

## POLYPHARMACY IN GERIATRIC PATIENTS UNDERGOING SURGERY – STRATEGIES TO REDUCE THE RISK OF IATROGENIC EVENTS

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### Abstract

As the elderly population is increasing globally, more and more geriatric patients are expected to undergo surgical interventions. With age, the incidence of comorbidities is also higher, with these patients being in a significant proportion subject to polypharmacy. The present paper is a comprehensive review of the prevalence, cause, and specific risks associated with polypharmacy in the elderly undergoing elective surgical procedures. The possible implications on hospital stay, perioperative morbidity, and healthcare expenditure and the strategies to minimize the risk of adverse events in the perioperative course due to polypharmacy are presented. Polypharmacy has a high prevalence in older patients and can be attributed to multiple patient and doctor-related causes. Adverse drug reactions are significantly associated with the number of personal medications and represent an avoidable cause of perioperative morbidity. The most frequent polypharmacy complications are falls, cardiac events, hemorrhages, postoperative cognitive impairment, and delirium. Preoperative polypharmacy management in geriatric patients should include a comprehensive medication review and a multidisciplinary approach. Further directions of study include strategies for deprescribing and implementing software tools to assess inappropriate drug associations and help clinicians minimize the risk of drug interactions.

### Rezumat

Cum la nivel global media de vârstă este din ce în ce mai mare, se așteaptă ca tot mai mulți pacienți geriatrici să fie supuși intervențiilor chirurgicale. Odată cu vârsta, incidența comorbidităților este, de asemenea, mai mare, acești pacienți fiind într-o proporție semnificativă supuși polimedicatiei. Ne-am propus realizarea unei prezentări cuprinzătoare a prevalenței, cauzelor și riscurilor specifice asociate polimedicatiei la persoanele în vârstă care suferă proceduri chirurgicale electivă. Administrarea concomitentă a unui număr mare de medicamente are o prevalență ridicată la pacienții vârstnici și poate fi atribuită mai multor cauze legate de pacient și de medic. Reacțiile adverse la medicamente sunt asociate în mod semnificativ cu numărul de medicamente individuale și reprezintă o cauză evitabilă a morbidității perioperatorii. Cele mai frecvente complicații ale polimedicatiei sunt căderile, evenimentele cardiace, sângerările, afectarea cognitivă postoperatorie și delirul. Gestionarea preoperatorie a polifarmaciei la pacienții geriatrici trebuie să includă o revizuire cuprinzătoare a medicamentelor și o abordare multidisciplinară. Alte direcții de studiu includ strategii pentru implementarea instrumentelor software ce pot evalua asociațiile inadecvate de medicamente, ajutând astfel clinicienii să minimizeze riscul interacțiunilor medicamentoase.

**Keywords:** polypharmacy, geriatric, adverse event, risk management, surgery, patient safety, quality of care

### Introduction

Polypharmacy, defined by the World Health Organization as the concurrent use of multiple medications in the same person or the administration of an excessive number of drugs [1, 2], has become a major public health challenge nowadays, being a significant burden in healthcare expenditure. While there is no consensus regarding the definition of

polypharmacy, most studies consider the limit of 5 or more concomitant medications, with excessive polypharmacy of hyperpolypharmacy when 10 or more medications are prescribed [1-4]. It is associated with an increased risk of drug-drug interactions (DDIs), which have adverse effects on patient health, the efficacy of medications, and increased medical costs.

Elderly patients frequently associate multiple diseases and are particularly vulnerable to being exposed to the effects of polypharmacy, considering that the current treatment protocols for the most common chronic conditions, such as hypertension, ischemic heart diseases, or diabetes, involve the simultaneous administration of 2 or more drugs.

A study by Moriarty *et al.* showed that polypharmacy is on an increasing trend, especially in older individuals over 65 years of age, rising from 17.8% in 1997 to 60.4% in 2012 [3]. In a systematic review of Delara [2], the prevalence of polypharmacy in patients over 65 years, varied between 37 and 54%, while Bhagavathula found a prevalence of 49%, with hyperpolypharmacy in 31% in older adults in India [4].

While polypharmacy is to some extent unavoidable in geriatric patients, inappropriate or excessive polypharmacy is commonly associated with adverse health outcomes, such as the increased risk of death, falls, drug interactions, non-adherence, and hospitalization [5-7].

In the case of planning a surgical intervention, which requires a specific perioperative medication protocol, polypharmacy management is necessary to improve patient safety.

## Materials and Methods

The paper is a comprehensive review regarding the inadequate polypharmacy in geriatric patients, the possible implications on hospital stay, perioperative morbidity, and healthcare expenditure, and the strategies to prevent adverse events and increase patients' safety. A search was performed on PubMed/Medline and Google Scholar for all papers published between 2000 and 2022, by the terms: "polypharmacy" OR "multiple medications" AND "geriatric" OR "elderly" AND "surgery". After duplication removal, articles and book chapters available in full text in the English language were analysed.

## Results and Discussion

### *Risk factors for polypharmacy in geriatric patients*

With a WHO prediction of 20% population aged over 65 years of age globally by 2050, aging is a growing concern worldwide [8]. With increasing the life expectancy of the elderly, one can expect that the proportion of individuals taking more than 5 medications is on increasing trend. Several causes are associated with increased polymedication: increased number of comorbidities with age, easier availability of newer medication and curiosity toward it [9], self-medication with herbal supplements, vitamins, or over-the-counter painkillers, sleep medication, without the awareness of drug interactions.

The development of the pharma industry has led to the appearance on the health market of a very large number of medicines and nutritional supplements,

whose beneficial role in the treatment of various ailments is supported by clinical studies. However, the results of the studies are often obtained on young adults, without any associated comorbidities. In the case of geriatric patients, the prescription of the medication must take into account the associated pathology and the competing medication that can reduce the pharmacological action of a particular drug or expose the patient to the risk of adverse effects and the patient's life expectancy [10].

Patients that underwent multiple consults often accumulate more prescriptions, from every physician, without a proper correlation among them. In other cases, a side effect of the current medication might be interpreted as a new pathological condition and the doctor could add a new drug to compensate for the symptoms [9, 11].

A dysfunctional patient-doctor relationship can also be involved. Poor patient knowledge of the prescribed personal medication may result in unnecessary duplication or incorrect addition, in subsequent consultations. On the other hand, the physician might have the incorrect impression that the patient wants to leave the consultation with a prescription, and may add unnecessary medication. Incomplete information about the regimen and time of administration, failure to follow up on the patient's evolution, and adjust periodically the medication list are also frequent causes that lead to polymedication [8-11].

### *Syndromes of the elderly and implications on drugs pharmacokinetics and actions*

Geriatric syndromes are considered the consequence of age-related physiological changes, and various environmental stressors, but also of the associated chronic pathology. The discrete functional changes of the elderly, which do not correspond to the inclusion in a certain pathological entity, are gathered under the name of "geriatric syndromes" [12]. Among these, the best known is frailty, that is, the increased vulnerability of the elderly to the action of stressful factors, such as acute infections, surgical interventions, etc. Other syndromes of the elderly include cognitive dysfunction, malnutrition or depression, sleep disorders, changes in appetite, falls, and dizziness, often coexisting and significantly affecting the quality of life of the elderly patient [13, 14].

On the one hand, these functional changes are the consequence of the presentations to doctors from different specialties and can be the cause of polypharmacy, but on the other hand, they will have implications for the pharmacokinetics of the prescribed medication. With age, there are specific body changes that might interfere with drug pharmacokinetics and action: reduced body weight, gastrointestinal disorders, lower renal excretion, or limited hepatic enzyme activities. Shi *et al.* show that two-thirds of elderly patients have a slightly limited renal function, this being correlated with the presence of cardiovascular

diseases and other risk factors, with an impact on renal clearance [15]. Also, the decrease in lean mass and hydric compartment, with the relative increase in adipose tissue mass, produces changes in the distribution of various therapeutic agents at the tissue level [16]. Studies show an important variability of inter-individual response to therapy in the case of elderly patients. The

complexity of interactions between comorbidity, polypharmacy and age-related changes in pharmacokinetics justify an increased caution in administering medication in the elderly [15, 16], with these patients being particularly susceptible to the adverse effects of medication, as well as drug interactions.

**Table I**  
Risk factors for polypharmacy in geriatric patients

|                           |   |
|---------------------------|---|
| Patient-related factors   | Age<br>Number of comorbidities<br>Self-medication<br>Multiple consultations<br>Insufficient knowledge of current personal medication  |
| Physician related factors | Treating a side-effect of another drug with a newly added drug<br>Incomplete information regarding treatment and follow-up<br>Unnecessary medication due to the misguided impression that the patient is expecting a prescription |
| General factors           | Increased life expectancy and aging of the population worldwide<br>Availability of many new pharma products   |

*The most common drug interactions in elderly patients undergoing surgery*

Depending on the mechanism, pharmacodynamic and pharmacokinetic drug interactions are distinct. In pharmacokinetic interactions, the level of one drug is affected by another drug, while pharmacodynamic interactions typically result from interactions (synergistic and/or antagonistic effects) at the site of action of the cell. Therefore, in theory, clinically significant drug interactions occur more frequently with drugs that have a limited therapeutic range [17].

The cytochrome P450 (CYP) system has emerged as an important determinant of the incidence of several drug-drug interactions (DDIs) that can result in toxicity of the drug, reduced pharmacological effect and adverse drug reaction. The CYP superfamily of mono-oxygenases metabolizes various medications. 75% of medicines are eliminated *via* phase I hepatic metabolism and 70% by CYP enzymes. High plasma levels of a substrate drug due to co-administration of a metabolism-inhibiting medicine may cause substantial side effects.

Based on this, determining whether the medications are enzyme substrates, inducers, or inhibitors helps avoid clinically relevant interactions. Co-morbidity, age, gender, genetics, polypharmacy and narrow therapeutic index medications increase DDI probabilities [18].

Drug interactions can be divided into 4 classes: Class A: probably without clinical significance; Class B: clinical relevance cannot be determined with certainty; Class C: the interaction may alter the mode of action of the drug, but this can be well controlled by individual dose adjustment; Class D: interaction may lead to serious adverse effects, prevent the effect, or altered effects are difficult to control by dose adjustment [17]. Drug interactions are worse in elderly individuals owing to polypharmacy, decreased metabolism and clearance of medications, and underlying comorbid

conditions. Sorting out mild from serious medication interactions in elderly patients is difficult [19].

Interactions may occur not only between medicines, but also between medicines and foods or between medicines and diseases [17].

An Egyptian study group examined the nature of drug interactions in a Surgical Intensive Care Unit. The most common DDIs detected with were combinations between analgesics and other classes of drugs (acetaminophen and fentanyl, phenytoin and metronidazole, fentanyl and midazolam, phenytoin and acetaminophen, metronidazole and acetaminophen, enoxaparin and acetaminophen, metronidazole and phenytoin, and phenytoin and ranitidine) [20].

Tramadol is also one of the most commonly administered opioid analgesics in intensive care units. It interacts specifically with antidepressants and anti-psychotics, causing severe serotonin syndrome. If the patient is on carbamazepine, it should be stopped while tramadol is being taken, as it reduces its analgesic effect. Pre-operative administration of ketoconazole and erythromycin to prevent certain microbial infections should be avoided, as both are CYP3A4 inhibitors, which increase the plasma concentration of tramadol and the risk of adverse reactions [21].

Another example of important interactions encountered in elderly patients undergoing surgery is that between oral anticoagulants (acenocoumarol, warfarin, clopidogrel) and non-steroidal anti-inflammatory (NSAI) drugs and aspirin, resulting in an increased risk of bleeding accidents, due to displacement of anticoagulant from plasma proteins. Combining NSAIDs and oral anti-diabetic medications can result in hypoglycemic episodes [22].

Low molecular mass heparins (*e.g.* enoxaparin, dalteparin) are frequently recommended in the prevention of venous thromboembolic disease associated with surgery. Their administration should be strictly supervised in

case of existing chronic treatment with NSAID, aspirin, anticoagulants or other thrombolytics, because of the risk of bleeding [23, 24].

Many elderly patients take proton pump inhibitors (PPIs) on an ongoing basis. High gastric pH inhibits the absorption of the antifungal compounds itraconazole and ketoconazole significantly. Patients receiving PPIs should not receive either of these medications unless the PPI is discontinued. Dipyridamole is another substance commonly administered to the elderly that may be impacted by PPI use [27]. The absorption of nifedipine, digoxin and alendronate is enhanced when gastric pH is elevated. The effect is modest for digoxin and nifedipine, but alendronate bioavailability is twofold in the presence of elevated gastric pH [19]. Due to the multiple medications used by geriatric patients, general anesthetics should be administered under strict supervision. The concurrent use of benzodiazepines, parasympathetics, and inhalation anesthetics prolongs anesthesia and decreases respiratory rate. The interaction of neostigmine with analgesics can result in a heart attack [25].

#### *Specific risks of polypharmacy in geriatric patients admitted for surgery*

Many studies raise concerns regarding the increasing prevalence of polypharmacy in the elderly, and the possible associated healthcare effects, such as toxic reactions, loss of medication efficacy, or treatment failure. Geriatric patients are more frequently exposed to polypharmacy in a hospital environment [9, 26, 27]. Several studies reported that there is a strong correlation between the incidence of adverse drug events (ADEs) and the number of drugs taken by a person, raising from 13% with two medications, to 58% with 5 medications and 82% in cases when more than 7 medications were prescribed [27]. The most frequent prescribed classes of medication that are linked to adverse events are: anti-platelets (16%); diuretics (15.9%); non-steroidal anti-inflammatory drugs (11%) and anti-coagulants (8.3%) [26].

The use of potentially inappropriate medications for older people is associated with worse health outcomes owing to the occurrence of ADEs and drug interactions, leading to increased healthcare costs [28]. In a study on 250 senior patients of Lertkovit *et al.*, admitted for elective major surgery, the prevalence of polypharmacy was 74% [29]. Moreover, the drug therapy unrelated to surgery was well correlated with the number of associated comorbidities and adverse events in the perioperative period, such as postoperative cognitive dysfunction and delirium [30]. Abe *et al.* found that polypharmacy at admission was an independent factor for prolonged hospitalization in gastrointestinal surgery [31].

However, interrupting patients' medicine in the preoperative course should be avoided, as it may add significant risk to the surgery and further complicate the outcome. In a large prospective study by Kennedy

*et al.* [32] on 1027 patients admitted to a general surgery center, 12% of patients whose cardiovascular medication was discontinued developed cardiac complications during their admission. ACE inhibitors were most frequently associated with fatal outcomes. Sleep medication discontinuation was reported to be associated with dizziness and confusion, which mimics postoperative cognitive dysfunction and delirium. The reintroduction of patients' regular medicines early in their postoperative course was found to be associated with decreased in-hospital postoperative complications and mortality [33].

#### *Strategies of polypharmacy management*

With the new achievements of modern medicine and the increase in life expectancy, the older population segment is currently growing worldwide. Senior patients have surgical interventions more frequently than at younger ages. Several studies showed that geriatric patients who take multiple medications, especially high-risk medication, are more exposed to experiencing adverse events after surgery and even die, and most of these are preventable [33-36]. Ethical norms focus on beneficence before anything, including a comprehensive benefits/risks assessment and prioritization of benefits in curative [37]. In this context, there are increasing efforts and research to identify high-risk and potentially inappropriate medications (PIMs) and, in possible, to initiate a deprescribing process in the preoperative period in case of scheduled surgery.

The current approach in the case of elective surgery in the elderly includes a multidisciplinary preoperative approach, including a geriatrist, an internal medicine specialist, and an anesthesiologist, to assess an individualized evaluation, in terms of frailty, functional and organ limitations, cognitive dysfunction, and medication, known as comprehensive geriatric assessment [38]. A careful anamnesis is required to document the preoperative personal medication of the patient, to prevent possible drug interactions. Difficulties can be encountered in patients with cognitive impairment or acute conditions. In these conditions, the help of the patient's relatives or documentation in the electronic medical record could be very useful.

Special interest in the preoperative period should be paid in medications that may precipitate adverse events such as falls, delirium, hemorrhages, or potentially inappropriate drugs, on the base of risk/benefit evaluation [38, 39]. If needed, changes or dose alterations of the patient's medication should be performed by the internist, to minimize the risk of postoperative complications [29-41].

Get an accurate inventory of current medications, including prescription and non-prescription drugs, to manage polypharmacy. When a patient has many physicians, uses different pharmacies, has just been hospitalized, and has comorbid diseases that affect cognitive and physical function, this might be difficult. Despite doctors' best efforts, patient intake and medical

record entries sometimes differ. A “brown bag” evaluation, in which patients bring all prescription and over-the-counter drugs to the appointment, is a crucial “procedure” for primary care clinicians. Pharmacy calls and home and family health nurse prescription evaluations commonly corroborate drug usage. Clinic appointments should include periodic “brown bag” assessments of each medicine to determine efficacy, tolerability and suitability. 63% of potentially preventable adverse medication events were caused by doctors not reacting to drug-related symptoms and 37% by patients not reporting symptoms. “Brown bag” evaluations may prevent adverse medication occurrences by encouraging patient discussion about each medicine [19].

Several computerized programs to help clinicians during the medication review process and identify inappropriate prescriptions and to generate alerts for possible drug-to-drug interactions, such as Screening Tool of Older Persons' Prescriptions (STOPP), Screening Tool to Alert to Right Treatment (START), the Medication Appropriateness Index [42-45]. In a study by Forget *et al.* [45], using a software instrument Med Saver to identify the risk of inappropriate medication in patients that were planned for cardiac surgery, 78% of the study group had alerts for possible medication-associated risks, which imposed either deprescribing or changes in patient's medication.

**Table II**

Pre-operative medication review in elderly. examples of the potential post-operative risk of specific adverse events [46-50]

| Type of possible effect                       | Medication classes  |
|---|---|
| Fall-inducing                                 | Antihypertensive agents<br>Diuretics<br>B blockers<br>Sedatives and hypnotics<br>Neuroleptics and antipsychotics<br>Antidepressants<br>Benzodiazepines<br>Nonsteroidal anti-inflammatory drugs  |
| Delirium, Postoperative cognitive dysfunction | Anti-cholinergic<br>Antidepressants<br>Anti-convulsivants (valproic acid, phenytoin, carbamazepine)<br>Antihistamines<br>H2-blockers (famotidine, ranitidine, cimetidine)<br>Steroids<br>Non-steroidal anti-inflammatory medication<br>Digoxin<br>Opioids<br>Sedative hipnotics (benzodiazepines, barbiturates) |
| Postoperative gastrointestinal hemorrhages    | Anticoagulation medication<br>Antiplatelet medications<br>Aspirin<br>Steroids<br>Complex antithrombotic therapy<br>Non-steroidal anti-inflammatory medication   |

The alerts ranged from high (should be reconsidered right away and stopped as soon as possible) to intermediate (there is a potential risk, deprescribing should be taken into account), and low, advising for stopping mostly because of a lack of evidence for effectiveness [45]. Based on these findings, the authors support the idea that the medication review for elective surgery should be performed in an outpatient facility and should be based on a comprehensive discussion between the anesthetist/internist and the patient [45]. On this basis, an update of the patient's prescription and if necessary deprescribing could be safely initiated.

*Oral surgery and polypharmacy in the elderly*

In our research, we found there is a bi-dimensional interrelation between polypharmacy and oral surgery in geriatric patients. Several studies revealed that

polypharmacy was associated with poor oral health status [51-53]. This association might be due to adverse drug reactions or interactions among multiple medications. The most frequent encounter is dry mouth as a result of anticholinergic medication. Hyposalivation impacts oral health by multiple mechanisms, including microbial changes that led to caries, periodontitis, loss of teeth, impaired masticatory function, and a higher risk of aspiration pneumonia among elderly patients [52, 53].

On the other hand, dental specialists should be aware that in most cases, the elderly are taking multiple medications, and a careful anamnesis must be performed before any treatment. Anti-platelet and anticoagulation medication should be evaluated for the potential hemorrhagic risk during surgical maneuvers, but other

medications may also be of interest due to drug-to-drug reactions when antibiotics or anti-inflammatories are prescribed [54, 55].

## Conclusions

Polypharmacy in the elderly is often encountered and, in most cases, it is a necessary condition due to the associated comorbidities. However, many factors lead to duplications or unnecessary medications, that could generate prolonged hospital stays, and increased perioperative morbidity and mortality. Careful medication review in a multidisciplinary approach may significantly improve surgical outcomes.

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## Conflict of interest

The authors declare no conflict of interest.

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