THE PREVALENCE OF POLYPHARMACY AND PRESCRIPTION OF POTENTIALLY INAPPROPRIATE MEDICATIONS IN THE ELDERLY

BY

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Submitted in fulfillment of the requirements for the degree

Master in Medicine (MMED) in Internal Medicine

at the

Department of Internal Medicine

Faculty of Health Sciences at the University of the Free State

Submission Date: March 2021

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DECLARATION OF AUTHORSHIP

I, Dr. GS Isaacs, declare that the Master's Degree mini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree qualification in Internal Medicine at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education.

DR. GS ISAACS **12 April 2021**

AUTHOR'S CONTRIBUTIONS

The contributions of each author are stipulated below:

Author	Role in the study
Dr. GS Isaacs [Researcher]	Study concept and design, data collection, interpretation of data, draft of the article
Dr. M Harmse [Supervisor]	Supervision, study conception and design, revising critically for clinical content, give final approval of the version to be submitted
Mr. C van Rooyen [Biostatistician]	Analysis of data

All researchers declare that they have no conflict of interest and that no other situation of real, potential or apparent conflict of interest is known to them. They undertake to inform the University of the Free State of any change in these circumstances.

ACKNOWLEDGEMENTS

This study would not have been completed without the assistance of the persons mentioned below. My sincere thanks and appreciation to:

- My study leader, Dr. M Harmse, specialist physician, Faculty of Health Sciences, University of the Free State, for her guidance, support and expertise.
- Mr. Cornel van Rooyen for assisting with the biostatistical analysis of the study.
- Prof. TRP Mofokeng, Head of Department of Internal Medicine, Faculty of Health Sciences, University of the Free State for his support and guidance.
- The nursing staff Universitas academic hospital's geriatric outpatient clinic at Universitas Academic Hospital for their assistance during the data collection period.

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ABSTRACT

Background: The proportion of the elderly population, considered to be the main consumers of medicine, is on the increase. High multimorbidity prevalence in elderly increases the risk for appropriate- and inappropriate polypharmacy. Polypharmacy increase the risk for adverse drug reactions and drug events, drug-interactions and is associated with an increased risk of patient harm. Polypharmacy in the elderly correlates with potentially inappropriate medication prescription.

Objectives: To determine the prevalence of polypharmacy and potentially inappropriate medication (PIM) prescription at the geriatric outpatient clinic, Universitas Academic Hospital between 1 January 2015 and 31 December 2019.

Methods: A retrospective descriptive analytical study evaluating chronic medication prescriptions of all participants aged 65 years and older that attend the geriatric outpatient clinic at Universitas Academic Hospital over a 5-year period. Prescriptions were reviewed for quantity of medicines prescribed per participant and potentially inappropriate medication prescription.

Results: A total of 786 participants were included in the study. The majority of patients were aged between 75 and 84 years. The prevalence of polypharmacy was 84.3% of which the majority was female. A mean number of 9.5 medications were prescribed, ranging from 0 to 23 medications. Overall PIM prevalence was 90.2%. Proton pump inhibitors, amitriptyline, insulin sliding scale, promethazine, doxazosin, digoxin and antipsychotics were the most frequently prescribed PIMs. The three most frequently used PIMs in the category of drugs to be used with caution in older adults were aspirin, the loop diuretic furosemide and tramadol. Fifty-two participants (6.6%) were on a combination of ≥ 3 drugs which can lead to potentially clinically important drug-drug interactions**.**

Conclusion: A high prevalence of both polypharmacy and PIM was found. Limited data is available for the South African geriatric population.

Word Count: 279

Key words: polypharmacy, geriatric, elderly, potentially inappropriate medication, multimorbidity, Beers criteria

ABBREVIATIONS AND DEFINITIONS

Geriatric:	Relates to a person aged 65 years and older[6].
Elderly /Older adult:	Synonymously with geriatric and refers to a person aged ≥ 65 years[6].
Multimorbidity (MM):	Co-existence of ≥ 2 chronic health conditions[7].
Polypharmacy (PP):	Concurrent use of ≥ 5 different prescription medications[6,7,18].
Appropriate polypharmacy:	Optimization of pharmacological treatment agents prescribed to individuals with multiple- and/or complex diseases and conditions, where medicine usage in accordance with best evidence[7,12].
PIM:	Potentially Inappropriate Medication The use of medication for which the risk of patient harm outweigh benefit, particularly with the availability of safer alternatives[45,46].
Beers list or criteria:	A screening tool consisting of listed criteria intended to guide safe prescribing in all ambulatory- institutionalized- and acutely ill geriatric patients, with the exception of elderly managed in palliative and hospice care settings. It is used to identify PIM[47,54,56,57].
AGS:	American Geriatric Society
AHCA:	American Health Care Association
ADR:	Adverse Drug Reaction[30] Noxious, unintended response to medication or lack of drug efficacy at normal- or higher drug dosages.

ADE:	Adverse Drug Event[30] Any unfavorable or unintended medical occurrence temporarily associated with medicine use which does not definitely indicate a causal medication relationship.
Deprescribing:	Medication -tapering, -withdrawing or discontinuing aiming to reduce use of inappropriate- and/or ineffective medication, adverse effects and potentially problematic polypharmacy[23,70].
Hyperpolypharmacy (HPP):	Concurrent use of 10 or more medications[43].

CHAPTER 1

LITERATURE REVIEW

The elderly population is on the rise[1]. In 2011 it was estimated that more than 60% of the global population is made up of the geriatric population (individuals aged ≥65 years)[2]. Although developed countries have, on average, an older population, it is estimated that in less than 30 years, by 2050, approximately 8 in 10 of the world's elderly will reside in less developed areas[1,3]. The growth rate amongst the elderly (aged ≥ 60 years) in South Africa has increased from 1.1% to 3.0% in 2002-2003 and in 2019 – 2020 respectively[1]. Improvement in management of communicable diseases such as the human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), malaria and tuberculosis added to the increase in life-expectancy of the elderly[4]. In South Africa the proportion of elderly, aged 60 years and older, was estimated to be 9.1% (5.43million) in 2020, a 1.5% increase from the elderly population size of 7.6% in 2002[1].

Elderly are the main consumers of medication[5]. With increasing age, it is safe to assume accumulation of chronic underlying non-communicable diseases in individuals, leading to an increased likelihood to prescribe multiple medications[6,7,8]. The elderly requires careful consideration from prescribing physicians. Common health conditions and geriatric syndromes in the elderly population includes type 2 diabetes mellitus, hypertension, ischemic cerebrovascular incidents, heart disease, cognitive impairment, depression, cataracts, joint-, respiratory- and gastro-intestinal abnormalities[9,10,11]. Continuous identification or diagnosis of new conditions over a period of time puts the geriatric population at risk of using multiple prescription drugs concurrently and continuously.

Multimorbidity (MM), the co-existence of ≥ 2 chronic health conditions in an individual, is prevalent in elderly[10,11]. In the ageing population the incidence of multiple chronic diseases and degenerative conditions increases as well as the prevalence of prescribing multiple drugs. MM increases therapeutic management complexity for both patients and health professionals and may have a negative impact on health outcomes[7]. A decrease in the quality of life, self-rated health, mobility and functional ability and an increase in hospitalisations, physiological distress, burdening of health care resources, health care costs and mortality has been associated with MM[7]. Treatment regimens,

sometimes combining pharmacological and non-pharmacological management, for elderly patients living with MM can easily become overwhelming and burdensome for both health care professionals and patients with resultant uncoordinated and fragmented care[12]. Most drug prescriptions are written in the primary health care setting and expanding knowledge about MM, polypharmacy and potentially inappropriate medication (PIM) prescription at this care level might contribute to the solution of health problems in the elderly[13,14].

After the age of 65 years most elderly spend a large proportion of their remaining life exposed to polypharmacy[15]. Life expectancy at birth in South Africa is rising with an improvement to 62,5 years and 68,5 years in males and females[1]. Females have greater longevity but higher disability rates and poorer health, a phenomenon which is described as the "male-female health-survival paradox" [16,17]. This paradox contributes to the increased risk of females to be exposed to polypharmacy for more number of years and a larger percentage of their life[15].

The definition of polypharmacy is diverse with lack of a distinct universally agreed upon definition. This makes assessment and consideration for prescription medication safety and –efficacy in clinical practice demanding for health care workers[7]. The most commonly used definition of polypharmacy is the concurrent use of five or more different prescription medications[6,7,18]. The cut-off point of 5 or more medications has good discriminative properties to identify elderly at an increased risk of harm[19]. However, the numerical value of drugs prescribed do not indicate appropriateness of therapy, as all prescribed and non-prescription medication may be clinically indicated and appropriate for the patient[18]. Physicians tend to forget to enquire about the use of over-the-counter drugs and the elderly typically do not mention the use of drugs bought over-the-counter during the consultation[18]. The concept of polypharmacy and the risk for patient harm is associated with both quantity and appropriateness of medications[18]. Polypharmacy can be classified into "appropriate" or "inappropriate/ problematic" polypharmacy[7,12,20]. The classification and definitions of polypharmacy are summarized in Table 1.

Polypharmacy classification
Appropriate polypharmacy
Medication optimization for an individual with multiple- and/or complex diseases and conditions, where medications are prescribed in accordance to best evidence[7,12].
Problematic/ Inappropriate polypharmacy
Inappropriately prescribing multiple medications and/or where the deliberate benefit or risk for harm of the medicines are not realized[12].

Table 1: Classification of polypharmacy

Polypharmacy risk factors, other than the presence of MM, in the elderly population, include:

1. Individual patient consulting various physicians resulting in various different prescriptions, described as poly-clinic or poly-doctor management[21].
2. Self-medication and ease of getting non-prescription, "over the counter" medication[22].
3. The tendency of the physician towards prescribing many medicines[23].
4. Herbal preparation use, often undisclosed to physicians[24].
5. Poor patient knowledge of drug indication for use, side effects and interactions[25].
6. Inadequate communication and coordination between physician, patient and/or caregiver[21].
7. Treating side-effects of one drug with another drug ("prescribing cascade") [26].
8. Medication prescription not based on a diagnosis but rather on individual symptoms.
9. A trend to discontinue medication if a desired effect is not immediately evident and initiating a new medication, a tendency seen frequently during hospital admissions [27].
10. Failure to reduce or discontinue medication ("deprescribing") [28].
11. Automatic repeated prescription of medications that are known to both patient and physician and automated refill services[29].
12. The absent-mindedness of the physician to inquire and of the patient to inform about the medication.

13. Inclination to use medication acquired from acquaintances[18].

14. Tendency to use medication prescribed for previous symptoms or illnesses[21].

Hospitalisation in preceding six months, female gender, depression, low level of education and consulting $\geq$ 5 physicians a year have also been reported to increase the risk of polypharmacy in the geriatric population[18]. Females, compared to males, are at a higher risk for MM development resulting in a higher susceptibility for polypharmacy and associated drug-disease and drug-drug interactions[30]. Polypharmacy is associated with frailty in older people. Mortality risk and disability incidence are higher in frail elderly with polypharmacy compared to non-frail elderly with polypharmacy[31].

More than 20 years ago, the yearly cost of medication misuse and polypharmacy in the United States was calculated to be more than $177 billion[23]. Data on the financial burden of polypharmacy for South Africa is lacking.

To prescribe appropriately in the geriatric population is a difficult and complex process. Age-related physiological changes affect pharmacokinetic- and pharmacodynamic medication profiles[5,21]. Elderly are omitted from, or underrepresented in, clinical trials done prior to medication authorisation and marketing[20,33] resulting in absent or limited availability of pharmacokinetic-, efficacy-, safety- and risk/benefit analysis specifically for an elderly target population[20,33]. Identification of inappropriate polypharmacy will decrease the risk for adverse health outcomes[18].

In elderly with MM polypharmacy is driven by initiation of multiple individual drugs proven to reduce morbidity and mortality risk in specific diseases. Evidence for risk reduction and medication recommendation for a specific disease is often determined from people without MM and concurrent polypharmacy[12]. The" law of diminishing returns" describes a likely reduction in the absolute benefit made by individual additional drugs with the use of multiple preventative drugs[12].

Problematic polypharmacy arise when medication is used without a good evidence base for the intended use or if risk of harm from medication is likely to outweigh the benefits, or where 1 or more of the following apply[12]:

- Drug-drug interaction renders the drug combination hazardous.
- "Pill burden" or overall medicine-taking demand is unacceptable to the patient.
- Difficulty in achieving clinical useful medication adherence due to overall medicine-taking demand.
- Drugs prescribed to treat other medication related side effects, where alternative options are available to reduce the quantity of prescribed medication.

The risk and incidence of drug-interactions and side-effects is increased by the concurrent use of multiple drugs[12]. Physicians can fall into the "prescribing cascade" trap where another drug is initiated for the sole purpose of treating another drug's side- effect/s[26]. The newly initiated drug has the potential to cause a new side-effect profile. Detection of adverse drug reactions in the geriatric population, compared to a younger population, is challenging. The elderly often have an atypical presentation with non-specific side-effects, such as falls, confusion, depression and constipation[34]. Adverse drug reactions (ADR) or adverse drug events (ADE) are three times more prevalent in geriatric patients[30]. ADR probability among geriatric patients is estimated to be 6% with the use of two concurrent drugs, 50% with five drugs and increasing to 100% with the simultaneous use of eight or more drugs[35].

In 2017, the World Health Organization (WHO) Third Global Patient Safety Challenge, Medication without harm, included the appropriate and effective management of polypharmacy in order to protect patients from harm as an early priority. The aim of this challenge is to globally reduce severe, avoidable, medication-related harm by 50% over 5 years by improving the medication process including prescribing, medication use and -monitoring [36].

Medication effect is dependent on pharmacokinetic and pharmacodynamic factors. Age-related normal physiological changes result in unique and altered pharmacokinetics and pharmacodynamics and prescribing to an elderly person can become complex[18,20,26]. Herbal medication use in the elderly population is highly prevalent and potential interactions with prescription medication have been reported, however knowledge on concurrent herbal medication and non-prescription- as well as prescription medication use is lacking[24]. Physicians should also consider, the often neglected, pharmacokinetics and pharmacodynamics of over-the counter medication in the ageing

patient. Pharmacokinetics include the drug absorption, distribution across compartments, metabolism and finally drug excretion. Pharmacodynamics can be defined as the response of the body to the drug, end-organ responsiveness to medication or the length and intensity of the drug's pharmacological effect on target cells. Pharmacodynamics is affected by receptor binding, post receptor effects and chemical interaction. Changes in drugs effect are caused by both changes in drug – receptor and drug – organ interactions in the elderly.

Age-related pharmacokinetic and pharmacodynamics changes in the elderly population can be summarized as follows[5,21,37,38]:

1. Absorption: Although not associated with clinically significant decreased absorption, elderly has decreased gastric acid secretion and a decreased small-bowl surface area[39]. Absorption of drugs via simple diffusion are not affected by age-related changes, however drugs depending on active transport mechanisms are poorly absorbed[40].

2. Distribution: Body composition changes in an elderly person. An increase in adipose tissue results in larger distribution volume of lipid soluble drugs leading to a longer elimination half-life, a longer time to achieve drug steady-state concentration (drug amount entering system equal to drug amount eliminated) and prolonged drug action[41]. A decrease in total body water reduces the volume of distribution of water soluble drugs resulting in higher plasma drug concentration and an increased toxicity risk[5]. Decreased serum albumin concentrations, due to various reasons, are frequently observed in elderly. In low albumin states the unbound and pharmacologically active proportion of highly protein-bound drugs increase with resultant increased drug effect and risk for toxicity[41].

3. Metabolism: Decreased hepatic blood flow leads to reduced extraction, increased bioavailability and prolonged drug effect duration of drugs that undergo extensive first pass metabolism[42]. Phase I drug metabolism reactions decline in the elderly resulting in increased free drug concentrations and greater toxicity risk. Phase II metabolism is unaffected by age[42].

4. Excretion: Renal blood flow, glomerular filtration rate and tubular secretion rate declines with age[5].

In the elderly pharmacodynamics are affected by a decrease in receptor density, changes in receptor

binding, less efficient receptor functioning, increased receptor response and altered biochemical reactions. Declining parasympathetic control enhances unwanted anticholinergic drug effects. Elderly patients are at risk of developing confusion, sedation and depression with the use of anticholinergic and other prescription drugs at therapeutic dosages due to increased brain sensitivity resulting from a physiological decline in brain receptors, decreased cerebral blood flow and increased blood-brain barrier permeability. A reduction in homeostatic mechanisms such as an impaired thirst mechanism, diminished plasma volume and vasomotor regulation increase the elderly's risk for adverse and toxic reactions (e.g. development of postural hypotension with the use of antihypertensive agents). Impairment of glucose counter-regulation make elderly susceptible to sulphonylurea-induced hypoglycemia. Pharmacodynamic action of different drugs acting at the same or interrelated receptor sites leads to different effects. The effect can be either additive (summation of effects of concurrent drug), synergistic (drug effect enhanced by another drug) or antagonistic (drug effect inhibits by another drug) [43].

Polypharmacy is a risk factor for inappropriate prescribing or PIM (Potential Inappropriate Medication) prescription[44]. PIM encompasses the use of medication for which the risks for an individual outweigh the benefits, particularly when a safer alternative is available[45,46]. PIM also includes the misuse of medicine, including inappropriate dose and duration[4546]. Due to the existence of MM the geriatric population is at risk for PIM prescription. Age-related altered pharmacokinetics and pharmacodynamics contribute to certain drugs being classified as PIM for elderly[46]. Adverse drug reactions, more admissions to hospital and increased mortality have been associated with PIM use in the geriatric population[46,47].

Polypharmacy and PIM prescription prevalence increases with age[48,49]. In the elderly population PIM prevalence reaches 40% in Europe and the United States[50]. In 2004 a potentially inappropriate prescription prevalence of 30% was reported in an elderly population attending SA public sector primary health care facilities[51]. More recently, the prevalence of potentially inappropriate prescription (PIP) in elderly Nigerian and South African patients attending outpatient clinics of one University teaching hospital in both Nigeria and South Africa was 35.2% and 29.6% respectively[52].

In 2016 a cross-sectional analysis from medical claims data in older South Africans found a PIP prevalence of 13%[53]. Residents of nursing homes tend to be more vulnerable to PIM use. Common

complications and adverse events described are delirium, hip fractures, increased risks of falls, more frequent hospitalizations and death[54].

The direct correlation between polypharmacy and PIM lead to the development of multiple screening tools to aid physicians in safer prescribing[55,56].

The American Geriatric Society (AGS) Beers Criteria is the most widely used screening for PIM. It consists of listed criteria intended to guide safe prescribing in all ambulatory- institutionalized- and acutely ill geriatric patients, with the exception of elderly managed in palliative and hospice care settings[57,58]. The Beers criteria was developed in the United States in 1991 by Dr. Beers et al in order to improve the care of elderly residing in assisted living facilities by studying the complexity of safe and appropriate medications in the older adult[54,56]. The American Geriatrics Society stewarded Beers criteria since 2011. It has produced 3 yearly criteria updates since 2012, the latest update was in2019[56,57,58]. The AGS Beers Criteria is an explicit list of PIMs that are typically best avoided by elderly in most circumstances or under specific situations, such as certain diseases or conditions. The criteria are intended for use in adults 65 years and older. The 2019 update aims to improve elderly care by reducing PIM exposure. The American Health Care Association (AHCA) prescribing recommendations emerged from the Beers criteria. According to AHCA concurrent use of nine or more drugs increased adverse event risk in the elderly[59,60].

The Beers list prescribing guidance hinge on the following: Clinical condition or disease, usual pharmacological agents prescribed to manage the condition or disease, medication use or avoidance recommendations, quality of evidence-based recommendations and literature review based recommendation strength[57,58]. AGS Beers criteria intention is to ameliorate and individualize drug selection; upskill physician and patients; lessen adverse drug events; and to provide an instrument for quality of care assessment, medication related financial burden determination and for evaluating medication use patterns in elderly[57,58]. The Beers criteria contains both prescription- and "over-the-counter" drugs.

The Beers List is segmented into tables with six main categories. The first category table includes medications which are best avoided by older adults *in most circumstances*. The rationale for avoiding the drug classes are individually explained in the table. A total of 30 discrete criteria of medications or -classes are included in this category. The second category table includes medications which typically should be avoided in elderly *with certain specified medical conditions* as

potential drug-disease or drug-syndrome interactions may exacerbate the underlying disease or syndrome. Specific drug-disease and drug-syndrome exacerbations related to the specified medications are rationalized in the table. The third category table includes medications which should be used *with caution* in the elderly. The rationale for cautious use of the individual drug classes is explained. The second and third categories include 16 criteria specific and more than 40 medications or –classes. The fourth category table includes combinations of drugs which should be avoided in elderly due to potentially *clinically important drug-drug interactions*. The increased risk of specific clinical events related to different drug combinations are rationalized in the table. The fifth category table includes medications that require drug dose adjustment or drug discontinuation *based on renal function*. This table notates creatinine clearance (ml/min) at which action is required for each individual drug as well as specific risks associated with individual drug use below noted creatinine clearance level. Each of the five tables has an additional column for each PIM / PIM class where recommendations are given for an individual drug / drug class or drug combination that should definitely be avoided. This column notes exceptions to the rule related to individual patients. All of the recommendations in the tables are followed by columns detailing the individual quality of evidence (high-, moderate- and low-quality evidence) and strength of the recommendation (strong or weak). Table 6 additionally added in the updated criteria includes drugs with strong anticholinergic properties. (See Appendix F for the complete Beers criteria).

Physicians should apply the Beers criteria for patients with good comprehension and expertise, taking into account to specific needs for each individual elderly.

Beers criteria is a valuable tool that should be used within the greater milieu of other strategies aimed at ameliorating pharmacological care for older adults. The approach to drug prescription and -use in elderly should be comprehensive. Beers criteria should be considered as one of the components to aid in prescribing and should be used in conjunction with other tools and management approaches to enhance drug efficacy and –safety and lower patients' risk for harm. There are several limitations to the criteria as limited evidence is available for the benefits and harms of medications in the elderly population. Thus, decisions on criteria development and constitution were frequently made based on best-available evidence, rather than definitive verification[57].

Several other criteria and screening tools have been developed or modified to consider national

actuality due to inconsistencies found among countries in aspects that influence drug prescriptions, such as medication availability, clinical- and prescription practices, socioeconomic class and medication regulation[13]. Examples of other screening tools include[18]:

- Inappropriate Prescribing in the Elderly Tool (IPET)
- Improved prescribing for the elderly tool (IPET)[63]
- Medication Appropriateness Index (MAI)[18,64]
- Screening Tool for Older Person's Prescriptions (STOPP)[65]
- Screening Tool to alert Doctors to the Right Treatment (START)[65]
- PRISCUS list (Priscus: Latin for old and vulnerable elderly) [47,66]
- Fit for the Aged (FORTA)[62]
- European Union List of Potential Inappropriate Medications (EU (7)-PIM List)[13]
- Norwegian General Practice (NORGEP)
- Brazilian Consensus on Potentially Inappropriate Medications (BCPIM)[13,18,20,47]

Inappropriate Prescribing for the Elderly Tool (IPET), developed in 1997 by the Canadian Consensus Panel aimed to set forward medication-related adverse reactions and medication-disease interactions, currently evidence based medicine do not support some of the initial recommendations[18]. The Improved Prescribing for the Elderly Tool, also abbreviated as IPET was developed from the older IPET criteria and published in 2000[63]. The more recent IPET criteria evaluates 14 succinct categories of frequently encountered inappropriate prescribing instances in clinical practice[63]. Strong emphasis is placed on cardiovascular-, psychotropic- and non-steroidal anti-inflammatory drugs whilst drugs from other categories are under-represented. Shortcomings in this criteria, such as the suggested avoidance of beta-blockers in patients with cardiac failure patients and the avoidance of benzodiazepine with long half-lives in all situations, limits the application outside Canada[63].

Medication Appropriateness Index (MAI), published in 1992, evaluate appropriate prescribing of individual medication based on ten criteria[18,64]. Each drug is individually evaluated and rated as completely appropriate, marginally appropriate or completely inappropriate based on drug

indication, effectiveness, correct dose, correct and practical directions, clinically significant drug-drug or drug-disease interactions, redundant duplication with other drugs, therapy time span acceptability and if the drug is of the lowest cost compared to other equal utility alternatives. MAI encompasses drug prescribing elements that can be applied to any drug and to any medical disease but implementation in everyday clinical practice is limited by the time consuming nature of MAI single drug rating (approximately 10 minutes for each drug evaluated) and the requirement of comprehensive clinical information, medical comprehension and clinical judgement[64].

The comprehensive Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START)criteria, validated in 2008 in Ireland and Britain and used in other European countries, made significant advances in pharmacological management[65]. STOPP criteria classify 65 potentially inappropriate drugs according to physiological systems, explain why prescription might be inappropriate and define PIM in terms of frequently experienced drug-drug and drug-disease interactions. Discrete components highlight analgesic medication use, drug class prescription duplications and drugs that adversely affect elderly with an increased fall risk[65]. START criteria identify 22 potentially inappropriate under prescribing instances in which life expectancy and functional status favours prescription in the absence of contra-indications to prescription[65].

PRISCUS list, a list of PIM for older adults, was developed specifically for use in Germany[47,66]. Alternative approved pharmaceutical agents and different prescribing practices restricted the use of PIM criteria lists from other countries.

Fit for the Aged (FORTA) list, also developed in Germany, rates single drugs into four categories based on the individual patient's indication for use. Categories are determined by efficacy- and safety evidence as well as overall age appropriateness. Drugs can be rated into categories of indispensable with clear benefit, proven but possible safety concerns or limited efficacy, questionable efficacy or safety and drugs to clearly avoid[62].

The main goal of potentially inappropriate medication screening tools is to refine the care of the individual geriatric patient by minimizing PIM exposure to potentially inappropriate medications, serving both as an educational tool and quality control measure[56].

For the purposes of this study we will be using the Beers criteria to identify PIM. South Africa does not have a country specific screening tool for PIM.

Prevention should be the first cornerstone to avoid polypharmacy. Multidimensional geriatric assessments lie the foundation for prevention and management of polypharmacy. Golden rules for prescribing includes careful and patient individualised consideration prior to drug initiation, prescribing with maximum knowledge about patient morbidity as well as drug effects, frequent surveilling for medication efficacy and side-effects and continued reviewing of medication to terminate, to reduce dosage or to replace with safer alternative. When prescribing it is important to consider the "maximum benefit with least risk" as all medications convey some degree of risk[18].

Better prescribing practices have been reported among female physicians[67], physicians younger than 60 years[68] and physicians who have had additional geriatric training[54,69]. Deficiency of focused geriatric pharmacotherapy educational initiatives had been recognized as a limitation to appropriate prescribing in the elderly[54]. Prescribing practices may be influenced by institutional restrictions to specific drugs or relation between individual physicians and pharmaceutical corporations[54].

Deprescribing refers to the process of medication -tapering, -withdrawing or discontinuing with the aim to reduce use of inappropriate- and/or ineffective medication, adverse effects and potentially problematic polypharmacy[23,28,70]. Deprescribing certain varieties of PIMs (e.g. nonsteroidal anti-inflammatory drugs, benzodiazepines) can improve patient outcomes and can be performed harmlessly[23]. Deprescribing aims to improve quality of life without causing withdrawal effects or worsening of underlying disease and to effectively reduce pill burden whilst maintaining control of chronic conditions[70]. Deprescribing might aid in alleviating the adverse drug event (ADE) burden observed in the elderly population. In a South African study conducted at the emergency unit of Groote Schuur Hospital, Cape town, elderly prescribed ≥ 5 medications were more likely to develop ADE's with warfarin and medications from the angiotensin-converting enzyme inhibitor- and non-steroid anti-inflammatory classes independently increasing ADE risk in this population group[71]. This study demonstrated that polypharmacy in the geriatric population also contribute to an increased health care burden, experienced not only in the outpatient and inpatient setting, but also in emergency units[71].

Information obtained from this research project can be used to identify prescribing practices in elderly patients attending the Universitas Academic Hospital geriatric outpatient clinic. This information might assist in future to draft recommendations for safe prescribing guidelines in the elderly at Universitas Academic Hospital. It will also serve as a platform to educate not only health professionals but also patients on the consequences of polypharmacy and PIM prescriptions.

RESEARCH QUESTIONS

What is the prevalence of:

a) Polypharmacy of chronic medications (use of 5 or more prescription drugs) in patients attending the geriatric outpatient clinic, Universitas Academic Hospital, Bloemfontein.
b) Potentially inappropriate medications (PIM) chronically prescribed at the geriatric outpatient clinic, Universitas Academic Hospital, Bloemfontein.

AIM OF STUDY

- To determine the prevalence of polypharmacy and potentially inappropriate medication (PIM) chronically prescribed at the geriatric outpatient clinic, Universitas Academic Hospital, between 1 January 2015 and 31 December 2019. Drugs prescribed for ≥ 6 months consecutively were used to determine chronic polypharmacy- and chronic PIM prescription prevalence.

STUDY OBJECTIVES

- To determine the difference in chronic polypharmacy prevalence between age groups (65 – 69 years, 70 – 74 years, 75 – 79 years, 80 – 84 years, 85 – 89 years, ≥ 90 years).
- To determine the difference in chronic polypharmacy prevalence between elderly male and female.
- To identify the most common potentially inappropriate medications chronically (≥ 6 months) prescribed between 1 January 2015 and 31 December 2019.

HYPOTHESIS

The majority of patients attending the geriatric outpatient clinic is known with multimorbidity and is on multiple medications (polypharmacy) and potentially inappropriate medications (PIM) for elderly.

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CHAPTER 2

ARTICLE

The publishable article was prepared according to the journal submission guidelines for the *South African Medical Journal (SAMJ).*

Title

The prevalence of polypharmacy and prescription of potentially inappropriate medications in the elderly

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ABSTRACT

Background: The proportion of the elderly population, considered to be the main consumers of medicine, is on the increase. High multimorbidity prevalence in elderly increases the risk for appropriate- and inappropriate polypharmacy. Polypharmacy increase the risk for adverse drug reactions and drug events, drug-interactions and is associated with an increased risk of patient harm. Polypharmacy in the elderly correlates with potentially inappropriate medication prescription.
Objectives: To determine the prevalence of polypharmacy and potentially inappropriate medication (PIM) prescription at the geriatric outpatient clinic, Universitas Academic Hospital between 1 January 2015 and 31 December 2019.
Methods: A retrospective descriptive analytical study evaluating chronic medication prescriptions of all participants aged 65 years and older that attend the geriatric outpatient clinic at Universitas Academic Hospital over a 5-year period. Prescriptions were reviewed for quantity of medicines prescribed per participant and potentially inappropriate medication prescription.
Results: A total of 786 participants were included in the study. The majority of patients were aged between 75 and 84 years. The prevalence of polypharmacy was 84.3% of which the majority was female. A mean number of 9.5 medications were prescribed, ranging from 0 to 23 medications. Overall PIM prevalence was 90.2%. Proton pump inhibitors, amitriptyline, insulin sliding scale, promethazine, doxazosin, digoxin and antipsychotics were the most frequently prescribed PIMs. The three most frequently used PIMs in the category of *drugs to be used with caution* in older adults were aspirin, the loop diuretic furosemide and tramadol. Fifty-two participants (6.6%) were on a combination of ≥ 3 drugs which can lead to potentially clinically important drug-drug interactions.
Conclusion: A high prevalence of both polypharmacy and PIM was found. Limited data is available for the South African geriatric population.

Word Count: 279

Key words: polypharmacy, geriatric, elderly, potentially inappropriate medication, multimorbidity, Beers criteria

INTRODUCTION

The elderly population is on the rise.[1] In 2011 it was estimated that more than 60% of the global population is made up of the geriatric population (individuals aged 65 years and older).[2] Although developed countries have, on average, an older population, it is estimated that by the year 2050 approximately 8 in 10 of the world's elderly will reside in less developed areas.[1,3] The growth rate amongst the elderly (aged ≥ 60 years) in South Africa has increased from 1.1% to 3.0% in 2002-2003 and in 2019 – 2020 respectively.[1] In South Africa the proportion of elderly, aged 60 years and older, was estimated to be 9.1% (5.43million) in 2020, a 1.5% increase from the elderly population size of 7.6% in 2002.[1] Elderly are the main consumers of medication.[4] With increasing age, it is safe to assume multimorbidity (MM; co-existence of two or more chronic health conditions), resulting in an increased likelihood to prescribe multiple medications.[5-7] Polypharmacy (most commonly defined as the concurrent use of five or more drugs) is driven by initiation of multiple individual drugs proven to reduce morbidity and mortality risk in specific diseases. Evidence for risk reduction and medication recommendation for a specific disease is often determined from people without MM and concurrent polypharmacy.[8] The 'law of diminishing returns' describes a likely reduction in the absolute benefit made by individual additional drugs with the use of multiple preventative drugs.[8] The cut-off point of five or more medications has good discriminative properties to identify elderly at an increased risk of harm.[9] Concurrent use of multiple drugs increases the risk and incidence of drug-drug- and drug-disease interactions and adverse drug reactions and –events.[8] Ensuring safe and effective use of multiple medicine is the key aim in the healthcare for the individual patient.[5,6,8] Identification of inappropriate polypharmacy will decrease the risk for adverse health outcomes.[10] After the age of 65 years most elderly spend a large proportion of remaining life exposed to polypharmacy.[11] Females have greater longevity but higher disability rates and poor health, a phenomenon described as the 'male-female health-survival paradox.[12,13] This paradox contributes to the increased risk of females to be exposed to polypharmacy and associated drug-disease and drug-drug interactions for more absolute years and a larger proportion of their life.[11,14]

Polypharmacy is a risk factor for inappropriate prescribing or PIM (Potential Inappropriate Medication) prescription.[15] PIM encompasses the use of medication for which the risks for an individual outweigh the benefits, particularly when a safer alternative is available.[16,17] Due to the existence of MM the geriatric population is at risk for PIM prescription. Age-related altered pharmacokinetics and pharmacodynamics contribute to certain drugs being classified as PIM for elderly.[17] Adverse drug reactions, more admissions to hospital and increased mortality have been associated with PIM use in the geriatric population.[17,18] Polypharmacy and PIM prescription prevalence increases with age.[19,20] In the elderly population PIM prevalence reaches 40% in Europe and the United States.[21] In 2004 a potentially inappropriate prescription prevalence of 30% was reported in an elderly population attending SA public sector primary health care facilities.[22] More recently, the prevalence of potentially inappropriate prescription (PIP) in elderly Nigerian and South African patients attending outpatient clinics of one University teaching hospital in both Nigeria and South Africa was 35.2% and 29.6% respectively.[23] In 2016 a cross-sectional analysis from medical claims data in older South Africans found a PIP prevalence of 13%.[24] Residents of nursing homes tend to be more vulnerable to PIM use. Common complications and adverse events described are delirium, hip fractures, increased risks of falls, more frequent hospitalizations and death.[25] Polypharmacy correlation with PIM prescription lead to development of screening tools to aid in safe prescribing for elderly.[26,27] The widely used American Geriatric Society (AGS) Beers Criteria is an explicit list of PIMs that are typically best avoided by older adults in most circumstances or under specific situations, such as certain diseases or conditions and PIMs to

be used with caution in elderly.[27-29] The latest 2019 update aim to improve elderly care by reducing PIM exposure.[27-29] PIM deprescribing may improve patient outcomes[30] aid in alleviating the adverse drug event (ADE) burden observed in emergency care settings in the elderly population. [31]

The aim of the study was to determine the prevalence of polypharmacy and potentially medication (PIM) chronically prescribed at the geriatric outpatient clinic, Universitas Academic Hospital, between 1 January 2015 and 31 December 2019. Drugs prescribed for ≥ 6 months consecutively were used to determine chronic polypharmacy- and chronic PIM prescription prevalence. Secondary objectives included determining prevalence difference between gender and age groups and identifying most common PIMs prescribed.

METHODS

A retrospective descriptive analytical study was conducted at the tertiary geriatric outpatient clinic, Universitas Academic Hospital, Bloemfontein. Study participants were recruited from patient files from the geriatric outpatient clinic. Copies of chronic medication prescriptions, written by the attending outpatient clinic physician, of all participants aged 65 years and older, who were prescribed medication from the list of essential drug medications (EDL) available in the state sector between 1 January 2015 and 31 December 2019 were included in the study. Chronic medication prescriptions where the prescribed drugs are not available from the list of EDL in the state sector, private pharmacy prescriptions and single drug prescriptions where the medication was prescribed for less than a one-month period were excluded. Participants who had no copy of the chronic medication prescription written during the study period available in the clinic file were excluded.

The Health Sciences Research Ethics Committee (HSREC), University of the Free State granted approval to conduct the study (ethics number UFS-HSD2020/0320/2605).

Data was collected from individual geriatric clinic patient files. Patient files are available in storing cabinets in the geriatric outpatient clinic, Universitas Academic Hospital, Bloemfontein. The files of all patients were evaluated to identify patients who attended the clinic between 1 January 2015 and 31 December 2019. Copies of the chronic medication prescriptions are retained in patients' individual clinic files each time a new prescription is issued. Prescription copies were evaluated for study participation according to the inclusion- and exclusion criteria. Only the last prescription written during the above mentioned time period was used to collect data.

Chronic polypharmacy was determined by the number of medications prescribed ≥ 6 months consecutively, for each participant. We defined polypharmacy as five or more medications.

Data on PIM prescription was collected under the following headings:

a) PIMs best avoided in most circumstances in older adults
b) PIMs to be used with caution in older adults
c) PIM combination drug prescription which can lead to potentially clinically important drug-drug interactions
d) PIMs that require drug dose adjustment/ discontinuation based on renal function

Under each heading the unique PIM or PIM class, as identified by the AGS Beers criteria and

available on EDL list in the state sector, was specified. Presence of PIM prescription and PIM combination drug prescription was captured via a yes or no answer.

This study only evaluated medications that are available in the public sector on the essential drug list (EDL). The most recent Free State EDL was obtained from the Universitas Academic Hospital pharmacy. Only data on PIMs available on the EDL in the public sector was captured. Participants receiving medication from private pharmacies, and therefore PIMs available in the private but not public sector were excluded in this study.

A data collection form designed with REDCap® (Research Electronic Data Capture) software was used. Study data was collected and managed using the REDCap® database hosted at the University of the Free State. REDCap® is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external source.[32,33]

The researcher entered all data into the database. The data was exported in Excel format for statistical analysis. Statistical Analysis Software (SAS) System was used for the analysis of data. The Chi-square test was used for the analysis of comparative data.

RESULTS

A total of 786 participants (70% female; 30% male) who attended the geriatric outpatient clinic between 1 January 2016 and 31 December 2019 were included in the study.

The majority of the participants were aged between 75 and 84 years (26 % and 28% for age groups 75-79 years and 80 – 84 years respectively). Only 6% of participants were aged between 65 and 69 years and 7% were 90 years and older. The mean age at last consultation was 79.9 years, ranging from 65.9 to 99.1 years with a standard deviation of 6.4 years. Age group distributions of patients at the last consultation are demonstrated in Figure 1.

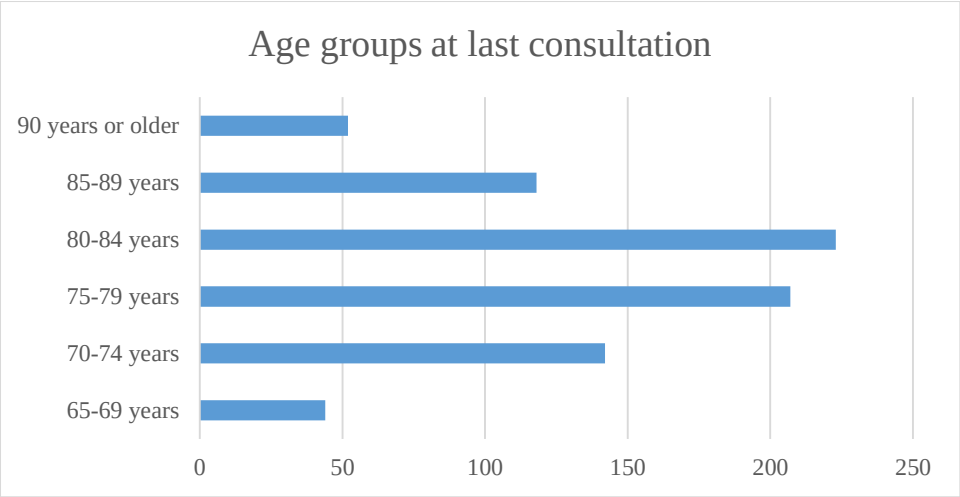


Figure 1: Age groups at last consultation

The minimum number of medications prescribed per participant was zero with a maximum number of 23. A total of 30 participants (4%) were not prescribed any chronic medication, only one participant was prescribed 23 chronic medications. A mean number of 9.5 medications were prescribed with a standard deviation of 4.7 medications. Of the participants 84.3% (n=663) had polypharmacy (five or more medications) and 15.7% (n=123) did not have polypharmacy. Ninety-six participants (12%) were prescribed 10 medications and 326 participants (41%) were prescribed 11 or more medications.

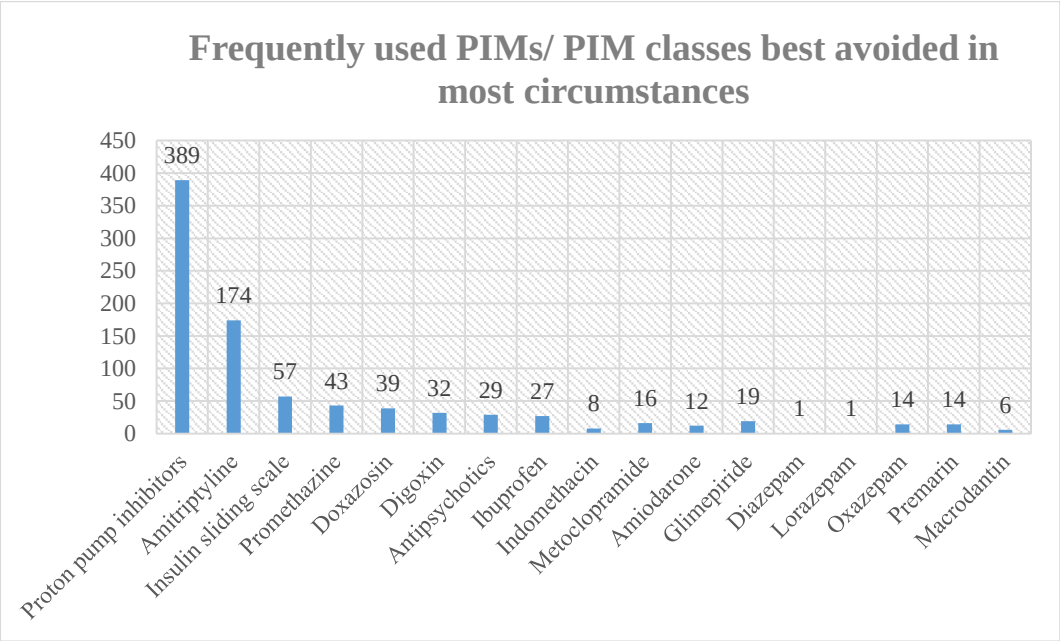
Table 1 shows the distribution of polypharmacy between the different age groups. In each age group more than 80% of participants had polypharmacy. The p-value for the different age groups was 0.857 which showed no statistical significance between the groups. A significant statistical higher prevalence of polypharmacy (p=0.031) was observed in females (n=474, 86%) compared to males (n=189, 80%).

Table 1: Polypharmacy prevalence by age group.

Age group	Polypharmacy		
	No	**Yes**	**Total**
65-69 years	8 (18.2%)	36 (81.8%)	44
70-74 years	23 (16.2%)	119 (83.8%)	142
75-79 years	31 (15%)	176 (85%)	207
80-84 years	36 (16.1%)	187 (83.86)	223
85-89 years	20 (17%)	98 (83%)	118
90 years or older	5 (9.6%)	47 (90.4%)	52
Total	123	663	786

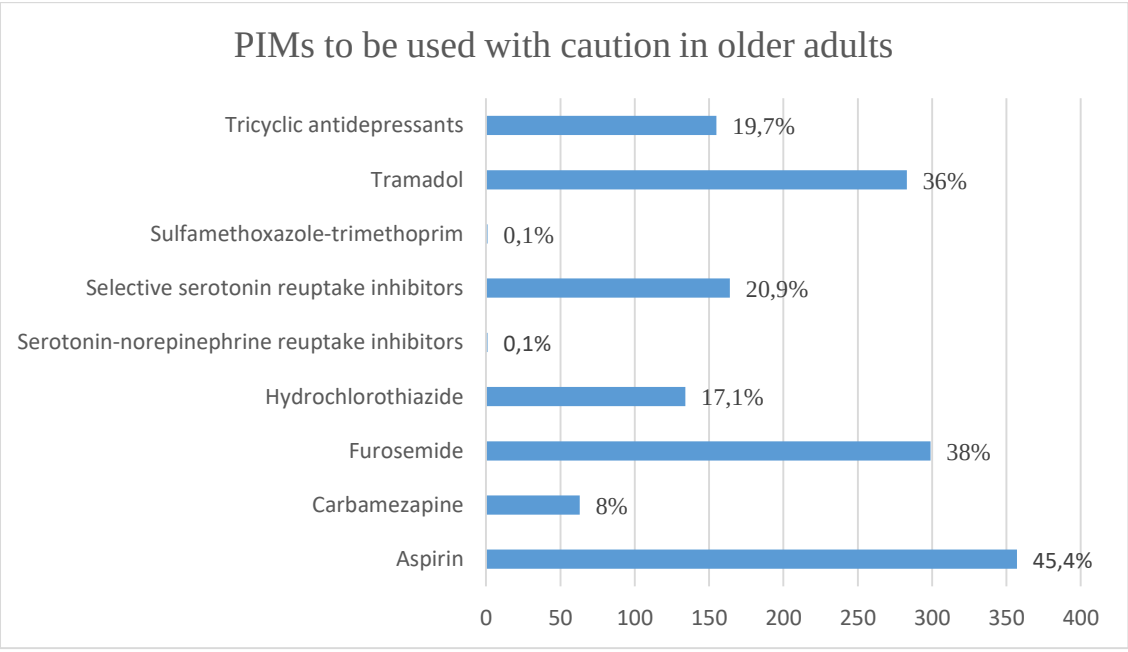
Most frequently used PIMs and PIM classes that are *best avoided in most circumstances* in older adults were: Proton pump inhibitors (n=389, 49.5%), the tricyclic antidepressant amitriptyline (n=174, 22.1%), insulin sliding scale (n=57, 7.3%), promethazine (n=43, 5.5%), doxazosin (n=39, 5%), digoxin (n=32, 4.1%) and antipsychotics (n=29, 3. 7%). Ibuprofen was prescribed to 3,4% (n=27) and indomethacin to 1% (n=8) of participants. The non-steroidal anti-inflammatory drug, ketorolac, did not appear on any prescription. Metoclopramide was chronically prescribed to 16 (2%), amiodarone to 12 (1,5%) and glimepiride to 19 (2,4%) participants. A total of 14 participants (1,8%) were prescribed a short-acting benzodiazepine. Intermediate- and long-acting benzodiazepine prescription was identified in only a single participant in the respective categories. Oral conjugated oestrogens were prescribed in 14 participants (1,8%), no testosterone prescription was identified. No participant received methyldopa or nifedipine with prazosin only prescribed to one participant. Prescription of chlorphenamine, hyoscine butylbromide and nitrofurantoin prophylaxis were less than 1%. See Figure 2.

Figure 2: Frequently used PIMs/ PIM classes best avoided in most circumstances



The three most frequently used PIMs in the category of drugs *to be used with caution* in older adults were aspirin (n=357, 45.4%), the loop diuretic furosemide (n=299, 38%) and tramadol (n=283, 36%). Figure 3 summarises the prevalence of other PIMs prescribed from the category of drugs to be used with caution.

Figure 3: PIMs to be used with caution in older adults



Tramadol (n=282, 35,9%) followed by spironolactone (n=97, 12,3%) and colchicine (n=32, 4,1%) were the drugs most frequently prescribed in the category for which a drug dose adjustment or discontinuation of the treatment should be made based on the renal function. Pregabalin was prescribed for 18 (2,3%) and duloxetine for 3 (0,4%) participants. Levetiracetam prescription was only identified in a single participant.

Fifty-two participants (6.6%) were on a combination of ≥ 3 drugs *which can lead to potentially clinically important drug-drug interactions*. Medication prescriptions included combinations from the following medication classes: Tricyclic antidepressants, sertonin-norepinephrine reuptake inhibitors (SNRIs), antipsychotics, antiepileptic's, benzodiazepines and opioids. The combination of doxazosin or prazosin with furosemide was prescribed for 19 participants (2.4%). None of the participants were given a combination of the following: Angiotensin receptor blockers and angiotension-converting-enzyme inhibitors; Chlorphenamine and promethazine; Oral corticosteroids and on-steroidal anti-inflammatory drugs; Lithium and angiotensin-converting enzyme inhibitors or furosemide; Phenytoin and sulfamethoxazole/trimethoprim.

The overall PIM prevalence in the study was 90.2%. Seventy-seven of the participants had no prescription for a PIM.

DISCUSSION

Polypharmacy, a gradually increasing global health problem in the geriatric setting [34], was prevalent in elderly attending the geriatric outpatient clinic, Universitas hospital. Polypharmacy prevalence in the study population was 84.3%. Local data on the prevalence of polypharmacy in the elderly in South Africa is lacking in the public- and private health care sector. A recent study among patients aged 60 years and older attending a South-West Nigerian geriatric center reported a point polypharmacy prevalence of only 23,8% with an average of four medications consumed without gender difference.[35] Despite heterogeneity in the numerical definition of polypharmacy a cut-off point of 5 or more different medications have good discriminative properties to identify elderly at an increased risk of harm, geriatric syndrome intensification[9], functional outcome decline[9], decreased quality of life[36] and a significant increased fall and associated injury likelihood.[37]

Polypharmacy prevalence in the study was significantly higher in females compared to males (p=0.031). Previous studies identified female gender as a risk factor for polypharmacy.[38,39] Females have greater longevity but higher disability rates and poor health, a phenomenon described as the 'male-female health-survival paradox'.[12,13] This paradox contributes to the increased risk of females to be exposed to polypharmacy for more absolute years and a larger proportion of their life.[11]

A study recently conducted among cardiovascular patients attending an Ethiopian university specialised outpatient clinic concluded that older age is a determinant of polypharmacy. Polypharmacy was found to be nearly two times more likely in the elderly, aged 65 years and above.[40] The largest proportion of the study population was aged between 75 and 84 years.

More than 80 % of participants in each of the age groups in our study had polypharmacy prescriptions, no statistical significance difference was identified between the groups. A Swedish study identified a dramatic increase in polypharmacy prevalence with age, reaching a peak prevalence of 80% in elderly aged 90 and above but found polypharmacy exposure likelihood to remain stable after the age of 85 years.[41] An Italian study found a steep medication burden increase until age 85-90 years followed by a substantial burned decline.[42]

The mean number of medications prescribed to participants in the study was 9.5. A previous study in 2007 on the geriatric profile at Universitas hospital, Bloemfontein identified an average use of 6 medications in admitted elderly above 65 years, patients admitted to non-internal medicine departments was also included in the study.[43] In geriatric patients the well-described phenomenon of hyperpolypharmacy (HPP), defined as concurrent use of 10 or more different medications, is linked to increased hospitalisation-, disability- and mortality risk.[44] Consumption of a greater quantity of different medications increase the risk for negative medication-related variables like drug-drug interactions, higher anticholinergic treatment burden, adverse reactions and lower drug regime adherence.[27] In the study prescription of 10 medications and 11 or more medications was 12% and 41% respectively.

Due to the existence of MM the geriatric population is at risk for both polypharmacy and PIM prescription.[17] Polypharmacy can be further classified into "appropriate" or "inappropriate/ problematic" as drug quantity in isolation does not indicate if medication is clinically indicated and appropriate for individual patients.[6,8] A limitation was that the study did not evaluate individual patient diagnosis to determine the presence of MM and polypharmacy appropriateness.

PIM use in the geriatric population has been associated with adverse drug reactions, more hospital admissions and increased mortality.[17,18]

In the elderly population PIM prevalence reached 40% in Europe and the United States.[21] In 2004 a potentially inappropriate prescription prevalence of 30% was reported in an elderly population attending SA public sector primary health care facilities.[22] More recently, the prevalence of potentially inappropriate prescription (PIP) in elderly Nigerian and South African patients attending outpatient clinics of one University teaching hospital in both Nigeria and South Africa was 35.2% and 29.6% respectively.[23] The PIM prevalence of 90.8% in this study is significantly higher than in these studies. The reasons for these possible differences may be explored (eg study tool methods, measurement scales, confounders, population differences, etc).

In 2016 a cross-sectional analysis from medical claims data in older South Africans found a PIP prevalence of 13%.[24]

A study conducted by Van Heerden et al in the South African private sector had similar findings to this study in that females have a higher rate of inappropriate medication prescribing than males.[24]

Studies that assessed inappropriate prescribing report that the most common potentially inappropriate medications prescribed include amitriptyline, benzodiazepines, doxazosin, proton pump inhibitors, NSAIDS, digoxin, antihistamines and oestrogen. In agreement with these studies the most frequently prescribed PIMs in our population were proton pump

inhibitors, followed by amitriptyline, insulin sliding scale, promethazine, doxazosin, digoxin and antipsychotics. The study conducted by van Heerden *et al* also showed that females were more likely to be exposed to proton pump inhibitors.[24]

An increased risk of falling in the elderly has been linked to the use of benzodiazepines, antidepressants, antipsychotics, antihypertensives and diuretics.[45] In a South African study warfarin, angiotensin-converting enzyme inhibitors and non-steroid anti-inflammatory drugs independently increased ADE risk in the geriatric population.[31].

The study had limitations. The study was conducted from evaluating copies of prescriptions and not from physician or patient interviews. Data on specific diagnosis and presence of multimorbidity was not captured in order to aid in evaluating medication for appropriateness. Over the counter medications and prescriptions written by physicians other than geriatric clinic physicians were not included in the study. It is possible that some participants were on more medication than captured. Beers criteria application was only done for medication available on state sector EDL and appearing from the Beers Criteria Antiretroviral treatment does not form part of the Beers criteria and it is possible that may also result in potentially inappropriate drug-drug interactions. Although polypharmacy was compared between males and females, PIMs in our population were not compared by gender. Laboratory data in renal function was not captured to apply to the medications in the category for which a drug dose adjustment or discontinuation of the treatment should be made based on the renal function.

The study contributes to the knowledge of local South African polypharmacy and PIM prevalence data in elderly attending a tertiary geriatric clinic in a public health care setting. Data from future research on polypharmacy and PIM prevalence in other health care levels can be compared against the study data. The study can help guide physicians in safe prescribing. This information might assist in future to draft recommendations for safe prescribing guidelines in the elderly at Universitas Academic Hospital. It will also serve as a platform to educate not only health professionals but also patients on the consequences of polypharmacy and PIM prescriptions. It is proposed that polypharmacy and PIM prevalence at the geriatric clinic, Universitas Academic Hospital, be reviewed in future to determine changes in prevalence and evaluate as new drugs become available on EDL.

More than 20 years ago, the yearly cost of medication misuse and polypharmacy in the United States was calculated to be more than $177 billion.[30] Data on the financial burden of polypharmacy for South Africa is lacking. Data from this study can be used to aid in local financial burden determination.

CONCLUSION

Limited data is available on polypharmacy and PIM prescription and use in the South African geriatric population attending all levels of care in private and public health settings. In this study, a high prevalence of polypharmacy and PIM was found. PIM prevalence was

significantly higher than studies conducted in Europe, the United States and Africa. There is a need for further research amongst the geriatric population with regards to multimorbidity (looking specifically at frailty as well), polypharmacy and PIMs.

ACKNOWLEDGEMENTS

Dr. M. Harmse, for technical and editorial preparation of the manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

DISCLAIMER

The content presented in this article is solely the responsibility of the authors and does not necessarily represent the official views of the institution.

AUTHORS' CONTRIBUTIONS

G.I. and M.H. designed the study. G.I. collected and interpreted data under supervision of M.H. Data analysed by C.V. M.H. assisted with conceptualisation and approval of the protocol.

M.H. prepared the initial draft of the article. All the authors viewed and approved the final version of the article.

FUNDING

The research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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APPENDICES

Appendix A: Letter of approval from Health Sciences Research Ethics Committee

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

13-May-2020

Dear Dr Gavin Isaacs

Ethics Clearance: **The prevalence of polypharmacy and prescription of potentially inappropriate medications in the elderly.**

Principal Investigator: **Dr Gavin Isaacs**

Department: **Internal Medicine Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2020/0320/2605**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00011992; REC 230408-011; IORG 0010096; FWA 00027947
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa

Appendix B: Permission from Free State Department of Health

health
Department of Health
FREE STATE PROVINCE

04 May 2020

Dr G Isaacs
Dept. of Internal Medicine
UFS

Dear Dr G Isaacs

Subject: The prevalence of polypharmacy and prescription of potentially inappropriate medication in the elderly.

- Please ensure that you read the whole document. Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Universitas Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** scheelats@fshealth.gov.za / makenamr@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Institution Manager on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- **As part of feedback you will be required to present your study findings/results at the Free State Provincial health research day**

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 7/05/2020

Appendix C: Permission from Head of Department

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

3 February 2020

The Chairperson,
Ethics Committee,
Faculty of Health Sciences
University of the Free State

TO WHOM IT MAY CONCERN

RE: The Prevalence of Polypharmacy and prescription of Potentially Inappropriate Medications in the Elderly.

I hereby grant Dr GS Isaacs (2011060783), permission to conduct research in the Geriatric division, Department internal Medicine.

Kind regards

Dr TRP Mofokeng
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MBChB (UCT), Cert Endocrinolog + Med(SA)
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Appendix D: Copy of research protocol approved by HSREC

The prevalence of polypharmacy and prescription of potentially inappropriate medications in the elderly.

Protocol for a mini-dissertation submitted in fulfillment of the requirements for the degree

Master of Medicine in Internal Medicine

Department of Internal Medicine

Faculty of Health Sciences at the University of the Free State

CANDIDATE

Dr GS Isaacs

Registrar: Department of Internal Medicine

Faculty of Health Sciences

University of the Free State

Student number: 2011060783

STUDY LEADER

Dr M Harmse

Consultant: Department of Internal Medicine

Faculty of Health Sciences

University of the Free State

Table of Contents

1 Introduction to protocol

The elderly population is on the increase. With the increase in age comes an increase in chronic underlying conditions[1–3]. The care of patients with multimorbidity (multiple medical conditions) is the greatest challenge now faced by the health service, as it can create overly complex health care for some of the most vulnerable in society[2]. The resulting polypharmacy (use of multiple medicines) can be appropriate or inappropriate and the key healthcare aim for the individual patient is to ensure the safe and effective use of their multiple medicines[2].

In this research project, the researcher will look to determine the prevalence of polypharmacy and potentially inappropriate medication (PIM) of patients that attended the Geriatric Clinic at Universitas Academic Hospital, Bloemfontein from 1 January 2015 and 31 December 2019.

Information obtained from this research project can be used to identify prescribing practices in elderly patients which can assist in the drafting of recommendations for safe prescribing guidelines in the elderly at Universitas Academic Hospital. It will also serve as a platform to educate not only health professionals but also patients on the consequences of polypharmacy and PIM prescriptions.

There is a need to address polypharmacy management as a public health issue, as multimorbidity does not just affect the elderly.

A similar study regarding polypharmacy and PIM prescribing in the elderly was conducted at the Universitas Academic Hospital Geriatric Clinic in 2014. Unfortunately the study was not submitted for publication.

2 Background to the research problem

2.1 Definitions

Geriatric:	Relates to a person aged 65 years and older[1].
Elderly / Older adult:	For the purposes of this study these terms are used synonymously with geriatric and refers to a person aged 65 years and older[1].
Multimorbidity:	The co-existence of two or more chronic health conditions[2].
Polypharmacy:	Concurrent use of five or more different prescription medications[1,2,4].
Appropriate Polypharmacy:	Optimisation of medications for patients with complex and/or multiple conditions where medicine usage agrees with best evidence[2].
PIM:	Potentially Inappropriate Medications The use of medication for which the risks outweigh the benefits, particularly when a safer alternative is available[5,6].
Beers List:	A screening tool consisting of a list of criteria to guide prescribing practices among adults 65 years and older in all ambulatory, acute, and institutionalised settings of care, except for the hospice and palliative care settings. It is used to identify PIM[7–10].

2.2 Literature review

The elderly population is on the increase. The geriatric population (age 65 and over) currently comprises more than 60% of the world's population. It is estimated that by the year 2050 nearly 8 in 10 of the world's older population will be living in the world's less developed areas[1]. With increasing age it is safe to assume an increase in chronic underlying conditions which is associated with the likelihood of an increase in prescribing medications[1–3]. Continuous identification or diagnosis of new conditions over a period of time puts the geriatric population at risk of polypharmacy. Multimorbidity, defined as the co-existence of two or more chronic health conditions, is common in the older population. This increases the complexity of therapeutic management for both patients and health professionals, and may have a negative impact on health outcomes[2].

There is large heterogeneity in the definition of polypharmacy and a lack of a clear universal definition. This makes it challenging for health professionals to assess and consider efficacy and safety issues within the clinical setting[2]. A recent systematic review by showed that the most commonly used definition of polypharmacy is the concurrent use of five or more different prescription medications[1,2,4]. Polypharmacy is a concept that is associated with both quantity and appropriateness of medications[4]. It can be classified into "appropriate" or "inappropriate/ problematic" polypharmacy[2,3,11].

The use of multiple drugs means multiple or higher incidence of drug-interactions or side-effects. Physicians commonly tend to fall into the "prescribing cascade" trap. This means prescribing a drug for the sole purpose of treating another drug's side-effect/s[8]. The newly initiated drug has the potential to cause a new side-effect profile.

The pharmacokinetics and pharmacodynamics of an elderly person is unique and prescribing to an elderly person can become complex[3,4,8]. Often physicians tend to forget to enquire about over-the-counter drugs and the elderly typically do not mention the use of over-the-counter drugs during the consultation[4].

Polypharmacy is a risk factor for inappropriate prescribing or PIM (Potential Inappropriate Medication). PIM encompasses the use of medication for which the risks outweigh the benefits, particularly when a safer alternative is available[5,6]. The use of PIM in the geriatric population has been associated with adverse drug reactions, increased hospital admissions and mortality[6,7].

Residents of nursing homes tend to be more vulnerable to PIMs. Common complications/ adverse events described are delirium and increased risks of falls[10].

As there is a direct correlation between polypharmacy and PIM, multiple screening tools have been developed over the years in order to aid physicians in safer prescribing[8,9].

The most widely used screening tool is the America Geriatric Society (AGS) Beers List. It consists of a list of criteria to guide prescribing practices among older adults[7–10]. The Beers list was developed in the United States in 1991 by Dr Beers et al in order to improve the care of nursing home residents by studying the issue of safe and appropriate medications in the older adult[8,10]. It has been updated several times since then with the latest update in 2019[7,8].

The Beers List is segmented into tables with five main categories. The first category table includes medications which is best avoided by older adults *in most circumstances*. The rationale for avoiding the drug classes are individually explained in the table. The second category table includes medications which typically should be avoided in elderly *with certain specified medical conditions* as potential drug-disease or drug-syndrome interactions may exacerbate the underlying disease or syndrome. Specific drug-disease and drug-syndrome exacerbations related to the specified medications are rationalized in the table. The third category table includes medications which should be used *with caution* in the elderly. The rationale for cautious use of the individual drug classes are explained. The fourth category table includes combinations of drugs which should be avoided in elderly due to potentially *clinically important drug-drug interactions*. The increased risk for specific clinical events related to different drug combinations are rationalized in the table. The fifth

category table includes medications that require drug dose adjustment or drug discontinuation *based on renal function*. This table notate creatinine clearance (ml/min) at which action is required for each individual drug as well as specific risks associated with individual drug use below noted creatinine clearance. Each of the five tables has an additional column for each PIM / PIM class where recommendations are given if an individual drug / drug class or drug combination should definitely be avoided. This column note exception to the rule related to individual patients. All of recommendations in the tables are followed by columns detailing the individual quality of evidence (high-, moderate- and low-quality evidence) and strength of the recommendation (strong or weak)[7].

The Beers List contains not only prescription drugs but also over-the-counter drugs. It is important to note that the Beers criteria should be used in conjunction with both the knowledge and expertise of the practitioner, as well as the individual needs of the patient[8]. See Appendix A for the complete Beers Criteria.

Screening tools, other than the AGS Beers List, are also available.

Examples of other screening tools:

- Inappropriate Prescribing in the Elderly Tool (IPET)
- Medication Appropriateness Index (MAI)
- Screening Tool for Older Person's Prescriptions (STOPP)
- Screening Tool to alert Doctors to the Right Treatment (START)
- PRISCUS (Latin for old and venerable elderly)
- Fit for the Aged (FORTA)[3,4,9]

IPET was developed by the Canadian Consensus Panel to set out adverse drug reactions and drug-disease relations[4]. STOPP/ START has been validated in Ireland and Britain and has been used in other European countries. PRISCUS list is being used in Germany[3]. The MAI screening tool questions medications in terms of their indications rather than their appropriateness[4].

The main goal of these screening tools is to improve the care of the elderly by reducing their exposure to potentially inappropriate medications, as both an educational tool and quality measure[8]. For the purposes of this study we will be using the Beers List to identify PIM.

A similar study regarding polypharmacy and potential inappropriate prescribing in the elderly was conducted at the Universitas Academic Hospital Geriatric Clinic in 2014. The study results showed that 75 percent of the study population fulfilled the criteria for polypharmacy and 29 percent of the medication was deemed inappropriate as per the Beers criteria. Unfortunately the study was not submitted for publication.

3 Study question

What is the prevalence of:

a) Polypharmacy (use of 5 or more prescription drugs) in patients attending the Geriatric outpatient clinic, Universitas Academic Hospital, Bloemfontein

b) Potentially inappropriate medications (PIM) prescribed at the Geriatric outpatient clinic, Universitas Academic Hospital, Bloemfontein

4 Aim of study

- To determine the prevalence of polypharmacy and potentially inappropriate medication (PIM) prescription at the Geriatric Clinic Universitas Academic Hospital between 1 January 2015 and 31 December 2019. Only drugs prescribed chronically for ≥ 6 months consecutively will be used to determine polypharmacy- and PIM prescription prevalence.

5 Study objectives

- To determine the difference in polypharmacy prevalence between age groups (65 – 69 years, 70 – 74 years, 75 – 79 years, 80 – 84 years, 85 – 89 years, ≥ 90 years)
- To determine the difference in polypharmacy prevalence between elderly male and female
- To identify the most common potentially inappropriate medications chronically (≥ 6 months) prescribed between 1 January 2015 and 31 December 2019.

6 Methodology

6.1 Study design

This will be a retrospective descriptive analytical study.

6.2 Study location and population

The study will be conducted at the Geriatric outpatient clinic, Universitas Academic Hospital, Bloemfontein. Study participants will be recruited from the Geriatric outpatient clinic's files. Each patient has a copy of their latest prescription, written by the attending clinic physician, in their individual clinic file. Copies of chronic medication prescriptions of all patients that attended the Geriatric outpatient clinic between 1 January 2015 and 31 December 2019 will be analyzed for study eligibility. The population size is estimated at approximately 100 – 150 patients.

6.3 Sampling

No sampling of the study population will be used. Chronic medication prescription copies of all patients that attended the Geriatric Clinic between 1 January 2015 and 31 December 2019 will be included provided adherence to the inclusion- and exclusion criteria.

6.4 Inclusion criteria

Copies of chronic medication prescriptions, written by the attending clinic physician, of:

1. Patients that attended the Geriatric outpatient clinic, Universitas Academic hospital, Bloemfontein, between 1 January 2015 and 31 December 2019.
2. Patients aged 65 years and older.
3. Patients who receive medication from the list of essential drug medications (EDL) available in the state sector.

Should a prescription have a combination of drugs prescribed for different time periods, the prescription will be included for evaluation but only data on drugs prescribed for ≥ 6 consecutive months will be captured for analysis.

6.5 Exclusion criteria

Copies of chronic medication prescriptions, written by the attending clinic physician:

1. If the last clinic visit was prior to 1 January 2015, the patient will not be included in the study.
2. No copy of the chronic medication prescription available in the clinic file.
3. Patients aged younger than 65 years.
4. Single drug prescriptions where the medication was prescribed for less than a one-month period.
5. Chronic medication prescriptions where the prescribed drugs are not available in state sector.
6. Private pharmacy prescriptions.

6.6 Measurement

The data for this study will be retrospectively collected from the individual clinic files. Clinic files are available in storing cabinets in the Geriatric outpatient clinic, Universitas Academic Hospital, Bloemfontein. The files of all patients will be evaluated in order to identify patients who attended the clinic between 1 January 2015 and 31 December 2019. Copies of the chronic medication prescriptions are retained in the patients' individual clinic file every time a new prescription is issued. Prescription copies will be evaluated for study participation according to the inclusion-and exclusion criteria. Only the last prescription written during above mentioned time period will be used to collect data. Demographic data that needs to be collected includes the chronological age of the participant and the sex.

Polypharmacy will be determined by noting down the number of chronically prescribed medications, prescribed ≥ 6 months consecutively, for each participant. We will use the definition of five or more concurrent medication prescription to identify polypharmacy.

Data on PIM prescription will be collected under the following headings:

a) PIMs best avoided in most circumstances in older adults
b) PIMs to be used with caution in older adults
c) PIM combination drug prescription which can lead to potentially clinically important drug-drug interactions
d) PIMs that require drug dose adjustment / discontinuation based on renal function

Under each heading the unique PIM or PIM class, as identified by the AGS Beers list criteria, will be noted. Presence of PIM prescription and PIM combination drug prescription will be captured via a yes or no answer.

For my study I will only be evaluating medications that are available in the state sector on the essential drug list (EDL). The most recent Free State EDL was obtained from the Universitas Academic Hospital pharmacy. Only data on PIMs available on the EDL in public sector will be captured. Participants receiving medication from private pharmacies, and therefore PIMs available in private but not public sector are excluded in this study.

A data collection form was designed with the REDCap® (Research Electronic Data Capture) software. Study data will be collected and managed using the REDCap database hosted at the University of the Free State. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources[12,13].

The researcher will enter the data in the database. The researcher and study leader will have full access to the study records at all times during the data collection period. The data will be exported in Excel format for statistical analysis.

6.7 Errors in methodology

The filing system at the Geriatric Clinic could pose challenges during the collection of data. Missing or incomplete copy of chronic medication prescriptions might result in difficulties collecting data.

6.8 Pilot Study

A pilot study will be conducted on 10 patient files to evaluate the feasibility of the data sheet. If no changes are made to the data sheet these 10 patients will be included in the study.

7 Data analysis

Data analysis will be done with the help of the Department of Biostatistics, University of the Free State.

8 Implementation of findings

This study will be done for qualification purposes.

9 Time Schedule

Submission to Health Sciences Research Ethics Committee	March 2020
Approval from Free State Department of Health	April2020
Data collection	May 2020
Data analysis	June 2020
Writing of report/ article	June/July 2020

10 Budget

Costs for this research project will be covered by the researcher.

Item	Cost
Photocopies and stationery	R200
Data	R300
Total Costs	R500

11 Ethics

The research protocol will be submitted to the Health Sciences Research Ethics Committee (HSREC) at the Medical Faculty of the University of the Free State for review and approval. Approval to conduct the research study will also be obtained from the Free State Department of Health before commencing with the study.

The patient records will be managed with confidentiality. Clinical records will not leave the premises of the Geriatric Clinic at Universitas Academic Hospital. In order to ensure confidentiality no identifiable information will be captured on the data sheet.

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13 Appendices

APPENDIX A: 2019 AMERICAN GERIATRICS SOCIETY (AGS) BEERS CRITERIA®(7)

Table 1

2019 AGS Beers Criteria for Potentially Inappropriate Medication use in Older Adults

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Anticholinergics[a]				
First-generation antihistamines	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity	Avoid	Moderate	Strong
Brompheniramine				
Carbinoxamine				
Chlorpheniramine				
Clemastine				
Cyproheptadine	Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate.			
Dexbrompheniramine				
Dexchlorpheniramine				
Diphenhydramine (oral)				
Doxylamine				
Hydroxyzine				
Meclizine				
Promethazine				
Pyrilamine				
Triprolidine				
Antiparkinsonian agents	Not recommended for prevention or treatment of extrapyramidal symptoms with antipsychotics; more effective agents available for treatment of Parkinson disease	Avoid	Moderate	Strong
Benztropine (oral)				
Trihexyphenidyl				
Antispasmodics	Highly anticholinergic; uncertain effectiveness	Avoid	Moderate	Strong
Atropine (excludes ophthalmic)				
Belladonna alkaloids				
Clidinium-chlordiazepoxide				
Dicyclomine Homatropine (excludes ophthalmic)				
Hyoscyamine				
Methscopolamine				
Propantheline				
Scopolamine				
Antithrombotics				
Dipyridamole, oral short-acting (does not apply to the extended-release combination with aspirin)	May cause orthostatic hypotension; more effective alternatives available; lack of harm across studies for use in cardiac stress testing	Avoid	Moderate	Strong
Antiinfectives				
Nitrofurantoin	Potential for pulmonary toxicity, hepatotoxicity, and peripheral neuropathy, especially with long-term use; safer alternatives available	Avoid in individuals with creatinine clearance <30 mL/min or for long-term suppression	Low	Strong
Cardiovascular				
Peripheral alpha-1 blockers for treatment of hypertension	High risk of orthostatic hypotension and associated harms, especially in older adults; not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile	Avoid use as an antihypertensive	Moderate	Strong
Doxazosin				
Prazosin				
Terazosin				

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Central alpha-agonists Clonidine for first-line treatment of hypertension Other CNS alpha-agonists Guanabenz Guanfacine Methyldopa Reserpine (>0.1 mg/day)	High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension	Avoid as first-line antihypertensive Avoid other CNS alpha-agonists as listed	Low Low	Strong Strong
Disopyramide	May induce heart failure in older adults because of potent negative inotropic action; strongly anticholinergic; other antiarrhythmic drugs preferred	Avoid	Low	Strong
Dronedarone	Worse outcomes have been reported in patients taking dronedarone who have permanent atrial fibrillation or severe or recently decompensated heart failure.	Avoid in individuals with permanent atrial fibrillation or severe or recently decompensated heart failure	High	Strong
Digoxin for first-line treatment of atrial fibrillation or of heart failure	Use in atrial fibrillation: should not be used as a first-line agent in atrial fibrillation, because there are safer and more effective alternatives for rate control supported by high-quality evidence. Use in heart failure: evidence for benefits and harms of digoxin is conflicting and of lower quality; most but not all of the evidence concerns use in HFrEF. There is strong evidence for other agents as first-line therapy to reduce hospitalizations and mortality in adults with HFrEF. In heart failure, higher dosages are not associated with additional benefit and may increase risk of toxicity. Decreased renal clearance of digoxin may lead to increased risk of toxic effects; further dose reduction may be necessary in those with stage 4 or 5 chronic kidney disease.	Avoid this rate control agent as first-line therapy for atrial fibrillation Avoid as first-line therapy for heart failure If used for atrial fibrillation or heart failure, avoid dosages >0.125 mg/day	Atrial fibrillation: low Heart failure: low Dosage >0.125 mg/day: moderate	Atrial fibrillation: strong Heart failure: strong Dosage >0.125 mg/day: strong
Nifedipine, immediate release	Potential for hypotension; risk of precipitating myocardial ischemia	Avoid	High	Strong
Amiodarone	Effective for maintaining sinus rhythm but has greater toxicities than other antiarrhythmics used in atrial fibrillation; may be reasonable first-line therapy in patients with concomitant heart failure or substantial left ventricular hypertrophy if rhythm control is preferred over rate control	Avoid as first-line therapy for atrial fibrillation unless patient has heart failure or substantial left ventricular hypertrophy	High	Strong
Central nervous system				
Antidepressants, alone or in combination Amitriptyline Amoxapine Clomipramine Desipramine Doxepin >6 mg/day Imipramine	Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≤6 mg/day) comparable to that of placebo	Avoid	High	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Nortriptyline Paroxetine Protriptyline Trimipramine				
Antipsychotics, first (conventional) and second (atypical) generation	Increased risk of cerebrovascular accident (stroke) and greater rate of cognitive decline and mortality in persons with dementia Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (eg, behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others	Avoid, except in schizophrenia or bipolar disorder, or for short-term use as antiemetic during chemotherapy	Moderate	Strong
Barbiturates Amobarbital Butabarbital Butalbital Mephobarbital Pentobarbital Phenobarbital Secobarbital	High rate of physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages	Avoid	High	Strong
Benzodiazepines *Short and intermediate acting:* Alprazolam Estazolam Lorazepam Oxazepam Temazepam Triazolam *Long acting:* Chlordiazepoxide (alone or in combination with amitriptyline or clidinium) Clonazepam Clorazepate Diazepam Flurazepam Quazepam	Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents; in general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults May be appropriate for seizure disorders, rapid eye movement sleep behavior disorder, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, and perioperative/procedural anesthesia	Avoid	Moderate	Strong
Meprobamate	High rate of physical dependence; sedating	Avoid	Moderate	Strong
Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (ie, "Z-drugs") Eszopiclone Zaleplon Zolpidem	Nonbenzodiazepine benzodiazepine receptor agonist hypnotics (ie, Z drugs) have adverse events similar to those of benzodiazepines in older adults (eg, delirium, falls, fractures); increased emergency room visits/hospitalizations; motor vehicle crashes; minimal improvement in sleep latency and duration	Avoid	Moderate	Strong
Ergoloid mesylates (dehydrogenated ergot alkaloids) Isoxsuprine	Lack of efficacy	Avoid	High	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Endocrine				
Androgens Methyltestosterone Testosterone	Potential for cardiac problems; contraindicated in men with prostate cancer	Avoid unless indicated for confirmed hypogonadism with clinical symptoms	Moderate	Weak
Desiccated thyroid	Concerns about cardiac effects; safer alternatives available	Avoid	Low	Strong
Estrogens with or without progestins	Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women	Avoid systemic estrogen (eg, oral and topical patch)	Oral and patch: high	Oral and patch: strong
	Evidence indicates that vaginal estrogens for the treatment of vaginal dryness are safe and effective; women with a history of breast cancer who do not respond to nonhormonal therapies are advised to discuss the risks and benefits of low-dose vaginal estrogen (dosages of estradiol <25 µg twice weekly) with their healthcare provider	Vaginal cream or vaginal tablets: acceptable to use low-dose intravaginal estrogen for management of dyspareunia, recurrent lower urinary tract infections, and other vaginal symptoms	Vaginal cream or vaginal tablets: moderate	Topical vaginal cream or tablets: weak
Growth hormone	Impact on body composition is small and associated with edema, arthralgia, carpal tunnel syndrome, gynecomastia, impaired fasting glucose	Avoid, except for patients rigorously diagnosed by evidence-based criteria with growth hormone deficiency due to an established etiology	High	Strong
Insulin, sliding scale (insulin regimens containing only short- or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin)	Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting. Avoid insulin regimens that include only short- or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin. This recommendation does not apply to regimens that contain basal insulin or long-acting insulin.	Avoid	Moderate	Strong
Megestrol	Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults	Avoid	Moderate	Strong
Sulfonylureas, long acting Chlorpropamide Glimepiride Glyburide (also known as glibenclamide)	Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes SIADH Glimepiride and glyburide: higher risk of severe prolonged hypoglycemia in older adults	Avoid	High	Strong
Gastrointestinal				
Metoclopramide	Can cause extrapyramidal effects, including tardive dyskinesia; risk may be greater in frail older adults and with prolonged exposure	Avoid, unless for gastroparesis with duration of use not to exceed 12 weeks except in rare cases	Moderate	Strong
Mineral oil, given orally	Potential for aspiration and adverse effects; safer alternatives available	Avoid	Moderate	Strong
Proton-pump inhibitors	Risk of Clostridium difficile infection and bone loss and fractures	Avoid scheduled use for >8 weeks unless for high-risk patients (eg, oral corticosteroids or chronic NSAID use), erosive esophagitis, Barrett esophagitis, pathological hypersecretory condition, or demonstrated need for maintenance treatment (eg, because of failure of drug discontinuation trial or H2 receptor antagonists)	High	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Pain medications				
Meperidine	Oral analgesic not effective in dosages commonly used; may have higher risk of neurotoxicity, including delirium, than other opioids; safer alternatives available	Avoid	Moderate	Strong
Non–cyclooxygenase-selective NSAIDs, oral: Aspirin >325 mg/day Diclofenac Diflunisal Etodolac Fenoprofen Ibuprofen Ketoprofen Meclofenamate Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin	Increased risk of gastrointestinal bleeding or peptic ulcer disease in high-risk groups, including those >75 years or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents; use of proton-pump inhibitor or misoprostol reduces but does not eliminate risk. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occur in ~1% of patients treated for 3–6 months and in ~2%–4% of patients treated for 1 year; these trends continue with longer duration of use. Also can increase blood pressure and induce kidney injury. Risks are dose related.	Avoid chronic use, unless other alternatives are not effective and patient can take gastroprotective agent (proton-pump inhibitor or misoprostol)	Moderate	Strong
Indomethacin Ketorolac, including parenteral	Increased risk of gastrointestinal bleeding/peptic ulcer disease and acute kidney injury in older adults. Indomethacin is more likely than other NSAIDs to have adverse CNS effects. Of all the NSAIDs, indomethacin has the most adverse effects.	Avoid	Moderate	Strong
Skeletal muscle relaxants Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine	Most muscle relaxants poorly tolerated by older adults because some have anticholinergic adverse effects, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults questionable	Avoid	Moderate	Strong
Genitourinary				
Desmopressin	High risk of hyponatremia; safer alternative treatments	Avoid for treatment of nocturia or nocturnal polyuria	Moderate	Strong

Abbreviations: CNS, central nervous system; HFrEF, heart failure with reduced ejection fraction; NSAID, nonsteroidal anti-inflammatory drug; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
[a]The primary target audience is the practicing clinician. The intentions of the criteria include (1) improving the selection of prescription drugs by clinicians and patients; (2) evaluating patterns of drug use within populations; (3) educating clinicians and patients on proper drug usage; and (4) evaluating health outcomes, quality-of-care, cost, and utilization data.
[b]See also criterion on highly anticholinergic antidepressants.

Table 2

2019 AGS for PIM Use in Older Adults Due to Drug-Disease or Drug- Syndrome Interactions That May Exacerbate the Disease or Syndrome

Disease or Syndrome	Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Cardiovascular					
Heart failure	Avoid: Cilostazol	Potential to promote fluid retention and/or exacerbate heart failure (HF)	As noted, avoid or use with caution	Cilostazol: low	Cilostazol: strong
	Avoid in heart failure with reduced ejection fraction: Nondihydropyridine CCBs (diltiazem, verapamil)	and COX-2 inhibitors, nondihydropyridine CCBs, thiazolidinediones (TZDs) likely to increase mortality in older adults with heart failure (cilostazol and dronedarone)		Nondihydropyridine CCBs: moderate NSAIDs: moderate COX-2 inhibitors: low Thiazolidinediones: high Dronedarone: high	Nondihydropyridine CCBs: strong NSAIDs: strong COX-2 inhibitors: strong Thiazolidinediones: strong Dronedarone: strong
	Use with caution in patients with heart failure who are asymptomatic; avoid in patients with symptomatic heart failure: NSAIDs and COX-2 inhibitors				
	Thiazolidinediones (pioglitazone, rosiglitazone)				
	Dronedarone				
Syncope	ACIDSIs	ACIDSIs cause bradycardia and should be avoided in older adults whose syncope may be due to bradycardia. Nonselective peripheral alpha-1 blockers can cause orthostatic blood pressure changes and should be avoided in older adults whose syncope may be due to orthostatic hypotension. Tertiary TCAs and the antipsychotics listed increase the risk of orthostatic hypotension or bradycardia.	Avoid	ACIDSIs, TCAs, and antipsychotics: high Nonselective peripheral alpha-1 blockers: high	ACIDSIs and TCAs: strong Nonselective peripheral alpha-1 blockers and antipsychotics: weak
	Nonselective peripheral alpha-1 blockers (ie, doxazosin, prazosin, terazosin)				
	Tertiary TCAs				
	Antipsychotics: Chlorpromazine Thioridazine Olanzapine				
Central nervous system					
Delirium	Anticholinergics (see Table 7 and full criteria available on www.geriatricscareonline.org) Antipsychotics[a] Benzodiazepines Corticosteroids (oral and parenteral)[a] H2-receptor antagonists Cimetidine Famotidine Nizatidine Ranitidine Meperidine Nonbenzodiazepine benzodiazepine receptor agonist hypnotics: eszopiclone, zaleplon, zolpidem	Avoid in older adults with or at high risk of delirium because of potential of inducing or worsening delirium Avoid antipsychotics for behavioral problems of dementia and/or delirium unless nonpharmacological options (eg, behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others. Antipsychotics are associated with greater risk of cerebrovascular accident (stroke) and mortality in persons with dementia.	Avoid	H2-receptor antagonists: low All others: moderate	Strong
Dementia or cognitive impairment	Anticholinergics (see Table 7 and full criteria available on www.geriatricscareonline.org) Benzodiazepines Nonbenzodiazepine benzodiazepine receptor agonist hypnotics Eszopiclone	Avoid because of adverse CNS effects Avoid antipsychotics for behavioral problems of dementia and/or delirium unless nonpharmacological options (eg, behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or	Avoid	Moderate	Strong

Disease or Syndrome	Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
	Zaleplon Zolpidem Antipsychotics, chronic and as-needed use[c]	others. Antipsychotics are associated with greater risk of cerebrovascular accident (stroke) and mortality in persons with dementia.			
History of falls or fractures	Antiepileptics Antipsychotics[b] Benzodiazepines Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics Eszopiclone Zaleplon Zolpidem Antidepressants: TCAs SSRIs SNRIs Opioids	May cause ataxia, impaired psychomotor function, syncope, additional falls; shorter-acting benzodiazepines are not safer than long-acting ones. If one of the drugs must be used, consider reducing use of other CNS-active medications that increase risk of falls and fractures (ie, antiepileptics, opioid-receptor agonists, antipsychotics, antidepressants, nonbenzodiazepine and benzodiazepine receptor agonist hypnotics, other sedative/hypnotics) and implement other strategies to reduce fall risk. Data for antidepressants are mixed but no compelling evidence that certain antidepressants confer less fall risk than others.	Avoid unless safer alternatives are not available; avoid antiepileptics except for seizure and mood disorders Opioids: avoid except for pain management in the setting of severe acute pain (eg, recent fractures or joint replacement)	Opioids: moderate All others: high	Strong
Parkinson disease	Antiemetics Metoclopramide Prochlorperazine Promethazine All antipsychotics (except quetiapine, clozapine, pimavanserin)	Dopamine-receptor antagonists with potential to worsen parkinsonian symptoms Exceptions: Pimavanserin and clozapine appear to be less likely to precipitate worsening of Parkinson disease. Quetiapine has only been studied in low-quality clinical trials with efficacy comparable to that of placebo in five trials and to that of clozapine in two others.	Avoid	Moderate	Strong
Gastrointestinal					
History of gastric or duodenal ulcers	Aspirin >325 mg/day Non–COX-2–selective NSAIDs	May exacerbate existing ulcers or cause new/additional ulcers	Avoid unless other alternatives are not effective and patient can take gastroprotective agent (ie, proton-pump inhibitor or misoprostol)	Moderate	Strong
Kidney/urinary tract					
Chronic kidney disease stage 4 or higher (creatinine clearance <30 mL/min)	NSAIDs (non-COX and COX selective, oral and parenteral, nonacetylated salicylates)	May increase risk of acute kidney injury and further decline of renal function	Avoid	Moderate	Strong

Disease or Syndrome	Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Urinary incontinence (all types) in women	Estrogen oral and transdermal (excludes intravaginal estrogen) Peripheral alpha-1 blockers Doxazosin Prazosin Terazosin	Lack of efficacy (oral estrogen) and aggravation of incontinence (alpha-1 blockers)	Avoid in women	Estrogen: high Peripheral alpha-1 blockers: moderate	Estrogen: strong Peripheral alpha-1 blockers: strong
Lower urinary tract symptoms, benign prostatic hyperplasia	Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence (see Table 7 and full criteria available on www.geriatricscareonline.org)	May decrease urinary flow and cause urinary retention	Avoid in men	Moderate	Strong

Abbreviations: AChEI, acetylcholinesterase inhibitor; CCB, calcium channel blocker; CNS, central nervous system; COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]The primary target audience is the practicing clinician. The intentions of the criteria include (1) improving the selection of prescription drugs by clinicians and patients; (2) evaluating patterns of drug use within populations; (3) educating clinicians and patients on proper drug usage; and (4) evaluating health-outcome, quality-of-care, cost, and utilization data.

[b]May be required to treat concurrent schizophrenia, bipolar disorder, and other selected mental health conditions but should be prescribed in the lowest effective dose and shortest possible duration.

[c]Excludes inhaled and topical forms. Oral and parenteral corticosteroids may be required for conditions such as exacerbation of chronic obstructive pulmonary disease but should be prescribed in the lowest effective dose and for the shortest possible duration.

Table 3

2019 AGS Beers Criteria for PIMs: Drugs To Be Used With Caution in Older Adults

Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Aspirin for primary prevention of cardiovascular disease and colorectal cancer	Risk of major bleeding from aspirin increases markedly in older age. Several studies suggest lack of net benefit when used for primary prevention in older adult with cardiovascular risk factors, but evidence is not conclusive. Aspirin is generally indicated for secondary prevention in older adults with established cardiovascular disease.	Use with caution in adults ≥70 years	Moderate	Strong
Dabigatran Rivaroxaban	Increased risk of gastrointestinal bleeding compared with warfarin and reported rates with other direct oral anticoagulants when used for long-term treatment of VTE or atrial fibrillation in adults ≥75 years.	Use with caution for treatment of VTE or atrial fibrillation in adults ≥75 years	Moderate	Strong
Prasugrel	Increased risk of bleeding in older adults; benefit in highest-risk older adults (eg, those with prior myocardial infarction or diabetes mellitus) may offset risk when used for its approved indication of acute coronary syndrome to be managed with percutaneous coronary intervention.	Use with caution in adults ≥75 years	Moderate	Weak
Antipsychotics Carbamazepine Diuretics Milnacipran Oxcarbazepine SNRIs SSRIs TCAs Tramadol	May exacerbate or cause SIADH or hyponatremia; monitor sodium level closely when starting or changing dosages in older adults	Use with caution	Moderate	Strong
Dextromethorphan/quinidine	Limited efficacy in patients with behavioral symptoms or dementia (does not apply to treatment of PBA). May increase risk of falls and concerns with clinically significant drug interactions. Does not apply to treatment of pseudobulbar affect.	Use with caution	Moderate	Strong
Trimethoprim-sulfamethoxazole	Increased risk of hyperkalemia when used concurrently with an ACEI or ARB in presence of decreased creatinine clearance	Use with caution in patients on ACEI or ARB and decreased creatinine clearance	Low	Strong

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PBA, pseudobulbar affect; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VTE, venous thromboembolism.

*The primary target audience is the practicing clinician. The intentions of the criteria include (1) improving the selection of prescription drugs by clinicians and patients, (2) reducing patterns of drug use within populations, (3) educating clinicians and patients on proper drug usage, and (4) evaluating health outcomes, quality of care, cost, and utilization data.

Table 4.

2019 AGS Beers Criteria for Potentially Clinically Important Drug-Drug Interactions That Should Be Avoided in Older Adults

Object Drug and Class	Interacting Drug and Class	Risk Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
RAS inhibitor (ACEIs, ARBs, aliskiren) or potassium-sparing diuretics (amiloride, triamterene)	Another RAS inhibitor (ACEIs, ARBs, aliskiren)	Increased risk of hyperkalemia	Avoid routine use in those with chronic kidney disease stage 3a or higher	Moderate	Strong
Opioids	Benzodiazepines	Increased risk of overdose	Avoid	Moderate	Strong
Opioids	Gabapentin, pregabalin	Increased risk of severe sedation-related adverse events, including respiratory depression, and death	Avoid; exceptions are when transitioning from opioid therapy to gabapentin or pregabalin, or when using gabapentinoids to reduce opioid dose, although caution should be used in all circumstances.	Moderate	Strong
Anticholinergic	Anticholinergic	Increased risk of cognitive decline	Avoid; minimize number of anticholinergic drugs (Table 7)	Moderate	Strong
Antidepressants (TCAs, SSRIs, and SNRIs) Antipsychotics Antiepileptics Benzodiazepines and nonbenzodiazepines, benzodiazepine receptor agonist hypnotics (ie, "Z-drugs") Opioids	Any combination of three or more of these CNS-active drugs[a]	Increased risk of falls (all) and of fracture (benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonist hypnotics)	Avoid total of three or more CNS-active drugs[a]; minimize number of CNS-active drugs	Combinations including benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonist hypnotics or opioids: high All other combinations: moderate	Strong
Corticosteroids, oral or parenteral	NSAIDs	Increased risk of peptic ulcer disease or gastrointestinal bleeding	Avoid if not possible; provide gastrointestinal protection	Moderate	Strong
Lithium	ACEIs	Increased risk of lithium toxicity	Avoid; monitor lithium concentrations	Moderate	Strong
Lithium	Loop diuretics	Increased risk of lithium toxicity	Avoid; monitor lithium concentrations	Moderate	Strong
Peripheral α-1 blockers	Loop diuretics	Increased risk of urinary incontinence in older women	Avoid in older women, unless conditions warrant both drugs	Moderate	Strong
Phenytoin	Trimethoprim-sulfamethoxazole	Increased risk of phenytoin toxicity	Avoid	Moderate	Strong
Theophylline	Cimetidine	Increased risk of theophylline toxicity	Avoid	Moderate	Strong
Theophylline	Ciprofloxacin	Increased risk of theophylline toxicity	Avoid	Moderate	Strong
Warfarin	Amiodarone	Increased risk of bleeding	Avoid when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	Ciprofloxacin	Increased risk of bleeding	Avoid when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	Macrolides (excluding azithromycin)	Increased risk of bleeding	Avoid when possible; if used together, monitor INR closely	Moderate	Strong

Object Drug and Class	Interacting Drug and Class	Risk Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Warfarin	Trimethoprim-sulfamethoxazole	Increased risk of bleeding	Avoid when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	NSAIDs	Increased risk of bleeding	Avoid when possible; if used together, monitor closely for bleeding	High	Strong

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CNS, central nervous system; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; RAS, renin-angiotensin system; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]CNS-active drugs: antiepileptics; antipsychotics; benzodiazepines; nonbenzodiazepine, benzodiazepine receptor agonist hypnotics; TCAs; SSRIs; SNRIs; and opioids.

Table 5

2019 AGS Beers Criteria for Medications That Should Be Avoided or Have Their Dosage Reduced With Varying Levels of Kidney Function in Older Adults

Medication Class and Medication	Creatinine Clearance at Which Action Required, mL/min	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Anti-infective					
Ciprofloxacin	<30	Increased risk of CNS effects (eg, seizures, confusion) and tendon rupture	Doses used to treat common infections typically require reduction when CrCl <30 mL/min	Moderate	Strong
Trimethoprim-sulfamethoxazole	<30	Increased risk of worsening of renal function and hyperkalemia	Reduce dose if CrCl 15-29 mL/min Avoid if CrCl <15 mL/min	Moderate	Strong
Cardiovascular or hemostasis					
Amiodarone	<30	Increased potassium and decreased sodium	Avoid	Moderate	Strong
Apixaban	<25	Lack of evidence for efficacy and safety in patients with a CrCl <25 mL/min	Avoid	Moderate	Strong
Dabigatran	<30	Lack of evidence for efficacy and safety in individuals with a CrCl <30 mL/min. Label dose for patients with a CrCl 15-30 mL/min based on pharmacokinetic data.	Avoid; dose adjustment advised when CrCl >30 mL/min in the presence of drug-drug interactions	Moderate	Strong
Cefotetan	<60	QTc prolongation and torsade de pointes	Reduce dose if CrCl 30-59 mL/min Avoid if CrCl <29 mL/min	Moderate	Strong
Edoxaban	15-50 <15 or >95	Lack of evidence of efficacy or safety in patients with a CrCl <50 mL/min	Reduce dose if CrCl 15-50 mL/min Avoid if CrCl <15 or >95 mL/min	Moderate	Strong
Enoxaparin	<30	Increased risk of bleeding	Reduce dose	Moderate	Strong
Fondaparinux	<30	Increased risk of bleeding	Avoid	Moderate	Strong
Rivaroxaban	<50	Lack of efficacy or safety evidence in patients with a CrCl <50 mL/min	Non-valvular atrial fibrillation: reduce dose if CrCl 15-50 mL/min; avoid if CrCl <15 mL/min Venous thromboembolism treatment and for VTE prophylaxis with hip or knee replacement: avoid if CrCl <30 mL/min	Moderate	Strong
Spironolactone	<30	Increased potassium	Avoid	Moderate	Strong
Triamterene	<30	Increased potassium and decreased sodium	Avoid	Moderate	Strong
Central nervous system and analgesics					
Carisoprodol	<30	Increased gastrointestinal adverse effects (nausea, dizziness)	Avoid	Moderate	Weak
Gabapentin	<60	CNS adverse effects	Reduce dose	Moderate	Strong
Levetiracetam	≤80	CNS adverse effects	Reduce dose	Moderate	Strong
Pregabalin	≤60	CNS adverse effects	Reduce dose	Moderate	Strong
Tramadol	<30	CNS adverse effects	Immediate release: reduce dose Extended release: avoid	Low	Weak
Gastrointestinal					
Cimetidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Ranitidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Nizatidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Famotidine	<50	Mental status changes	Reduce dose	Moderate	Strong

Medication Class and Medication	Creatinine Clearance at Which Action Required, mL/min	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Hyperuricemia					
Colchicine	<30	Gastrointestinal, neuromuscular, bone marrow toxicity	Reduce dose; monitor for adverse effects	Moderate	Strong
Probenecid	<50	Loss of effectiveness	Avoid	Moderate	Strong

Abbreviations: CNS, central nervous system; CrCl, creatinine clearance; QTc, corrected QT interval; VTE, venous thromboembolism.

APPENDIX B: DATA COLLECTION FORM

Confidential

Data Sheet

Record ID	_____
Gender	○ Male ○ Female
Date of Birth	_____
Date of last consultation	_____
Age at last consultation (years)	_____
Age groups	○ 65-69 years ○ 70-74 years ○ 75-79 years ○ 80-84 years ○ 85-89 years ○ 90 years or older
Number of prescribed medication at last consultation	_____
Polypharmacy?	○ Yes ○ No

PIMs best avoided in most circumstances in older adults (tick all applicable)	☐ Allergex (Chlorpheniramine) ☐ Phergan (Promethazine) ☐ Buscopan (Hyoscyamine) ☐ Macrodantin (Nitrofurantoin) ☐ Cardura (Doxazosin) ☐ Minipress (Prazosin) ☐ Methyldopa ☐ Digoxin (1st line rx of AF or HF) ☐ Nifedipine, immediate release ☐ Amiodarone ☐ Amitriptyline ☐ Clomipramine ☐ Antipsychotics (first and second generation) ☐ Phenobarbital ☐ Lorazepam ☐ Oxazepam ☐ Clorazepate ☐ Diazepam ☐ Testosterone ☐ Premarin ☐ Insulin, sliding scale ☐ Glimepiride ☐ Glyburide (glibenclamide) ☐ Metaclopramide (maxalon) ☐ Proton pump inhibitors ☐ Aspirin >325 mg/day ☐ Ibuprofen ☐ Indomethacin ☐ Ketorolac, incl parenteral ☐ Orphenadrine ☐ Desmopressin
PIMs to be used with caution in older adults (tick all applicable)	☐ Aspirin (for primary prevention of CVS disease and colorectal ca) ☐ Carbamazepine (Tegretol) ☐ Lasix (Furosemide) ☐ Hydrochlorthiazide ☐ Serotonin-norepinephrine reuptake inhibitors (SNRIs) ☐ Selective Serotonin reuptake inhibitors (SSRIs) ☐ Tricyclic antidepressants (TCAs) ☐ Tramadol ☐ Bactrim
PIMS that require drug dose adjustment or discontinuation based on renal function	☐ Spironolactone ☐ Cymbalta (Duloxetine) ☐ Levetiracetam (Keppra) ☐ Pregabalin ☐ Tramadol ☐ Colchicine

PIM combination drug prescription which can lead to potentially clinically important drug-drug interactions	Yes	No
Angiotensin receptor blockers (ARB)/Angiotensin-converting-enzyme inhibitors (ACE)	○	○
Opioids/Benzodiazepines	○	○
Opioids/Lyrica	○	○
Allergex/Phenergan	○	○
TCA/SSRI/SNRI/antipsychotics/antiepileptics/benzos/opioids (combination of 3 or more)	○	○
Corticosteroids/Non-steroidal anti-inflammatory drug (NSAIDS)	○	○
Lithium/ACE	○	○
Lithium/Lasix	○	○
Cardura or Minipress/ Lasix	○	○
Phenytoin/Bactrim	○	○
Warfarin/Macrolides(exd Zithromax)	○	○
Warfarin/Bactrim	○	○
Warfarin/NSAIDs	○	○

Appendix E: Data Collection Form

Data Sheet

Record ID	_____
Sex	◯ Male ◯ Female
Date of Birth	_____
Date of last consultation	_____
Age at last consultation (years)	_____
Age groups	◯ 65-69 years ◯ 70-74 years ◯ 75-79 years ◯ 80-84 years ◯ 85-89 years ◯ 90 years or older
Number of prescribed medication at last consultation	_____
Polypharmacy?	◯ Yes ◯ No

PIMs best avoided in most circumstances in older adults (tick all applicable)	☐ Allergex (Chlorpheniramine) ☐ Phergan (Promethazine) ☐ Buscopan (Hyoscyamine) ☐ Macrodantin (Nitrofurantoin) ☐ Cardura (Doxazosin) ☐ Minipress (Prazosin) ☐ Methyldopa ☐ Digoxin (1st line rx of AF or HF) ☐ Nifedipine, immediate release ☐ Amiodarone ☐ Amitriptyline ☐ Clomipramine ☐ Antipsychotics (first and second generation) ☐ Phenobarbital ☐ Lorazepam ☐ Oxazepam ☐ Clorazepate ☐ Diazepam ☐ Testosterone ☐ Premarin ☐ Insulin, sliding scale ☐ Glimepiride ☐ Glyburide (glibenclamide) ☐ Metaclopramide (maxalon) ☐ Proton pump inhibitors ☐ Aspirin >325 mg/day ☐ Ibuprofen ☐ Indomethacin ☐ Ketorolac, incl parenteral ☐ Orphenadrine ☐ Desmopressin
PIMs to be used with caution in older adults (tick all applicable)	☐ Aspirin (for primary prevention of CVS disease and colorectal ca) ☐ Carbamazepine (Tegretol) ☐ Lasix (Furosemide) ☐ Hydrochlorthiazide ☐ Serotonin-norepinephrine reuptake inibitors (SNRIs) ☐ Selective Serotonin reuptake inhibitors (SSRIs) ☐ Tricyclic antidepressants (TCAs) ☐ Tramadol ☐ Bactrim
PIMS that require drug dose adjustment or discontinuation based on renal function	☐ Spironolactone ☐ Cymbalta (Duloxetine) ☐ Levetiracetam (Keppra) ☐ Pregabalin ☐ Tramadol ☐ Colchicine

PIM combination drug prescription which can lead to potentially clinically important drug-drug interactions	Yes	No
Angiotensin receptor blockers (ARB)/Angiotensin-converting-enzyme inhibitors (ACE)	○	○
Opioids/Benzodiazepines	○	○
Opioids/Lyrica	○	○
Allergex/Phenergan	○	○
TCA/SSRI/SNRI/antipsychotics/antiepileptics/benzos/opioids (combination of 3 or more)	○	○
Corticosteroids/Non-steroidal anti-inflammatory drug (NSAIDS)	○	○
Lithium/ACE	○	○
Lithium/Lasix	○	○
Cardura or Minipress/ Lasix	○	○
Phenytoin/Bactrim	○	○
Warfarin/Macrolides(excl Zithromax)	○	○
Warfarin/Bactrim	○	○
Warfarin/NSAIDs	○	○

Appendix F: 2019 American Geriatrics Society (AGS) Beers Criteria[57]

Table 1

2019 AGS Beers Criteria for Potentially Inappropriate Medication use in Older Adults

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Anticholinergics[b]				
First-generation antihistamines Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Dimenhydrinate Diphenhydramine (oral) Doxylamine Hydroxyzine Meclizine Promethazine Pyrilamine Triprolidine	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate.	Avoid	Moderate	Strong
Antiparkinsonian agents Benztropine (oral) Trihexyphenidyl	Not recommended for prevention or treatment of extrapyramidal symptoms with antipsychotics; more effective agents available for treatment of Parkinson disease	Avoid	Moderate	Strong
Antispasmodics Atropine (excludes ophthalmic) Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine Homatropine (excludes opthalmic) Hyoscyamine Methscopolamine Propantheline Scopolamine	Highly anticholinergic, uncertain effectiveness	Avoid	Moderate	Strong
Antithrombotics				
Dipyridamole, oral short acting (does not apply to the extended-release combination with aspirin)	May cause orthostatic hypotension; more effective alternatives available; IV form acceptable for use in cardiac stress testing	Avoid	Moderate	Strong
Anti-infective				
Nitrofurantoin	Potential for pulmonary toxicity, hepatotoxicity, and peripheral neuropathy, especially with long-term use; safer alternatives available	Avoid in individuals with creatinine clearance <30 mL/min or for long-term suppression	Low	Strong
Cardiovascular				
Peripheral alpha-1 blockers for treatment of hypertension Doxazosin Prazosin Terazosin	High risk of orthostatic hypotension and associated harms, especially in older adults; not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile	Avoid use as an antihypertensive	Moderate	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Central alpha-agonists Clonidine for first-line treatment of hypertension Other CNS alpha-agonists Guanabenz Guanfacine Methyldopa Reserpine (>0.1 mg/day)	High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension	Avoid as first-line antihypertensive Avoid other CNS alpha-agonists as listed	Low Low	Strong Strong
Disopyramide	May induce heart failure in older adults because of potent negative inotropic action; strongly anticholinergic; other antiarrhythmic drugs preferred	Avoid	Low	Strong
Dronedarone	Worse outcomes have been reported in patients taking dronedarone who have permanent atrial fibrillation or severe or recently decompensated heart failure.	Avoid in individuals with permanent atrial fibrillation or severe or recently decompensated heart failure	High	Strong
Digoxin for first-line treatment of atrial fibrillation or of heart failure	Use in atrial fibrillation: should not be used as a first-line agent in atrial fibrillation, because there are safer and more effective alternatives for rate control supported by high-quality evidence. Use in heart failure: evidence for benefits and harms of digoxin is conflicting and of lower quality; most but not all of the evidence concerns use in HFrEF. There is strong evidence for other agents as first-line therapy to reduce hospitalizations and mortality in adults with HFrEF. In heart failure, higher dosages are not associated with additional benefit and may increase risk of toxicity. Decreased renal clearance of digoxin may lead to increased risk of toxic effects; further dose reduction may be necessary in those with stage 4 or 5 chronic kidney disease.	Avoid this rate control agent as first-line therapy for atrial fibrillation Avoid as first-line therapy for heart failure If used for atrial fibrillation or heart failure, avoid dosages >0.125 mg/day	Atrial fibrillation: low Heart failure: low Dosage >0.125 mg/day: moderate	Atrial fibrillation: strong Heart failure: strong Dosage >0.125 mg/day: strong
Nifedipine, immediate release	Potential for hypotension; risk of precipitating myocardial ischemia	Avoid	High	Strong
Amiodarone	Effective for maintaining sinus rhythm but has greater toxicities than other antiarrhythmics used in atrial fibrillation; may be reasonable first-line therapy in patients with concomitant heart failure or substantial left ventricular hypertrophy if rhythm control is preferred over rate control	Avoid as first-line therapy for atrial fibrillation unless patient has heart failure or substantial left ventricular hypertrophy	High	Strong
Central nervous system				
Antidepressants, alone or in combination Amitriptyline Amoxapine Clomipramine Desipramine Doxepin >6 mg/day Imipramine	Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≤6 mg/day) comparable to that of placebo	Avoid	High	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Nortriptyline Paroxetine Protriptyline Trimipramine				
Antipsychotics, first (conventional) and second (atypical) generation	Increased risk of cerebrovascular accident (stroke) and greater rate of cognitive decline and mortality in persons with dementia Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (eg, behavioral interventions) have failed or are not possible *and* the older adult is threatening substantial harm to self or others	Avoid, except in schizophrenia or bipolar disorder, or for short-term use as antiemetic during chemotherapy	Moderate	Strong
Barbiturates Amobarbital Butabarbital Butalbital Mephobarbital Pentobarbital Phenobarbital Secobarbital	High rate of physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages	Avoid	High	Strong
Benzodiazepines *Short and intermediate acting:* Alprazolam Estazolam Lorazepam Oxazepam Temazepam Triazolam *Long acting:* Chlordiazepoxide (alone or in combination with amitriptyline or clidinium) Clonazepam Clorazepate Diazepam Flurazepam Quazepam	Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents; in general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults May be appropriate for seizure disorders, rapid eye movement sleep behavior disorder, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, and periprocedural anesthesia	Avoid	Moderate	Strong
Meprobamate	High rate of physical dependence; sedating	Avoid	Moderate	Strong
Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (ie, "Z-drugs") Eszopiclone Zaleplon Zolpidem	Nonbenzodiazepine benzodiazepine receptor agonist hypnotics (ie, Z drugs) have adverse events similar to those of benzodiazepines in older adults (eg, delirium, falls, fractures); increased emergency room visits/ hospitalizations; motor vehicle crashes; minimal improvement in sleep latency and duration	Avoid	Moderate	Strong
Ergoloid mesylates (dehydrogenated ergot alkaloids) Isoxsuprine	Lack of efficacy	Avoid	High	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Endocrine				
Androgens Methyltestosterone Testosterone	Potential for cardiac problems; contraindicated in men with prostate cancer	Avoid unless indicated for confirmed hypogonadism with clinical symptoms	Moderate	Weak
Desiccated thyroid	Concerns about cardiac effects; safer alternatives available	Avoid	Low	Strong
Estrogens with or without progestins	Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women	Avoid systemic estrogen (eg, oral and topical patch)	Oral and patch: high	Oral and patch: strong
	Evidence indicates that vaginal estrogens for the treatment of vaginal dryness are safe and effective; women with a history of breast cancer who do not respond to nonhormonal therapies are advised to discuss the risks and benefits of low-dose vaginal estrogen (dosages of estradiol <25 μg twice weekly) with their healthcare provider	Vaginal cream or vaginal tablets: acceptable to use low-dose intravaginal estrogen for management of dyspareunia, recurrent lower urinary tract infections, and other vaginal symptoms	Vaginal cream or vaginal tablets: moderate	Topical vaginal cream or tablets: weak
Growth hormone	Impact on body composition is small and associated with edema, arthralgia, carpal tunnel syndrome, gynecomastia, impaired fasting glucose	Avoid, except for patients rigorously diagnosed by evidence-based criteria with growth hormone deficiency due to an established etiology	High	Strong
Insulin, sliding scale (insulin regimens containing only short- or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin)	Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting. Avoid insulin regimens that include only short- or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin. This recommendation does not apply to regimens that contain basal insulin or long-acting insulin.	Avoid	Moderate	Strong
Megestrol	Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults	Avoid	Moderate	Strong
Sulfonylureas, long acting Chlorpropamide Glimepiride Glyburide (also known as glibenclamide)	Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes SIADH Glimepiride and glyburide: higher risk of severe prolonged hypoglycemia in older adults	Avoid	High	Strong
Gastrointestinal				
Metoclopramide	Can cause extrapyramidal effects, including tardive dyskinesia; risk may be greater in frail older adults and with prolonged exposure	Avoid, unless for gastroparesis with duration of use not to exceed 12 weeks except in rare cases	Moderate	Strong
Mineral oil, given orally	Potential for aspiration and adverse effects; safer alternatives available	Avoid	Moderate	Strong
Proton-pump inhibitors	Risk of *Clostridium difficile* infection and bone loss and fractures	Avoid scheduled use for >8 weeks unless for high-risk patients (eg, oral corticosteroids or chronic NSAID use), erosive esophagitis, Barrett esophagitis, pathological hypersecretory condition, or demonstrated need for maintenance treatment (eg, because of failure of drug discontinuation trial or H2-receptor antagonists)	High	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Pain medications				
Meperidine	Oral analgesic not effective in dosages commonly used; may have higher risk of neurotoxicity, including delirium, than other opioids; safer alternatives available	Avoid	Moderate	Strong
Non–cyclooxygenase-selective NSAIDs, oral: Aspirin >325 mg/day Diclofenac Diflunisal Etodolac Fenoprofen Ibuprofen Ketoprofen Meclofenamate Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin	Increased risk of gastrointestinal bleeding or peptic ulcer disease in high-risk groups, including those >75 years or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents; use of proton-pump inhibitor or misoprostol reduces but does not eliminate risk. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occur in ~1% of patients treated for 3-6 months and in ~2%-4% of patients treated for 1 year; these trends continue with longer duration of use. Also can increase blood pressure and induce kidney injury. Risks are dose related.	Avoid chronic use, unless other alternatives are not effective and patient can take gastroprotective agent (proton-pump inhibitor or misoprostol)	Moderate	Strong
Indomethacin Ketorolac, includes parenteral	Increased risk of gastrointestinal bleeding/peptic ulcer disease and acute kidney injury in older adults Indomethacin is more likely than other NSAIDs to have adverse CNS effects. Of all the NSAIDs, indomethacin has the most adverse effects.	Avoid	Moderate	Strong
Skeletal muscle relaxants Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine	Most muscle relaxants poorly tolerated by older adults because some have anticholinergic adverse effects, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults questionable	Avoid	Moderate	Strong
Genitourinary				
Desmopressin	High risk of hyponatremia; safer alternative treatments	Avoid for treatment of nocturia or nocturnal polyuria	Moderate	Strong

Abbreviations: CNS, central nervous system; HFrEF, heart failure with reduced ejection fraction; NSAID, nonsteroidal anti-inflammatory drug; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

[a]The primary target audience is the practicing clinician. The intentions of the criteria include (1) improving the selection of prescription drugs by clinicians and patients; (2) evaluating patterns of drug use within populations; (3) educating clinicians and patients on proper drug usage; and (4) evaluating health-outcome, quality-of-care, cost, and utilization data.

[b]See also criterion on highly anticholinergic antidepressants.

Table 2

2019 AGS for PIM Use in Older Adults Due to Drug-Disease or Drug-Syndrome Interactions That May Exacerbate the Disease or Syndrome

Disease or Syndrome	Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Cardiovascular					
Heart failure	Avoid: Cilostazol	Potential to promote fluid retention and/or exacerbate heart failure (NSAIDs and COX-2 inhibitors, nondihydropyridine CCBs, thiazolidinediones); potential to increase mortality in older adults with heart failure (cilostazol and dronedarone)	As noted, avoid or use with caution	Cilostazol: low	Cilostazol: strong
	Avoid in heart failure with reduced ejection fraction: Nondihydropyridine CCBs (diltiazem, verapamil)			Nondihydropyridine CCBs: moderate	Nondihydropyridine CCBs: strong
				NSAIDs: moderate	NSAIDs: strong
	Use with caution in patients with heart failure who are asymptomatic; avoid in patients with symptomatic heart failure: NSAIDs and COX-2 inhibitors			COX-2 inhibitors: low	COX-2 inhibitors: strong
	Thiazolidinediones (pioglitazone, rosiglitazone)			Thiazolidinediones: high	Thiazolidinediones: strong
	Dronedarone			Dronedarone: high	Dronedarone: strong
Syncope	AChEIs	AChEIs cause bradycardia and should be avoided in older adults whose syncope may be due to bradycardia. Nonselective peripheral alpha-1 blockers cause orthostatic blood pressure changes and should be avoided in older adults whose syncope may be due to orthostatic hypotension. Tertiary TCAs and the antipsychotics listed increase the risk of orthostatic hypotension or bradycardia.	Avoid	AChEIs, TCAs, and antipsychotics: high	AChEIs and TCAs: strong
	Nonselective peripheral alpha-1 blockers (ie, doxazosin, prazosin, terazosin)			Nonselective peripheral alpha-1 blockers: high	Nonselective peripheral alpha-1 blockers and antipsychotics: weak
	Tertiary TCAs				
	Antipsychotics: Chlorpromazine Thioridazine Olanzapine				
Central nervous system					
Delirium	Anticholinergics (see Table 7 and full criteria available on www.geriatricscareonline.org.)	Avoid in older adults with or at high risk of delirium because of potential of inducing or worsening delirium	Avoid	H2-receptor antagonists: low	Strong
	Antipsychotics[a] Benzodiazepines	Avoid antipsychotics for behavioral problems of dementia and/or delirium unless nonpharmacological options (eg, behavioral interventions) have failed or are not possible *and* the older adult is threatening substantial harm to self or others. Antipsychotics are associated with greater risk of cerebrovascular accident (stroke) and mortality in persons with dementia.		All others: moderate	
	Corticosteroids (oral and parenteral)[c]				
	H2-receptor antagonists Cimetidine Famotidine Nizatidine Ranitidine				
	Meperidine				
	Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics: eszopiclone, zaleplon, zolpidem				
Dementia or cognitive impairment	Anticholinergics (see Table 7 and full criteria available on www.geriatricscareonline.org)	Avoid because of adverse CNS effects Avoid antipsychotics for behavioral problems of dementia and/or delirium unless nonpharmacological options (eg, behavioral interventions) have failed or are not possible *and* the older adult is threatening substantial harm to self or	Avoid	Moderate	Strong
	Benzodiazepines				
	Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics Eszopiclone				

Disease or Syndrome	Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
	Zaleplon Zolpidem Antipsychotics, chronic and as-needed use[b]	others. Antipsychotics are associated with greater risk of cerebrovascular accident (stroke) and mortality in persons with dementia.			
History of falls or fractures	Antiepileptics Antipsychotics[b] Benzodiazepines Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics Eszopiclone Zaleplon Zolpidem Antidepressants TCAs SSRIs SNRIs Opioids	May cause ataxia, impaired psychomotor function, syncope, additional falls; shorter-acting benzodiazepines are not safer than long-acting ones. If one of the drugs must be used, consider reducing use of other CNS-active medications that increase risk of falls and fractures (ie, antiepileptics, opioid-receptor agonists, antipsychotics, antidepressants, nonbenzodiazepine and benzodiazepine receptor agonist hypnotics, other sedatives/hypnotics) and implement other strategies to reduce fall risk. Data for antidepressants are mixed but no compelling evidence that certain antidepressants confer less fall risk than others.	Avoid unless safer alternatives are not available; avoid antiepileptics except for seizure and mood disorders Opioids: avoid except for pain management in the setting of severe acute pain (eg, recent fractures or joint replacement)	Opioids: moderate All others: high	Strong
Parkinson disease	Antiemetics Metoclopramide Prochlorperazine Promethazine All antipsychotics (except quetiapine, clozapine, pimavanserin)	Dopamine-receptor antagonists with potential to worsen parkinsonian symptoms Exceptions: Pimavanserin and clozapine appear to be less likely to precipitate worsening of Parkinson disease. Quetiapine has only been studied in low-quality clinical trials with efficacy comparable to that of placebo in five trials and to that of clozapine in two others.	Avoid	Moderate	Strong
Gastrointestinal					
History of gastric or duodenal ulcers	Aspirin >325 mg/day Non–COX-2–selective NSAIDs	May exacerbate existing ulcers or cause new/additional ulcers	Avoid unless other alternatives are not effective and patient can take gastroprotective agent (ie, proton-pump inhibitor or misoprostol)	Moderate	Strong
Kidney/urinary tract					
Chronic kidney disease stage 4 or higher (creatinine clearance <30 mL/min)	NSAIDs (non-COX and COX selective, oral and parenteral, nonacetylated salicylates)	May increase risk of acute kidney injury and further decline of renal function	Avoid	Moderate	Strong

Disease or Syndrome	Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Urinary incontinence (all types) in women	Estrogen oral and transdermal (excludes intravaginal estrogen) Peripheral alpha-1 blockers Doxazosin Prazosin Terazosin	Lack of efficacy (oral estrogen) and aggravation of incontinence (alpha-1 blockers)	Avoid in women	Estrogen: high Peripheral alpha-1 blockers: moderate	Estrogen: strong Peripheral alpha-1 blockers: strong
Lower urinary tract symptoms, benign prostatic hyperplasia	Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence (see Table 7 and full criteria available on www.geriatricscareonline.org)	May decrease urinary flow and cause urinary retention	Avoid in men	Moderate	Strong

Abbreviations: AChEI, acetylcholinesterase inhibitor; CCB, calcium channel blocker; CNS, central nervous system; COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]The primary target audience is the practicing clinician. The intentions of the criteria include (1) improving the selection of prescription drugs by clinicians and patients; (2) evaluating patterns of drug use within populations; (3) educating clinicians and patients on proper drug usage; and (4) evaluating health-outcome, quality-of-care, cost, and utilization data.

[b]May be required to treat concurrent schizophrenia, bipolar disorder, and other selected mental health conditions but should be prescribed in the lowest effective dose and shortest possible duration.

[c]Excludes inhaled and topical forms. Oral and parenteral corticosteroids may be required for conditions such as exacerbation of chronic obstructive pulmonary disease but should be prescribed in the lowest effective dose and for the shortest possible duration.

Table 3

2019 AGS Beers Criteria for PIMs: Drugs To Be Used With Caution in Older Adults

Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Aspirin for primary prevention of cardiovascular disease and colorectal cancer	Risk of major bleeding from aspirin increases markedly in older age. Several studies suggest lack of net benefit when used for primary prevention in older adult with cardiovascular risk factors, but evidence is not conclusive. Aspirin is generally indicated for secondary prevention in older adults with established cardiovascular disease.	Use with caution in adults ≥70 years	Moderate	Strong
Dabigatran Rivaroxaban	Increased risk of gastrointestinal bleeding compared with warfarin and reported rates with other direct oral anticoagulants when used for long-term treatment of VTE or atrial fibrillation in adults ≥75 years.	Use with caution for treatment of VTE or atrial fibrillation in adults ≥75 years	Moderate	Strong
Prasugrel	Increased risk of bleeding in older adults; benefit in highest-risk older adults (eg, those with prior myocardial infarction or diabetes mellitus) may offset risk when used for its approved indication of acute coronary syndrome to be managed with percutaneous coronary intervention.	Use with caution in adults ≥75 years	Moderate	Weak
Antipsychotics Carbamazepine Diuretics Mirtazapine Oxcarbazepine SNRIs SSRIs TCAs Tramadol	May exacerbate or cause SIADH or hyponatremia; monitor sodium level closely when starting or changing dosages in older adults	Use with caution	Moderate	Strong
Dextromethorphan/ quinidine	Limited efficacy in patients with behavioral symptoms of dementia (does not apply to treatment of PBA). May increase risk of falls and concerns with clinically significant drug interactions. Does not apply to treatment of pseudobulbar affect.	Use with caution	Moderate	Strong
Trimethoprim-sulfamethoxazole	Increased risk of hyperkalemia when used concurrently with an ACEI or ARB in presence of decreased creatinine clearance	Use with caution in patients on ACEI or ARB and decreased creatinine clearance	Low	Strong

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PBA, pseudobulbar affect; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VTE, venous thromboembolism.

*The primary target audience is the practicing clinician. The intentions of the criteria include (1) improving the selection of prescription drugs by clinicians and patients; (2) evaluating patterns of drug use within populations; (3) educating clinicians and patients on proper drug usage; and (4) evaluating health-outcome, quality-of-care, cost, and utilization data.

Table 4

2019 AGS Beers Criteria for Potentially Clinically Important Drug-Drug Interactions That Should Be Avoided in Older Adults

Object Drug and Class	Interacting Drug and Class	Risk Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
RAS inhibitor (ACEIs, ARBs, aliskiren) or potassium-sparing diuretics (amiloride, triamterene)	Another RAS inhibitor (ACEIs, ARBs, aliskiren)	Increased risk of hyperkalemia	Avoid routine use in those with chronic kidney disease stage 3a or higher	Moderate	Strong
Opioids	Benzodiazepines	Increased risk of overdose	Avoid	Moderate	Strong
Opioids	Gabapentin, pregabalin	Increased risk of severe sedation-related adverse events, including respiratory depression and death	Avoid; exceptions are when transitioning from opioid therapy to gabapentin or pregabalin, or when using gabapentinoids to reduce opioid dose, although caution should be used in all circumstances.	Moderate	Strong
Anticholinergic	Anticholinergic	Increased risk of cognitive decline	Avoid; minimize number of anticholinergic drugs (Table 7)	Moderate	Strong
Antidepressants (TCAs, SSRIs, and SNRIs) Antipsychotics Antiepileptics Benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (ie, "Z-drugs") Opioids	Any combination of three or more of these CNS-active drugs[a]	Increased risk of falls (all) and of fracture (benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonist hypnotics)	Avoid total of three or more CNS-active drugs[a]; minimize number of CNS-active drugs	Combinations including benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonist hypnotics or opioids: high All other combinations: moderate	Strong
Corticosteroids, oral or parenteral	NSAIDs	Increased risk of peptic ulcer disease or gastrointestinal bleeding	Avoid; if not possible, provide gastrointestinal protection	Moderate	Strong
Lithium	ACEIs	Increased risk of lithium toxicity	Avoid; monitor lithium concentrations	Moderate	Strong
Lithium	Loop diuretics	Increased risk of lithium toxicity	Avoid; monitor lithium concentrations	Moderate	Strong
Peripheral α-1 blockers	Loop diuretics	Increased risk of urinary incontinence in older women	Avoid in older women, unless conditions warrant both drugs	Moderate	Strong
Phenytoin	Trimethoprim-sulfamethoxazole	Increased risk of phenytoin toxicity	Avoid	Moderate	Strong
Theophylline	Cimetidine	Increased risk of theophylline toxicity	Avoid	Moderate	Strong
Theophylline	Ciprofloxacin	Increased risk of theophylline toxicity	Avoid	Moderate	Strong
Warfarin	Amiodarone	Increased risk of bleeding	Avoid when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	Ciprofloxacin	Increased risk of bleeding	Avoid when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	Macrolides (excluding azithromycin)	Increased risk of bleeding	Avoid when possible; if used together, monitor INR closely	Moderate	Strong

Object Drug and Class	Interacting Drug and Class	Risk Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Warfarin	Trimethoprim-sulfamethoxazole	Increased risk of bleeding	Avoid when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	NSAIDs	Increased risk of bleeding	Avoid when possible; if used together, monitor closely for bleeding	High	Strong

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CNS, central nervous system; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; RAS, renin-angiotensin system; SNRI, serotonin- norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
[a]CNS-active drugs: antiepileptics; antipsychotics; benzodiazepines; nonbenzodiazepine, benzodiazepine receptor agonist hypnotics; TCAs; SSRIs; SNRIs; and opioids.

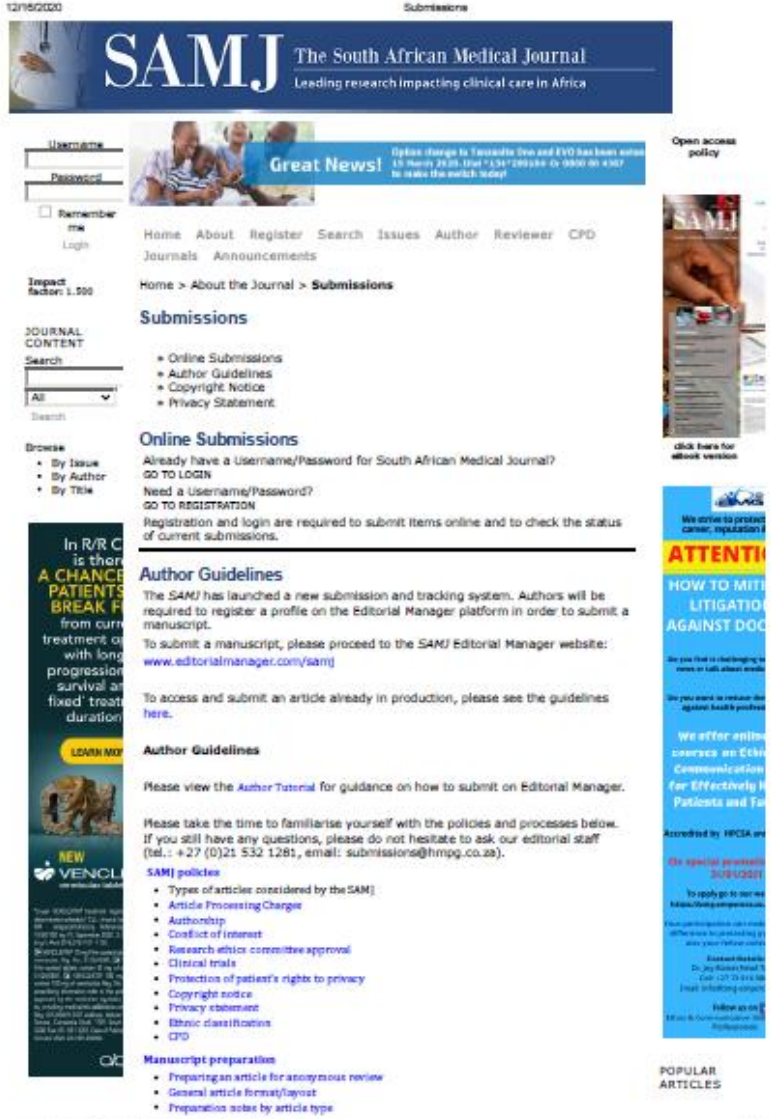
Table 5

2019 AGS Beers Criteria for Medications That Should Be Avoided or Have Their Dosage Reduced With Varying Levels of Kidney Function in Older Adults

Medication Class and Medication	Creatinine Clearance at Which Action Required, mL/min	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Anti-infective					
Ciprofloxacin	<30	Increased risk of CNS effects (eg, seizures, confusion) and tendon rupture	Doses used to treat common infections typically require reduction when CrCl <30 mL/min	Moderate	Strong
Trimethoprim-sulfamethoxazole	<30	Increased risk of worsening of renal function and hyperkalemia	Reduce dose if CrCl 15-29 mL/min Avoid if CrCl <15 mL/min	Moderate	Strong
Cardiovascular or hemostasis					
Amiloride	<30	Increased potassium and decreased sodium	Avoid	Moderate	Strong
Apixaban	<25	Lack of evidence for efficacy and safety in patients with a CrCl <25 mL/min	Avoid	Moderate	Strong
Dabigatran	<30	Lack of evidence for efficacy and safety in individuals with a CrCl <30 mL/min. Label dose for patients with a CrCl 15-30 mL/min based on pharmacokinetic data.	Avoid; dose adjustment advised when CrCl >30 mL/min in the presence of drug-drug interactions	Moderate	Strong
Dofetilide	<60	QTc prolongation and torsade de pointes	Reduce dose if CrCl 20-59 mL/min Avoid if CrCl <20 mL/min	Moderate	Strong
Edoxaban	15-50 <15 or >95	Lack of evidence of efficacy or safety in patients with a CrCl <30 mL/min	Reduce dose if CrCl 15-50 mL/min Avoid if CrCl <15 or >95 mL/min	Moderate	Strong
Enoxaparin	<30	Increased risk of bleeding	Reduce dose	Moderate	Strong
Fondaparinux	<30	Increased risk of bleeding	Avoid	Moderate	Strong
Rivaroxaban	<50	Lack of efficacy or safety evidence in patients with a CrCl <30 mL/min	Nonvalvular atrial fibrillation: reduce dose if CrCl 15-50 mL/min; avoid if CrCl <15 mL/min Venous thromboembolism treatment and for VTE prophylaxis with hip or knee replacement: avoid if CrCl <30 mL/min	Moderate	Strong
Spironolactone	<30	Increased potassium	Avoid	Moderate	Strong
Triamterene	<30	Increased potassium and decreased sodium	Avoid	Moderate	Strong
Central nervous system and analgesics					
Duloxetine	<30	Increased gastrointestinal adverse effects (nausea, diarrhea)	Avoid	Moderate	Weak
Gabapentin	<60	CNS adverse effects	Reduce dose	Moderate	Strong
Levetiracetam	≤80	CNS adverse effects	Reduce dose	Moderate	Strong
Pregabalin	<60	CNS adverse effects	Reduce dose	Moderate	Strong
Tramadol	<30	CNS adverse effects	Immediate release: reduce dose Extended release: avoid	Low	Weak
Gastrointestinal					
Cimetidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Famotidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Nizatidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Ranitidine	<50	Mental status changes	Reduce dose	Moderate	Strong

Medication Class and Medication	Creatinine Clearance at Which Action Required, mL/min	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Hyperuricemia					
Colchicine	<30	Gastrointestinal, neuromuscular, bone marrow toxicity	Reduce dose; monitor for adverse effects	Moderate	Strong
Probenecid	<30	Loss of effectiveness	Avoid	Moderate	Strong

Abbreviations: CNS, central nervous system; CrCl, creatinine clearance; QTc, corrected QT interval; VTE, venous thromboembolism.



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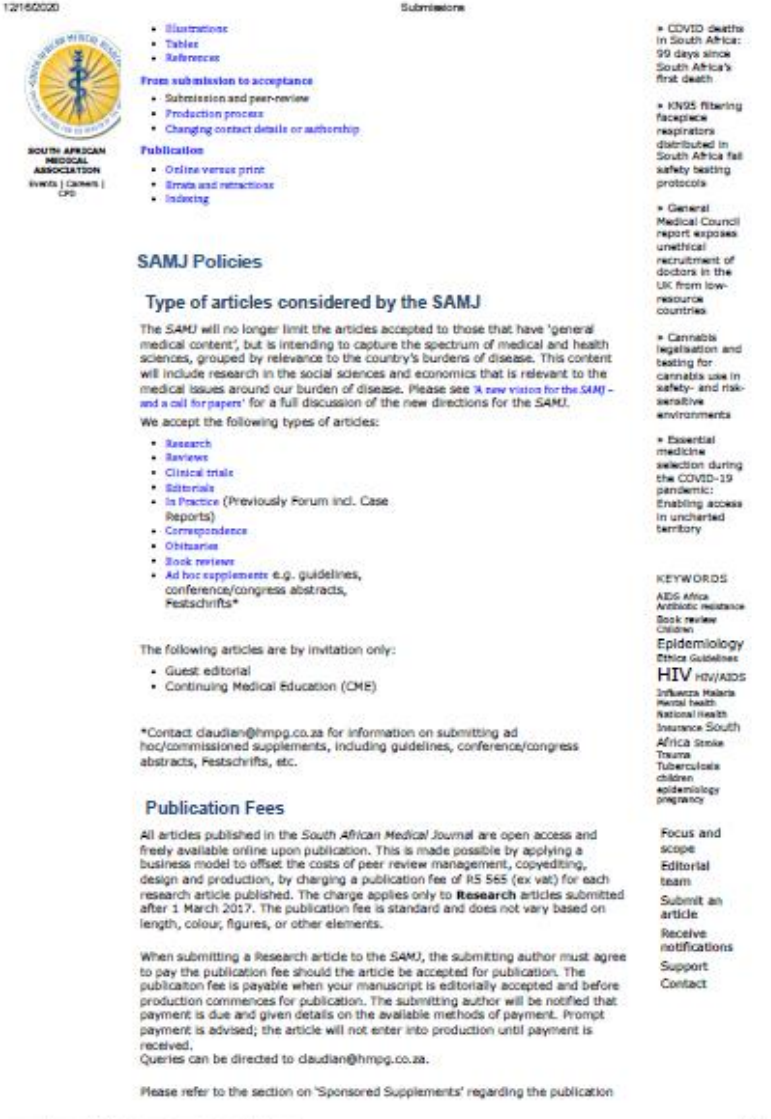

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- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

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Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies

- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 – 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)82 452 2860)

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 – 3 000 words

- Each article requires an abstract of ±200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail

address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

- Case report
- Clinical practice
- Clinical alert
- Issues in medicine
- Issues in public health
- Healthcare delivery
- Medicine and the environment
- Medicine and the law
- Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style

- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.

All guidelines should be structured according to Agree II.

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 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.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.

- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
  - Alongside 'url =' copy the URL between { }.
  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjc.182
- *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, 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: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. 866B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format*: Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(In press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process

*Manuscripts accepted at this point are limited to Editorials, Correspondence, Obituaries, Book reviews, Abstracts
**Some minor revisions may be requested

Production process

Please note that there is a 6-month waiting time for publication, once an article has been sent to the production team.

The following process will follow:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Publication

Online v. print

The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition , containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online

- The full text of all accepted articles is published in full online, open access.
- Citation information of each article is based on its online publication.
- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print

- Not all articles will be selected for print.
- An article may be selected for print in a different month from that in which it was published online.
- Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish anerratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of SAMA. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

The *SAMJ* has an impact factor of 1.5.

Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

- Index Medicus (Medline/PubMed)
- ExcerptaMedica (EMBASE)
- Biological Abstracts (BIOSIS)
- Science Citation Index (SciSearch)
- Current Contents/Clinical Medicine
- Scopus
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

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Contact claudian@samedical.org for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

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Appendix H: Turnitin Report

turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	Mariette Harmse
Assignment title:	Submit your chapter or thesis here (draft)
Submission title:	Isaacs MMed
File name:	GS_Isaacs_MMED_20_April.docx
File size:	5.53M
Page count:	109
Word count:	11,993
Character count:	73,681
Submission date:	21-Apr-2021 03:22PM (UTC+0200)
Submission ID:	1565595425

THE PREVALENCE OF POLYPHARMACY AND PRESCRIPTION OF POTENTIALLY INAPPROPRIATE MEDICATIONS IN THE ELDERLY

MMED GS Isaacs

ORIGINALITY REPORT

18%	15%	14%	8%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

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	the use of potentially inappropriate medications by older adults in primary health care", Research in Social and Administrative Pharmacy, 2018 Publication	
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	Mohile, Cynthia Owusu, Heidi D. Klepin, Stuart M. Lichtman, Ajeet Gajra, Rupal Ramani, Vani Katheria, Laura Zavala, and Arti Hurria. "Polypharmacy and Potentially Inappropriate Medication Use in Older Adults with Cancer Undergoing Chemotherapy: Effect on Chemotherapy-Related Toxicity and Hospitalization During Treatment", Journal of the American Geriatrics Society, 2014. Publication	
28	cora.ucc.ie Internet Source	<1 %
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31	"Developing Drug Products in an Aging Society", Springer Science and Business Media LLC, 2016 Publication	<1 %
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