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Chapter

Elderly and Polypharmacy: Physiological and Cognitive Changes

Daniela A. Rodrigues, Maria Teresa Herdeiro, Adolfo Figueiras, Paula Coutinho and Fátima Roque

Abstract

Population ageing is one of the most significant social transformations of the twenty-first century. The increase in average life expectancy was a successful challenge achieved in the modern world. However, nowadays a new challenge arises for all society: achieving a better quality of life for increasing people's life. The comorbidities associated with ageing make elderly prone to polypharmacy. On the other hand, physiological and cognitive changes interfere with drugs' pharmacodynamics and pharmacokinetics contributing to drug-related problems which have been reported to account for a large percentage of emergency treatment and hospitalizations of older people, increasing the costs with health in the most aged regions. In order to reduce the use of potentially inappropriate medicines in this population, strategies and tools have been developed in recent years to assess the appropriateness medication use in the elderly.

Keywords: polypharmacy, elderly, pharmacodynamics, pharmacokinetics, potentially inappropriate medication

1. Introduction

Ageing is an inevitable process characterized by declining functions and increased susceptibility to certain diseases. Biologically, ageing results from a variety of molecular and cellular damage over time, leading to a gradual decrease in physical and mental capacity, increasing the risk of illness and death [1]. The fragility acquired by the elderly population with ageing is related to the gradual decrease of the physiological reserve and the failure of the homeostatic mechanisms. Thus, a cumulative decline is promoted in several physiological systems, and there is an exhaustion of the body's reserves, starting to have a greater vulnerability to changes in health status [2]. The mechanisms associated with ageing are determined by environmental factors but also by genetic factors, which regulate the expression of genes that can be especially important for this process [3].

With ageing, many chronic diseases arise, requiring the use of a higher number of drugs. Polypharmacy, defined as the use of five or more drugs, is a significant public health problem, particularly in the older adults, since it is responsible for the increase of adverse drug reactions (ADR) and, frequently, for the rise of the morbidity and mortality in this population [4]. There are many other important

issues related to the problem of polypharmacy, such as the interaction between drugs, organization and adherence to treatment [4].

Through the normal ageing process, changes occur with impact on the pharmaco-dynamics and pharmacokinetics of drugs. These changes may be related to the function of particular organs, homeostatic mechanisms and also to the ability to respond to specific receptors, causing greater vulnerability and susceptibility to ADR in older patients [5] frequently associated with the use of potentially inappropriate medication (PIM) in this population [6]. The inappropriate prescription in older patients occurs when the risk of adverse effects exceeds the clinical benefit, especially when there are more effective alternatives available [7]. The use of PIM is a public health challenge because it has high prevalence rates in different health contexts [8].

Although older adults are the primary consumers of medicines, the truth is that clinical trials are usually carried out on younger people, and the physiological changes that occur with ageing are not considered. With the rise of older people in the world, the needs associated with the resources of health systems will continue to increase, and several challenges will arise.

Over the past few years, to reduce the use of PIM in the older population, strategies and tools of explicit and implicit criteria have been developed to evaluate the appropriateness of medication use in the older patients. These criteria are useful tools for clinical practice, as a support for clinical decision.

2. Physiological and pharmacological changes in the elderly

The normal ageing process implies the occurrence of several physiological, biological, physical and psychological changes, which can affect the elderly patient' quality of life and modify the ability to reach the best health outcomes [9]. The changes caused by ageing are associated with complex pathophysiology, variability in organ function and the presence of comorbidities, specific to this population [2]. When young, the human body has a sizeable physiological reserve to sustain the function of most organs. However, in early adulthood, the first physiological changes that can affect drug effects begin to occur, and the decline of cellular activity becomes a gradual and continuous process. In older adults, this reserve is increasingly diminished with decreasing in homeostatic mechanisms activity [10].

All of these factors contribute to the frailty of older adults making them more prone to drug-related problems. Most older people can experience significant changes in drug pharmacokinetics and pharmacodynamics due to age-related physiological changes and become more susceptible and vulnerable to adverse effects [7].

2.1 Age-related changes in pharmacokinetics

The bioavailability of a drug depends on many factors and all stages of pharmacokinetics (absorption, distribution, metabolism and excretion) and can be modified with ageing [9, 11]. A summary of the main pharmacokinetics changes can be consulted in **Table 1**.

There are several available routes of administration. However, the most common is the oral route. Although ageing is associated with decreased gastric emptying and peristalsis, in the absence of pathology, the absorption of most drugs does not decrease with age [9]. However, the presence of pathologies that affect the gastrointestinal organs can affect absorption. Furthermore, food intake can also affect drugs' absorption. The fraction of the drug dose administered that reaches the bloodstream, after oral administration, can be influenced by several other factors,

Pharmacokinetics	Physiological changes	Drug examples
Absorption	Increased gastric pH Decreased gastrointestinal motility Decreased intestinal permeability Decreased gastrointestinal blood flow	Antacids H2-receptor antagonists Proton pump inhibitors Anticholinergic drugs
Distribution	Decreased lean body mass Increased fat body mass Decreased body water	Benzodiazepines
Metabolism	Decreased liver volume Decreased blood flow Decreased hepatic clearance rates	Propranolol Morphine
Excretion	Reduced renal blood flow Decreased glomerular filtration rates Increased urea excretion Decreased creatinine production Decreased renal clearance rates	Thiazides Loop diuretics ACEI ARBs Aliskiren Digoxin Potassium-sparing agents Beta-blockers NSAIDs

ACEI, angiotensin conversion enzyme inhibitors; ARBs, angiotensin II receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 1.
Impact physiological changes and pharmacokinetics in older adults [9, 11–13].

such as gastric pH, gastrointestinal motility, intestinal permeability and mucosal integrity, function and expression of drug carriers and gastrointestinal blood flow [11].

Drugs absorption after intramuscular or subcutaneous administration can be modified in older patients because there is a reduction in blood perfusion of the tissues [12].

After absorption, the drug enters the bloodstream and is distributed through the body. The distribution will influence the amount of active substance available to prosecute an effect at a specific target. Factors such as the extent of binding to tissues and plasmatic proteins, changes in body composition and protein synthesis can affect the distribution of drugs [11]. The volume of distribution can be affected by the proportions of lean body mass and fat body mass. With ageing, there is a reduction in the amount of body water and an increase in fat, so there are changes in the distribution of drugs that depend on lipid solubility. Also, the half-life of a drug increases with the volume of distribution. Thus, a decrease in the volume of distribution for hydrophilic drugs results in higher plasma concentrations and a lower half-life in older patients. Some examples are drugs such as digoxin and theophylline. As the volume of distribution increases, the half-life of liposoluble drugs increases, affecting, for example, long-acting benzodiazepines that can accumulate in the body [12].

Metabolism consists of converting an active substance in simpler and more polar substances, called metabolites. These metabolites are inactive or have modified activity. In the case of prodrugs, metabolism is necessary to convert the prodrug in an active drug. Therefore, hepatic metabolism is essential for the elimination of drugs from the body. Hepatic metabolism depends on hepatic blood flow, the transport of the drug from the blood to the hepatocytes and the ability to metabolize the drug [11]. It can be difficult to predict changes in liver metabolism for each patient. In addition to age, the nutritional status of the elderly also affects the rate of metabolism of the drug [12]. Moreover, the increase of inflammatory conditions in older adults can compromise the enzymes associated with the metabolism of many

drugs. Frailty is associated with higher inflammatory markers and a reduction in the activity of esterases (enzymes class that catalyse hydrolysis reactions) [5].

With ageing, the composition of gut microbiome also changes. Intestinal bacteria play a role in the metabolism of drugs as they, being mostly anaerobic, participate in chemical reactions of reduction and hydrolysis of molecules. The changes caused by this phenomenon occur mainly in frailty older adults and long-term nursing homes residents. They have a decreased enzyme induction capacity, which can lead to an increase in genetic silencing with age. Also, external factors such as exposure to environmental contaminants are responsible for altering gene expression. These changes reflect the differential biological ageing [5].

Most drugs are eliminated through the kidneys, and in older adults, the ability to concentrate urine is reduced, consequently, there is a need for a higher amount of urine to excrete the same amount of toxic waste compared to young adults. The decline in renal function is mainly due to the decrease in the glomerular filtration rate (GFR) and the reduction in renal blood flow. With ageing, the decline in glomerular filtration is quite evident. The decreased in renal function increases the risk of ADR, and therefore, special attention should be given when prescribing, to older patients, drugs excreted by kidneys. For drugs that have a narrow therapeutic index and are excreted through the kidneys, such as digoxin, metformin and lithium, it is especially important to adjust and monitor the treatment [12].

This decrease in GFR can be explained by an increase in urea excretion and a reduction in creatinine production in older adults. The renal plasma flow is reduced by 50%, and the kidney's ability to increase baseline GFR by at least 20% (the renal reserve) also decreases significantly with ageing [13].

Sodium reabsorption is reduced in the older adults, and drugs that promote the excretion of salt and water, such as thiazides and loop diuretics, can induce hyponatraemia, hypovolaemia and renal failure. Also, renal excretion of potassium is significantly reduced with ageing, so drugs such as angiotensin-converting-enzyme inhibitor (ACEI), angiotensin II receptor blockers (ARBs), aliskiren, digoxin, potassium-sparing agents, beta-blockers and nonsteroidal anti-inflammatory drugs (NSAIDs) can induce hyperkalaemia [13].

2.2 Age-related changes in pharmacodynamics

Age-related pharmacodynamic changes may also occur. However, these are more difficult to study than pharmacokinetic changes because there is low evidence of the mechanism underlying these changes.

Many response measures are subjective and can be influenced by several factors. These changes represent how drugs react in the body after absorption. The central nervous system (CNS) and the cardiovascular system, as well as the homeostatic mechanisms, are the most affected with the ageing process. Since most medicines used by the older adults have strong anticholinergic properties, the principal ADR that occur in this population are confusion, drowsiness and an increased risk of falls and fractures [14]. Due to all the physiological changes, an older adult's ability to recover from an illness is often diminished, and symptoms may remain partially for a long time.

Age-related pharmacodynamic changes are associated with receptors (number, activity and expression) and with the ability to signal transduction and changes in homeostatic mechanisms [15].

Thus, in the older adults, there is an impaired circulatory response, an increased risk of falls and fractures, changes in thermoregulation mechanisms, laryngeal reflexes compromised with increased risk of aspiration or pneumonia, dehydration and bleeding due to changes in vascular stability and impaired cognitive ability. Therefore, drugs with sedative effects can considerably increase the risk of ADR in older patients [16].

Considering the drugs that act in the CNS, there is an increased sensitivity to the action of benzodiazepines, which can cause a high degree of sedation and impaired psychomotor performance in older adults, making them more favourable to the occurrence of falls and fractures. With increasing age, the ability to respond to anti-psychotic drugs also increases, so there is an increased risk of anticholinergic and extrapyramidal effects, orthostatic hypotension and adverse cerebrovascular effects. The increase in the response capacity to antidepressants also increases the risk of anticholinergic effects in the elderly, being responsible for causing gastrointestinal bleeding and hyponatraemia. These population also have an increased sensitivity to intravenous and inhaled anaesthetic and opioid medications, with an increased risk of respiratory depression and reduced tolerability to these drugs. Furthermore, with ageing, there is an increased sensitivity to the adverse effects caused by lithium, increasing the risk of neurotoxic effects in these population [10, 17].

Concerning drugs that act on the cardiovascular system, the main pharmacody-namic changes associated with age are related to the reduction of the baroreceptor response to low blood pressure and the increase in the sinoatrial suppressive effect, interfering with the administration of calcium channel blocker drugs, causing an effect that can lead to the occurrence of orthostatic hypotension, falls and a decrease in heart rate. With ageing, there is a change in the signal transduction of the beta receptor and negative regulation of the beta-adrenergic receptors, so that there may be a reduction in the effectiveness of beta-blocking agents at doses considered normal. The reduction in GFR causes a decrease in the capacity of diuretic and natriuretic responses. NSAIDs reduce the effects of diuretics, and there is a compromise in adaptive and homeostatic mechanisms, thus reducing the effectiveness of diuretics in doses considered normal, and a high risk of hypoka-laemia, hypomagnesaemia and hyponatraemia may occur. NSAIDs can also reduce the effects of ACEI. Since older patients are more sensitive to warfarin, there is an increased risk of bleeding when taking anticoagulant drugs [10, 17].

The presence of comorbidities is also responsible for pharmacodynamic changes during the ageing process. For example, the presence of psychiatric disorders such as schizophrenia, depression and dementia can alter the function of several neu-rotransmitters [16].

3. Polypharmacy and inappropriate medication in older patients

Pharmacotherapy can improve the quality of life, cure, prevent and relieve the symptoms of many pathologies. However, there is a growing concern that many older people are taking an inappropriately high number of medications [18]. Polypharmacy consists of the use of several drugs by the same patient and appears as a response to the increase in health-related problems, particularly in older adults. There is no consensual definition for polypharmacy; however, most studies consider the con-sumption of five or more drugs per day per person [19]. In older patients, polyphar-macy has been associated with a wide range of negative health outcomes, including falls, ADR effects, changes in physical and cognitive ability, hospital readmission and mortality. It has also been associated with increasing costs in health [4, 18].

Besides, older adults often self-medicate themselves to improve their quality of life. This is a concern because the use of home medicines and herbal products, as well as the diet, can interfere with their health, due to the many drug interactions that can occur [20].

The inappropriate use of medicines by older patients who suffer from multiple diseases is a public health problem due to its impact on morbidity, quality of life and the improper use of health resources. There is an increase in hospital readmissions

and the occurrence of ADR, leading the older patients to have difficulties in carrying out their daily activities, progressively losing their autonomy and, consequently, with loneliness and social isolation [4, 21]. Polypharmacy and multiple comorbidities are also associated with a lack of therapeutic compliance by older patients. The non-adherence may represent a risk because adverse health outcomes could occur like hospitalization and mortality [22].

Polypharmacy represents a challenge for health professionals, and it is essential to improve patients' knowledge about their medication because beliefs about drugs are a strong predictor of adherence. If the patient knows what medicines he is using, the reason for pharmacotherapy and believe about its benefit, the adherence problem will be improved. In practice, the main goal is to achieve an ideal pharmacotherapy by reducing the number of drug-related problems (DRP).

The probability of a drug interaction occurring also increases with ageing due to the higher number of drugs used by older patients. These interactions have negative effects on health, and therefore, health professionals must be alert to possible interactions and must prevent them from occurring [23].

Most of the medications are considered appropriate for older patients, as long as they are used in the correct dosage and for the period strictly necessary. However, since older adults are more susceptible to the adverse effects of drugs, as a result of changes on pharmacokinetics and pharmacodynamics, special care by health professionals is needed when treating older patients.

Having more than one prescriber increases the risk of inappropriate medications use. Thus, it is crucial to implement medication review procedures and that the most frailty older adults have a clinician with knowledge of all their pharmacotherapy and improve communication with caregivers [23].

Some studies have shown that some measures can be implemented to decrease polypharmacy and its adverse effects, improving the quality of the prescription, such as educational programmes for patients and professionals and the creation of multidisciplinary teams of health professionals [24].

4. Improve pharmacotherapy in older patients

To improve the pharmacotherapy in older patients, the available tools must be friendly to improve the use by the health professionals.

According to Wooten [25–27], 10 rules must be followed by the physician's when prescribing, especially in older patients: (1) know the patient and use the patient's most current medical record; (2) follow the tenets of evidence-based medicine, but understand the limitations of the evidence; (3) understand the potential pharmacokinetic and pharmacodynamic changes that can occur in older adults, and use this specific patient information to make prudent prescribing decisions; (4) recognize and investigate patient factors that may contribute to medication problems; (5) avoid the prescribing cascade, if possible; (6) prescribe and recommend only those medications/drug classes for which have a thorough understanding of the pharmacology; (7) identify, anticipate and monitor potential drug interactions before they become a problem; (8) establish a monitoring plan for each medication prescribed for both efficacy and toxicity; (9) properly counsel patients/caregivers on all of the patient's medications, and ensure that the patient understands the pharmacotherapy plan; and (10) assess and address compliance issues.

Clinical decision support includes a variety of tools and interventions that can be computerized or noncomputerized. Clinical decision support systems (CDSS) are characterized as tools for information management and include several clinical guidelines.

In the last decades, the focus has been on tools to provide specific recommendations to patients, called advanced CDSS. These may include, for example, checking interactions between drug-disease, drug-drug, individualized dosing support and advice on laboratory tests during drug treatment [28]. The creation and implementation of this type of tools are responsible for increasing the quality of care and improving health outcomes, reducing the likelihood of errors and adverse effects. Thus, it is possible to reduce uncertainty and increase the reproducibility of decisions, increasing efficiency, cost-effectiveness and the satisfaction of the patients and caregiver [29].

For reducing prescription errors in older patients, other measures can be taken, such as implementing an educational system to train prescription, especially in young doctors who have less practice, and also in hospitals, where this type of errors are more frequent [30]. In many hospitals, pharmacists are responsible for identifying errors in the prescription of medications and must report them immediately to the medical team. Sometimes, the environment involving prescribing physicians may influence the prescription process, leading to some errors. So, all the conditions must be met so that the physician can carry out the prescription in the best possible way, making simple changes such as reducing background noise and promoting more effective communication between all health professionals and with patients. Upon admission of the older patients to the hospital, it is advisable to carry out a reconciliation of the medication in which all medicines used should be checked. The importance and suitability of each medicine for the patient should be assessed, as well as the needs of adding a new list with the latest medications, explaining reasons. This list must be updated and given to the next health professional responsible for the patient [30]. There is currently a validated tool used to provide physicians with a method for obtaining their patients' medication history, the structured history taking of medication use (SHiM). The SHiM consists of 16 questions and reveals the potential to avoid discrepancies in patients' medication histories [31].

Another way to improve pharmacotherapy for older patients is to use criteria that were created to identify PIM as tools to support clinical decision support as described above.

4.1 Criteria used as tools to reduce potentially inappropriate medications in the elderly

To reduce the use of PIM in older patients, strategies and tools have been developed in recent years to assess the appropriateness of medication use in this population. The created criteria can be classified as explicit, implicit or mixed. Explicit criteria are lists of drugs that can be applied with minimal information and clinical judgement. These do not consider individual differences between patients. In contrast, the implicit criteria consider the patient's therapeutic regimen and are based on the judgement of a health professional, being specific to each patient. The mixed criteria, on the other hand, consist of a combination of the previous two, allowing to obtain advantages from both [8].

In 1991, Beers et al. [32] were the first ones to introduce the concept of PIM and to propose a list of PIM for the older adults. These criteria, developed to help healthcare professionals to assess the quality of prescription in older patients, were initially intended for psychiatric patients. In 2011, the American Geriatrics Society (AGS) assumed the responsibility for these criteria and became compromised to update them regularly, and in 2012 [33] the criteria were updated. After that, criteria have been updated, and new, improved versions appeared in 2015 [34] and recently in 2019 [35]. A consensus panel was created with several experts to define what these criteria would be and what individual aspects should be considered.

However, there are drugs not included in these criteria, and that may also be potentially inappropriate for older patients.

Many other attempts have been proposed using implicit or explicit criteria. For example, the Medication Appropriation Index (MAI) measures the appropriation of prescriptions for elderly patients [36]. That is an implicit tool that consists of making a structured assessment of the patient's medications across 10 criteria worded as questions. The 10 items are essential to evaluate the potential of DRP.

Also, according to European standards, the EURO-FORTA List was created in 2018 and is based on the FORTA List that has been validated for Germany and Austria. The EURO-FORTA List is an implicit tool and consists of 264 drugs/drug classes organized in 26 groups according to clinical diagnosis or symptoms [37].

On the other hand, explicit tools, such as the Screening Tool to Alert to Right Treatment (START) and Screening Tool of Older Person's Prescriptions (STOPP) criteria, originally created in 2008 [38], are adapted to European prescription standards. Over time, the START/STOPP criteria have been updated, with the most recent version (version 2) being published in 2015 [39]. These criteria are used as tools to help researchers and professionals to identify 81 PIM and 34 potential prescribing omissions (PPO). Although the STOPP criteria are classified as explicit, according to studies carried out recently in Portugal, for only 29 of the 81 STOPP criteria, a judgement can be made only with the patient's medication profile information. This means that 52 of the STOPP criteria require additional information (i.e., duration of treatment, previous medication, current medical conditions, medical history and laboratory data) [40].

In 2015, the EU (7)-PIM List, an explicit criteria tool, was developed by experts from seven European countries (Germany, Finland, Estonia, Holland, France, Spain and Sweden) that allows the identification and comparison of PIM in these countries [41]. The EU (7)-PIM List development process was based on the participation of several European experts in two Delphi rounds. Some PIM concepts were defined considering the dose, the time of use or the therapeutic scheme, and the final list consists of 282 PIM.

In addition to these criteria, there are many other PIM lists in several countries, such as LaRoche (France) [42, 43], the PRISCUS list (Germany) [44], the Austrian consensus panel list [45], the NORGEP criteria (Norway) [46] and the Canada national consensus panel list [47].

Figure 1 is a flowchart that represents the steps that must be taken by health professionals when prescribing medications to the elderly, including the moment when they should consult the currently available PIM identification criteria.
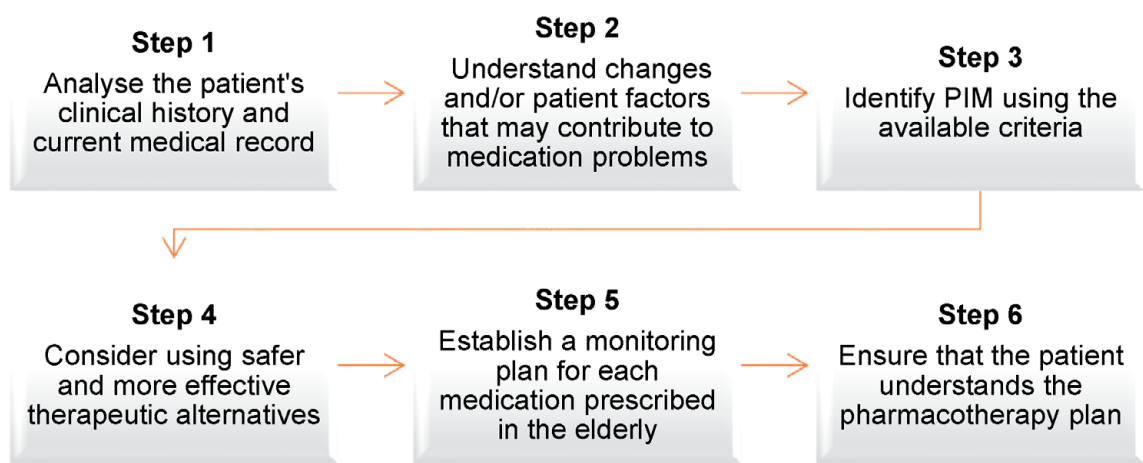

Step 1
Analyse the patient's clinical history and current medical record

Step 2
Understand changes and/or patient factors that may contribute to medication problems

Step 3
Identify PIM using the available criteria

Step 4
Consider using safer and more effective therapeutic alternatives

Step 5
Establish a monitoring plan for each medication prescribed in the elderly

Step 6
Ensure that the patient understands the pharmacotherapy plan

Figure 1.
Flowchart of the operating procedure of the expected steps during prescription for older patients.

5. Conclusions

There are many physiological and pathophysiological changes associated with ageing that can affect the disposition of a drug. However, there are many variations among individuals. Thus, health professionals should be more alert during a prescription to older patients and monitor their health status with individual attention.

One of the main factors responsible for variability in older patients is genetics since the structure, function and expression of most of the enzymes involved in metabolism can be affected due to genetic polymorphism, which will modify the therapeutic effect of certain drugs. Thus, the concept of individualized therapy, which analyses for each subject, genetic and non-genetic factors to optimize the treatment for each patient according to their characteristics, is increasingly common.

In general, older patients have a higher sensitivity to drug therapy, so recommendations for the appropriate prescription of drugs in the elderly population should be considered.

The incorporation of the described criteria in the CDSS has been successful in the detection of PIM. Persistent changes in medication were recorded in 8.7% of the alerts generated [48]. These data suggest that CDSS alerts are a useful tool for implementing guidelines related to the identification of PIM for older patients and for helping physicians during the prescription process, improving healthcare practices.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

ACEI	angiotensin conversion enzyme inhibitors
ADR	adverse drug reaction
AGS	American Geriatrics Society
ARBs	angiotensin II receptor blockers
CDSS	clinical decision support systems
CNS	central nervous system
DRP	drug-related problem
GFR	glomerular filtration rate
MAI	medication appropriation index
NSAIDs	nonsteroidal anti-inflammatory drugs
PIM	potentially inappropriate medication
PPO	potential prescribing omissions

| START | screening tool to alert to right treatment |
| STOPP | screening tool of older person's prescriptions |

A. Glossary

Adverse drug reactions	A response to a medicinal product which is noxious and unintended [49]
Bioavailability	The fractional extent to which a dose of drug reaches its site of action or a biological fluid from which the drug has access to its site of action [50]
Drug-related problems	An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes [51]
Pharmacodynamic	Biochemical and physiological effects of drugs and their mechanisms of action [50]
Pharmacokinetic	The absorption, distribution, metabolism and excretion of a drug that occurs since the moment when the drug enters the body [50]
Polypharmacy	The concurrent use of multiple medications. Although there is no standard definition, polypharmacy is often defined as the routine use of five or more medications. This includes over-the-counter, prescription and/or traditional and complementary medicines used by a patient [52]
Potentially inappropriate medication	Medicines where the potential risk is greater than the potential benefit, especially when safer alternatives are available [41]
Prodrugs	Inactive drug that undergo metabolism to an active drug [50]

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