

Review Article

AGEING EFFECTS ON PHARMACOLOGICAL THERAPY

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Abstract

The ageing process involves several functional and structural changes, an increased vulnerability to stressors and a variable degree of disability. Providing health care for this age group aims to maintain its functional independence, to prevent disabilities and, first of all, demands the investigation of pathological conditions, possibly associated with high morbidity, also known as the geriatric syndromes. They can contribute to an inappropriate use of medication associated with side effects or drug interactions, polypharmacy, underuse of necessary treatments, lack of monitoring or reduced adherence to treatment. On the other hand, these risks could be managed, by considering the specific geriatric features when deciding the therapeutic approach.

Keywords: elderly, geriatric syndromes, inappropriate medication use

Rezumat

Procesul de îmbătrânire presupune diverse modificări structurale și funcționale, creșterea vulnerabilității față de acțiunea factorilor de stress și un grad variabil de dizabilitate. Scopul asistenței de sănătate a vârstnicului vizează menținerea independenței funcționale și prevenirea deficiențelor, ceea ce presupune în primul rând, controlul unor aspecte patologice asociate cu morbiditate crescută, supranumite în literatură sindroame geriatrice. Acestea pot contribui la o farmacoterapie necorespunzătoare, care include prescrierea unor medicamente cu risc crescut de reacții adverse sau de interacțiuni medicament-boală, polimedicatie, subutilizarea medicamentelor necesare, absența monitorizării terapiei sau aderența redusă la tratament. Totodată, problemele de terapie medicamentoasă ale vârstnicului, ar putea fi gestionate, prin luarea în considerare a particularităților geriatrice în cadrul demersurilor de individualizare a terapiei.

Cuvinte-cheie: vârstnic, sindroame geriatrice, terapie inadecvată

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Introduction

The ageing process is the result of several anatomical and functional changes, which disrupt the body's regulatory mechanisms, make more difficult to attain the homeostatic state and increase its vulnerability during stressful situations [1]. The World Health Organization established the threshold of 65 years old for defining the elderly, but the amazing individual variability, with significant differences regarding the degree of disability, and also the absence of a biological marker for senescence, allow for a more complex approach of this growing population [2, 3].

It is widely accepted that older patients either hospitalised, living in the nursing homes or in the community, are frequently exposed to medications side effects; 27.6% of their total could be prevented, 42.2% of the fatal ones could be prevented and the majority take place during the prescribing and the monitoring phase of the medication use process, with 20% of them being the consequence of patients non-adherence [4].

When choosing the best therapeutic option for an elderly patient, it is important to consider the physiologic changes and the most common disease states that can modify the individual response to medications, among which, there are several confirmed examples, frequently associated with inappropriate use. The purpose of this paper is to make a short presentation of the complex relationship between pharmacological therapy and ageing process consequences.

Physiologic changes that influence the elderly response to medications

The age-related structural and functional changes can modify the response to therapy and the absence of controlled studies including old and especially very old (over 80 years old) or disabled patients make more difficult the choice of an appropriate treatment for this population.

At the absorption level, there is a decrease in the pepsin and gastric acid secretion (40% of the elderly have hypochlorhidria), with a slowed gastric emptying and intestinal transit time, and a reduced blood flow at this level. The pH changes can reduce the absorption for iron supplements, ketoconazole or itraconazole or can enhance the disaggregation of the enteric coated tablets. Skin dryness causes delayed transcutaneous absorption for fentanyl, testosterone or estradiol [2, 5].

25-30% of the total body water and muscle mass is reduced in the elderly, with a similar scale increase of the total body fat, which allow for an extension of the volume of distribution for the lipophilic medications (diazepam or systemic lipophilic anaesthetics), increasing their half-life and their toxicity. The drug-efflux activity of the P-glycoprotein localised at the haemato-encephalic barrier level and the concentrations of the plasmatic proteins involved in medication transport are reduced, which can increase the concentration of the free and pharmacological active fraction of the administered medications [2, 6].

The liver's volume and vascularisation are significantly decreased in the elderly [5, 7], increasing the bioavailability of risperidone, diazepam, alprazolam, propranolol, simvastatine, amitriptyline, fluoxetine, sertraline or carbamazepine [1, 2]. Some of the CYP450 isoenzymes (1A2, 2C9, 2C19, 2D6, 2E1, 3A3 /4) have a diminished activity, while the function of the enzymes involved in phase II metabolic reactions is preserved [7]. The doses of oral anticoagulants, required to attain a therapeutic INR are usually lower than those needed for the adult population, as a consequence of the reduced hepatic synthesis of coagulation factors [2].

Beginning with the age of 40, the renal function progressively decreases, irrespectively of the presence of pathologies which could impair it [8], but on the other hand, these changes are not considered mandatory, as almost a third of the elderly maintain a normal renal function [5, 6]. The process of estimation of the glomerular filtration rate using the creatinine plasmatic level, needs to take into consideration the reduced muscular mass of the elderly with the subsequent diminished creatinine production [1, 5, 8]. The Cockcroft-Gault or the Modification of Diet in Renal Disease (MDRD) formulas can be used for estimating the renal functioning of the elderly, although each one has limitations in its applicability to these patients [2, 6, 9, 10]. However, a significant number of old persons, especially women, have an estimated creatinine clearance which could erroneously be interpreted as a moderate stage of chronic kidney disease, if other signs of renal impairment are not carefully investigated [8, 9]. It becomes important to regularly monitor the renal function of the elderly which could allow for a prompt intervention to prevent the morbidity associated with renal failure and also to adjust the dose of drugs eliminated through the renal route [9, 11]. Other modifications at the renal level allow for difficulties in adaptation to sudden changes of the electrolytes and water balance, favouring hyponatremia, hyperkalemia and dehydration, all of which could also accentuate certain medications (diuretics, medications influencing the renin-angiotensin system) side effects [2].

The variable cellular loss, reduced signal transmission and changes in the balance of neuromediators concentrations, increase the time necessary to learn new information or to make decisions, favour the manifestations of Alzheimer and Parkinson disease or change the sleeping patterns [5]. They also explain the increased permeability of the haemato-encephalic barrier associated with dementia and the pronounced sensitivity to the benzodiazepines, opioids, antiepileptics or anticholinergic medication side effects [2]. Acute stressful events (infections, dehydration, overdose or interactions with medications influencing the central nervous system function) are often associated with changes of the mental status including delirium [5].

Changes in the baroreceptors responsiveness and reduced arterial wall elasticity favour the orthostatic hypotension [5, 6] and also an increased incidence of systolic hypertension [1]; peripheral nervous system transformations allow for an increased risk for QT interval prolongation and a reduced effort capacity [12]. This way, the orthostatic hypotension or the arrhythmias associated with tricyclic antidepressants, antipsychotics, diuretics or angiotensin converting enzyme inhibitors become probable side effects in this population.

The geriatric syndromes

The term of “*geriatric syndromes*” refers to some of the most frequent health conditions presented by the elderly patients. They are associated with multiple risk factors including older age, baseline cognitive and functional impairment or reduced mobility. Their presence can promote further morbidity, disability, hospitalizations and death, by increasing the vulnerability to environmental changes and by inducing a reduced quality of life [13]. Frequent examples include frailty, cognitive function decline (including delirium and dementia), falls, urinary incontinence, malnutrition, sleep disturbances or pain.

The geriatric syndrome of frailty is defined as a state of increased vulnerability to stressors (present in everyday life or acute ones, as sudden disease, trauma or hospitalizations) and reduced functional reserve, which impair the individual's ability to cope [14, 15]. 7% of those over 65 years old and 30% of those over 80 years old are frail or, depending on the definition used, its incidence could be from 33 to 88% of the elderly population [16, 17]. It is important to note that the changes that determine frailty may not manifest as an overt disease state, easily recognizable and that its aetiology is multifactorial (genetic, biological, physical, psychological, social and environmental) [18]. The criteria and methods which could be used to evaluate the frailty status of an individual are still debated: phenotypic criteria based on identifying compromised energetics include low grip strength, low energy, slowed walking speed, low physical activity and unintentional weight loss. Another approach is to count the number of deficits presented by the individual patient (disability, diseases, physical and cognitive impairments, psychosocial risk factors, and geriatric syndromes) and to establish the frailty index [15, 18]. Diseases that can be associated with frailty are heart failure, myocardial infarction, rheumatoid arthritis, peripheral vascular diseases, chronic obstructive pulmonary disease, diabetes, iron deficiency, thyroid disorders, pain or sarcopenia, although this association is not mandatory and depends on the degree of control of the therapeutic objectives [17, 18]. At a molecular level, frailty is caused by a complex interaction of impaired hormonal, immunologic, oxidative stress defence mechanisms or autonomic nervous system pathways [14]. It is a dynamic and sometimes a reversible process, as almost 25% of the elderly presenting with a new disability can have a complete recovery [16].

The ageing process is associated with a gradual and unintentional reduction of the body mass index (BMI), represented especially by loss of muscular tissue, i.e. sarcopenia (even 3kg per decade) and caused by proteic malnutrition [19]. Its prevalence can be as high as 85% for the elderly living in nursing homes or 15% for those living in the community, and can be identified for 50% of the 85 years old persons. Comorbidities, psychological and social factors can be associated with malnutrition: depression (the most frequent cause for the institutionalized elderly), dysphagia, cancer, heart failure, infection, alcoholism, dementia and reduced cognitive status (reduced ability to prepare meals), social isolation and bereavement, anorexia, poverty, dental problems, nausea [19-21]. Closely related to the elderly weight loss is the concept of age-related anorexia, caused by peripheral and central changes that modify the satiety threshold, the taste and smell

perceptions, with subsequent reduced interest for food [14, 19]. Screening for malnutrition in the elderly involves regular calculation of the BMI (results under 22kg/m² or a 7, 5% weight loss in the last 3 months suggesting an increased risk for hospitalization) or the use of validated malnutrition assessment tools as the Mini Nutritional Assessment. The frequency of the assessment varies, from once a year for the community dwelling elderly, to once every 3 months for those in the nursing homes or weekly for those with prolonged hospitalizations [21, 22]. Until now, the available pharmacological interventions (proteic supplementation, cyproheptadine, dexamethasone, cannabinoids) have not been associated with significant or persistent weight gain, but on the other hand it is important to regularly review the medication possibly favouring malnutrition [19].

Falls as a geriatric syndrome exclude those that are a consequence of violence, loss of consciousness, secondary to stroke or epilepsy [23-25]. Occasional or isolated falls occur most often because of extrinsic factors or environmental hazards (inadequate lighting, uneven surfaces, raised threshold or slippery surfaces) which cause 33-50% of falls and represent modifiable risk factors [26]. Recurrent falls (2 or more falls in the last 6 months) are related to altered visual or vestibular functions, reduced cognitive performance and musculoskeletal function, orthostatic hypotension, nocturia, dehydration, cardiopulmonary disorders, peripheral neuropathy, delirium and parkinsonism, polypharmacy, medications with sedative or hypotensive side-effects [19, 23, 26]. Approximately 30% of community dwelling older adults have at least one fall per year, women and the elderly living in the nursing homes being the most frequent fallers. Fractures (90% are the result of falls), physical impairment, increased risk for repeated falls, depression, anxiety, reduced quality of life or death are some of the possible consequences [20, 25]. Individualized, multidisciplinary interventions, vitamin D and calcium supplementation, replacing pharmacological treatments associated with increased fall risk are some of the possible interventions intended to prevent falls [25, 27].

Pain is a prevalent symptom in the elderly population, with 35.7% of those aged 60-69 years and 56.1% of those 90-99 years experiencing pain every day. For the elderly in the nursing homes or in the long-term facilities, 49-83% of the individuals report pain, but the analgesic use is 27-44%. Osteoarthritis of at least one joint, back pain, fracture associated pain, neuropathic pain and cancer pain are the most frequently encountered types [28, 29]. Pain of the older patients is considered under-reported, under-treated, and still perceived as a normal characteristic of the ageing process. Old people have a higher pain threshold, a lower pain tolerance, impaired pain modulating mechanisms are more inclined to central sensitisation [30]. The lack of pain control reduces quality of life, mobility, quality and duration of sleep, causes functional dependence for activities of daily living [28, 31]. Therapeutic choices need to consider potential side effects that would cause further impairment, as the anticholinergic and sedative effects of opioids or cardiovascular and renal effects of non-steroidal anti-inflammatory drugs. The assessment of pain requires special considerations in patients with dementia, when validated instruments assessing changes in behaviour are used [30, 31].

Drug related problems specific to the elderly population

The elderly population is at increased risk for drug related problems, which represent 30% of the reported reasons for its admission to the hospital, being more frequently associated with disability and death [32].

Inappropriate medication use in the elderly population refers to the use of medications favouring an increased risk for side effects or interactions between therapy and concomitant comorbidities, polypharmacy, underuse of necessary medications, lack of monitoring, reduced patient adherence to the recommended therapies. To prevent the unwanted consequences related to the inappropriate medication use in the elderly, several standardized and validated instruments have been conceived and proposed for use in everyday geriatric practice. The examples refer to explicit (criterion based: Beers, McLeod, IPET, Laroche, START and STOPP criteria, ACOVE, PRISCUS) and implicit criteria (judgement based: MAI criteria), some of them suggesting alternatives or management options for the potential problems identified (table I) [33-42].

Table no I. Published criteria of inappropriate medication use in the elderly.

Criteria / references	Explicit or implicit?	Country / year	Does it evaluate medication misuse*?	Does it evaluate medication underuse?	Does it offer solutions?
Beers et al. ³⁴	Explicit	USA/ 2003	yes	no	no
McLeod et al. ³⁵	Explicit	Canada /1997	yes	no	yes
^a IPET ⁴⁰	Explicit	Canada /2000	yes	no	no
Laroche et al. ⁴¹	Explicit	France / 2008	yes	no	yes
^b START ³⁶	Explicit	Ireland / 2007	no	yes	yes (implicit)
^c STOPP ³⁶	Explicit	Ireland / 2008	yes	no	sometimes
^d ACOVE ³⁷	Explicit	USA / 2004	yes	yes	yes (implicit)
^e PRISCUS ³⁹	Explicit	Germany / 2010	yes	no	yes
^f MAI ⁴²	Implicit	USA / 1992	yes	no	no

* misuse relates to the use of medications frequently associated with side-effects or disease interactions when used in the elderly.

^a Improved Prescribing in the Elderly Tool

^b Screening Tool to Alert doctors to Right i.e. appropriate Treatments

^c Screening Tool of Older People's potentially Inappropriate Prescriptions

^d Assessing Care of Vulnerable Elders

^e Latin term for "old and venerable"

^f Medication Appropriateness Index

These lists have in common several types of geriatric drug related problems:

- anticholinergic medications (as a therapeutic effect or as a side effect) like first generation antihistaminics, tricyclic antidepressants, anticholinergic antispasmodics, some antipsychotics. They can cause cardiac effects (tachycardia, orthostatic hypotension), central nervous system effects (sedation, hallucination, agitation, delirium, confusion), urinary retention, mucosal dryness, thermoregulation abnormalities, increased ocular pressure, all of which suggest the suitability of safer alternatives if available. However, more recent literature states that tricyclic antidepressants could be used in the elderly in a reduced dosage, for the treatment of neuropathic pain,
- sedative medications, which can favour falls, or which can induce confusion states, in the elderly demented patients: benzodiazepines (especially long half-life molecules), barbiturics (except anticonvulsant use), tricyclic antidepressants, first generation antipsychotics, opioids as first choice analgesics,
- non steroidal anti-inflammatory drugs, frequently used for the management of osteoarthritis pain (10-20% of the old population is using or just completed such a treatment). They are not a contraindication in the elderly, but a short period use with the minimum doses would have a greater cardiovascular, digestive or renal safety,
- for digoxine, a daily dose of 0, 125mg is recommended in order to avoid severe cardiovascular side-effects in the presence of renal disease [33-44].

Underuse of evidence-based therapies, proved to reduce morbidity and mortality of several chronic diseases, is a frequent drug related problem among the older patients, especially among those older than 85 years old [38]. For example, 64 to 100% of the older patients have in average, one indication without treatment, irrespective of the total number of medications received, with underuse being more frequent than misuse, among those taking daily, more than 8 medications [45]. Half of the medications underused would be necessary for the management of cardiovascular diseases [46]. Common examples of underused are: statins for the primary prevention of myocardial infarction or for the secondary prevention of stroke [38], oral anticoagulants for stroke prevention in atrial fibrillation [47, 48], angiotensin converting enzyme inhibitors for the management of heart failure or hypertension associated with diabetes [37, 38, 49], beta-blockers and aspirin after myocardial infarction [37, 38], aspirin for those with diabetes or angina [37, 38], calcium in osteoporosis [37, 38, 49], acetaminophen as first choice therapy in osteoarthritis [49].

57% of the older women in the United States are taking more than 5 medications daily, 12% are receiving more than 10. In Europe, 51% of the elderly are taking more than 6 medications daily. Prescribed medications can be used concomitantly with over the counter medications or with herbal products, increasing the number of pharmacologically active administered molecules [45]. Therefore, polypharmacy is another one of the frequently encountered drug related problems of the elderly patients, as it is associated with increased morbidity and mortality. For example, prescriptions analysis containing 5 or more medications showed that 21% presented therapeutic duplications and 12%

contained interacting medications [50]. It lacks a clear definition and it can be considered a geriatric syndrome. It can be described as the administration of four or more medications, as the use of multiple unnecessary medications or within the same chemical class, as the administration of more medications that are clinically indicated [51, 52]. On the other hand, polypharmacy seems inevitable considering the multiple pathologies of the elderly and the evidence based prescribing which requires the use of multiple prophylactic therapies.

Lack of therapy monitoring is either the first, either the second cause for drug related problems in the elderly (next to the prescribing ones), according to studies done in nursing homes or in community dwelling elderly [53-55]. It becomes especially important for medications with a low therapeutic index or in the case of patients with polypharmacy and it can involve laboratory tests, clinical examination or regular medication review [56].

Non-adherence is the third most frequent type of drug related problem in the non-institutionalized elderly, who administer only 50% of the recommended therapies [55, 57]. Predictors for non-adherence which could be influenced through targeted interventions, are their health status (severe conditions or impaired cognitive function), the degree of social isolation, of functional independence and mobility or the living conditions. On the other hand, a complex medication regimen, the lack of information regarding treatment or symptomatic side effects increase the risk for non-adherence [58].

Conclusions

Drug therapy remains for the moment, the most important type of intervention meant to prevent disability and mortality among the elderly, although it is essential to acknowledge the subtle differences from the adult population, from which most of the drug use information is obtained, and also the differences inside the elderly subgroups. There is a continuous search of a mathematical model which could give an estimate of the individual degree of disability with the subsequent possibility of drug therapy adjustment. For the moment, the best approach would probably be an individualized and multidisciplinary one, with frequent reassessment of the benefit to risk ratio.

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