Chapter

Pharmacovigilance in Older Adults

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Abstract

Polypharmacy and physiological changes inherent to the aging process can cause significant modifications in the pharmacokinetic and dynamic regimens of drugs, making the elderly more susceptible to adverse drug effects. Adverse drug reactions (ADR) in older adults have a significant impact on hospital admissions, increasing hospital stay and healthcare costs. Most common ADR in this population are dose-related and predictable. However, they can be difficult to diagnose as they often have nonspecific symptoms. This could be minimized by decreasing the use and prescription of potentially inappropriate medication and being aware of possible drug interactions. Besides, being older patients underrepresented in clinical trials and due to their physiological modifications, serious or atypical ADR are more common in this age range. To minimize harm in older adults, effective pharmacovigilance must be encouraged.

Keywords: Elderly, Medication, Adverse Drug Reactions, Drug Safety, Pharmacovigilance

1. Introduction

The World Health Organization [WHO] estimates that more than half of medicines are either inappropriately prescribed, dispensed, or sold, as the vast majority of patients fail to take their medication properly [1]. Adding the fact that no drug, taken correctly, is completely risk-free, it becomes of the outmost importance to permanently monitor its safety, to ensure that, throughout its life cycle, the benefits of each drug outweigh the risks of its use [2]. Pharmacovigilance intends to promote patient care and safety as well as an effective assessment of the risk–benefit profile of drugs [3].

With declining fertility rates and greater and better access to health care, the population aged, and the number of older adults has increased globally [4].

Aging is a risk factor for the development of chronic diseases, and to an increased incidence of pathologies such as cardiovascular diseases, strokes, cancer, or dementias. In this sense, the older population is the age group that most needs health care and medicines [5, 6]. Polypharmacy, commonly defined as the concomitant use of at least five drugs, is thus prevalent in this age group [7, 8].

Associated with aging, pharmacodynamic and pharmacokinetic changes occur at physiological level, which implies modified pharmacological responses [9]. The older are much more susceptible to adverse reactions and drug interactions than any other age group [7, 8].

Since people aged 65 and older are underrepresented in clinical trials pharmacovigilance becomes essential to allow continuous monitoring of safety and the assessment of the benefit/risk of drugs in this population [10].

2. Physiological and pharmacological modifications

The impact of aging on the human organism brings together complex changes at the molecular, cellular and tissue levels in all systems of the organism, and the effects of the most varied existing environmental factors [11, 12].

The physiological changes associated with the aging process weaken the older population. These can cause significant changes in the pharmacokinetic and dynamic regimens of medications, making them more susceptible to adverse effects [13].

2.1 Age-related changes in pharmacokinetics

With aging, pharmacokinetics processes suffer modifications [9]. Bioavailability, the extent and rate at which the active substance enters the systemic circulation to reach the action site, can be modified [9, 14].

Absorption of most drugs does not appear to decrease significantly with age, but different pathologies of the digestive system may affect drug absorption [9]. Nevertheless, drugs administered intramuscularly or subcutaneously may have their absorption modified, due to the reduction in blood perfusion of the tissues [15].

After absorption, the drug enters the bloodstream and is distributed to different tissues and organs. With the increase in fat mass and reduction in the volume of water, the volume of distribution of fat-soluble medications increases [as does the half-life of the same], as in the case for the long-acting benzodiazepines [15, 16]. In contrast, water-soluble drugs may have a lower volume of distribution, with an increase in plasma concentrations, that can be toxic, as happens with gentamicin, digoxin, theophylline, and cimetidine [9, 16]. In addition to body composition, the two main proteins involved in the transport of drugs: albumin, which binds to acidic drugs [e.g. warfarin, digoxin, lorazepam], and α1-acid glycoprotein, which binds mainly to basic drugs [ex: lidocaine, propranolol] may have their plasma concentrations altered in older population with comorbidities [15, 17].

Although other organs can metabolize drugs, the liver is the main organ involved in the process. Metabolism consists of converting an active substance in simpler and more polar substances, called metabolites, from phase I and II reactions. These metabolites are inactive or have modified activity. In the liver, maintaining its functions during aging, there are changes that can reduce its functionality [18]. The hepatic volume decreases 20–30%, and the hepatic blood flow 20–50%. There is a reduction in the first-pass hepatic effect, and thus the bioavailability of drugs that are subjected to extensive first-pass metabolism may be increased, while others, which need activation in the liver, may be reduced [15]. In addition, the hepatic clearance of drugs subjected to limited flow metabolism [e.g., propranolol and amitriptyline] can be reduced by more than 40%. Age can significantly affect the pharmacokinetics of drugs with a narrow therapeutic index [reduced margin between an effective dose and a toxic dose]. Inflammatory conditions can also affect the function of the enzymes involved in metabolism. The microbial ecosystem also stands out, with many clinically relevant drugs being co-metabolized by microflora. With changes in the composition of the intestinal microbiome, the drug's metabolism can also be altered with harmful consequences [19].

Excretion is also affected by the aging process. The kidney is the main organ in the removal of drugs and their metabolites and the pharmacokinetics are strongly influenced by the progressive loss of kidney function with age, thereby decreasing the excretion of drugs [20, 21]. Due to these changes, a decline in total clearance with age is expected for drugs predominantly excreted by this pathway. With the decrease in clearance, serum levels will increase, potentially causing ADR [22]. Therefore, the dosage of these drugs must be guided by kidney function and the glomerular filtration rate [GFR]. In addition, polypharmacy can increase the risk of kidney dysfunction, overloading the kidneys to excrete several drugs and their metabolites at the same time [23].

2.2 Age-related changes in pharmacodynamics

In older adults' sensitivity, meaning the effects of the same concentration of a particular drug at the site of action, vary significantly when comparing with young or adult persons. This difference can be justified by changes in drug-receptor interaction, signal transduction, adaptive homeostatic responses and, among more fragile patients, by comorbidities [24, 25]. Although age-related pharmacokinetic changes are predictable, the complex interaction between pharmacokinetic changes and homeostatic changes makes it a difficult topic to study [15].

The most relevant pharmacodynamic changes are at the central nervous system [CNS] and cardiovascular level [15]. Older adults often demonstrate an exaggerated response to psychoactive drugs due to an underlying age-related decline in CNS function, and are also more prone to adverse effects with cognitive impairment, including confusion and drowsiness. At the cardiovascular level, they may experience a greater decline in blood pressure after administration of calcium channel blockers with or without dihydropyridine, which may be the result of related changes with age in the reflex of the baroreceptors, as well as a decreased clearance of these drugs [25, 26]. In addition, β-adrenergic receptors decrease in numbers and have less sensitivity and also show changes in the G-protein involved in signal transduction. As a result, β-adrenergic activity in vascular, cardiac and respiratory tissue decreases, altering the effect of β-blocking agents and β-agonists in general [26, 27].

Pharmacodynamics not only affects the therapeutic effects of the drug but can also change the magnitude of the effect with subsequent adverse effects [20, 25]. These changes in pharmacokinetics and pharmacodynamics can thus make the older population more prone and susceptible to ADRs, either in normal therapeutic doses or by drug interactions mechanisms [27].

3. Adverse drug reactions in older adults

As previous mentioned, physiological aging causes pharmacodynamic and pharmacokinetic changes, imposing different pharmacological responses [9]. The drug could trigger iatrogenic problems in the geriatric patient, increasing the risk of possible ADR [28].

The vast majority of ADRs can be divided in 2 types:

- Dose-dependent, more frequent at higher doses, which can occur in any individual when exposed to a sufficient dose of the drug: Type A - Augmented, representing almost 80% of all ADR in older patients [29, 30]

- Immune mediated or non-immunological hypersensitivity reactions, not dependent on the dose, which can occur in predisposed individual. These

reactions are therefore unpredictable and more serious, usually detected only after the drug enters the market: Type B - Bizarre, representing 20% of all ADRs in older patients [29–32].

Drugs associated with type A reactions are generally of low therapeutic index and are commonly used in older patients and therefore most ADRs in this age group are type A reactions with predictable pharmacological effect [30, 33]. Known homeostatic dysregulation, age-related changes in pharmacokinetics and pharmacodynamics and drug interactions make ADRs definitely or possibly preventable in this population. However, ADRs can be difficult to diagnose in older patients as they often have nonspecific symptoms, whether falls, fatigue, cognitive decline, or constipation, all of which have different etiologies [7]. Despite the difficulties it is estimated an average prevalence of 11% of ADR [33].

Most common ADRs causing hospitalization in older patients are related to Gastrointestinal complications [Gastrointestinal bleeding, peptic ulcer, erosive gastritis, nausea, vomiting]; Cardiovascular disorders [Hypotension, bradycardia, falls, arrhythmias] Metabolic/endocrine complications [Hypoglycemia]; Renal and urinary disorders [Renal impairment, acute renal failure]; Electrolyte disorders [Hypokalemia, hyperkalemia, hyponatremia]; Nervous system disorders [Depressed level of consciousness, mental status changes] [34]. Studies have shown that beta-blockers, antibiotics, oral anticoagulants, digoxin, ACE inhibitors, antineoplastics, calcium entry blockers, opioids, oral antidiabetics and most frequently NSAIDs as the main drug classes causing ADR hospitalization in older adults [33, 35].

3.1 The healthcare impact of ADR in older patients

ADRs cause a significant burden in healthcare services, representing 6.5% in hospital admissions, being responsible for death of 0.15% of the patients admitted. Besides, patients admitted with ADRs were significantly older than patients without ADRs, as hospitalization due to NSAIDs complications increases exponentially with aging, having an important impact in healthcare resources. The median prevalence of ADRs leading to hospitalization is 10%. Although some hospitalizations related to ADRs are inevitable, it is estimated that only 18.6–28% of ADR cases that caused hospitalization in older patients were considered inevitable. Severe ADRs are related mostly to hematological disorders and acute renal failure [33, 34].

Polypharmacy is one of the main risk factors for ADR in this population. The risk of ADR increases by 13% in patients taking two drugs to 58% when taking five and to 82% when taking seven or more drugs [4, 7]. Drug interactions, common in polypharmacy, can cause synergistic toxicity and thus be risk factors, such as the combination of corticosteroids and NSAIDs. Polypharmacy leads to problems in medication adherence and correct administration representing a risk for adverse events or ADR [31, 36, 37].

ADRs also have a strong economic impact in the health system. The costs involved in treatment are mainly associated with hospitalization, prolonged hospital stay and additional clinical investigations- Studies point to an average of 8 additional hospital stay days and costs of approximately 706 M € per year [38, 39]. Regarding avoidable ADRs, costs per hospitalization vary between € 2,851 - 9,015, with length of hospital stay between 4.2 and 13 days. In outpatient, the costs resulting from avoidable ADRs ranged between € 174 and € 8,515 [38]. Particularly in the elderly, an average cost of emergency care of 333 US $ is pointed, with severe ADR patients costing $ 691 per patient and $ 7,529 per patient with severe ADR during hospitalization [40].

ADRs can trigger cascades of prescription when new drugs are prescribed for problems resulting from another medication, which is usually an unknown ADR, increasing therapeutic costs, in addition to increasing the risk of new ADRs. Fever, hemorrhage, diarrhea and arrhythmia are those with the greatest economic burden in a hospital environment; and NSAIDs, antibiotics, anticoagulants and antineoplastics are the main classes involved in ADRs related costs [39].

Most drugs are suitable for the older, as long as they are used in the correct dose and for the necessary period. However, since they are more susceptible to adverse events, the potential risk of certain drugs may outweigh the potential benefit. When safer alternatives are available, these drugs are considered inappropriate [PIM] [28, 41].

3.2 Potentially inappropriate medication for older adults

In recent years, in order to reduce inappropriate prescribing, and in turn, to reduce the prevalence of PIM in older population, explicit and implicit criteria strategies and tools have been developed, being very useful in clinical practice, as decision support- Explicit criteria consists in lists of drugs applied with minimal information and clinical evaluation, not considering individual differences between patients, representing important alert mechanisms on the possibility of the inappropriate use of a medication just by itself, as where implicit criteria focus on the patient's therapeutic regimen and clinical evaluation. Associating these criteria with information management tools such as Clinical decision support systems [CDSS] can allow improvements in patient therapy. These CSSDs, usually computerized, can verify interactions between medicine-disease or medicine-medicine, also detecting PIM [36].

Among the criteria most applied in research within this theme, Beers criteria stands out. In 1991, Beers and his research colleagues met with geriatric and pharmaceutical specialists to list the drugs to be avoided by older people. Explicit criteria were defined, considering 30 drugs/pharmacological groups considered inappropriate. These criteria have since been repeatedly reformulated and updated according to new information in the literature. Currently, these criteria are divided into 5 lists: Potentially inappropriate to be avoided in the elderly; Potentially inappropriate in the elderly due to drug–drug and/or drug-disease interactions; Those that should be prescribed with caution in the elderly; Combinations of drugs known to cause "drug–drug" interactions; Drugs to be avoided or whose dose adjustment is necessary when prescribed in elderly people with impaired renal function [42, 43]. However, its application in Europe is limited, where several of the drugs identified in these criteria are not commercialized in this continent and some of the drugs marketed in Europe are inappropriate and are not on the Beers list [44].

START/ STOPP criteria is also currently used. The STOPP [Screening Tool of Older Person's potentially inappropriate Prescriptions] criteria are 80 parameters organized by physiological systems. The START [Screening Tool to Alert doctors to Right Treatment], on the other hand, identify potentially beneficial omissions [which should be prescribed to the elderly], with 34 criteria divided into six physiological systems [44]. STOPP/START have advantages over Beers because they are significantly associated with adverse drug reactions. In addition, they are more in line with the European reality, also having greater sensitivity demonstrated for the identification of inappropriate prescriptions. Although the STOPP criteria is explicit, only 29 of the 81 STOPP criteria can be applied only with information on the patient's medication profile [36].

Recently, in order to develop a European list of potentially inappropriate drugs, 27 experts from 7 countries in Europe came together, creating the EU [7] -PIM list, with

282 drugs from 34 pharmacological classes in which it is found, for each drug, the justification for its inadequacy, as well as dose adjustments/special considerations of use [when applicable] and possible alternatives to that drug [45].

The EU [7]-PIM list has been used in some studies in Europe that show a range between 40.9 [Sweden] and 87% [Portugal] of older adults having PIM prescribed by the physician. Proton bomb inhibitors, Bromazepam, Diazepam, Lorazepam and Alprazolam are the most common [46].

ADRs related to PIMs were observed in some studies, with digoxin, benzodiazepines, and imipraminic antidepressants, being the most common. In hospitalized older patients, NSAIDs were the most common types of PIM-ADRs, inducing upper gastrointestinal bleeding. Benzodiazepines inducing falls with fractures and depressed mental status, as well as digoxin >0.125 mg/day inducing cardiac arrhythmias and visual disturbances due to digoxin poisoning are also common in hospital context [47, 48].

4. Promoting drug safety in older adults

Older adults have a higher chronic diseases burden and consume more prescription drugs than any other age group. Besides drug–drug interactions, the prevalence of concurrent use of prescription drugs and herbal medicinal products [HMPs] by older adults is significant, and can also lead to serious ADR, as risk of bleeding due to the use concomitant use of *Ginkgo biloba*, garlic or ginseng with antithrombotics [49].

4.1 Older participants in clinical trials

Including older patients in the clinical trial process is important, as on average older adults carry 60% of the national disease burden but represent only 32% of participants in Phase II and III clinical trials [50, 51]. This population is underrepresented, especially the >75-year-old. and current guidelines recommend to have a significant number of older participants in the trials [that can be estimated with the help of epidemiological studies targeting the disease that the drug intends to treat] in order to assess the risk–benefit ratio of the drug in this age group. Phase I trials might not need older participants, but phase II and III clinical trials should include them, to assess dosage, safety, adverse effects, and effectiveness [52, 53]. Decentralized clinical trials could facilitate the appropriate inclusion of these patients [50].

Nevertheless, including this age group implies some methodological considerations. As it exists a progressive impairment of the renal or hepatic function or drug–drug interactions, an appropriate assessment of pharmacokinetic profiles and pharmacodynamic endpoints are needed [54, 55]. Besides, since they have a high risk of cognitive function impairment, determining adverse CNS events is of the outmost relevant clinical importance during the trial design. Aware of these needs, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use [ICH] developed guidelines for studies in special populations, namely older adults, aiming for a sufficient representation in phase III. It is advisable 100 minimum participants and, when the disease is associated with aging, older people should form most of the participants [55, 56].

These studies should compare older and younger patients or evaluate drug disease interaction studies in older adults. Population pharmacokinetic analyses intends to determine the sources and correlation of variability of the drug concentration in the target patient population, comparing the older with the young group.

Safety and efficacy should also be of the outmost importance, as outcomes must be explored to provide evidence base support to the dose selection during drug approval, impacting regulatory procedures. Finding significant differences in safety and efficacy outcomes between young and older patients, pharmacokinetic studies plays an important role to understand these differences and assess benefit–risk of a drug administration [55–57].

4.2 Medication labelling

After drug development, providing quality information to health care professionals about the safe and effective use of drugs in geriatric patients is fundamental. And so, it is required by the Food and Drug Administration [FDA] and the European Medicines Agency [EMA] that the labeling of these drugs must have safety and efficacy information for the older. Particularly for EMA, it is mandatory to present on the Summary of Product Characteristics [SmPC] and the Patient Information Leaflet information regarding dosage, frequency and seriousness of ADR, or the need of monitoring in this population [57, 58].

4.3 Pharmacovigilance in older patients

Pharmacovigilance plays a key role in ADR detection in post authorization period, improving the safe and rational drug use and thereby improving patient care [59, 52]. In 2012, new legislation came into force within EU, creating the Pharmacovigilance Risk Assessment Committee and giving a central role to pharmacovigilance. A significant increase in the participation of health professionals and patients in the system was seen, and the electronic transmission of information from Pharmacovigilance became mandatory in November 2005, with EudraVigilance being the system for analyzing and managing information on suspected ADR, allowing the electronic exchange of reports of ADR cases, used by the various partners of the European regulatory network to monitor the safety of medicines [60].

A strong pharmacovigilance system can perform safety surveillance with processes, tools, and experts to monitor ADRs from medication taken by older patients. During this post-authorization surveillance, safety risks may be detected, particularly in patients with comorbidity and polypharmacy, suffering physiologic changes inherent to the aging process [61, 62]. Adequate pharmacovigilance systems considering HMPs is also necessary to increase the likelihood of ADR detection, and appropriately identify and manage older patients at risk [49, 63].

Risk management plans [RMP] must also be submitted to EMA when applying for a marketing authorization, including relevant information on medicine's safety profile, how the risks will be prevented or minimized and how to promote knowledge regarding safety and efficacy of a determined drug.. The elaboration of this document allows the understanding of safety concerns in older adults, planning how to reduce the possibility of suffering ADR. The RMP must be modified whenever it is determined important safety risks, as well as the labeling [54, 64].

Nevertheless, signal detection using spontaneous reporting systems is one of the most important sources for safety monitoring in post authorization "real-life" setting, especially in populations underrepresented in preapproval clinical trials such as older adults [61, 62]. Even tough underreporting, low sensitivity and selectivity are disadvantages to be considered regarding this reporting system, the fact that broadens all medicines on the market throughout all the life cycle, in all patients, not interfering with prescription habits, not only allows the identification of common ADR, as well as rare, unexpected ADRs in groups and scenarios not studied, as

the older patients. This makes spontaneous reporting a fundamental report system for the safety monitoring of approved medicines [60, 65]. Due to the widespread of under-reporting of ADRs to spontaneous reporting systems, including serious or severe ADRs, the use of new technology is a great opportunity to empower patients to report, such as the programmes WEB-RADR [66] in Europe and Medwatch [67] in the United States. Although these tools were developed to facilitate reporting by both healthcare professionals and patients, a better understanding of the relation that the older patients have with health technologies is need [68].

In the European Economic Area [EEA], the electronic transmission of information from Pharmacovigilance became mandatory in November 2005, with EudraVigilance being the system for analyzing and managing information on suspected ADR, facilitating electronic exchange of individual case safety reports between EMA, national competent authorities, marketing authorization holders and sponsors of clinical trials in the EEA, as it allows early detection and evaluation of possible safety signals [60, 69].

EudraVigilance allows researchers and/or interested readers to perform same analysis in the ADR database EudraVigilance of the EMA, even though with different levels of access for different stakeholders. As some studies explore national databases, some studies have explored EudraVigilance database, accessing suspected medication and common ADR reported in older adults. Antineoplastic and immunomodulating agents, Nervous system, Cardiovascular system, Blood, and blood forming organs represent a significant part of suspected medication spontaneously reported in elderly. Rash, Confusional state, Dizziness, Pruritus, Pyrexia, Thrombocytopenia, Diarrhea, Vomiting, Dyspnea and Nausea are the most reported Preferred Terms in elderly spontaneous cases [62, 70, 71].

5. Conclusions

Older adults, having comorbidities, in polypharmacy regimens, associated with physiological age-related changes, are more susceptible to ADRs. With the demographic aging being a reality worldwide, the healthcare demand increases, as well as drug safety vigilance efforts.

Only recently older people start to have a significant presence in clinical trials. Pharmaceutical companies and the regulatory agencies joined efforts to provide evidence on the benefits and harms of medicines in older patients, giving more importance to efficacy and safety during drug development targeting diseases mostly related with aging or chronic diseases.

Pharmacovigilance regulatory agencies at a local and national level should promote monitoring and reporting programs of adverse effects observed, particularly in older populations, adding reliable safety data and identifying age related.

Drug safety studies in this age group need to be constantly improved to present evidence-based data to enhance quality of prescriptions in a highly healthcare demanding age group.

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Conflict of interest

The authors declare no conflict of interest.

Appendices and Nomenclature

ADR	Adverse drug reaction
CDSS	Clinical decision support systems
CNS	Central nervous system
EEA	European Economic Area
EMA	European Medicines Agency
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
NSAID	Non-steroid anti-inflammatory drug
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
WHO	World Health Organization

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