2)	0.212	0.00
Glibenclamide	9409	3724 (39.6)	5685 (60.4)	<0.001	0.07
Haloperidol	549	357 (65.0)	192 (35.0)	0.601	0.00
Hydroxyzine	1813	1249 (68.9)	564 (31.1)	0.012	0.00
Hyoscine and combinations	7492	4832 (64.5)	2660 (35.5)	0.003	0.00

thereof					
Ibuprofen and combinations thereof	34162	19649 (57.5)	14513 (42.5)	<0.001	0.05
Imipramine	2561	1863 (72.8)	698 (27.2)	<0.001	0.01
Indomethacin	3611	2361 (65.4)	1250 (34.6)	0.372	0.00
Insulin	18715	6966 (37.2)	11749 (62.8)	<0.001	0.11
Ketoprofen	1464	922 (63.0)	542 (37.0)	0.012	0.00
Ketorolac	2671	1524 (57.1)	1147 (42.9)	<0.001	0.01
Lorazepam	10615	7483 (70.5)	3132 (29.5)	<0.001	0.01
Loxapine	9	9 (100.0)	-	0.032	0.00
Mefenamic acid	1121	714 (63.7)	407 (36.3)	0.091	0.00
Meloxicam	41030	28353 (69.1)	12677 (30.9)	<0.001	0.02
Meperidine	228	151 (66.2)	77 (33.8)	0.964	0.00
Meprobamate and combinations thereof	27894	19326 (69.3)	8568 (30.7)	<0.001	0.02
Methocarbamol	1609	1080 (67.1)	529 (32.9)	0.379	0.00
Methyldopa	3950	2862 (72.5)	1088 (27.5)	<0.001	0.01
Methyltestosterone	2	-	2 (100.0)	0.048	0.00
Metoclopramide	7971	4944 (62.0)	3027 (38.0)	<0.001	0.01
Naproxen	1786	1161 (65.0)	625 (35.0)	0.335	0.00
Nifedipine	465	304 (65.4)	161 (34.6)	0.747	0.00
Nitrofurantoin	4296	3619 (84.2)	677 (15.8)	<0.001	0.03
Olanzapine	1871	1316 (70.3)	555 (29.7)	<0.001	0.01
Orphenadrine and combinations thereof	4371	2730 (62.5)	1641 (37.5)	<0.001	0.01
Oxazepam	11732	8527 (72.7)	3205 (27.3)	<0.001	0.02
Paliperidone	10	10 (100.0)	-	0.024	0.00
Pentazocine	9	5 (55.6)	4 (44.4)	0.505	0.00
Phenobarbitone	697	409 (56.7)	288 (41.3)	<0.001	0.01
Pimozide	35	32 (91.4)	3 (8.6)	0.002	0.00
Piroxicam	4221	2586 (61.3)	1635 (38.7)	<0.001	0.01
Prazosin	977	458 (46.9)	519 (53.1)	<0.001	0.02
Promethazine and combinations thereof	3727	2324 (62.4)	1403 (37.6)	<0.001	0.01
Propafenone	540	269 (49.8)	271 (50.2)	<0.001	0.01
Propantheline	74	59 (79.7)	15 (20.3)	0.013	0.00
Quetiapine	4977	3268 (65.7)	1709 (34.3)	0.527	0.00
Reserpine	454	344 (75.8)	110 (24.2)	<0.001	0.01
Risperidone	6873	4378 (63.7)	2495 (36.3)	<0.001	0.01
Sotalol	1736	890 (51.3)	846 (48.7)	<0.001	0.02
Spironolactone	3260	1780 (54.6)	1480 (45.4)	<0.001	0.02
Temazepam	2393	1516 (63.4)	877 (36.6)	0.005	0.00
Terazosin	250	23 (9.2)	227 (90.8)	<0.001	0.03
Testosterone	290	10 (3.5)	280 (96.5)	< 0.001	0.03
Triazolam	1774	1104 (62.2)	670 (37.8)	0.001	0.01
Trifluoperazine	168	136 (81.0)	32 (19.0)	< 0.001	0.01
Trimipramine	706	505 (71.5)	201 (28.5)	0.002	0.00

Triprolidine and combinations thereof	1158	635 (54.8)	523 (45.2)	< 0.001	0.01
Ziprasidone	114	87 (76.3)	27 (23.7)	0.021	0.00
Zolpidem	0	-	-		

*All values are Cramér's *V* statistics, except where clearly stated otherwise.
†Fisher's exact test.

Table 4. Prevalence of the10 most inappropriately prescribed drugs per prescriber group

Prescriber	**Total study population (*N*)**	**GPs *n* (%)**	**Pharmacy *n* (%)**	**Specialists *n* (%)**	**Other *n* (%)**	***p*-value**	**Effect size***
Beers criteria item						<0.001	0.09
Alprazolam	29896	24073 (80.5)	-	4536 (15.2)	1287 (4.3)		
Amiodarone	17433	9820 (56.3)	-	7324 (42.0)	289 (1.7)		
Amitriptyline and combinations thereof	36509	28095 (77.0)	-	6793 (18.6)	1621 (4.4)		
Diclofenac	36062	22205 (61.6)	10200 (28.3)	2732 (7.6)	925 (2.6)		
Doxazosin	14816	10499 (70.9)	1 (0.0)	4109 (27.7)	207 (1.4)		
Oestrogen and combinations thereof	69894	56978 (81.5)	106 (0.2)	11368 (16.3)	1442 (2.1)		
Ibuprofen	34162	16347 (47.9)	12351 (36.2)	2312 (6.8)	3152 (9.2)		
Insulin	18715	11971 (64.0)	-	6492 (34.7)	252 (1.3)		
Meloxicam	41030	34544 (84.2)	-	5765 (14.1)	721 (1.8)		
Meprobamate and combinations thereof	27894	21956 (78.7)	71 (0.3)	4447 (15.9)	1420 (5.1)		

GPs = general practitioners.

*All values are Cramér's *V* statistics.

3.3 Manuscript two

Detecting potentially serious drug-drug interactions among South African elderly private health sector patients using the Matanović/Vlahović-Palčevski drug-drug interaction protocol

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Abstract
Objective: To determine the prevalence of potentially serious drug-drug interactions (DDIs) and their relationship with sex and age, among elderly in South Africa.
Methods: A cross-sectional study was conducted using medicine claims data for 2013, for a total of 103,420 medical aid beneficiaries' ≥65 years. Potentially serious DDIs were counted using the Matanović/Vlahović-Palčevski drug-drug interaction protocol, when two potential interacting drugs were supplied for overlapping days during a 30-day period. Chi-square test was used to determine the association between the prevalence of potentially serious DDIs and sex or age group.
Key findings: In total, 65 of the 70 Matanović/Vlahović-Palčevski comprehensive protocol for drug-drug interactions were possible in South Africa at the time of the study. A total of 331,655 potentially serious drug-drug interactions were identified among 912,712 prescriptions, at a mean 0.36 (SD 0.7) (95% CI, 0.36-0.37) drug-drug interactions per prescription. There was no association between the mean number of drug-drug interactions per prescription and sex ($P< 0.001$, Cohen's d-value=0.10) or age groups ($F (3, 912,712) = 1093.05$, $P<0.001$; Cohen's d-value ≤ 0.16). The most frequent interacting drug combinations were between central nervous system drugs (30.6%), antihypertensives and nonsteroidal anti-inflammatory drugs (23.5 %), diuretics and nonsteroidal anti-inflammatory drugs (8.3%), angiotensin-converting enzyme inhibitors and potassium supplements (4.9%) and nonsteroidal anti-inflammatory drugs/aspirin and corticosteroids (4.8%).
Conclusion: The Matanović/Vlahović-Palčevski comprehensive drug-drug interaction tool might be a useful initial screening tool that can be employed by prescribers and pharmacists alike in the South African private health sector, in finding and preventing the most common potentially serious drug-drug interactions in practice.

Keywords: Potentially serious drug-drug interactions; older people; Matanović/Vlahović-Palčevski drug-drug interaction list, pharmaceutical claims data; South Africa

Introduction

In 2011, 4.1 million individuals (8.0%) of the total South African population were aged 60 years and older,[1] with the number of patients older than 60 years with medical aid increasing from 6.5% in 2011 to 7.1% in 2013.[2] Although elderly patients represent only a small fraction of the entire population, they are regarded as the largest per capita consumers of prescription medication. For instance, elderly patients take, on average, three to four times more medicine items than the general population.[3] This can be attributed to the higher prevalence of disease and comorbidities in this age group[4] which, in turn, can lead to a higher number of medication items needed to treat these conditions, and subsequently, an increased risk for developing drug interactions.[5,6]

Several explicit screening tools or criteria are available to determine the appropriateness of prescribing for elderly patients.[7]In 2012, Matanović and Vlahović-Palčevski developed a comprehensive tool to identify potentially serious drug-drug interactions (DDIs) in the elderly.[8] This protocol consists of four sections namely (1) drugs with an unfavourable benefit/risk ratio, (2) drugs with a questionable efficacy, (3) drugs to be avoided with certain diseases/conditions, and (4) potentially serious DDIs.[8]The latter section consists of a list of 70 potentially clinically important DDIs.[8]

Data regarding the prevalence of DDIs among the South African elderly patients are limited. The purpose of this study was therefore to determine the prevalence of potentially serious DDIs and their relationship with sex and age, among elderly South African patients by using the Matanović/Vlahović-Palčevski drug-drug interaction protocol.

Methods

A cross-sectional analysis was conducted using a database obtained from a South African Pharmaceutical Benefit Management (PBM) company. The database for the period 1 January to 31 December 2013 contained pharmaceutical claims information for a total of 809,857 patients. Of these, 103,420 patients (12.8 %) on the database were 65 years and older, representing 7.1% of the total medical aid industry across South Africa during 2013.[2] We queried data fields for patient demographic information (patients' sex and date of birth) and pertinent prescription information (drug trade name, days' supply, month, and treatment date). Patients' date of birth and treatment date were used to calculate the age of patients on the day of treatment. Patients were then divided into four equally sized groups ($65 \leq$ group $1 \leq 68$ years; $68 <$ group $2 \leq 72$; $72 <$ group $3 \leq 78$; and group $4 > 78$ years).

We assumed that consumption started the same day the prescribed medication was dispensed (i.e. 'treatment date'). Because a patient could receive more than one drug per prescription and more than one prescription per month, the variables 'month' and 'day's supply' were used to group all medication dispensed within one calendar month, of which day's supply overlapped, as one prescription. This was accomplished using the treatment dates and number of days' supply for each prescription. Potentially serious DDIs were counted when the days' supply for two potentially interacting medications as listed by the Matanović/Vlahović-Palčevski drug-drug interaction protocol, overlapped.

Variables were characterized using 95% confidence intervals, descriptive statistics such as proportions/ratios for categorical variables, and means and standard deviations for continuous variables. An independent two-sample *t*-test was used to assess the statistical significance

ofdifferences in the mean number of prescriptions per patient and the mean number of drugs per prescription, between men and women. A one-way between-group analysis of variance (ANOVA) operationalised by the general linear model (GLM) with post-hoc comparisons using the Tukey HSD test was conducted to explore the impact of age groups on the mean number of prescriptions per patient and the mean number of drugs per prescription. To determine the association between the prevalence of the potentially serious DDIs and sex or age group, the Chi-square test was done.

Because statistical significance tests yielded small *p*-values (indicating significance) in most tests, we focused our interpretation on effect sizes which is independent of units and sample size.[9] Cohen's *d*-value was used to evaluate mean differences between groups (with significance defined as a level of at least 0.8), and Cramér's *V* statistic (defined as a level of at least 0.5) was used for associations between categorical variables. Statistical analyses were performed using SAS Software, version 9.3 (Cary (NC): SAS Institute Inc.; 2002).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was conducted with the approval of a NHREC-registered Research Ethics Committee (Ethics number: 00179-14-S1) and the board of directors of the PBM.

Results

Table 1 shows the general characteristics of the study population (N = 103,420 patients).The mean (SD) age of the patients was 74.1 (SD 6.7) years. There was an evident prevalence of women in the study population, with prevalence increasing with age from 54.8%in patients below the age of 68 years, to 60.6% in patients older than 78 years. Women received proportionally more prescriptions and drugs during the study period (58.0% and 59.0%, respectively). Prevalence of both prescriptions and drugs in women increased with age, however, there was no significant difference between men and women with regard to the mean number of prescriptions per patient ($P < 0.001$, Cohen's *d*-value=0.08) or the mean number of drugs per prescription ($P < 0.001$, Cohen's *d*-value=0.03). Analysis by one-way ANOVA with post-hoc comparisons using Tukey HSD test showed that there was a statistically significant difference between the age groups at the $p<0.05$ level with regard to the mean number of prescriptions per patient [$F(3, 103,420)=199.42$, $P<0.001$] and the mean number of drugs per prescription [$F(3, 912,713)=2452.00$, $P<0.001$]. Despite reaching statistical significance, however, the actual difference in means between the age groups was quite small. The effect sizes, calculated using Cohen's *d*-value, was < 0.3.

Insert Table 1

The prevalence of potentially serious DDIs, stratified by sex and age group are described in Table 2. In total, 331,655 potentially serious DDIs (involving 235,870 prescriptions) were identified among a total of 912,713 prescriptions (Table 2). A mean 0.36 (SD 0.7) (95% CI, 0.36-0.37) potentially serious DDIs were encountered per prescription. Women encountered proportionally more interactions than men, however, the difference was not practically significant ($P < 0.001$; Cramér's $V = 0.05$). Although there was an increase in the total prevalence of potentially serious DDIs from 59.7% among women below the age of 68 years to 66.8% amongst those older than 78 years, the difference between the age groups were not practically significant ($P <0.001$; Cramér's $V = 0.06$) (Table 2). There was also no difference

with regard to the mean number of potentially serious DDIs per prescription between the sexes (P<0.001, Cohen's d-value =0.10) or age groups (F(3, 912,712)= 1093.05, P<0.001; Cohen's d-value ≤ 0.16).

Insert Table 2

Table 3 shows the frequency of the potentially serious DDIs encountered. The potentially serious DDI with the highest prevalence was the interaction among different central nervous system (CNS)drugs (31.4%), followed by interactions between antihypertensives + nonsteroidal anti-inflammatory drugs (NSAIDs) (24.1%), diuretics + NSAIDs (8.5%), angiotensin converting enzyme (ACE) inhibitors + potassium supplements(5.1%) and NSAIDs/aspirin + corticosteroids (5.0%)(Table 3). Within the category of potentially serious DDIs among different CNS drugs, the drug pairs most frequently identified was zolpidem/alprazolam (16.3%), followed by zolpidem/amitriptyline (15.5%) and zolpidem/citalopram(14.5%). The antihypertensive drugs + NSAID pairs most frequently identified was bisoprolol/meloxicam (4.9%), followed by amlodipine/meloxicam (4.6%), and bisoprolol/celecoxib (4.4%) (data not shown in tables).

Insert Table 3

Discussion

In the absence of data regarding DDIs among the South African elderly patients, this study aimed to determine the prevalence of potentially serious DDIs and their relationship with sex and age, among elderly South African patients by using the Matanović/Vlahović-Palčevski drug-drug interaction protocol. There were a number of key findings: Firstly, we determined that approximately one in every four (~26%) prescriptions for medications for elderly patients in our study population contained at least one potentially serious DDI. Although DDIs were independent of sex and age group, women encountered proportionally more potential interactions than men, and there was a trend of an increase in the total prevalence of potentially serious DDIs by age group. The most frequent interacting drug combinations were central nervous system drugs (30.6%), antihypertensives and nonsteroidal anti-inflammatory drugs (23.5%), diuretics and nonsteroidal anti-inflammatory drugs (8.3%), angiotensin-converting enzyme inhibitors and potassium supplements (4.9%) and nonsteroidal anti-inflammatory drugs/aspirin and corticosteroids (4.8%).

Overall, the identification of potentially serious drug-drug interactions inapproximately 26% of the prescriptions is slightly higher than found by other database studies (ranging from 4.7-22%).[10-15] It should, however, be noted that we included all prescriptions for patients during the study period — prescriptions analysed may therefore have been repeat prescriptions, implying that a patient may have encountered the same interaction more than once. It is furthermore difficult to compare our findings with other studies in South Africa since only a few studies measuring the prevalence of DDIs in South African are available. One such study was conducted by Kapp *et al*.[16] in a primary healthcare setting in a sub-district in South Africa. The authors analysed patients' drug lists using Medscape's drug interaction checker for DDIs, showing that at least 42.0% of randomly selected patient prescriptions had at least one potential drug interaction, a further 5.3% had severe potential interactions and 0.5% received contraindicated combinations.[16] In agreement with these authors, our study underscores the importance of assessing medicine prescribed to older South African adults

for potential drug interactions. This becomes even more important as populations age across countries.

The potentially serious DDIs identified in our study were more prevalent among patients older than 78 years. Similar results were found in other published studies[10, 17] and the study by Kapp *et al*.[16] In contrast to the study by Kapp *et al*., however, we showed that proportionally more women encountered potentially serious DDIs. According to Verbrugge,[18] sex differentials and attitudes about symptoms, medical care, medicines and self-care are responsible for a higher medicine claim rate among females; for example, women are more frequently ill than men. These frequent symptoms lead to activity that is more restricted and subsequently to more physician and dentist visits and medication use by women. Hence, prescription claim rates per patient are normally higher for females than for males, [17,19] increasing the potential for encountering more drug interactions.

The most frequently encountered potentially serious DDIs identified in this study were all clinically significant pharmacodynamic DDIs. These finding are in agreement with previous reports.[10-11,14,20] The study conducted by Popović *et al.,* identified the combination of an ACE inhibitor with a potassium supplement as the most prevalent combination that might lead to serious DDIs, followed by the combination of NSAIDs with a diuretic. In female patients the most prevalent combination was antidepressants with NSAIDs.[20] The most common medication combination potentially leading to serious DDIs in our study included CNS drugs, in particular, the drug pairs zolpidem/alprazolam, zolpidem/amitriptyline and zolpidem/citalopram. Both amitriptyline (tricyclic antidepressant) and citalopram (selective serotonin reuptake inhibitor) are used for treatment of depression. Combining these items with zolpidem may lead to an enhancement of the CNS effects and an increased risk of experiencing adverse effects. Adverse effects associated with the use of zolpidem and alprazolam include delirium, falls and fractures, impaired cognitive functions and an increased risk for motor vehicle accidents. Frail, elderly patients have an increased risk for falls and fractures and the use of benzodiazepines in these patients lead to an increased risk for falls and fractures.[21-22] According to the Medicines and Related Substances Act (Act 101 of 1965), medical practitioners and dentists may prescribe schedule 5 (and specified Schedule 5) items but for not longer than 6 months. Where these items are used as anxiolytic, antidepressant or tranquilisers, the prescription may not be for longer than six months before the authorised prescriber has not consulted with a registered psychiatrist. If these items were prescribed by a psychiatrist, they must consult with another psychiatrist before giving a new prescription.[25] In the South African health care setting, patients tend to consult with multiple physicians at the same time which leads to an increase in items being prescribed without knowledge of what the other physician prescribed. This may lead to polypharmacy and an increase in the number of potential drug-drug interactions. The pharmacist thus plays a crucial role as gate-keeper to ensure that the use of medicine is rational and does not affect the patient negatively.

We also found that antihypertensives are commonly prescribed with NSAIDs, in particular, bisoprolol with meloxicam or celecoxib, and amlodipine with meloxicam. Both meloxicam and celecoxib are cyclo-oxygenase-2 (COX-2) selective inhibiting NSAIDs that may cause fluid retention, increased blood pressure and eventually an increased risk of heart failure when used with cardiovascular drugs.[23-24] Several NSAIDs can be purchased as over the-counter-drug analgesics in South Africa. Healthcare workers – in particular pharmacists, are therefore key players for finding and preventing these interactions. There is thus an urgent

need for DUR type analysis studies to identify and prevent these potential interaction and future studies may focus on the outcome of these potential interactions.

Strengths and limitations

Limitations that should be considered when interpreting the results include the fact that data from only one PBM were used. Consequently, results cannot be generalised to the total South African private health sector. However, this PBM was linked up to most of South Africa's pharmacies and 98% of all dispensing medical practitioners in the country at the time of the study. Consequently, we believe that this database can be considered a true representation of prescribing and dispensing practices in the country adding robustness to our study.

Furthermore, all prescriptions, including repeat prescriptions, for patients for the study period were included and thus may imply that a patient encountered the same potential DDI more than once, leading to a possible overestimate of potential DDIs. On the other hand, however, patients may have paid out-of-pocket for medicines, in which case a claim would not have been recorded on the database, resulting in a possible underestimation of potential DDIs. Finally, because we analysed pharmaceutical claims data, we could not assess the outcomes of the potentially serious DDIs.

Conclusion

To the best of our knowledge, this study is the first to report the prevalence of potentially serious DDIs among an elderly population in the South African private health sector according to the Matanović/Vlahović-Palčevski drug-drug interaction protocol. The Matanović/Vlahović-Palčevski drug-drug interaction protocol appears to be comprehensive screening tool drug-drug interaction tool that can be employed by prescribers and pharmacists in South Africa alike in finding and preventing potentially the most serious DDIs in practice.

Drugs of concern among the elderly patients in South Africa were the sedative hypnotics (benzodiazepines and other), antidepressants, antihypertensives and nonsteroidal anti-inflammatory drugs. We will be exploring the prescribing of these medicine items further in future research.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Table 1.Study population characteristics

Characteristic	Total study population, N	Women n(%)	Men n(%)
Number of patients, n (%)	103,420	59,077 (57.1)	44,343 (42.9)
Age group (years) n (%)			
≥65, ≤68	23,027	12,615 (54.8)	10,412 (45.2)
>68, ≤72	25,066	13,981 (55.8)	11,085 (44.2)
>72, ≤78	28,604	16,277 (56.9)	12,327 (43.1)
>78	26,723	16,204 (60.6)	10,519 (39.4)
Number of prescriptions, n (%)	912,713	529,540 (58.0)	383,173 (42.0)
Age group (years), n (%)			
≥65, ≤68	192,631	107,487 (55.8)	85,144 (44.2)
>68, ≤72	219,603	124,321 (56.6)	95,282 (43.4)
>72, ≤78	257,174	148,024 (57.6)	109,150 (42.4)
>78	243,305	149,708 (61.5)	93,597 (38.5)
Number of drugs, n (%)	4,228,398	2,492,951 (59.0)	1,735,447 (41.0)
Age group (years), n (%)			
≥65, ≤68	840,623	472,483 (56.2)	368,140 (43.8)
>68, ≤72	993,538	571,446 (57.5)	422,092 (42.5)

>72, ≤78	1,205,797	706,923 (58.6)	498,874 (41.4)
>78	1,188,440	742,099 (62.4)	446,341 (37.6)
Number of prescriptions per patient, mean (SD) (95% CI)	8.83 (3.6) (8.80-8.85)	8.96 (3.6) (8.93-8.99)	8.64 (3.7) (8.61-8.68)
Age group (years), mean (SD) (95% CI)			
≥65, ≤68	8.37 (3.8) (8.32-8.42)	8.52 (3.7) (8.46-8.59)	8.18(3.9) (8.10-8.25)
>68, ≤72	8.76 (3.7) (8.72-8.81)	8.89 (3.6) (8.83-8.95)	8.60(3.7) (8.53-8.67)
>72, ≤78	8.99 (3.6) (8.95-9.03)	9.09 (3.5) (9.04-9.15)	8.86(3.7) (8.79-8.92)
>78	9.11 (3.5) (9.06-9.15)	9.24 (3.4) (9.19-9.29)	8.90(3.7) (8.83-8.97)
Number of drugs per prescription, mean (SD) (95% CI)	4.37 (2.9) (4.36-4.37)	4.44 (3.0) (4.43-4.45)	4.26 (2.9) (4.25-4.27)
Age group (years), mean (SD) (95% CI)			
≥65, ≤68	4.13 (2.9) (4.11-4.14)	4.16 (3.0) (4.14-4.18)	4.09 (2.9) (4.07-4.11)
>68, ≤72	4.27 (2.9) (4.25-4.28)	4.34 (3.0) (4.32-4.36)	4.17 (2.8) (4.15-4.19)
>72, ≤78	4.42 (2.9) (4.41-4.43)	4.51 (3.0) (4.49-4.52)	4.29 (2.9) (4.28-4.31)
>78	4.60 (2.9) (4.59-4.61)	4.67 (3.0) (4.65-4.68)	4.49 (2.9) (4.47-4.51)

Table 2. Prevalence of drug interactions, stratified by sex and age group

	Total study population N	Women (%)	Men (%)
Total number of prescriptions with drug interactions, N	235,870	148,154 (62.8)	87,716 (37.2)
Age group (years), n (%)			
≥65, ≤68	43,659	26,121 (59.8)	17,538 (40.2)
>68, ≤72	52,804	32,221 (61.0)	20,583 (39.0)
>72, ≤78	67,335	42,293 (62.8)	25,042 (37.2)
>78	72,072	47,519 (65.9)	24,553 (37.1)
Total number of drug interactions, N	331,655	210,579 (63.5)	121,076 (36.5)
Age group (years), n (%)			
≥65, ≤68	59,450	35,495 (59.7)	23,955 (40.3)
>68, ≤72	73,027	45,123 (61.8)	27,904 (38.2)
>72, ≤78	95,405	60,641 (63.6)	34,764 (36.4)
>78	103,773	69,320 (66.8)	34,453 (33.2)
Number of drug interactions per prescription*, mean (SD) (95% CI)	0.36 (0.7) (0.36-0.37)	0.40 (0.8) (0.39-0.40)	0.32 (0.7) (0.31-0.32)
Age group (years), mean (SD) (95% CI)			
≥65, ≤68	0.31 (0.7) (0.30-0.31)	0.33 (0.7) (0.32-0.33)	0.28 (0.6) (0.28-0.29)

>68, ≤72	0.33 (0.7) (0.33-0.34)	0.36 (0.7) (0.36-0.37)	0.29 (0.7) (0.29-0.30)
>72, ≤78	0.37 (0.8) (0.37-0.38)	0.41 (0.8) (0.40-0.41)	0.32 (0.7) (0.32-0.33)
>78	0.42 (0.8) (0.42-0.43)	0.46 (0.8) (0.46-0.47)	0.37 (0.7) (0.36-0.37)

*** Calculated using the total number of prescriptions (Table 1) as denominator**

Table 3.Potentially serious drug-drug interactions

Interaction	Frequency, n (%)
Anti-arrhythmics	
Disopyramide – Cimetidine	0
Disopyramide – Macrolides (except azithromycin)	2 (0.001)
Procainamide – Amiodarone	0
Procainamide – Cimetidine	0
Procainamide – Trimethoprim and combinations thereof	0
Quinidine – Cimetidine	0
Quinidine – Fluvoxamine	0
Anti-epileptics	
Carbamazepine – Danazol	0
Carbamazepine – Verapamil	174 (0.1)
Carbamazepine – Diltiazem	48 (0.01)
Carbamazepine – Macrolides	95 (0.03)
Phenytoin – Isoniazid	0
Phenytoin – Quinidine	0
Phenytoin – Warfarin	234 (0.1)
Phenytoin – Omeprazole	200 (0.1)
Phenytoin – Cimetidine	11 (0.003)
Phenytoin – Theophylline	112 (0.03)
Phenytoin – Fluoxetine	45 (0.01)
Phenytoin – Amiodarone	124 (0.04)

Other drugs with low therapeutic index	
Digoxin – Verapamil	1,381 (0.4)
Digoxin – Amiodarone	1,224 (0.4)
Digoxin – Clarithromycin	144 (0.04)
Digoxin – Quinidine	0
Digoxin – Propafenone	35 (0.01)
Lithium – ACE-inhibitors	161 (0.05)
Lithium – Diuretics	147 (0.04)
Lithium – NSAIDs	121 (0.04)
Salicylates – Probenecid	2 (0.001)
Theophylline – Clarithromycin	1,087 (0.3)
Theophylline – Erythromycin	116 (0.03)
Theophylline – Cimetidine	95 (0.03)
Warfarin – Quinolones	1,072 (0.3)
Warfarin – Amiodarone	3,797 (1.1)
Warfarin – Macrolides	536 (0.2)
Warfarin – Sulfamethoxazole	99 (0.03)
Drug-drug interactions selected by Malone et al. as having greatest clinical importance (pharmacokinetic and pharmacodynamic)	
Benzodiazepines – Azole antifungal agents	1,550 (0.5)
Cyclosporine – Rifampin	1 (0.0003)
Ergot alkaloids – Macrolide antibiotics (except azithromycin)	4 (0.001)
MAO-inhibitors – Sympathomimetics (dopamine, ephedrine,	6 (0.002)

phenylephrine, pseudoephedrine)	
Meperidine – MAO inhibitors	0
Methotrexate – Trimethoprim	13 (0.004)
Nitrates – Sildenafil	5 (0.001)
SSRIs – MAO inhibitors	3 (0.001)
Theophylline – Fluvoxamine	5 (0.001)
Theophylline – Quinolones	1,849 (0.6)
Thiopurines – Allopurinol	10 (0.003)
Warfarin – NSAIDs	3,647 (1.1)
Warfarin – Thyroid hormones	6,312 (1.9)
Warfarin – Cimetidine	45 (0.01)
Warfarin – Barbiturates	32 (0.01)
Warfarin – Fibric acid and derivatives	394 (0.1)
Other clinically important drug-drug interactions (pharmacokinetic and pharmacodynamic)	
Atorvastatin/simvastatin – Amiodarone	6,808 (2.1)
Potassium – Potassium-sparing diuretics	7,188 (2.2)
Clopidogrel – PPIs	2,679 (0.8)
Levodopa – MAO inhibitors	23 (0.01)
SSRIs – Tramadol	3,926 (1.2)
SSRIs – Metoclopramide	724 (0.2)
HMG Co-A reductase inhibitors – Gemfibrozil	76 (0.02)
Atorvastatin/simvastatin – Macrolide antibiotics	3,867 (1.2)

Clinically significant pharmacodynamic drug-drug interactions	
ACE inhibitors – Potassium supplements	16,319 (4.9)
ACE inhibitors – Potassium-sparing diuretics	13,550 (4.1)
Verapamil – Beta-blockers	3,238 (1.0)
Diuretics – NSAIDs	27,359 (8.2)
Antihypertensive – NSAIDs	77,847 (23.5)
Warfarin – Antiplatelet agents	5,977 (1.8)
Antiplatelet agents – Antiplatelet agents	9,489 (2.9)
Anticholinergic - Anticholinergic	10,183 (3.1)
NSAIDs/Aspirin - Corticosteroids	15,998 (4.8)
CNS agents (e.g. diazepam) – CNS agents (e.g. codeine)	101,470 (30.6)

ACE angiotensin-converting enzyme; CNS central nervous system; MAO mono-amine oxidase; NSAIDs non-steroidal anti-inflammatory drugs; PPIs proton pump inhibitors; SSRIs selective serotonin reuptake inhibitors

3.4 Chapter summary

In this chapter, two manuscripts were presented addressing the objectives of the empirical investigation. The next chapter, which concludes the study, focuses on the conclusion, strengths and limitations of the study, and recommendations for future studies.

CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS

4.1 Introduction

In this final chapter, conclusions from the study are drawn with regard to the specific objectives. It first gives a brief overview of the outlay of the dissertation followed by a summary of the findings from the study. The strengths and limitations are outlined and the chapter will conclude with recommendations for future studies.

4.2 Dissertation outlay

This dissertation consists of four chapters with the findings of the empirical study presented in article format. Chapter 1 gives the background and justification of the study, the study aim and objectives, and the research methodology that was followed. It also includes the ethical considerations.

Chapter 2 consists of the literature review. It provides background information on prescribing for elderly patients and factors that influence the prescribing for this age group. The chapter includes background information on the Beers criteria and the Mimica Matanović and Vlahović-Palčevski comprehensive drug-drug interaction list as measures of inappropriate prescribing, which were applied in this study to determine the prevalence on potentially inappropriate prescribing and drug-drug interactions respectively.

Chapter 3 gives the results for and discusses the empirical investigation. The chapter consists of two manuscripts. Manuscript one was submitted to the South African medical journal and manuscript two was submitted to the International journal of pharmacy practice (see Annexure D).

A list of annexures contains all additional information not included in the different chapters.

4.3 Conclusions based on the objectives

The general aim of the study was to determine potentially inappropriate prescribing patterns for elderly patients in the private health sector of South Africa utilising different screening tools. The study was conducted through a literature review and an empirical investigation. The conclusions for the research objectives for each of the two aspects of the study are discussed below.

4.3.1 Conclusions from the literature review

The objectives of the literature review as outlined in Chapter one paragraph 1.2.1 were achieved in Chapter two. The following paragraphs summarise the findings.

- **To determine what appropriate prescribing for the elderly entails**

This objective was achieved in Chapter two, section2.2.

Prescribing can be regarded as rational or appropriate when the choice of the medicine item is based on its safety, efficacy, cost-effectiveness and convenience when compared to other medicine items for use in a specific patient (Shah *et al.,* 2011:248). Appropriate prescribing also entails maximum benefit and minimum harm to the patient (Lipworth *et al.,* 2011:1) based on distinct evidence-based proof that the item is well tolerated by the majority of patients (Parsons *et al.,* 2012:144). The aim of appropriate prescribing is to increase the use of treatment with available evidence on the effectiveness and to exclude medicine items that are not needed or have questionable efficacy and to avoid duplication of treatment. Providers should use their clinical knowledge and reasoning in the decision-making process regarding prescribing (Page *et al.,* 2010:84).

Inappropriate prescribing refers to prescriptions where the patient is at a higher risk of negative outcomes than potential benefit from the treatment (Maio *et al.,* 2010:219; Rancourt *et al.,* 2004:2) and where the cost of the treatment is not taken into consideration. Inappropriate prescribing may also include suboptimal prescribing practices (Parsons *et al.,* 2012:144) such as negative outcomes (drugs prescribed for no reason, drugs with increased potential to lead to adverse effects, treatment that is not cost-effective and that may lead to hospitalisation and an increase in resource utilisation) (Gallagher *et al.,* 2011:1176; Parsons *et al.,* 2012:144), the use of medicine for longer periods of time and at higher doses than indicated, the use of items with known drug-drug interactions, and the underutilisation of beneficial items which are not regarded to be suitable for use in elderly patients due to age-related changes (Gallagher *et al.,* 2007:13).

There are additional types of prescribing that may also be regarded as inappropriate. Underprescribing refers to the omission of items which has a clear indication without any clinical reason for stopping the treatment (Kuijpers *et al.,* 2007:131; O'Connor *et al.,* 2012:439). Overprescribing refers to the use of more than one similar item, the excess use of medicine items or the prescribing of unnecessary items (Gallagher *et al.,* 2007:114; Hajjar *et al.,* 2005:1518). Polypharmacy generates prescribing cascades where additional medicine items are prescribed to relieve symptoms of unrecognized adverse effects (O'Mahony *et al.,* 2012:423). Deprescribing refers to the process of stopping the use of some items with the

aim to minimize polypharmacy (Scott *et al.,* 2015:827). Misprescribing refers to the prescribing of medicine items that has a higher potential to cause adverse effects, including inaccurate dosing, frequency, route of administration, duration of treatment, and may be more likely to lead to serious drug-drug and drug-disease interactions (O'Connor *et al.,* 2012:438-439). Off-label prescribing may also be seen as a form of inappropriate prescribing as medicine items are prescribed for unregistered therapeutic indications (Jackson *et al.,* 2012:427). (Refer to paragraph 2.2).

- **To determine the factors influencing prescribing for the elderly and to determine which unique factors of elderly patients influence the medication prescribed to them**

This literature objective was answered in Chapter two, section 2.3.

Advanced age, polypharmacy, multiple comorbidities, impairment, social and emotional support and the financial position are all factors that influence inappropriate prescribing (Page *et al.,* 2010:76). Aspects to consider when prescribing for elderly patients include accurate drug indication, avoidance of drug contraindications, minimisation of interactions, minimisation of overprescribing and a related increase in potential medicine-related issues, switching to palliative pharmacotherapy where appropriate and getting value for money (O'Mahony *et al.,* 2012:424). (Refer to paragraph 2.3). Factors innate to the elderly that influence prescribing include physiological changes associated with aging, including pharmacokinetic and pharmacodynamic changes. External factors such as non-adherence, common among elderly patients, also influence prescribing for the elderly.

Several factors that contribute to non-adherence include factors pertaining to the patient, the medication, the relationship with the healthcare providers, factors pertaining to weakness in the healthcare system and the cost of the treatment (Hershberger & Tindall, 2007:21; Eaddy *et al.,* 2012:45). Interpersonal factors (such as physician-patient relationship), the patient's involvement in the decision-making process and the patient's attitude, beliefs, group norms and cultural variations (marital status, level of income, age and gender) also influence the prescribing for the elderly. Adherence may further be affected by impaired vision, hearing, ambulation or other functional abilities. Illiteracy and health beliefs of patients about the illness or prescribed medicine may also contribute to non-adherence (Martin *et al.,* 2005:191-194). Complex medicine regimens or polypharmacy, failure to see the advantages of taking the prescribed treatment, unnecessary drug interactions, packaging of medicine items, failure to adjust the treatment regimen to suite the way of living of the patient, failure to review the cost-effectiveness of the treatment and failure between healthcare professionals and the patient to develop a good therapeutic and helping relationship may also contribute to non-

adherence (Hershberger & Tindall, 2007:21-22). Lack of knowledge and unfamiliarity with treatment guidelines for the elderly patients may lead to underprescribing which is considered an important part of inappropriate prescribing (Lipworth *et al.,* 2011:1).

Strategies to improve prescribing in the elderly patient include feedback to clinicians about their prescribing practices (Lipworth *et al.,* 2011:2). All pharmacokinetic and pharmacodynamic changes should be considered when prescribing for the elderly patients (Gallagher *et al.,* 2007:114) as well as economic and clinical outcomes (Gupta *et al.,* 1996:184).(Refer to paragraphs 2.3.1 and 2.3.2).

- **To determine the prevalence and criteria for the measurement of inappropriate prescribing for elderly patients by analysing previous studies**

This literature objective was answered in Chapter two, section 2.5.

There are several tools and criteria available to evaluate the appropriateness of drugs prescribed for geriatric patients (Gallagher *et al.,* 2011:1176). These tools can be explicit, implicit or a combination of both. Implicit measures are based on clinicians' clinical judgement and knowledge, is very patient specific, needs access to large numbers of clinical data and well-trained clinicians to perform the evaluation (Parsons *et al.,* 2012:145). Explicit criteria, on the other hand, are based on specific criteria that were developed from evidence-based suggestions, published reviews, expert opinions and consensus methods where a limited degree of clinical judgement is needed. The Beers criteria are considered to be the gold standard for explicit criteria (Parsons *et al.,* 2012:145). (Refer to paragraph 2.5).

The literature review identified a total of 27 explicit, 7 implicit and 8 mixed approach tools. The Beers criteria adjusted for a specific country was used in numerous cases. Most of the explicit criteria were compiled by using the modified Delphi method. All of these tools need to be updated on a regular basis to ensure that the information stays current. The aim of most of the explicit criteria is to identify medicine items or classes thereof that should be avoided in elderly patients, to identify drug-drug or drug-disease interactions and to assess the overall quality of care in elderly patients. (Refer to Table 2.5). The implicit tools identified aims to detect underprescribing and drug omissions, identify patients that are at a higher risk of experiencing drug-related problems and to determine the appropriateness and assess the entire regimen of the individual patient. (Refer to Table 2.6). The tools with a mixed approach use a combination of both the implicit and the explicit criteria. The main aim of these tools is to assess the geriatric patient, identify potential medicine-related problems, educate physicians and pharmacists to reduce inappropriate prescribing and improve the overall prescribing for elderly patients. (Refer to Table 2.7).

According to the results of a Boolean search (refer to Table 2.10), the Beers criteria were the most popular criteria used to determine the prevalence of inappropriate prescribing. The prevalence of inappropriate prescribing when using the Beers criteria varied from 9.3% to 66.0%. The STOPP/START criteria were also frequently used with prevalence of inappropriate prescribing ranging from 10.3% to 60%. Other criteria used in studies included in the Boolean search included the FORTA criteria, WHO prescribing indicators, geriatric medication algorithm, McLeod criteria, Rancourt criteria, InterResident Assessment Instrument Minimum Data Set for nursing home care, Medicine Appropriateness Index, NORGEP criteria and the French potentially inappropriate medication list. (Refer to Table 2.10).

- **To compare different tools or criteria available to ensure appropriate medicine prescribing for elderly patients with regard to items listed in the different tools or criteria**

This literature objective was also answered in Chapter two, section 2.5.

The explicit, implicit and mixed criteria available to evaluate the appropriateness of drugs prescribed to elderly patients are outlined in Tables 2.5 to 2.7. Explicit criteria are applied as fixed specifications that do not consider individual characteristics of the individual patient whereas implicit criteria are based on clinical knowledge and do not have the consensus-based structure (Shelton *et al.,* 2000:441). The combination of implicit and explicit criteria is specific for the individual patient, supportive and provides a structured technique with the option for the reviewer to apply clinical knowledge when required (Shelton *et al.,* 2000:439). (Refer to paragraph 2.5).

According to the literature, Lindblad's criteria, STOPP/START, IPET and the Geriatric Medication Algorithm are easy to use (Mimica Matanović & Vlahović-Palčevski, 2012:1125-1126; Shelton *et al.,* 2000:442; Yogita & Priti, 2013:639), the ACOVE criteria are complicated to apply (Wenger *et al.,* 2007:S251) and the Beers criteria are the most extensively used (Chang & Chan, 2010:949). Polypharmacy, including underprescribing, is addressed in the ACOVE criteria, STOPP/START criteria, assessment of underutilisation of medicine, ARMOR and prescribing optimisations method for improving prescribing in the elderly (Drenth-van Maanen *et al.,* 2009:689; Haque, 2009:27; Wenger *et al.,* 2007:S247; Yogita & Priti, 2013:638). Criteria that suggest therapeutic alternatives include Austrian criteria, Laroche criteria, McLeod's criteria, the PRISCUS list and the Europe (EU) 7 PIMs list (Chang & Chan, 2010:949-950; Holt *et al.,* 2010:543; Mann *et al.,* 2012:160; Renom-Guiteras *et al.,* 2015:861), while Lindblad's criteria and NCQA involves drug-disease interactions (Albert *et al.,* 2010:409; Mimica Matanović & Vlahović-Palčevski, 2012:1125). Drug-drug interactions

are addressed in Malone's list (Malone *et al.,* 2004:65), while the NORGEP criteria can be used for cases where no clinical information is needed (Dimitrow *et al.,* 2011:1527). Rancourt's criteria do not take clinical information into consideration (Rancourt *et al.,* 2004:6).

Overall medicine usage is evaluated in the Winit-Watjana criteria (Winit-Watjana *et al.,* 2008:49), the prescribing indicators tool the Zhan criteria focus on drugs to avoid (Dimitrow *et al.,* 2011:1527; Yogita & Priti, 2013:639), and the Maio criteria and Terrell Computerized Decision Support System determine the prevalence of potentially inappropriate medicines (PIMs) (Maio *et al.,* 2010:225-226; Terrell *et al.,* 2009:1392).The Beers criteria, Maio criteria, TIMER and the Medication Management Outcomes Monitor need to be updated on a regular basis (Drenth-van Maanen *et al.,* 2009:689; Lee *et al.,* 2009:5-7; Maio *et al.,* 2010:226; National Guideline Clearinghouse, 2012). The Matsumura alert system focuses on overprescribing and is a web-based system (Matsumura *et al.,* 2009:556). Adverse drug reactions (ADRs) are taken into consideration in the American Medical Directors Association's Top 10 particular dangerous drug interactions list (American Medical Directors Association, 2011).

The quality of prescribing is better assessed when applying the FORTA criteria and Oborne's prescribing indicators (Frohnhofen *et al.,* 2011:1417; Oborne *et al.,* 1997:96), while Phadke's criteria and Cantrill's indicators can be useful when evaluating the prescription as a whole (Cantrill *et al.,* 1998:130; Yogita & Priti, 2013:646). The Medicine Appropriateness Index, Lipton's criteria and PMDRP are time consuming tools (Drenth-van Maanen *et al.,* 2009:689; Shelton *et al.,* 2000:442-443). Owen's steps for medicine-related problems as well as Barenholtz-Levy and Brown's model can be used to identify patients with medicine-related problems (Barenholtz-Levy, 2005:985; Brown *et al.,* 1998:696; Owens *et al.,* 1994:47). (Refer to Tables 2.5 to 2.7 for a complete description of all the available explicit, implicit and mixed approach criteria or screening tools available for assessing appropriateness of prescribing in the elderly patient).

The Beers criteria are the most commonly used criteria to evaluate the appropriateness of prescribing in the elderly patients. The Beers criteria are updated on a regular basis so that the information stays current. The Beers criteria are seen as the gold standard in determining appropriateness of prescribing in elderly patients and are widely applicable and therefore it was used in the empirical investigation of this study. The Mimica Matanović and Vlahović-Palčevski comprehensive drug-drug interaction list that was also used in this study is a combination of Malone's and Hanlon's lists for drug interactions with the addition of a few new interactions. The North-American and European tools were combined to complete the Mimica Matanović and Vlahović-Palčevski comprehensive drug-drug interaction list which

made it a very useful tool to determine the prevalence of drug-drug interactions in our study population.

To summarise, the aim of the literature review was to determine what prescribing appropriateness entails and to identify the tools and criteria available to assess the appropriateness of prescribing for elderly patients. The literature review also revealed that although inappropriate prescribing is common among elderly patients worldwide, limited information is available with regard to the prevalence of inappropriate prescribing among the South African elderly population. It provided data on the prevalence of inappropriate prescribing in other countries which can be used to compare the prevalence found in the private health sector of South Africa.

4.3.2 Conclusions from the empirical investigation

The objectives of the empirical investigation as outlined in Chapter one, paragraph 1.2.2 were achieved in Chapter three. The following paragraphs summarise the findings.

- **To determine the appropriateness of prescribing in patients 65 years and older on the database by application of the Beers criteria stratified by age, gender and prescriber**

This empirical objective was achieved in manuscript one.

A total of 103 420 patients 65 years and older were included in the study with a total of 1 544 268 prescriptions claimed for this age group. Although women received proportionally more prescriptions than men, there was no difference between the sexes in terms of average number of prescriptions claimed per patient. A total of 4 231 014 drugs were prescribed of which 2 494 560 (59%) were prescribed to women.

The 2012-Beers criteria applied to the claims data identified 562 852 (13%) potentially inappropriate drugs prescribed to a total of 71 206 (68.9%) of patients. The majority of patients received one potentially inappropriate drug (37.2%), 26.1% received two and 16.2% received three potentially inappropriate items. A further 11 % received five or more potentially inappropriate drugs.

Proportionally, more women (72.3%) received potentially inappropriate drugs than men (64.3%); however, this difference was not significant. The most frequently potentially inappropriate prescribed drug overall was oestrogen, followed by meloxicam, amitriptyline and combinations thereof, diclofenac, ibuprofen, alprazolam, meprobamate and combinations thereof, insulin, amiodarone and doxazosin. These items compare well to

those identified in other studies (Albert *et al.,* 2010; Azana Fernandez & Davila Barboza, 2013; Barry *et al.*, 2006; Bonk *et al.,* 2006; Brekke *et al.,* 2008; Chetty & Gray, 2004; Fialová *et al.,* 2005; Fick *et al.,* 2008; Golden *et al.,* 1999; Hamilton *et al*., 2011; Lechevallier-Michel *et al.,* 2005; Liu *et al.,* 2012; Lund *et al.,* 2015; Moraes *et al.*, 2013; NPS Medicinewise, 2013; Onder *et al.,* 2003; Parsons *et al.,* 2012; Pitkala *et al.,* 2002; Rancourt *et al.,* 2004; Ryan *et al.,* 2013; Van der Hooft *et al.,* 2005; Wahab *et al.,* 2012). These studies also identified items such as amitriptyline, benzodiazepines, doxazosin, proton-pump inhibitors, non-steroidal anti-inflammatory drugs, digoxin, antihistamines and oestrogen as the most frequently potentially inappropriately prescribed items. Women received significantly more oestrogen than men with a moderate association. For insulin and doxazosin men received significantly more prescriptions than women with a moderate association. For all the other items listed above, there was no practically significant difference between sexes.

General practitioners prescribed the largest number of inappropriate medicine to the elderly population, followed by the specialist group, pharmacists and other prescribers (which included psychiatrists, radiologists, oncologists and surgical medical professionals). The number of potentially inappropriately prescribed items per prescriber group differed significantly although the association was weak.

The prevalence of potentially inappropriate prescriptions in this study (13.0%) was less than that found by international studies (ranging from 20-40%) (NPS Medicinewise, 2013). It was also less than that found in another study (30%) that was conducted in the public sector primary healthcare facilities in South Africa (Chetty & Gray, 2004). A possible explanation for the difference in the prevalence of potentially inappropriate prescriptions may be due to the functions performed during real-time DUR process used by the PBM for claim processing.

Women in the study population tended to receive more inappropriate medicine items than men; however, no difference between the sexes was found in terms of average number of drugs prescribed per patient, which could have influenced this association.

In conclusion, the study showed that prescribing according to explicit criteria was common in elderly patients registered on the database. Women were more likely to be exposed to potentially inappropriate medicine items than their male counterparts. Explicit criteria cannot substitute clinical judgement based on the individual patient and therefore there is need of a prescribing measure in older adults in the South African health sector that can be used to encourage value-driven healthcare.

- **To determine the prevalence of potentially serious drug-drug interactions (DDIs) in patients 65 years and older on the database by application of the Mimica Matanović and Vlahović-Palčevski-comprehensive drug-drug interaction list, stratified by age and gender**

This empirical objective was achieved in manuscript two.

A total of 103 420 patients were included in this study with 59 071 (57.1%) women and 44 343 (42.9%) men. A total of 4 228 398 drugs were prescribed to these patients with 2 492 951 (59%) prescribed to female patients and 1 735 447 (41%) to male patients. Prevalence of both prescriptions and drugs in women increased with age; however, there was no significant difference between the sexes with regard to the mean number of prescriptions per patient or the mean number of drugs per prescriptions. There was a statistically significant difference between the age groups with regard to the mean number of prescriptions per patient and the mean number of drugs per prescription. Based on effect sizes, however, the actual difference in means between the age groups was quite small.

In total, 331655 (7.8%) drug interactions were identified among the 4 231 014 drugs prescribed on a total of 912 713 prescriptions (37.3%). Women encountered more interactions than men (63.5% *vs*.36.5%); however, the difference was not significant.

The most common DDIs identified in this study were all clinically significant pharmacodynamic drug-drug interactions. The drug-drug interaction with the highest prevalence was between central nervous system drugs and central nervous system drugs (30.6%), followed by antihypertensive drugs and non-steroidal anti-inflammatory drugs (23.5%), diuretics and non-steroidal anti-inflammatory drugs (8.3%), angiotensin converting enzyme inhibitors and potassium supplements (4.9%) and non-steroidal anti-inflammatory drugs/aspirin and corticosteroids (4.8%). Within the central nervous system drugs, the drug pairs most frequently identified was zolpidem/alprazolam (16.3%), followed by zolpidem/amitriptyline (15.5%) and zolpidem/citalopram (14.5%). The antihypertensive drugs plus non-steroidal anti-inflammatory drugs pairs most frequently identified were bisoprolol/meloxicam (4.9%), followed by amlodipine/meloxicam (4.6%) and bisoprolol/celecoxib (4.4%).

Approximately 26% of prescriptions for medications for elderly patients on the database contained at least one potential DDI, which was slightly higher than the range found by other database studies ranging from 4.7-22% (Egger *et al.,* 2003; Grönroos *et al.,* 1997; Linnarson, 1993; Magro *et al.,* 2007; Nobili *et al.,* 2009; Rosholm *et al.*, 1998). (Refer to manuscript two). A limited number of studies are available measuring the prevalence of DDIs in South

Africa. The DDIs identified in this study were more prevalent among patients older than 78 years. Similar results were found by other international studies (Eggar *et al.,* 2007; Nobili *et al.,* 2009). DDIs were higher among women. Possible explanations for these results might be that women outnumbered the men in this study and that women received proportionally more prescribed medication than men.

The study revealed that about one in four prescriptions for elderly patients from the study population contained a potentially serious DDI. Patients' sex and age were found to be weak predictors of potential DDIs as assessed using the Mimica Matanović/Vlahović-Palčevski comprehensive drug-drug interaction tool. Drugs of concern in patients were the sedative hypnotics (benzodiazepines and other), antidepressants, antihypertensives and nonsteroidal anti-inflammatory drugs. Sedative hypnotics may cause drowsiness and impair balance which may lead to an increased risk for falls in elderly patients, while antidepressants may lead to anticholinergic side effects which include confusion. It may also cause drowsiness and postural hypotension in elderly patients. Antihypertensive agents may cause postural hypotension in the elderly and NSAIDs should be used with care in patients with cardiac disease or renal impairment. Bleeding associated with NSAID use is also more common in elderly patients.

Inappropriate prescribing and drug-drug interactions were common among the study population. Female patients received more inappropriate prescriptions and had a higher prevalence of DDIs than their male counterparts. The prevalence of inappropriate prescriptions was the highest among patients between the ages of 72 and 78 years, whereas the prevalence of DDIs was the highest in patients older than 78 years.

Pharmacodynamic DDIs was the most prevalent of all DDIs identified in the study population with CNS drugs being the most frequent group involved in the DDIs.The most common CNS drugs pairs involved in DDIs in our study included zolpidem/alprazolam, zolpidem/amitriptyline and zolpidem/citalopram. Combining these items lead to an enhancement of the CNS effects and an increased risk of experiencing adverse effects. Adverse effects associated with the use of zolpidem and alprazolam include delirium, falls and fractures, impaired cognitive functions and an increased risk for motor vehicle accidents (Fick *et al.,* 2012; Hollingworth & Siskind, 2010).Both amitriptyline (tricyclic antidepressant) and citalopram (selective serotonin reuptake inhibitor) are used for treatment of depression. The use of zolpidem with these two items should be avoided as it may lead to additional impairment of cognitive and motor-functions, delirium and increased risk of falls in the elderly (Fick *et al.,* 2012).

The use of anti-inflammatory drugs were also high in the elderly population, and the study revealed that anti-inflammatory drugs (especially nonsteroidal anti-inflammatory drugs) was one of the groups of drugs most frequently involved in DDIs. Several NSAIDs can be purchased as over the-counter-drug analgesics in South Africa. Healthcare workers, in particular pharmacists, are therefore key players for finding and preventing these interactions.

The most frequently inappropriate prescribed drug was oestrogen. During the past decade there has been much debate regarding the safe use of hormone replacement therapy in elderly women, which could have resulted in confusion for prescribers (Mkele, 2014:27). The International Menopause Society published a universal agreement statement in the use of hormone therapy in menopause in 2013. In 2014 the South African Menopause Society (SAMS) revised the SAMS Council consensus statement on menopausal hormone therapy published in 2007. Similar recommendations were included in the revised edition and several other clinical benefits, including the use of non-hormonal alternatives for management of vasomotor symptoms, were incorporated (Guidozzi *et al.,* 2014:537). Further studies should assess the influence of these guidelines on the prescribing of oestrogen among elderly women.

Of all the prescribers, the general practitioners were the group that prescribed the highest number of inappropriate items. The results of the study also revealed that although there is a clear need for a prescribing tool for elderly patients in the South African health sector, it is important to remember that the use of such a tool cannot substitute clinical judgement based on the need of the individual patient.

4.4 Study limitations and strengths

Several limitations apply to this study. Data from only one PBM was used, and therefore only members of the medical schemes administered by the selected PBM were represented in the study. The population covered included only members from certain healthcare plans. Subjects may have gone in and out of eligibility, which may have led to subjects and data being missed. The database used only included claims for medicine items. In most of the administrative databases, only the demographic data and those that are needed for financial management may be accurate. The ICD-10 codes were not always available and it may not be clear whether a diagnosis or treatment was new or whether a coded diagnosis was comorbidity or a complication.

A further limitation is that only a sample of private health sector data was included in this study. However, the private health sector comprises about 16% of the total health sector.

The PBM used provided services to 35 medical schemes and 5 capitation provider clients, administered by 15 different healthcare administrators. The PBM was at the time of the study linked up to most of South Africa's pharmacies and 98% of all dispensing medical practitioners and processed over 300 000 real-time claims and 30 000 prescribers' transactions on a daily basis. (Refer to paragraph 1.3.2.2).

Not all types of potentially inappropriate medications were addressed in the Beers criteria as it does not comprehensively address the need of the individual patient receiving palliative and hospice care (Yogita & Priti, 2013:639). Only medicine items listed that was available in South Africa at the time of the study (i.e. 102 of the 143 Beers criteria items) was included. (Refer to manuscript one).

The prevalence of DDIs was determined using only the Mimica Matanović and Vlahović-Palčevski comprehensive drug-drug interaction list, and other potential DDIs as listed in other reference guides (refer to paragraph 4.3.2) were not included in the study. Exclusion of these other potential DDIs might have led to a lower prevalence of DDIs in elderly patients.

Strengths of the empirical study included that data from a well-known PBM was used. The PBM has certain validation processes in place to ensure the validity and the reliability of the data. The database is updated on a regular basis which ensures that the data is current and valid. (Refer to paragraph1.3.2.3). Other strengths of the study include that all patients aged 65 years and older that were active members of the medical schemes at the time of the study were included in the study. Only paid claims were included in the study. (Refer to paragraph 1.3.2.4).

4.5 Recommendations

The results of this study underscore the importance of adapting the Beers criteria list to fit the needs of a prescribing measure in older adults in the South African health sector to encourage value-driven healthcare. Further studies in the South African private health sector are needed to clarify the dynamics of sex differences in interactions between healthcare providers and patients resulting in women being prescribed more medications.

From the study, the following recommendations are made:

- Validation of the Beers criteria and Mimica Matanović and Vlahović-Palčevski comprehensive drug-drug interaction list for the South African healthcare setting.

- Determining which screening criteria are the most suitable for database-type analysis in South Africa.

- Further studies applying different screening tools to other study populations to get a better representation of the prevalence of inappropriate prescribing in the different healthcare settings of South Africa.

- Developing a list of prescribing guidelines or potentially inappropriate medicines for elderly patients that is specific to the South African healthcare environment.

4.6 Chapter summary

This chapter summarised the conclusions based on the literature and empirical objectives. In addition the limitations and strengths of the study were discussed. Finally recommendations were made for future research. Hereby the final chapter of this dissertation is concluded.

ANNEXURE A: ANNEXES TO CHAPTER ONE AND TWO

Table A.1 Beers criteria for potentially inappropriate medication use in older adults (PL detail document, 2012; Fick *et al*., 2012:619-623)

Medication	Recommendation	Rationale
Anticholinergics (excluding tricyclic antidepressants)		
First-generation antihistamines as single agent or part of combination products: Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Diphenhydramine (oral) Doxylamine Hydroxyzine Promethazine Triprolidine	Avoid	Highly anticholinergic Clearance reduced with increased age Tolerance develops when used as hypnotic Increased risk of confusion, dry mouth, constipation and other anticholinergic effects and toxicity
Antiparkinson agents: Benztropine (oral) Trihexyphenidyl	Avoid	More effective agents are available for treatment of Parkinson's disease Not recommended for prevention of extrapyramidal symptoms with antipsychotics
Antispasmodics: Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine Hyoscyamine	Avoid, except in short-term palliative care to decrease oral secretions	Highly anticholinergic Effectiveness is uncertain

Medication	Recommendation	Rationale
Propantheline Scopolamine		
Antithrombotics		
Dipyridamole (oral, short-acting)	Avoid	May cause orthostatic hypotension More effective alternatives are available Intravenous form is acceptable for use in cardiac arrest testing
Ticlopidine	Avoid	Safer and more effective alternatives are available
Anti-infective		
Nitrofurantoin	Avoid for long-term suppression Avoid in patients with a creatinine clearance <60ml/min	Potential for pulmonary toxicity Safer alternatives are available Lack of efficacy in patients with creatinine clearance 60ml/min due to inadequate drug concentrations in the urine
Cardiovascular		
Alpha-1 blockers: Doxazosin Prazosin Terazosin	Avoid use as an antihypertensive	High risk of orthostatic hypotension Not recommended as routine treatment for hypertension Alternative agents have a better benefit-risk profile
Alpha agonists: Clonidine Guanabenz Guanfacine Methyldopa Reserpine (>0.1mg/day)	Avoid clonidine as first-line antihypertensive Avoid others	High risk of central nervous system effects May cause bradycardia and orthostatic hypotension Not recommended as routine treatment for hypertension
Anti-arrhythmic drugs (class Ia, Ic and III): Amiodarone Dofetilide	Avoid antiarrhythmic drugs as first-line treatment for atrial fibrillation	Rate control yields better balance of benefits and harms than rhythm control for most older adults Amiodarone is associated with multiple toxicities,

Medication	Recommendation	Rationale
Dronedarone Flecainide Ibutilide Procainamide Propafenone Quinidine Sotalol		including thyroid disease, pulmonary disorders, and QT interval prolongation
Disopyramide	Avoid	Is a potent negative inotrope - induces heart failure Strongly anticholinergic Other safer alternative antiarrhythmic drugs preferred
Dronedarone	Avoid in patients with permanent atrial fibrillation or heart failure	Rate control is preferred over rhythm control for atrial fibrillation Worse outcomes have been reported in patients who have permanent atrial fibrillation taking dronedarone
Digoxin >0.125mg/day	Avoid	In heart failure patients, higher doses do not provide any additional benefit Risk of toxicity may be increased Decreased renal clearance may increase risk of toxicity
Nifedipine (immediate release)	Avoid	May cause hypotension May precipitate myocardial infarction
Spironolactone >25mg/day	Avoid in patients with heart failure or with a creatinine clearance 30ml/min	The risk of hyperkalaemia is higher in heart failure if the patients are taking >25mg/day
Central nervous system		
Tertiary TCAs, alone or in combination: Amitriptyline Chlordiazepoxide-amitriptyline	Avoid	Highly anticholinergic May cause sedation May cause orthostatic hypotension

Medication	Recommendation	Rationale
Clomipramine Doxepin >6mg/day Imipramine Perphenazine-amitriptyline Trimipramine		The safety profile of low-dose doxepin (≤ 6mg/day) is comparable to that of placebo
First and second generation antipsychotics First generation (conventional) agents: Chlorpromazine Fluphenazine Haloperidol Loxapine Molindone Perphenazine Pimozide Promazine Thioridazine Thiothixene Trifluoperazine Triflupromazine Second generation (atypical) agents: Aripiprazole Asenapine Clozapine Iloperidone Lurasidone Olanzapine Paliperidone Quetiapine Risperidone Ziprasidone	Avoid use for behavioural problems or dementia unless non-pharmacologic options have failed and patient is threat to self or others	Increased risk of cerebrovascular accident Increased mortality in persons with dementia

Medication	Recommendation	Rationale
Thioridazine Mesoridazine	Avoid	Highly anticholinergic Greater risk of QT-interval prolongation
Barbiturates: Amobarbital Butabarbital Butalbital Mephobarbital Pentobarbital Phenobarbital Secobarbital	Avoid	High rate of physical dependence Tolerance to sleep benefits Greater risk of overdose at low dosages
Benzodiazepines Short- and intermediate acting Alprazolam Estazolam Lorazepam Oxazepam Temazepam Triazolam Long-acting Chlorazepate Chlordiazepoxide Chlordiazepoxide-amitriptyline Clidinium-chlordiazepoxide Clonazepam Diazepam Flurazepam Quazepam	Avoid any type of benzodiazepines for the treatment of insomnia, agitation or delirium	Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents Increase risk of cognitive impairment, delirium, falls, fractures and motor vehicle accidents in older adults May be appropriate for seizure disorders, rapid eye movement sleep disorders, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, periprocedural anaesthesia and end-of-life care
Chloral hydrate	Avoid	Tolerance occurs within 10 days Risk outweighs the benefit in light of overdose with doses only three times the recommended

Medication	Recommendation	Rationale
		dose
Meprobamate	Avoid	High rate of physical dependence Very sedating
Non-benzodiazepine hypnotics: Eszopiclone Zolpidem Zaleplon	Avoid chronic use (>90 days)	Adverse events are similar to those of benzodiazepines in older adults Shows minimal improvement in sleep latency and duration
Ergot mesylates Isoxsuprine	Avoid	Lack of efficacy
Endocrine		
Androgens: Methyltestosterone Testosterone	Avoid unless indicated for moderate to severe hypogonadism	Contraindicated in men with prostate cancer Potential for cardiac problems
Desiccated thyroid	Avoid	Concerns about cardiac effects Safer alternatives available
Oestrogens with or without progestin	Avoid oral and topical patch Topical vaginal cream: acceptable to use low-dose intra-vaginal oestrogen for the management of dyspareunia, lower urinary tract infections and other vaginal symptoms	Evidence of carcinogenic potential (breast and endometrium) Lack of cardioprotective effect and cognitive protection in older women Vaginal oestrogens for the treatment of vaginal dryness are safe and effective in women with breast cancer, especially at dosages of estradiol<25mcg twice weekly
Growth hormone	Avoid, except as hormone replacement following pituitary gland removal	Effect on body composition is small Associated with oedema, arthralgia, carpal tunnel syndrome, gynecomastia and impaired fasting glucose
Insulin (sliding scale)	Avoid	Higher risk of hypoglycaemia without improvement in hyperglycaemia management regardless of care setting

Medication	Recommendation	Rationale
Megestrol	Avoid	Minimal effect on weight Increases risk of thrombotic events and possible death
Sulfonylureas: Chlorpropamide Glyburide	Avoid	Chlorpropamide – associated with prolonged half-life in older adults, can cause hypoglycaemia and is associated with syndrome of inappropriate antidiuretic hormone secretion Glyburide – associated with higher risk of severe prolonged hypoglycaemia in older adults
Gastrointestinal		
Metoclopramide	Avoid, unless for gastroparesis	Can cause extrapyramidal effects including tardive dyskinesia Risk may be further increased in frail older adults
Mineral oil (orally)	Avoid	May cause aspiration and adverse effects Safer alternatives are available
Trimethobenzamide	Avoid	One of the least effective antiemetic drugs Can cause extrapyramidal effects
Pain medications		
Meperidine	Avoid	Not effective in dosages commonly used May cause neurotoxicity Safer alternatives are available
Non-cyclooxygenase-selective nonsteroidal anti-inflammatory drugs oral Aspirin >325mg/day Diclofenac Diflunisal Etodolac Fenoprofen Ibuprofen Ketoprofen Meclofenamate	Avoid chronic use unless other alternatives are not effective and patient can take gastro-protective agents such as a proton pump inhibitor or misoprostol	Increases risk of gastrointestinal bleeding or peptic ulcer disease in high-risk groups including those ≥75 years old, or taking oral or parenteral corticosteroids, anticoagulants, or platelet agents Use of proton pump inhibitor or misoprostol reduces, but does not eliminate the risk

Medication	Recommendation	Rationale
Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin		
Indomethacin Ketorolac (includes parenteral)	Avoid	Increased risk of gastrointestinal bleeding or peptic ulcer disease in high-risk groups Indomethacin has the most adverse effects of all the nonsteroidal anti-inflammatory drugs.
Pentazocine	Avoid	Causes central nervous system adverse effects including confusion and hallucinations more commonly than other narcotic drugs Is a mixed agonist and antagonist Safer alternatives are available
Skeletal muscle relaxants: Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine	Avoid	Poorly tolerated by older adults Anticholinergic adverse effects include sedation and increased risk of fracture Effectiveness of dosages tolerated by older adults is questionable

Table A.2 Beers criteria for potentially inappropriate medications to be used with caution in older adults (PL detail document, 2012)

Medication	Recommendation	Rationale
Aspirin for primary prevention of cardiac events	Use with caution in adults ≥ 80 years old	Not sufficient evidence of benefit versus risk in individuals ≥ 80 years old
Dabigatran	Use with caution in adults ≥ 75 years old or if CrCl < 30 ml/min	Increased risk of bleeding compared with warfarin in adults ≥ 75 years old Insufficient evidence for efficacy and safety in patients with CrCl < 30 ml/min
Prasugrel	Use with caution in adults ≥ 75 years old	Greater risk of bleeding Risk may be offset by benefit in highest-risk older patients
Antipsychotics Carbamazepine Carboplatin Cisplatin Mirtazapine Serotonin-norepinephrine reuptake inhibitors Selective serotonin reuptake inhibitors Tricyclic antidepressants Vincristine	Use with caution	May exacerbate or cause syndrome of inappropriate antidiuretic hormone secretion or hyponatremia Need to monitor sodium level closely when starting or changing dosages in older adults due to increased risk
Vasodilators	Use with caution	May exacerbate episodes of syncope in individuals with history of syncope

Scopolamine = Hyoscine (South Africa)

Table A.3 Potentially serious drug–drug interactions in the elderly (Mimica Matanović & Vlahović-Palčevski, 2011)

1. Clinically significant pharmacokinetic drug-drug interactions
Anti-arrhythmic
Disopyramide– cimetidine Disopyramide– macrolides (except azithromycin) Procainamide– amiodarone Procainamide– cimetidine Procainamide– trimethoprim Quinidine– cimetidine Quinidine– fluvoxamine
Anti-epileptics
Carbamazepine– danazol Carbamazepine– diltiazem Carbamazepine – macrolides Carbamazepine – verapamil Phenytoin – amiodarone Phenytoin – cimetidine Phenytoin – fluoxetine Phenytoin – isoniazid Phenytoin – omeprazole Quinidine – phenytoin Theophylline – phenytoin Warfarin – phenytoin
Other drugs with low therapeutic index:

Digoxin – clarithromycin Digoxin – amiodarone Digoxin – propafenone Digoxin – quinidine Digoxin – verapamil Lithium – ACE inhibitors Lithium – diuretics Lithium – NSAIDs Procainamide – cimetidine Salicylates – probenecid Theophylline – cimetidine Theophylline – erythromycin, clarithromycin Warfarin – amiodarone Warfarin – macrolides Warfarin – quinolones Warfarin – sulfamethoxazole
2. Drug-drug interactions selected by Malone *et al.*(2004) as having greatest clinical importance (pharmacokinetic and pharmacodynamic)
Benzodiazepines – azole antifungal agents Cyclosporine – rifampin Ergot alkaloids – macrolide antibiotics (except azithromycin) MAO inhibitors – sympathomimetics (dopamine, ephedrine, phenylephrine, pseudoephedrine) Meperidine – MAO inhibitors Methotrexate – trimethoprim Nitrates – sildenafil SSRIs – MAO inhibitors Theophylline – fluvoxamine Theophylline – quinolones Thiopurines – allopurinol Warfarin – fibric acid derivatives Warfarin – NSAIDs

Warfarin – cimetidine Warfarin – thyroid hormones Warfarin – barbiturates
3. Other clinically important drug-drug interactions (pharmacokinetic and pharmacodynamic)
Atorvastatin/simvastatin – amiodarone Potassium – potassium-sparing diuretics Clopidogrel – PPIs Levodopa – MAO inhibitors SSRIs – metoclopramide SSRIs – tramadol HMG Co-A reductase inhibitors – gemfibrozil Atorvastatin/simvastatin – macrolide antibiotics
4. Clinically significant pharmacodynamic drug-drug interactions
ACE inhibitors – potassium-sparing diuretics ACE inhibitors– potassium supplements Anticholinergic – anticholinergic Antihypertensive – NSAIDs CNS agents (e.g. diazepam) – CNS agents (e.g. codeine) Diuretics – NSAIDs NSAIDs, aspirin – corticosteroids Verapamil – beta blockers Warfarin – antiplatelet agents Antiplatelet agent – antiplatelet agent

Table A.4 Checklist to ensure validity and reliability of the database used (adapted from Hall *et al*., 2011)

Consideration	Aspect	Checklist item	Approach
Database selection	Population covered	Is the study population appropriate in terms of size, coverage and representativeness?	Refer to target population and study population section 3.1.2.3.
	Capture of study variables	Are all exposures, outcomes and other variables captured in detail without bias and are they accessible for research?	Refer to data analysis, data analysis plan and statistical analysis section 3.1.3.
	Continuous and consistent data capture	Were there any changes or breaks in the data collection over time for individual patients or the whole population during the observation period? Were there any inconsistencies in healthcare provision or the capturing of study variables across the database population?	Refer to target population and study population section 3.1.2.3. Prescribing patterns for a one-year period will be evaluated.
	Record duration and data latency	Are the average patient record duration and the time between the occurrence of the exposure and the data collection long enough for the study event?	Refer to target population and study population section 3.1.2.3. Data from 2013 will be used.
	Database expertise	Is the expertise (in-house or elsewhere) to use the resource available?	Assistance will be received from the relevant personnel of the North-West University.
Use of multiple resources	Multiple resources linked to increase breadth of patient information	Can data resources be linked?	Refer to section 3.1.2.2 for data elements that will be extracted from the database for each patient. For this study, only one database will be used.

Consideration	Aspect	Checklist item	Approach
	Multiple resources linked to increase numbers	Are the data sources and the data system compatible in metrics, policy and terminology?	Only one database will be used.
Use of multiple resources continued	Linkage	Is reliable person matching possible for sufficiently large proportions of the database population? Are experience and techniques available and can duplicates be identified?	Only one database will be used.
	Data storage and analyses	Should a central or distributed model be used?	A central model should be used.
Extraction and analysis of the study population	Specification of extraction	Is it specified in detail how to extract the: study population and variables; code lists and non-coded systems; Retrieval and merging of additional external data; and output and final analysis?	Refer to sections 3.1.2.2 and 3.1.2.3.
Privacy and security	Compliance with privacy and security policy	Have all relevant local, regional and national policies been complied with?	Refer to ethical considerations sections 4.1.2 and 4.1.3.
	Limited use of identifying information	Are all direct identifiers removed or masked? Whose responsibility is it to ensure privacy?	Refer to section 4.1.2.
	Secure data storage and transfer	Is there a formal data security policy? Has the policy been adhered to?	Refer to section 4.1.3.
	Review of policy and procedures	Are regular privacy reviews adhered to? Has the use of a new database, collection of additional patient or	Refer to section 4.1.3.

Consideration	Aspect	Checklist item	Approach
		physician data, use of multiple resources, or narrative data impacted confidentiality?	
Quality and validation procedures	Overall database	Have appropriate general quality checks been done?	Refer to section 3.1.2.2.1, (Paragraph three).
	Study population	Which study-specific quality checks are needed with regard to the extraction process, data merging, study variables and assumptions? Did an independent programmer review the annotated programming code?	Refer to section 3.1.2.2 for elements (fields) that will be extracted from the database. Refer to section 3.1.2.3 for the inclusion and exclusion criteria.
	Testing	Checks can be external, logical or internal. Checks should be cross-sectional, longitudinal and up to date.	Refer to section 3.1.2.2.1. (Paragraph three).
Documentation	Format	Are all the rules of Guidelines for Good Pharmacoepidemiology Practices followed (including storage and indexing)?	Refer to sections 4.1.2 and 4.1.3 for ethical considerations.
	Specifics	Have extraction specifications, output, quality testing, merging resources, responsibility for privacy and annotated programming code for data extraction and final analysis been documented?	Refer to section 3.1.2.2 for data elements (fields) that will be extracted from the database.

ANNEXURE B: AUTHOR GUIDELINES FOR THE SOUTH AFRICAN MEDICAL JOURNAL (MANUSCRIPT ONE)

Instructions for Authors:
(http://www.samj.org.za/index.php/samj/about/submissions#authorGuidelines Date of access: 21 Jan. 2016).

Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields. *References should be limited to no more than 15.* Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results,* and *Conclusion.*

Scientific letters will be considered for publication as shorter ***Research articles***.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the *SAMJ* peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Forum articles must be accompanied by a short description (50 words) of the affiliation details/interests of the author(s). Refer to recent forum articles for guidance. Please provide an accompanying abstract not exceeding 150 words.

Book reviews should be about 400 words and must be accompanied by the publication details of the book.

Obituaries should be about 400 words and may be accompanied by a photograph.

Guidelines must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed. A structured abstract not exceeding 250 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents. References, appendices, figures and tables must be kept to a minimum.

Guidelines exceeding 8 000 words will only be considered for publication as a supplement to the SAMJ*; the costs of which must be covered by sponsorship or advertising. The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.*

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

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If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

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Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

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One author:
Szeto HH. Simultaneous determination of meperidine and normeperidine in biofluids. *J Chromatogr* 1976; 125: 503–510.

Two authors:
Vu-Duc T, Vernay A. Simultaneous detection and quantitation of O6-monoacetylmorphine, morphine and codeine in urine by gas chromatography with nitrogen specific and/or flame ionization detection. *Biomed Chromatogr* 1990; 4(2): 65–69.

Three or more authors: Huestis MA et al. Monitoring opiate use in substance abuse treatment patients with sweat and urine drug testing. *J Anal Toxicol* 2000; 4(Suppl.3): 509–521.

Article in press:
Ladines CA et al. Impaired renal D1-like and D2-like dopamine receptor interaction in the spontaneously hypertensive rat. *Am J Physiol Regul Integr Comp Physiol* 2008 (in press).

Electronic publication ahead of print:
Teeuwen PHE. Doppler-guided intra-operative fluid management during major abdominal surgery: a systematic review and meta-analysis. *Int J Clin Pract* (accessed 21 November 2007, epub ahead of print).

Online serial:
Margolis PA et al. From concept to application: the impact of a community-wide intervention to improve the delivery of preventive services to children. Pediatrics [online] 2001; 108:e42. www.pediatrics.org/cgi/content/full/108/3/e42 (accessed 20 September 2001).

Corporate author:
The Cardiac Society of Australia and New Zealand . Clinical exercise stress testing. Safety and performance guidelines. *Med J Aust* 1996; 164: 282–284.

Anonymous author:
Anon. Coffee drinking and cancer of the pancreas. *BMJ* 1981; 283: 628.

Author with prefix and/or suffix in their name:
Humphreys Jnr, Sir Robert and Adams T. Reference style in the modern age. *J Bib Cit* 2008; 1: 1–10.

Article not in English:
Sokolov S et al. [Studies of neurotropic activity of new compounds isolated from *Rhodiola rosea* L.] Khim Farm Zh 1985; 19: 1367–1371 [in Russian].

Book references

Book by a single author or group of authors working together as a single author:
Cole MD, Caddy B. *The Analysis of Drugs of Abuse: An instruction manual*, 2nd edn. New York : Ellis Horwood, 1995.

An edited book:
Hoepfner E et al. eds. *Fiedler Encyclopedia of Excipients for Pharmaceuticals*, Cosmetics and Related Areas, 5th edn. Aulendorf: Editio Cantor Verlag, 2002.

An article in an edited book:
Sanders PA. Aerosol packaging of pharmaceuticals. In: Banker GS, Rhodes CT , eds. *Modern Pharmaceutics*. New York : Marcel Dekker, 1979: 591–626.

A book in a series:
Scott RPW. Chromatographic Detectors – *Design, Function, and Operation*. Chromatographic Science Series, 73, Cazes J, ed. New York : Mercel Dekker, 1966.

Other references

Article in conference proceedings:
Dumasia MC et al. LC/MS analysis of intact steroid conjugates: a preliminary study on the quantification of testosterone sulphate in equine urine. In: Auer DE, Houghton E, eds. *Proceedings of the 11th International Conference of Racing Analysts and Veterinarians*. Newmarket : R & W Publications (Newmarket), 1966: 188–194.

Standard:
ISO 9002. *Quality Systems – Model for Quality Assurance in Production, Installation and Servicing Quality Management System*. Geneva : ISO, 1994.

Offline database or publication:
Dictionary of Natural Products. CD-ROM. London : Chapman & Hall/CRC, 2003.

Milazzo S et al. Laetrile treatment for cancer. *Cochrane Database of Systematic Reviews*, issue 2. London : Macmillan, 2006.

Dissertation:
Youssef NM. School adjustment of children with congenital heart disease. Pittsburgh, Pennsylvania: University of Pittsburgh, 1988 (dissertation).

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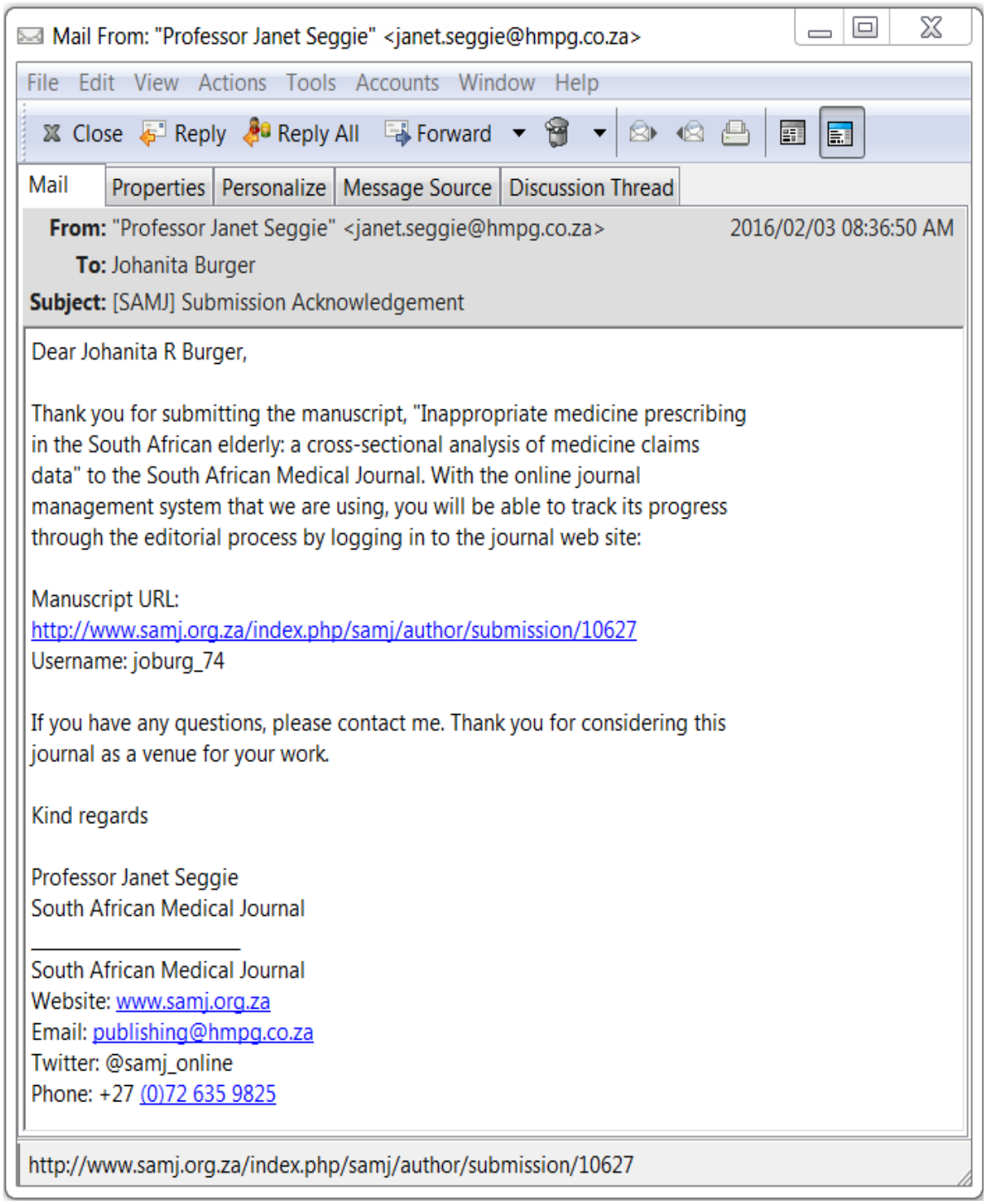

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Thank you for submitting the manuscript, "Inappropriate medicine prescribing in the South African elderly: a cross-sectional analysis of medicine claims data" to the South African Medical Journal. With the online journal management system that we are using, you will be able to track its progress through the editorial process by logging in to the journal web site:

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If you have any questions, please contact me. Thank you for considering this journal as a venue for your work.

Kind regards

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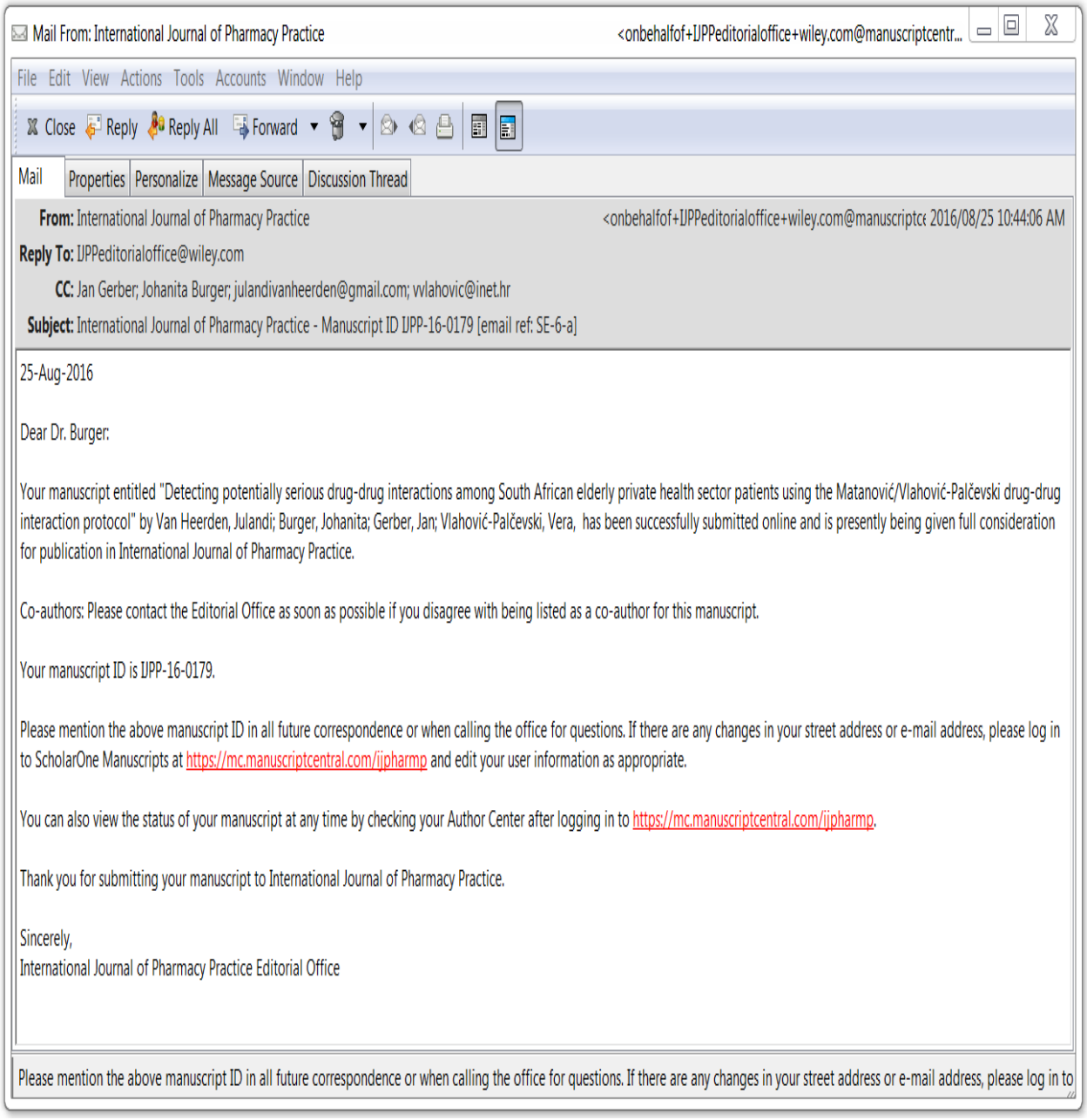

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25-Aug-2016

Dear Dr. Burger:

Your manuscript entitled "Detecting potentially serious drug-drug interactions among South African elderly private health sector patients using the Matanović/Vlahović-Palčevski drug-drug interaction protocol" by Van Heerden, Julandi; Burger, Johanita; Gerber, Jan; Vlahović-Palčevski, Vera, has been successfully submitted online and is presently being given full consideration for publication in International Journal of Pharmacy Practice.

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Acts *see* South Africa.

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