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Pharmacological aspects of elderly: an integrative literature review

Aspectos farmacológicos do idoso: uma revisão integrativa de literatura

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RESUMO: Os idosos constituem o grupo populacional que mais cresce de forma acelerada e descontrolada no Brasil, representando 14,3% da população geral. Associado a isto e ao aumento da expectativa de vida, mudança do padrão de adoecimento do pais e a medicalização no idoso, temas como a farmacologia do indivíduo idoso tornam-se essenciais na formação de um profissional da área da saúde. O processo normal do envelhecimento possui particularidades capazes de modificar as etapas da farmacocinética e a farmacodinâmica de um medicamento, predispondo o idoso às Reações Adversas a Medicamentos (RAM), cascata iatrogênica, uso de Medicamentos Potencialmente Inapropriados (MPI) e polifarmácia, processo do adoecimento, quedas e fraturas, delirium, hospitalização, institucionalização e até à morte. Baseado nisso, instrumentos ou listas de medicamentos considerados inadequados para uso em idosos foram criadas, cada uma com particularidades da comercialização de seu país. Visto isso, entende-se que o assunto é de extrema relevância na pratica clínica, e, quando utilizado de forma interdisciplinar, melhora a qualidade de serviços, formação de profissionais da área da saúde e permite a prevenção de eventos iatrogênicos.

Descritores: Idoso; Farmacologia. Envelhecimento; Lista de medicamentos potencialmente inapropriados/utilização; Efeitos colataterais e reações adversas à medicamentos; Serviços de saúde para idosos.

ABSTRACT: The elderly are the fastest growing population group in Brazil, accounting for 14.3% of the population. Associated with this and with the increase in life expectancy, changes in the country's pattern of illness and the medicalization of aging, issues such as pharmacology in elderly have become essential topics in the health professionals' training. The normal aging process has particularities that can modify the pharmacokinetic and pharmacodynamic properties of drugs, predisposing elderly to Adverse Drug Reactions (ADRs), iatrogenesis, use of Potentially Inappropriate Medications (PIM), polypharmacy, illness processes, falls and fractures, delirium, hospitalization, institutionalization and even death. Based on this, instruments or lists of medications considered inappropriate for elderly were created, each with particularities of the medication market of each country. Therefore, this subject is extremely relevant in clinical practice and when it is used in an interdisciplinary way, it improves the quality of services and the training of health professionals and allows the prevention of iatrogenic events.

Keywords: Aged; Pharmacology; Aging; Potentially inapropriate medications/utilization; Drug-related side effects and adverse reactions; Health services for the aged.

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INTRODUCTION

The World Health Organization (WHO) defines health as "*complete physical, mental and social well-being and not merely the absence of disease or infirmity*". However, most elderly suffer from one or more noncommunicable diseases (NCDs). These diseases are often not associated with functional limitations, meaning they can keep performing their normal activities. Based on this, the Brazilian National Health Policy for Elderly (PNSPI) stated that the health of this population is more associated with the condition of autonomy and independence than with the presence or absence of organic diseases[1].

Aging is a sequential, individual, cumulative, irreversible, universal, and non-pathological process of deterioration of a mature organism, and it is common to all members of a certain species. This process makes the organism increasingly incapable of responding to environmental stresses, thus increasing the possibility of death[2].

The aging process, associated with chronic degenerative diseases, generates a higher demand for health services, which in turn can lead to polypharmacy, Adverse Drug Reactions (ADRs) and other iatrogenic events[3-6]. Currently, elderly are the fastest-growing population in Brazil and the largest consumers of medications in the world. As a consequence, the country has become the fourth largest consumer of medications in the world, and the Brazilian pharmaceutical sector has become the largest in the world[7].

As a consequence of prescribed and non-prescribed (self-medication) use of medication, adverse drug reactions have become a major cause of admission to health services and a major public health problem. Based on this, the present study highlights the importance of studying the impact of the aging process and its influence on the pharmacology of elderly.

METHOD

This is an exploratory study and literature review aimed at addressing the impact of senescence on pharmacology in older adults. The databases NCBI/PubMed (National Center for Biotechnology Information), SciELO (Scientific Electronic Library Online) and Lilacs (Latin American and Caribbean Center on Health Sciences Information) were searched for the following descriptors: "Pharmacology", "Polypharmacy", "Potentially Inappropriate Medications", "Adverse Drug Reactions", "Placebo and nocebo effects", "elderly" "aging", and the corresponding descriptors in Portuguese and Spanish.

The present study was limited only by the type of access to the publications: only the studies with free access in the previously mentioned databases were selected. Only the articles whose abstracts addressed the subject studied were used in this research.

RESULTS

Eigtheen studies were included in this review article. Table 1 shows the distribution of the selected studies by authorship, country, year of publication, title, journal and database.

Table 1 – Distribution of selected studies according to authorship, country, year of publication, title, journal and database

Author/year, country	Title	Journal	Database		
			NCBI Pubmed	SciELO	Lilacs
Silva et al., 2011 Brazil	Mitochondrial metabolism, free radicals and aging	Brazilian Journal of Geriatrics and Gerontology	-	01	-
Silva et al., 2012 Brazil	Polypharmacy in geriatrics	AMRIGS Journal	-	-	01
Manso et al., 2015 Brazil	Inappropriate medication use in older adults with chronic diseases in a health plan in São Paulo, Brazil	Brazilian Journal of Geriatrics and Gerontology	-	01	-
Carvalho, 2007 Brazil	The polypharmacy in elderly in São Paulo –SABE Study – Health, Well-being and Aging	-	-	-	01
Secoli, 2010 Brazil	Polypharmacy: interaction and adverse reactions in the use of drugs by elderly people	Brazilian Journal of Nursing	-	01	-

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Sousa-Munoz et al., 2012 Brazil	Inappropriate geriatric prescriptions and poly-pharmacotherapy in medical clinic wards at a University Hospital	Brazilian Journal of Geriatrics and Gerontology	-	01	-
Quinalha et al., 2010 Brazil	Tools for assessing the pharmacotherapy of the elderly: a review	Brazilian Journal of Geriatrics and Gerontology	-	01	-
Beers et al., 1991 EUA	Explicit criteria for determining inappropriate medication use in nursing home residents	Arch Intern Med	01	-	-
American Geriatrics Society, 2012 EUA	American Geriatrics Society updated Beers criteria for potentially inappropriate medication use in elderly	J Am Geriatr Soc	01	-	-
American Geriatrics Society, 2015 EUA	American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in elderly	J Am Geriatr Soc	01	-	-
Silveira et al., 2009 Espanha	Inappropriate prescription in older patients: The STOPP/START criteria	Rev Esp Geriatr Gerontol	01	-	-
O'Mahony et al., 2014 Inglaterra	STOPP/START criteria for potentially inappropriate prescribing in elderly: version 2	Age and Ageing	01	-	-
Holt et al., 2010 Alemanha	Potentially inappropriate medications in the elderly: the PRISCUS list	Deutsches Arzteblatt Int	01	-	-
Oliveira et al., 2017 Brazil	Brazilian consensus of potentially inappropriate medication for elderly people	Geriatr Gerontol Aging	-	01	-
Lopes et al., 2016 Brazil	Use of potentially inappropriate medications by the elderly at home	Cien Saúde Coletiva	-	01	-
Foster et al., 2017 EUA	Comparative "nocebo effects" in elderly patients enrolled in cancer therapeutic trials: Observations from a 446-patient cohort	Cancer	01	-	-
Cruz et al., 2010 EUA	Placebo and nocebo effects in randomized double blind clinical trials of agentes for the treatment of fatigue in advanced cancer patients	Cancer	01	-	-
Hunter et al., 2005 EUA	Neurophysiologic correlates of side effects in normal subjects randomized to venlafaxine or placebo	Neuropsychopharmacology	01	-	-
Total:			**09**	**07**	**02**

DISCUSSION

People reach the peak of their body organic functions in their thirties and forties. Between the ages of 40 and 50 there is a stabilization, followed by a decline that starts at the age of 60. These functional alterations are called senescence or senectitude and are considered non-pathological. They correspond to the progressive loss of organ reserves in the organism of elderly. These physiological changes occur with the passage of time (e.g. appearance of wrinkles or white hair). It is different from senility, which is defined as a pathological process of aging that corresponds to a homeostatic imbalance of the organism, which raises the risk of morbidity and mortality among elderly[3,4,6].

Cellular aging

The biochemical, molecular and structural changes that occur in the body of elderly are called cellular aging. According to the free radical theory of aging, the interior of cells in the organism of elderly is different from young bodies due to the accumulation of proteins, lipids, carbohydrates and oxidized DNA. This justifies the structural alterations in which the transport of ions and nutrients are modified in the plasma membrane, the mitochondria form undesirable substances during the cellular metabolism due to the formation and accumulation of these substances and, the ribonucleic acids, located in the cellular nucleus, become more condensated making the mechanism of cell repair and division more difficult[8].

There are still other factors, such as: (1) hormesis induced by regular physical activity, (2) caloric restriction, (3) dietary intake of antioxidants and (4) increased production of antioxidants. These factors promote mitochondrial integrity and fuction, which can reduce oxidative and nitrosative stress, slow the aging process and increase longevity.

In elderly, there is also a reduction in the total amount of body water and in intracellular and extracellular components, which can lead to severe fluid loss and difficulty to replace lost fluids. As a result, the bioavailability of water-soluble drugs is altered, and their volume of distribution decreases. Liposoluble drugs, in turn, present an increase in the volume of distribution due to an increase in adipose tissue during the aging process[3,4,6].

All these processes lead to apoptosis and changes in cellular function, making elderly more vulnerable to illnesses[3,4,6].

Pharmacokinetics

Absorption, distribution, metabolism and excretion are the pharmacokinetic processes that suffer modifications during the aging process. These alterations produce changes in the concentration of some receptors. The liver and kidneys are the organs most affected in elderly, however, other structures are also modified[3,4,6,9].

Older adults may present problems from ingestion to excretion of drugs, due to lack of dentition, decrease in saliva production or other factors. Some drugs may also cause gastric lesions (gastritis) due to their adherence to gastric mucosa, or can have ineffective absorption due to low gastric hydrochloric acid secretion, esophageal and gastric peristalsis, perforation of the digestive tract, the condition of the absorptive surface, and the active transport in the membrane already discussed. It should be noted that slow peristalsis in older adults increases the contact period between the drug and the mucosal absorptive surface[3,4,6,9].

During the aging process, there is a decrease in the serum levels of plasma proteins. Albumin is one of these proteins, and the main repercussion of its decrease is an increased free fraction of drugs. This serum alteration causes problems in the transport of substances and increases the risk of drug intoxication[3,4,6,9].

In the liver there is a significant reduction in the number of hepatocytes and in liver mass, which leads to a decrease in blood flow. This justifies the 30% decrease in hepatic clearance, a decrease in oxidative and conjugative metabolism, and an increase in the plasma concentration of some drugs (propranolol, verapamil, lidocaine). Imipramine, amtriptyline, morphine and meperidine are drugs that do not have changes in plasma concentration due to liver function[3,4,6,9].

Due to the decreased activity of the liver enzyme system, there is a reduced production of the metabolites responsible for reducing the total drug blood level and thus obstructing the interaction with other organs[3,4,6,9].

Some drugs can be metabolized and eliminated by the liver and intestine, while others are excreted only by the kidneys. As consequences of renal aging we have a 30 to 40% loss of renal mass, a 60% decrease in the number of glomeruli, a decrease in blood flow, aging of the glomerular capsule, thickening of the tubular basement membrane (renal tubular atrophy), a decrease in creatinine clearance (1% per year) and a 30% to 40% decrease in Glomerular Filtration Rate (GFR) and in tubular secretion. As a result, drug elimination is impaired, leading to a prolonged effect of drugs primarily eliminated by the kidneys. Several authors recommend using the Cockcroft-Gault formula before prescribing a drug eliminated by the kidneys (mainly antibiotics) to an elderly. The elderly may still need dose adjustments due to the functional deterioration of the kidneys[3,4,6,9].

It should be noted that the reduction of the GFR is considered the main pharmacokinetic change in the normal aging process of an individual[3,6].

Table 2 shows the main age-related pharmacokinetic changes.

Table 2 - Pharmacokinetic changes related to the normal aging process and their clinical repercussions

Pharmacological Processes	Age-related Alterations	Clinical Repercussions
Absorption	↓ Number of absorptive cells	Intestinal atrophy
	↑ Gastric pH	Change in the absorption of drugs that require acidic dissolution
	↓ Motility of the digestive tract ↓ Gastrointestinal transit	May lead to changes in the absorption of medications (e.g. Levodopa and Penicillins)
	↓ Splenic blood flow	Absorption of liposoluble drugs and drugs that are metabolized during the first hepatic passage
Distribution	↓ Serum albumin	↑ Drug free fraction (e.g. Phenytoin), ↑ Risk of intoxication
	↓ Body water and lean body mass	↓ Volume of distribution of water-soluble drugs (e.g. Digoxin) ↓ Dose required to achieve plasma concentration
	↑ Mass of fat	↑ Volume of distribution and half life of liposoluble drugs (e.g. Benzodiazepines) ↑ Duration of effects after first dose and gradual build up of toxicity with drug accumulation in adipose tissue
Metabolism	↓ Hepatic blood flow	↓ First-pass metabolism ↓ Plasma levels
	↓ Liver mass ↓ Cytochrome p450 activity (Phase I drug metabolism)	↓ Hepatic oxidative metabolism → ↑ Half-life of drugs metabolized by the liver (e.g. quinidine)
Excretion	↓ Number of glomeruli ↓ Total renal mass ↓ Renal plasma flow ↓ Glomerular Filtration Rate (GFR) ↓ Tubular secretion	↓ Excretion of drugs by the kidney → ↑ half-life and ↑ serum level of drugs

Pharmacodynamics

Changes in homeostatic mechanisms and the decline of some organic functions in elderly are intrinsically associated with changes in drug sensitivity. Reduction of cerebral blood flow, orthostatic hypotension, renal and gastrointestinal dysfunction, age-associated baroreflex impairment, impaired thermoregulation, impaired cognitive ability, metabolic alterations and impaired immune response are some of these organic functions[4,9].

There are also modifications in the interaction between drugs and their receptors, which have an effect in the action of drugs. Alpha and beta adrenergic receptors, muscarinic acetylcholine receptors and GABA receptors are some of the receptors associated with different final effects of drugs used by elderly[9].

Due to these and other aspects of the aging process, elderly health should be approached in a comprehensive and multidimensional manner, with clinical reasoning for the different clinical manifestations that an elderly may present as a consequence of a drug.

Polypharmacy

The increase in life expectancy and the growth of up to 46% in the population aging rate during the last ten years have led to an increase in the prevalence of Chronic Non-communicable Diseases (NCDs). This predisposes elderly to polypharmacy, adverse drug reactions and inappropriate drug prescriptions[3,4,6,9,10,11].

Currently, polypharmacy is a major discussion topic in clinical practice and a very relevant theme in several specialties. There are many qualitative and quantitative definitions of polypharmacy. The qualitative definition is the most used in American studies; it defines polypharmacy as "*the prescription, administration or use of more drugs than what is clinically appropriate"*. On the other hand, Latin American and European studies adopt the quantitative definition, which is stated as "*the simultaneous use of multiple drugs*"[12].

There are also authors who consider as polypharmacy the use of any drug that is not prescribed[12].

Based on the prevalence criterion, the literature considers polypharmacy as the use of 5 or more types of medications[4,9,11,12].

In the literature, there are several subdivisions of polypharmacy, such as: minor (use of 2 to 4 medications) and major polypharmacy (use ≥5 medications); groups of 1 to 3, 4 to 5, 6 to 8 and 9 or more medications; and low (2 to 3 medications), moderate (4 to 5 medications) and high polypharmacy (>5 medications)[12].

The use of multiple drugs can damage the elderly health. According to the Ibero-American center, it is possible to classify these damages in three levels: (1) lower level effects are usually mild, cause few health problems and may pass unnoticed. They do not require additional treatment; (2) moderate level effects may lead to a deterioration in the clinical condition of the patient and require the association of treatments (3) higher level effects are potentially life threatening and can cause permanent damage[9].

The use of non-pharmacological treatments is not very common in Brazil, and access to medications is easy, which contributes to self-medication and leads to several consequences for the health of elderly[3].

There are several consequences of overmedication, such as increased health care costs both for the patient and for the health care system, increased rate of adverse drug events, use of potentially inappropriate medications, non-adherence to treatment, increased urinary incontinence, drug-drug interaction, drug-disease interaction, decreased functional capacity, multiple geriatric syndromes, hospitalization and institutionalization[3,4,12,13].

Iatrogenesis: adverse reactions

Iatrogenesis is any pathogenic effect brought about by medical practice and it is commonly represented by iatropharmacogeny. ADRs are the leading cause of iatrogenesis in medical practice. The risk of ADRs is up to 88% among elderly who use five or more medications[4,9,12].

Adverse drug reaction (ADR) is a noxious and unintentional response of the body to the use of a medication with a dose normally used in humans. Older adults account for 25% of hospital admissions due to acute, subacute or chronic ADR. ADRs are even more frequent when the medications used are considered inappropriate for elderly[4,13].

The drugs that most often cause ADRs include non-steroidal anti-inflammatory drugs (NSAIDs), beta blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), diuretics, digoxin, antilipidemic, central nervous system depressants, enzyme inducers (phenytoin and carbamazepine) and enzyme inhibitors (cimetidine and omeprazole)[13].

The main adverse reactions among elderly are mental confusion, falls, postural hypotension, urinary incontinence, faecal and urinary retention, parkinsonism symptoms that mimic Parkinson's disease (e.g. tremors, stiffness and bradykinesia), insomnia, and others. The morbimortality of ADRs related to the use of more than one drug is high, since these effects can be serious and even fatal in more susceptible individuals[4,13].

Potentially inappropriate medications: a world view on main lists and criteria

Changes in body composition and in renal and hepatic functions during the aging process lead to pharmacokinetic and pharmacodynamic changes in several drugs, as previously discussed. For this reason, older adults are considered the most susceptible to adverse drug events (ADRs) and to the use of Potentially Inappropriate Medications (PIMs).

PIMs are drugs that are prescribed by qualified professionals (physicians) and whose risk of adverse events outweighs the benefits, even when there are effective alternatives. These medications cause drug-drug and drug-disease interactions, as well as undesirable side effects that have an impact on the quality of life of elderly[3,4,6,9,11,14].

A drug may still be considered potentially inappropriate if there is an increased risk of adverse reactions, if the use of the drug aggravates the initial disease or if there is no scientific evidence about its therapeutic efficacy, since clinical trials for drug marketing authorization almost never have elderly as study population[4,9,11].

Given this, researchers have proposed instruments (lists or criteria) to detect potential iatrogenic risks of drugs in elderly. These instruments, also considered methods of quaternary prevention, are of great use in clinical practice. The first instrument created was the Beers criteria, published in 1991 by the American geriatrician Dr. Mark Howard Beers to list the drugs considered inappropriate for long-term use among elderly. Beers (1991) described his list as a worldwide consensus implemented in American clinical practice and used in several clinical epidemiological studies[3,4,15,16].

The 2012 version of the Beers criteria inaugurated a partnership with the American Geriatrics Society, which allowed for regular updates, more rigorous systematic reviews and a greater dissemination of the criteria. In addition, the Beers criteria began to categorize PIMs into two distinct groups: medications to avoid in older adults regardless of diseases or conditions and medications considered potentially inappropriate when used in elderly with certain diseases or syndromes. Currently, the Beers Criteria is in its fifth update (1991, 1997, 2003, 2012 and the last one in 2015)[17,18].

The 2015 review added a list of drug–drug interactions associated with harms in elderly, a list of drugs that should be avoided and drugs that should have their dose adjusted based on the individual's kidney function. This list is applicable to all older adults with the exclusion of those in palliative and hospice care (mode of palliative care for terminally ill patients)[18].

The STOPP/START criterion, first published in 2008 and updated in 2014, was recognized by the *European Union Geriatric Medicine Society*. It is an evidence-based tool that can detect potential prescribing omissions in drug

therapy for older adults. It is based on a set of two PIM lists, STOPP (*Screening Tool of Older Person's potentially inappropriate Prescriptions*) and START (*Screening Tool to Alert doctors to the Right Treatment*). This list, developed for the European reality, is capable of detecting a larger number of elderly using PIMs in Western Europe when compared to the Beers criteria. This is justified by the large number of drugs that are rarely prescribed or sold in the continent[19,20].

The PRISCUS list was another instrument created to evaluate PIMs. It was created by German researchers in 2010, specifically for use in Germany, because of differences in the drugs marketed, in prescribing behavior, and in therapeutic guidelines in the country. This list was created in four phases: (1) qualitative analysis of selected PIM lists for elderly from other countries; (2) literature search in the main databases; (3) development of a preliminary list of PIM for elderly, specifically adapted to the German market; and (4) generation of the PRISCUS list by consultation of experts (modified Delphi process). In this list, the drugs are categorized as PIM or drugs that require dose adjustment and laboratory monitoring [21].

Recently, the *Geriatrics, Gerontologic and Aging* Journal published the Brazilian Consensus of Potentially Inappropriate Drugs for Elderly, adapted to the Brazilian reality. This is the first Brazilian impact study, focused on the commercialization and prevalence of the drugs most prescribed in the country's clinical practice. The purpose of creating this instrument was to improve the quality and safety of prescriptions to patients susceptible to ADRs, that is, elderly[22].

The Brazilian Consensus of Potentially Inappropriate Medications for Elderly has become the solution to the lack of specific criteria for the clinical practice of the country, since many studies use the Beers criteria to analyze groups of elderly. It should be noted that only 60% of the drugs mentioned in the Beers criteria are marketed in Brazil, which creates bias in the results of several Brazilian studies[23].

The objective of the study was to validate the 2012 Beers criteria and the 2006 STOPP contents in order to elaborate national classification criteria of PIMs for elderly. In the first and second stages of the study, the authors used a modified Delphi process to create a preliminary list of medications (potentially inappropriate regardless of clinical conditions/diseases and potentially inappropriate depending on clinical conditions/diseases) and to gather suggestions. Subsequently, an electronic questionnaire was applied to gather scores from each specialist. A drug was classified as potentially inappropriate when it obtained a 95% Confidence Interval (95% CI) ≥ 4.0[22].

Tables 3 and 4 respectively show the main PIMs regardless of clinical conditions/diseases and the PIMs dependent on clinical conditions/diseases.

All of these PIM lists are used on a large scale in geriatric clinics and educational centers, for research and to develop quality indicators in health services.

Placebo-nocebo effect

By definition, the placebo-nocebo effect comes from an inert substance with no pharmacological properties that is associated with positive or negative adverse events. Both effects, Placebo and Nocebo, have a neurobiological origin in relation to the symptoms or the disease. It is known that the brain is able to influence the biochemical processes in the central nervous system, thus affecting the response to treatment[24].

The placebo effect corresponds to positive adverse events of a treatment. The positive expectation of an elderly about the treatment causes anxiety and stimulates central pathways. This psychobiological response activates the release of catecholamines and other biochemical substances that can cause relief or improvement of symptoms[24,25,26].

The Nocebo effect has the opposite definition. Negative and pessimistic expectations lead to the release of neurochemical substances that cause a response opposite to placebo, generating negative adverse events on the symptoms[24,25,26].

The placebo-nocebo effect is attributed mainly to non-pharmacological factors such as the physician-patient relationship, the desire for improvement, the patient's behavior and the expectations about the treatment. It is believed that other factors are involved in the placebo-nocebo effect, and age is one of them[24].

As previously discussed, elderly are more vulnerable to adverse reactions due to the particularities of the aging process. This occurs more frequently in older patients submitted to antineoplastic therapy. It is believed that the use of placebo in elderly with oncological disease may be beneficial against the adverse events of chemotherapy. Based on this, some researchers believe that neurobiological factors associated with senescence are involved in this response to placebo. The neurobiological response given by the immune system of elderly may be one of the main mechanisms related to positive and negative adverse effects; therefore, this topic should be further investigated in randomized clinical studies[24].

Based on our survey, some studies have shown divergent results regarding this discussion, indicating that aging does not significantly influence the placebo-nocebo effect, and that there should be clinical care regardless of age. However, it should be noted that there is no consensus in the literature on the influence of age on the placebo-nocebo effect. In addition, there is a lack of studies in the literature addressing this issue, mainly the nocebo effect, among elderly[27,28]. Therefore, new studies addressing this issue among elderly must be carried out in order to further explore the subject.

Table 3 – Potentially inappropriate medications regardless of clinical conditions/diseases, according to the Brazilian Consensus of Potentially Inappropriate Drugs for Elderly, 2017[23]

Class	Criteria
Central Nervous System and Psychotropic Medications	**Antiparkinsonian**: Biperiden, Trihexyphenidyl **First-generation Antihistamines**: Brompheniramine, Carbinoxamine, Cyproheptadine, Clemastine, Chlorpheniramine, Dexchlorpheniramine, Diphenhydramine, Dimenhydrinate, Doxylamine, Hydroxyzine, Meclizine, Promethazine, Triprolidine **First-generation Antipsychotics**: Chlorpromazinee, Fluphenazine, Haloperidol, Levomepromazine, Penfluridol, Periciazine, Pimozide, Pipotiazine, Sulpiride, Thioridazine, Trifluoperazine, Zuclopenthixol **Second-generation Antipsychotics**: Amisulpride, Aripiprazole, Clozapine, Olanzapine, Paliperidone, Quetiapine, Risperidone, Ziprasidone **Barbiturates**: Phenobarbital, Thiopental **Benzodiazepines:** Alprazolam, Bromazepam, Clobazam, Clonazepam, Chlordiazepoxide, Cloxazolam, Diazepam, Estazolam, Flunitrazepam, Flurazepam, Lorazepam, Midazolam, Nitrazepam **Neuroleptics**: Hypnotics **Non-benzodiazepine Hypnotics**: Zolpidem **Tertiary tricyclic antidepressants**: Amitriptyline, Imipramine, Nortriptyline, Clomipramine, Maprotiline Thioridazine
Cardiovascular System	**Alpha-1 Blockers**: Doxazosin, Prazosin, Terazosin **Central alpha agonists**: Clonidine, Methyldopa, Reserpine (>0.1 mg/day) **Antiarrhythmics**: Amiodarone, Propafenone, Quinidine, Sotalol Aspirin (>150 mg/day) Digoxin (>0.125 mg/day) Dipyridamole **Diuretics**: Bumetanide, Furosemide, Piretanide Nifedipine, Spironolactone (>25 mg/day) Ticlopidine
Endocrine System	**Estrogen**: with or without progesterone **Androgens** Chlorpropamide **Oral antidiabetic**: Glibenclamide **Growth hormone**: Somatropin
Gastrointestinal System	**Gastrointestinal Antispasmodic**: Hyoscyamine, Scopolamine Loperamide, Codeine Metoclopramide Mineral oil (oral) **Proton Pump Inhibitors**: Omeprazole, Pantoprazole, Lansoprazole, Rabeprazole, Esomeprazole, Tenatoprazole for> 8 weeks
Musculoskeletal System	**Muscle Relaxants**: Carisoprodol, Cyclobenzaprine, Orphenadrine **NSAIDs**: Aspirin (> 325 mg/day), Diclofenac, Etodolac, Fenoprofen, Ibuprofen, Ketoprofen, Meloxicam, Naproxen, Piroxicam Indomethacin Ketorolac **Systemic Corticosteroids** (>3 months): Betamethasone, Budesonide, Deflazacort, Dexamethasone, Fludrocortisone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone Colchicine: (prolonged use) **Opioids**: Alfentanil, Fentanyl, Hydromorphone, Methadone, Morphine, Nalbuphine, Oxycodone, Pethidine, Remifentanil, Sufentanil (prolonged use) **Pethidine**: Dolantin, Meperidine
Others	Nitrofurantoin Theophylline

Table 4 - Potentially inappropriate drugs dependent on clinical conditions/diseases, according to the Brazilian Consensus of Potentially Inappropriate Drugs for Elderly, 2017[23]

Clinical condition	Criteria
Hemorrhagic disorders	**Antithrombotic/Anticoagulants**: Aspirin. Clopidogrel, Dipyridamole, Warfarin
Cardiac conduction disorders	**Tricyclic antidepressants**: Amitriptyline, Imipramine, Nortriptyline, Clomipramine
Chronic constipation	**Antimuscarinics**: Oxybutynin, Darifenacin, Tolterodine, Solifenacin **Non-dihydropyridine calcium channel blockers**: Diltiazem, Verapamil **1st generation antihistamines**: Brompheniramine Dexbronpheniramine, Carbinoxamine, Cyproheptadine, Clemastine, Dexchlorpheniramine, Diphenhydramine, Dimenhydrinate, Doxylamine Hydroxyzine, Promethazine, Triprolidine **Anticholinergics and Gastrointestinal Antispasmodics**: Atropine, Dicyclomine, Homatropine, Scopolamine, Hyoscine **Antipsychotics**: Chlorpromazinee, Clozapine, Fluphenazine, Olanzapine, Pimozide, Promethazine, Thioridazine, Trifluoperazine **Tricyclic antidepressants**: Amitriptyline, Imipramine, Nortriptyline, Clomipramine **Opioids**: Morphine, Oxycodone, Codeine, Pethidine, Fentanyl, Sufentanil, Nalbuphine, Tramadol (>2 weeks) Antiparkinsonians: Biperiden, Trihexyphenidyl **Muscle Relaxants**: Carisoprodol, Cyclobenzaprine, Orphenadrine, Tizanidine
Chronic kidney disease (stages IV and V)	**NSAIDs**: Indomethacin, Diclofenac, Etodolac, Ketorolac, Aceclofenac, Piroxicam, Tenoxicam, Lornoxicam, Meloxicam, Ibuprofen, Naproxen, Ketoprofen, Mefenamic acid, Celecoxib, Parecoxib, Etoricoxib, Benzydamine, Nimesulide, Glucosamine, Chondroitin Triamterene
Chronic Obstructive Pulmonary Disease (COPD)	**Non-cardioselective beta blockers**: Carvedilol, Labetalol, Nadolol, Pindolol and Propranolol
Diabetes Mellitus and episodes of hypoglycemia (> 1 episode per month)	Beta blockers
Delirium	**Anticholinergics** **Benzodiazepines**: Alprazolam, Estazolam, Lorazepam, Chlordiazepoxide, Clonazepam, Diazepam, Flurazepam **Corticosteroids**: Dexamethasone, Prednisolone, Methylprednisolone, Betamethasone, Hydrocortisone **H2-receptor antagonists**: Cimetidine, Ranitidine, Famotidine, Nizatidine Pethidine **Hypnotic sedatives**: Zolpidem Thioridazine **Tricyclic antidepressants**: Amitriptyline Imipramine, Nortriptyline, Clomipramine
Dementia and cognitive impairment	**Antipsychotics**: Chlorpromazinee, Clozapine, Fluphenazine, Olanzapine, Pimozide, Thioridazine, Trifluoperazine **Benzodiazepines**: Alprazolam, Estazolam, Lorazepam, Chlordiazepoxide, Clonazepam, Diazepam, Flurazepam **Antimuscarinic**: Oxybutynin **Gastrointestinal antispasmodics**: Atropine, Dicyclomine, Homatropine, Scopolamine, Hyoscine H2-receptor antagonists: Cimetidine, Ranitidine, Famotidine, Nizatidine **Muscle Relaxants**: Carisoprodol, Cyclobenzaprine, Orphenadrine, Tizanidine **Opioids**: Morphine, Oxycodone, Codeine, Pethidine, Fentanyl, Sufentanil, Nalbuphine, Tramadol (prolonged use) **Tricyclic antidepressants**: Amitriptyline, Imipramine, Nortriptyline, Clomipramine Zolpidem **Antihistamines**: Brompheniramine, Carbinoxamine, Cyproheptadine, Clemastine, Diphenhydramine, Dimenhydrinate, Hydroxyzine **Antiparkinsonians**: Trihexyphenidyl, Biperiden
Glaucoma	**Antimuscarinic**: Oxybutynin Ipratropium **Tricyclic antidepressants**: Amitriptyline, Imipramine, Nortriptyline, Clomipramine

Table 4 - Potentially inappropriate drugs dependent on clinical conditions/diseases, according to the Brazilian Consensus of Potentially Inappropriate Drugs for Elderly, 2017[23] *Cont.*

Clinical condition	Criteria
Gout	**Thiazide Diuretics**: Hydrochlorothiazide, Chlorthalidone
Heart failure	**Non-dihydropyridine calcium channel blockers**: Diltiazem, Verapamil Cilostazol **NSAIDs**: Indomethacin, Diclofenac, Etodolac, Ketorolac, Aceclofenac, Piroxicam, Tenoxicam, Lornoxicam, Meloxicam, Ibuprofen, Naproxen, Ketoprofen, Mefenamic Acid, Celecoxib, Parecoxib, Etoricoxib, Benzydamine, Nimesulide, Glucosamine, Chondroitin **Thiazolidinediones**: Pioglitazone
History of breast cancer or venous thromboembolism	**Estrogens and Analogues**: Ethinylestradiol, Estradiol, Estriol, Promestriene, Diethylstilbestrol, Tibolone
History of fall or fractures	**Anticonvulsants**: Phenobarbital, Primidone, Phenytoin, Clonazepam, Carbamazepine, Oxcarbazepine, Valproic acid, Vigabatrin, Lamotrigine, Topiramate, Gabapentin, Pregabalin **1st generation antihistamines**: Brompheniramine, Dexbronpheniramine, Carbinoxamine, Cyproheptadine, Clemastine, Dexchlorpheniramine, Diphenhydramine, Hydroxyzine, Promethazine, Triprolidine **Antipsychotics**: Chlorpromazinee, Fluphenazine, Haloperidol, Pimozide, Thioridazine, Aripiprazole, Clozapine, Olanzapine, Paliperidone, Quetiapine, Risperidone, Ziprasidone **Benzodiazepines** **Non-benzodiazepine hypnotics**: Zolpidem **Opioids**: Morphine, Oxycodone, Codeine, Pethidine, Fentanyl, Sufentanil, Nalbuphine, Tramadol (prolonged use) **Selective serotonin reuptake inhibitors**: Fluoxetine, Citalopram, Paroxetine, Sertraline, Fluvoxamine, Escitalopram, Venlafaxine **Tricyclic antidepressants**: Amitriptyline, Imipramine, Nortriptyline, Clomipramine
History of peptic ulcer	**Non-COX-2 Selective NSAIDs**: Indomethacin, Diclofenac, Etodolac, Ketorolac, Aceclofenac, Piroxicam, Tenoxicam, Lornoxicam, Meloxicam, Ibuprofen, Naproxen, Ketoprofen, Mefenamic Acid, Celecoxib, Parecoxib, Etoricoxib, Benzydamine, Nimesulide, Glucosamine, Chondroitin **COX-2 Selective NSAIDs**: Celecoxib, Parecoxib, Etoricoxib
Hypertension (SAH)	**Non-COX-2 Selective NSAIDs** in older adults with moderate to severe hypertension: Indomethacin, Diclofenac, Etodolac, Ketorolac, Aceclofenac, Piroxicam, Tenoxicam, Lornoxicam, Meloxicam, Ibuprofen, Naproxen, Ketoprofen, Mefenamic acid, Celecoxib, Parecoxib, Etoricoxib, Benzydamine, Nimesulide, Glucosamine, Chondroitin
Insomnia	**Oral decongestants**: Pseudoephedrine, Phenylephrine **Stimulants**: Methylphenidate **Theobromines**: Theophylline, Caffeine
Symptoms affecting the urinary tract	Oral or inhaled anticholinergics (in men)
Parkinson's disease	**First-generation antipsychotics**: Chlorpromazinee, Fluphenazine, Haloperidol, Pimozide, Thioridazine **Second-generation antipsychotics**: Aripiprazole, Clozapine, Olanzapine, Paliperidone, Quetiapine, Risperidone, Ziprasidone Metoclopramide Promethazine
Postural hypertension	**Vasodilators**: Hydralazine, Minoxidil
Seizures	**Atypical antipsychotics**: Clozapine, Olanzapine **Conventional antipsychotics**: Chlorpromazinee, Thioridazine Bupropion Maprotiline Tramadol
Hyponatremia (<130 mEq/L)	**Selective serotonin reuptake inhibitors**: Fluoxetine, Citalopram, Paroxetine, Sertraline, Fluvoxamine, Escitalopram
History of syncope	**Anticholinesterases**: Donepezil, Rivastigmine, Galantamine **Peripheral alpha-blockers**: Doxazosin, Prazosin, Terazosin Chlorpromazinee Olanzapine Thioridazine **Tertiary tricyclic antidepressants**: Amitriptyline, Clomipramine, Imipramine

CONCLUSION

The physiological aging process has a great impact on pharmacology in elderly, which demonstrates the relevance of the topic addressed. Several countries have implemented instruments for the prevention of adverse drug reactions and for caution with potentially inappropriate medications in their clinical practice. Currently, studies addressing pharmacology in elderly and the use of these instruments are of great impact in health services and are useful to help health professionals to act in an interdisciplinary way and seek quality in the care of elderly.

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