

Potentially Inappropriate Medications and their Use in Elderly Populations Residing in Long-Term Care Facilities

A. R. Ganassin¹, V. T. G. de Matos², *M. C. Toffoli-Kadri¹

1.Center for Biological and Health Sciences, Federal University of Mato Grosso do Sul, Cidade Universitaria, P.O. Box 549, Campo Grande, Mato Grosso do Sul, Brazil.

2.Faculty of Medicine, Federal University of Mato Grosso do Sul, Rua Amazonas, 2952, Jardim Autonomista, Campo Grande Mato Grosso do Sul, Brazil.

ABSTRACT

In recent decades, an aging population has caused a demographic change brought on by factors such as the improvement in sanitary conditions and technological advances in the medical and pharmaceutical industries. However, the demands of specific care coupled with new family arrangements have led to increasing institutionalization of the elderly. Medications used in these populations are not always appropriate for their needs, as the socioeconomic difficulties of long-term care facilities for the elderly result in collective rather than individualized consultations, increasing the possibility of drug and iatrogenic interactions. Elderly residing in long-term care facilities require special attention, since they may present specific vulnerable characteristics such as advanced age, high number of diseases, frailty, polypharmacy, physical as well as psychological and social dependence, low functionality, among others. Furthermore, they present particularities regarding the use of medications due to organ functions are minimized by physiological changes that alter pharmacokinetics and pharmacodynamics. Thus, to support this practice, several instruments that classify potentially inappropriate medications for the elderly have emerged. In Brazil, most studies on drug use in the elderly are related to outpatient, hospital, or community settings. However, few studies have investigated risk factors related to medication usage in institutionalized elderly. This review aims to contribute to the rational use of medications in the elderly, in order to complement the knowledge of health professionals and, consequently, maximize therapeutic efficacy in this population.

Keywords: Elderly health, iatrogenic, long-term care facilities, rational drug use

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*Address for correspondence:

M. C. Toffoli-Kadri

Professor, Center for Biological and Health Sciences, Federal University of Mato Grosso do Sul, Cidade Universitaria, P.O. Box 549, Campo Grande, Mato Grosso do Sul, Brazil.

E-mail: monica.kadri@ufms.br

INTRODUCTION

Demographic studies have shown a steady increase in elderly populations worldwide. This growth is estimated to reach 80% over the next 25 years [1]. In Brazil, the 2010 census showed a population increase of approximately 21 million people compared to the census conducted in 2000. This number shows the increase in the Brazilian population during the period was 12.3%. Whereas in 2000, 5.9% of the population was in the age group above 65 years, by 2010, this figure increased to 7.4% [2]. In recent decades, Brazil has shifted from the typical profile of a young population to an aging population

characterized by multiple chronic illnesses in the older age groups [1].

The gradual increase in longevity and decreasing mortality are caused by factors such as improvements in sanitary conditions, quality of life and technological advances in the medical and pharmaceutical areas. These advancements collaborated to the prevention and cure of many previously fatal diseases, allowing for increased life expectancy [3,4].

According to the World Health Organization [5], the age group that encompasses elderly individuals varies between countries and over time as a reflection of social

differences or functional ability. Developed countries consider senior citizens as individuals aged over 65 years, while this status as an elderly individual is considered 60 years or older in Brazil [5,6]. Some authors suggest the age group above 75 years for studies in geriatrics. However, these designations are arbitrary due to the high heterogeneity in the elderly population and actual differences between chronological and physiological ages [5,7]. The aging of the Brazilian population follows the trend seen in developed countries by generating new social demands and providing ever-increasing challenges to health services. These changes make it imperative to redefine healthcare practices across the country [8-10].

The need for specialized care coupled with new family arrangements has contributed to the increasing institutionalization of the elderly [11]. The socioeconomic difficulties of long-term care facilities (LTCF) lead them to make collective rather than individualized consultations. Additionally, medications used are not always suitable for the posology required for the patient, increasing the chances of drug interactions and adverse and iatrogenic effects [8, 12].

Elderly residents of nursing homes need special attention, since certain aspects of these populations are quite characteristic, such as older age, high number of diseases, greater frailty, polypharmacy, physical as well as psychological and social dependence, low functionality, among others. Furthermore, they may present particularities in relation to drug use, given different organ functions are minimized by physiological changes. These changes alter the pharmacokinetics and pharmacodynamics and raise cautions in prescribing to them. Thus, to support this practice, several instruments that indicate potentially inappropriate medications (PIM) for the elderly have emerged.

In Brazil, most studies on the use of medications in the elderly are related to outpatient, hospital, or community settings. However, few studies have investigated risk factors related to medication usage in institutionalized elderly.

This review will contribute to the rational drug use in elderly populations in order to

supplement the knowledge of health professionals and maximize the benefit of the patient.

HEALTH CONDITIONS OF THE ELDERLY

Technological advances have provided the pharmaceutical industry with new discoveries and drug developments. These novelties combined with misinformation regarding their use contributes to the appearance of complications caused by ineffective treatment, drug interactions, iatrogenic diseases and adverse events, which lead to increased morbidity and treatment costs [13, 14].

The physiological changes associated with aging are numerous, affect different organs and are dependent on genetic, environmental and psychological influences. Such changes alone do not characterize disease and are considered normal; however, aging causes a loss in physiologic reserve, making individuals more vulnerable to disease or accidents in comparison to younger persons. Psychiatric, social and emotional alterations also can arise in this context and may foster depression and loneliness [15].

Diseases with diverse symptomatology and chronic degenerative diseases that often depend on prolonged or repeated drug therapy continue to emerge. These diseases are prone to the use of multiple medications concurrently, which increases the risk of adverse events in elderly patients [14, 16, 17].

It is important to remember the elderly have particularities regarding the use of medications, because the functions of different organs become minimized due to changes occurring in the body. These deviations promote changes in pharmacokinetics and pharmacodynamics [4, 14, 18].

Aging causes changes in the absorption, distribution, biotransformation and elimination of medications, which can potentiate their therapeutic effects and/or adverse effects [19,20].

The absorption of drugs may be impaired in elderly patients due to increasing gastric pH caused by the reduction of acid production resulting from decreasing number of gastric parietal cells. This increase enhances the absorption of alkali drugs and reduces the

absorption of acidic drugs. Aging also promotes a reduction in surface intestinal absorption and lower esophageal sphincter pressure and peristalsis as well as slows gastrointestinal emptying time [9, 15].

Distribution and biotransformation are also affected. The amount of water in the body decreases and reduces the volume of drug distribution [1].

The delivery of a drug is influenced by the flow of blood circulation in tissues, plasma protein binding and physicochemical drug properties. Furthermore, delivery is also influenced by lean and fat body mass, since adipose mass increases and lean mass decreases with increasing aging. The distribution volume is less for water soluble drugs and greater for liposoluble drugs [20]. Consequently, liposoluble drugs tend to accumulate in adipose tissue, increasing their plasma half-life and duration of action and causing the risk for adverse effects. For water-soluble drugs, the reduced distribution volume may increase the initial concentration in the central compartment, resulting in higher concentrations in the plasma [9].

Biotransformation can be affected by hepatic blood flow, which can be reduced even by as much as half in the elderly. This results in reduced first pass metabolism of drugs and increased bioavailability. On the other hand, for prodrugs, the activation of the first pass can be slower or reduced by aging [21].

Additionally, there is a decrease in the activity of cytochrome P450 enzymes responsible for the oxidative metabolism of pharmaceuticals. Thus, some medications may continue to exert their effects for a longer period of time than expected [22]. One example is diazepam, which has a half-life of 24 hours in younger patients and 90 hours in elderly patients [21].

Renal function is an important parameter for the excretion of pharmaceutical agents, and in the elderly, there is a progressive decline in this function with advancing age. Reduction in renal blood flow, tubular clearance, and creatinine clearance and increase in serum creatinine result in two clinically significant effects, increased half-life and increased serum levels of drugs [15].

For medications with a narrow therapeutic safety margin, such as digoxin, aminoglycosides and warfarin, serious side effects may occur in elderly patients if a dosage adjustment is not defined based on the value of creatinine clearance [9, 21].

In relation to pharmacodynamics, modifications in the number and/or receptor affinity to medications, signal transduction, especially for agents that depress the central nervous system, such as opioid analgesics, hypnotics and sedatives leads to greater sensitivity to these triggered effects [10, 15].

In this way, there remains a fine line between risks and benefits in the use of medications by the elderly population. Therefore, the problem cannot be attributed to the use of medication itself, but to their irrational use [8].

RATIONAL USE OF MEDICATIONS IN ELDERLY POPULATIONS

The concept of Rational Drug Use (RDU) was defined at the World Conference in Nairobi in 1985 as when "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community"[23].

Important criteria for RDU include accurate diagnosis, appropriate prescription, correct dispensing under appropriate conditions, timely availability, affordability, effective drug consumption by dosage and period of time indicated in defined intervals, safety and quality and patient compliance [24-26]. Indicators proposed by WHO RDU allow for the identification of current prescription profile and health care service quality and are classified as prescription indicators, patient care indicators and service indicators. Through these, it is possible: a) to describe the situation of a place in relation to the use of medications; b) to evaluate the quality of the process of diagnosis and treatment; c) to evaluate the practice of professionals, managers and users of the health care system, quantifying specific aspects of the behavior of care providers [27].

In Brazil, the National Drug Policy aims to guarantee the necessary safety, efficacy and quality of medicinal products, promoting

the rational use and access for the population to those it is considered essential [28]. This policy is the main instrument to guide health actions related to the use of medication [29].

Studies conducted in different countries during the last years on the safe and effective use of medications have demonstrated the irrational use of medications is a worldwide phenomenon and few prescriptions fit the WHO criteria [9, 30, 31].

Use of multiple medications, known as polypharmacy, is prevalent and can be necessary in many situations to improve symptoms, diseases and problems related to quality of life. However, this practice may also pose a risk for inappropriate prescriptions, non-adherence, adverse reactions and drug interactions [32, 33].

Polypharmacy has been characterized in various ways in the literature. Some consider this practice to be when there is use of multiple medications and/or administration of more drugs than are clinically indicated, representing unnecessary use [34]. Others have established the use of five or more medications as the reference point [15, 32, 35].

The frequency and predictors of polypharmacy are closely related to disease and disability in the afflicted elderly population. The prevalence of older people with multimorbidities varies between 35-80%, but may increase in the coming years with the aging population [32, 33].

Current clinical recommendations propose the use of multiple medication in certain chronic diseases, such as hypertension, coronary artery disease, heart failure, chronic obstructive pulmonary disease, chronic renal failure and diabetes mellitus [32, 33]. In the United States, between 25-50% of adults aged 65 years or older are estimated to consume five or more medications [15]. In Brazil, a cross-sectional study conducted in an interior city of São Paulo State involving 301 elderly in the community showed 23% of these residents were using five or more medications, with 4% using eight or more [36].

The Health, Wellbeing and Aging Study (Estudo Saúde, Bem-estar e

Envelhecimento- SABE) carried out in 1115 subjects aged 65 or more in the city of São Paulo found 84.3% of participants were using medications and the prevalence of polypharmacy was 36% [35]. Loyola Filho et al. [37] observed 72.1% of the 1598 seniors aged 60 years or more surveyed using at least one prescribed medication.

Reducing iatrogenic disease induced by medications is a concern for all health professionals due to the socioeconomic and clinical consequences [32]. The most common adverse effects due to use of medicines in elderly are mental confusion, nausea, changes in bowel habits, lethargy, dizziness, sedation and falling accidents. Many of these effects may be erroneously interpreted as resulting from degenerative processes associated with aging or disease symptoms, leading to the prescription of new drugs [15].

The task of prescribing medications to the elderly is difficult and complex and requires the establishment of treatment priorities [14].

For choosing a medication for a specific disease, the efficacy and safety should be evaluated, always opting for the one that provides defined clinical efficacy and acceptable safety. Prescribers should be aware of specific contraindications and adverse reactions in elderly patients and use the criteria of a convenient dosing schedule and access as the last criteria for selection. Medicines are considered appropriate for the elderly when there is clear evidence-based indication, good tolerability and cost effectiveness [38].

POTENTIALLY INAPPROPRIATE MEDICATIONS (PIM) FOR THE ELDERLY

The need for caution in prescribing medications for seniors has given rise to a number of tools to assist in the process. Such instruments are lists developed by experts in the field and include medications considered potentially inappropriate for the elderly.

Potentially inappropriate medications (PIM) are medications or classes of medications that should be avoided in elderly patients with 60 years of age or older. Medications are placed in this category when they have no evidence-based indication, do not present cost-

effectiveness, or there are safer alternatives [20, 39].

In this context, several instruments with different denominations, such as the French list [40], the Medication Appropriateness Index [41], the STOPP/START criteria [42], the PRISCUS list [43], the Korean list [44], IPET [45], ACOVE [46] and Beers criteria [39, 47-49], may be employed. Beers criteria are the most widely utilized by researchers worldwide [50, 51].

For the preparation of these instruments, the Delphi method was the common support tool which aims to seek the advice of a group of experts (doctors, pharmacists, nurses and other health professionals), accompanied by systematic review and use of evidence-based approach for the determination of a consensus on the use of the medication in elderly [52, 53].

The principle of this method is based on the elaboration of a questionnaire developed from a literature review with sufficient information to homogenize the language and facilitate the rationale. Then, the experts respond to questions individually and may add explanations and opinions. This questionnaire is circulated repeatedly among respondents, who present their ideas while preserving the anonymity and influence of the others [52, 54].

Responses are analyzed by coordinators with the aid of statistics, including or excluding new items and questions that were repeated for the next cycle. The experts are then able to reassess their responses based on the findings and justifications given by the group in the previous round. This process is repeated several times until the divergence of opinions is reduced to a satisfactory level and considered as a consensus among experts [52, 55].

PIM continue to be prescribed and used as first-line treatment for the most vulnerable of elderly, despite evidence of unsatisfactory results. Because of this, some countries are making use of PIM as an integral part of public policy practice and identification instruments have been incorporated for various quality measures [56].

CLASSIFICATION OF ELDERLY INAPPROPRIATE MEDICATION USE

French List

The French list of PIM was developed by a consensus of experts. Therefore, each criteria of the questionnaire was evaluated according to the Likert scale of (1) to (5) points, where (1) signifies *total agreement with inadequacy* and (5) signifies *total disagreement with inadequacy*. Items with a score (1) and (2) were kept in the list, while items (4) and (5) were excluded; items with scores of (3) of uncertain opinion were presented to experts again at another time. The questionnaire consisted of two categories, drugs that should be avoided in elderly patients as they were not effective or induce some type of risk and drugs to be used only in specific medical conditions.

The French list identified 34 medications inappropriate for elderly over 75 years of age, because at this age, pharmacokinetic and pharmacodynamic changes are more significantly likely to alter the response to the medication than at younger ages. Among the medications found, 25 were deemed unsuitable due to unfavorable risk/benefit, one was considered of questionable efficacy and eight were classified as having both unfavorable risk/benefit and questionable efficacy.

Among all medications or classes of medications in the French list, just a few were also proposed in the Beers criteria list, since those not available in France or considered harmful and ineffective were excluded [40].

Medication Appropriateness Index

The Medication Appropriateness Index (MAI) is an instrument that evaluates the elements of a prescription and is applicable for various medications, scenarios and clinical conditions. This index was developed by a clinical pharmacist and a geriatric doctor based on a literature review of assessment measures and medication evaluation scales [41] and was subsequently validated by Samsa et al. [57]. In this instrument, the prescription is evaluated for possible drug-related problems according to the key criteria: indication, effectiveness, dosage and concentration, instructions for proper administration of the medication,

convenience/practicality, drug interactions, drug-disease interaction, therapeutic duplicity, treatment duration and cost of the drug compared with other agents of the same efficacy and safety [41, 57].

STOPP/START Method

The STOPP (Screening Tool of Older Person's Prescriptions) method is a screening tool of potentially inappropriate medication prescriptions composed of 65 criteria accompanied by a concise explanation as to why the medication is inappropriate. The criteria for potentially appropriate medications, i.e. indicated medications, is found in the START (Screening Tool to Alert Doctors to Right Treatment) tool, which consists of 22 indicators for evidence-based appropriate prescribing of medications for diseases commonly found in elderly [42].

PRISCUS List

The German list for PIM called PRISCUS (from the Latin for "ancient", "old", "venerable") contains 83 medications distributed in 18 therapeutic drug classes. For cases in which the administration of a PIM is clinically necessary, this list contains recommendations for clinical practice, such as monitoring of laboratory values and adaptation of the dosage. Therapeutic alternatives are also listed [43].

Korean List

The Korean list is comprised of two major groups, one with PIM prescribed regardless of the disease or clinical condition and another with PIM as they relate to 29 diseases. Medications are then further classified into three subgroups: the first subgroup includes medications that should be avoided; the second, medication that should be monitored; and the third, medications with low risk. The level of drug inadequacy was determined by considering the clinical importance of the risk and the availability of alternative therapy. Levels are ranked on a scale of 1 (very low) to 4 (very high).

The list of disease-independent PIM prescriptions contains 57 medications. Of these, 42 medications were classified in the first subgroup, 13 in the second, and two in the third. Among the disease-dependent PIM prescriptions, 93 medications were included. Of these, 63 were in the first

subgroup, 28 in the second and three in the third [44].

Inappropriate Prescribing in the Elderly Tool

The Inappropriate Prescribing in the Elderly Tool (IPET) is also known as the *Canadian Criteria* and was first published in 2000. This tool updated the criteria for inappropriate prescribing previously published by McLeod et al. [58]. These criteria consist of 14 medication-disease interactions involving 45 PIM [45].

Assessing Care of Vulnerable Elders

Assessing Care of Vulnerable Elders (ACOVE) is a project that developed a questionnaire to identify vulnerable elderly. For this work, clinical conditions prevalent among the elderly were selected to measure and develop a set of evidence-based quality care indicators.

ACOVE contains 392 quality indicators, 26 different clinical conditions, 14 types of care procedures and covers the four healthcare domains of screening and prevention, diagnosis, treatment, and monitoring and continuity.

This tool can be used to evaluate the care provided to vulnerable elderly at the level of the health system, health plan or medical group. The quality indicators can be applied to identify areas of care that need improvement and form the basis of interventions to improve care [46].

Beers Criteria

In 1991, Beers et al. [39] published a list of criteria aimed at reducing the risk of iatrogenic and adverse reactions in institutionalized elderly based on consultations with pharmacology and geriatrics experts. Classifications were made for potentially inappropriate medications or medication classes for the elderly regardless of clinical condition.

In 1997, Beers [47] published a revision of those criteria in order to classify the elderly population according to the degree of frailty, independent of housing conditions (community, nursing home, or hospital). Thus, the following three categories were established: a) drugs to be avoided in the elderly in general, b) drugs to have the maximum dose adjusted according to the patient's age and c) drugs to be avoided for certain diseases.

The above criteria were revised again by Fick et al. [48]. These authors updated the list of diseases and medications, distributing medications into two groups: a) medications or classes of medications that should be avoided in the elderly, regardless of diagnosis or clinical condition due to the high risk of side effects and the existence of other safer medications and b) classes that should not be used in certain clinical circumstances. The total list comprised 48 medications or medication classes.

In 2012, Fick et al. [49] updated PIM groups described in 2003 and added a third group, which comprises the therapeutic classes and drugs that should be used with caution for elderly.

The careful consideration for the inclusion of a third group in the criteria adopted in 2003 was based on the consensus regarding the priority of using the medication under conditions in which it would not induce abuse or damage and requires greater care in prescribing.

To assess the quality of recommendation evidence and strength for the insertion of a medication or therapeutic class into the most recent list, Fick et al. [49] used the classification system and guidance of the *American College of Physicians' Guideline Grading System*, which is based on evaluation levels for recommendation, development and evolution of studies.

Evidence quality was considered *high* when the evaluations included consistent results from well-designed studies conducted in representative populations that directly assessed effects on health outcomes, randomized clinical trials of high quality or reproduced results, and observational studies with no significant methodological flaws. *Moderate* quality was attributed to insufficient evidence to determine the effects on health outcomes, but the number, size or consistency of included studies were of widespread routine practice or indirect nature. *Low* quality was considered when there was insufficient evidence to assess the effects on health outcomes because of limited number of studies, unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence or

lack of information on important health outcomes [49].

For the strength of recommendation, strong recommendation was considered when the risks and damages clearly exceeded the benefits, weak recommendation when the risks and damages were balanced with the benefits and recommendation insufficient when the evidence was insufficient to determine the benefits and risks [49].

LONG-TERM CARE FACILITIES FOR THE ELDERLY

Aging is not synonymous with disease, but advancing age progressively reduces functional capacity with consequent loss of autonomy and independence. For economic and/or health reasons, this loss can compromise significantly the condition of life for seniors [59].

The need for specific care coupled with new family arrangements and conditions where there are limitations on the capacity to provide the necessary care has contributed to the increasing institutionalization of the elderly in nursing homes, retirement homes, geriatric clinics and LTCF [8, 12]. Thus, it is possible to envision a new role for LTCF, in which they are no longer only part of the social assistance network but also a part of the health care network as well [11].

According to the definition described in the ordinance of the State Department of Social Services in Brazil (Secretaria de Estado de Assistência Social do Brasil - SEAS) nº 2.854/2000, LTCF are residential in character and designated for people aged 60 years or older with some degree of difficulty in performing daily activities. Also, LTCF are intended for those whose family does not have the financial, physical or emotional means to provide the necessary care [60].

In this sense, the need for attention related to the use of medications used by institutionalized elderly was demonstrated in a study by Correr et al. [61], which evaluated the prescriptions and their related risks in a LTCF in the city of Apucarana, Paraná. The authors found 13.5% of the medicines used were considered inadequate, and 51.3% drug interactions were identified that compromised the efficacy of treatment.

In a study of institutionalized elderly in Juiz de Fora, Minas Gerais, Fochat et al. [62] found 67.2% polymedicated elderly, 58 potential interactions and 219 PIM (7.8%). Aguiar et al. [4] identified the use of PIM (28.7%), polypharmacy (18.1%) and duplicate therapy (11.7%) in institutionalized elderly studied. Additionally, O'Mahony et al. [63] identified 60% of prescriptions with PIM in nursing homes in Ireland. The data demonstrate the need for improvement and quality assessment for drug therapy in order to promote rational drug use in this age group.

CONCLUSION

Drug treatment in the elderly is a major challenge for multiple reasons. The pharmacokinetic and pharmacodynamic changes that occur in the elderly can directly interfere with the adverse effects of medication and increase the risk of intoxication. Moreover, there are external factors that affect the pharmacotherapy of elderly, such as misuse, difficulties in adherence to treatment and the existence of PIM.

Medication is an important tool for restoring and maintaining the health of elderly patients, and thus, to be attentive to the quality of pharmacotherapy is to be attentive to health. As such, efforts to improve the selection, prescription and use of medications should be a priority for health professionals.

Methods exist for assessing the quality of medication use in the elderly. But considering the complexity that permeates the processes of "population aging", "medication use" and "institutionalized elderly", it is important to note that these methods are not intended to exhaust the possibilities of assessment and intervention in the pharmacotherapy of the elderly. Furthermore, the adjustment and adaptation of these methods to the Brazilian reality and their incorporation into evaluative health practices may constitute a key step in promoting rational drug use in the country.

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