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REVIEW

Medication use in older patients and age-blind approach: narrative literature review (insufficient evidence on the efficacy and safety of drugs in older age, frequent use of PIMs and polypharmacy, and underuse of highly beneficial nonpharmacological strategies)

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Abstract

Introduction The importance of rational drug therapy is increasing with the aging of the population. Since one of the main reasons for inappropriate drug prescribing is also the "age-blind" approach, which results in ageist practices, this narrative literature review focuses on the description of the main barriers related to insufficient individualization of drug regimens associated with such age-blind approaches.

Methodology A narrative literature review using the PubMed, WoS, Embase, and Scopus databases was conducted by the EU COST Action IS1402. Experts in different scientific fields from six countries (the Czech Republic, Spain, Portugal, Hungary, Serbia, and Turkey) worked in four specific areas: (1) underrepresentation of older adults in clinical trials and clinical and ethical consequences; (2) insufficient consideration of age-related changes and geriatric frailty in the evaluation of the therapeutic value of drugs; (3) frequent prescribing of potentially inappropriate medications (PIMs); and (4) frequent underuse of highly beneficial nonpharmacological strategies (e.g., exercise).

Results Older patients are underrepresented in clinical trials. Therefore, rigorous observational geriatric research is needed in order to obtain evidence on the real efficacy and safety of frequently used drugs, and e.g. developed geriatric scales and frailty indexes for claims databases should help to stimulate such research. The use of PIMs, unfortunately, is still highly prevalent in Europe: 22.6% in community-dwelling older patients and 49.0% in institutionalized older adults. Specific tests to detect the majority of age-related pharmacological changes are usually not available in everyday clinical practice, which limits the estimation of drug risks and possibilities to individualize drug therapy in geriatric patients before drug prescription. Moreover, the role of some nonpharmacological strategies is highly underestimated in older adults in contrast to frequent use of polypharmacy. Among nonpharmacological strategies, particularly physical exercise was highly effective in reducing functional decline, frailty, and the risk of falls in the majority of clinical studies.

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Conclusion Several regulatory and clinical barriers contribute to insufficient knowledge on the therapeutic value of drugs in older patients, age-blind approach, and inappropriate prescribing. New clinical and observational research is needed, including data on comprehensive geriatric assessment and frailty, to document the real efficacy and safety of frequently used medications.

Keywords Drug prescribing · Older patients · Ageism · Frailty · Age-related changes · Potentially inappropriate medications · Polypharmacy · Observational studies · Randomized controlled trials

Introduction

The world population is aging and advances in health technologies and science contribute to increasing longevity and prolonging of life expectancy in older patients. According to the World Health Organization (WHO), more than 20% of the world population will be over 60 years old and, particularly, the prevalence of very old patients (80+ years) will significantly increase by the year 2050 [1].

Unfortunately, drug-related problems in older patients are very frequent (up to 20–30% of hospitalizations) and often contribute to higher prevalence of frailty, disability, morbidity, mortality, and increased healthcare cost [2–4]. The European project PREDICT (Increasing the Participation of the Elderly in Clinical Trials, 7th Framework programme of the European Commission, 2009–2013) confirmed that there is a lack of specific evidence on the efficacy and safety of frequently used medications from randomized controlled trials (RCTs) for older patients, which represent the main medication users [5]. This problem of "evidence-biased geriatric medicine" creates a substantial barrier to appropriate drug prescribing in older adults. In 2000, Cohen, in his paper, confirmed that standard dosing for many frequently used medications recommended by SPCs (Summary Product Characteristics) should be adjusted to safer and equally effective low-dose drug regimens in the majority of older patients [6].

While, until today, ageism in the healthcare society was understood as systematic stereotyping, unfair treatment of older people or discrimination against older persons or certain age groups based on prejudices related to age itself [7], recent problems with ageism in the area of drug prescribing (conscious or unconscious) relates mainly to the "age-blind" approach [8]. This includes insufficient individualization of drug regimens with respect to age-related physiological, pathological, and pharmacological changes and with respect to the specific needs of geriatric patients. This also includes frequent prescribing of potentially inappropriate medications (PIMs) in higher age, risky polypharmacy, unnecessary exposure to medications having doubtful efficacy (e.g., pentoxifylline, low-dose piracetam), etc. [8]. Particularly, very old, frail, and disabled patients are the most disadvantaged group.

This review article focuses mainly on four particular areas of inappropriate medication use in older patients, namely:

Area 1. Underrepresentation of older adults in clinical trials, clinical and ethical consequences, and importance of new evidence from observational research,
Area 2. Insufficient consideration of the impact of age-related changes and geriatric frailty on the therapeutic value of drugs in daily clinical practice,
Area 3. Frequent use of high-risk medications in older patients in different settings of care, and
Area 4. Frequent underuse of some beneficial nonpharmacological strategies (e.g., physical exercise) in contrast to high prevalence of polypharmacy and PIM use.

In Central and Eastern Europe, a new scientific program EUROAGEISM H2020 project was funded for the period 2017–2021, called the FIP7 programme on "Inappropriate prescribing and availability of medication safety and medication management services in older patients in Europe". The aim of this project is to describe the situation in polypharmacy and inappropriate medication use in older patients in Central and Eastern Europe (the Czech Republic, Estonia, Lithuania, Slovak Republic, Hungary, Serbia, Croatia, and Albania) in comparison to other developed countries (Ireland, Portugal, Belgium, and Turkey) and some developing countries (India and Ethiopia) [9].

Methodology

The content of this review article is based on a narrative literature review conducted with the use of the PubMed, Web of Science, Embase, and Scopus databases in the period from April 2015 to October 2018, during the active works of the WG1b working group "Healthy clinical strategies for healthy ageing" under the EU COST Action IS1402 "Ageism - a multi-national, interdisciplinary perspective" [10]. In our literature review, we focused especially on foreign scientific articles, mostly RCTs, observational studies, and systematic or narrative literature reviews, published in journals with the impact factor or peer review journals since 2000. As "ageism" is not yet recognized by many studies as a specific key word, we also used other key words selective for areas 1–4 (refer to the Introduction and corresponding with the Results subsections). These key words were: ageism, inappropriate prescribing, inappropriate drug use, potentially inappropriate

medications, aged, geriatric patients, older patients, frailty, RCTs, clinical trials, underrepresentation, observational study/studies, age-related changes, negative outcomes, positive impact, nonpharmacological methods, physical activity, and physical exercise. Works on particular areas 1–4 have been summarized by experts from different fields (geriatric clinical pharmacy, pharmacology, social pharmacy, physical therapy, nursing, and pharmacoepidemiology) in cooperation with their local research teams in six countries (Czech Republic, Spain, Portugal, Hungary, Serbia, and Turkey).

Works on literature reviews were summarized by independently working research teams for sections 1–4, reviewed by other experts in the working group (minimum 2) and summarized as pre-final and final versions during face-to-face expert meetings of the EU COST Action IS1402. Cooperating research teams were not asked to record the number of searched and selected articles and sent to the center mainly pre-final and final versions of their contributions. Tables 1, 2, and 3 were summarized also from the identified literature sources.

Results

Underrepresentation of older adults in clinical trials, clinical and ethical consequences of this phenomenon, and importance of new evidence from observational research

It is known that older people respond differently to drug therapies and the risk of adverse drug events (e.g., drug interactions, adverse drug reactions, and other complications) is higher in this population due to age-related changes in pharmacokinetics and pharmacodynamics (for a comprehensive overview of pharmacological changes, see Table 1 [11–13]) and also due to frailty, higher degree of comorbidity, polypharmacy, and other risk factors [2–4, 14]. Up until now, controlled clinical trials have largely focused on the assessment of single treatment strategies or strategies applying maximally 2–3 drugs simultaneously, and mostly on non-geriatric subjects and/or subjects without multiple comorbid conditions. There is evidence of underrecruitment of older patients in clinical trials, including clinical trials testing therapies specifically used for the treatment of disorders of older age [5, 15–17].

Beers and colleagues (2014) from the Medical Center of Utrecht University reviewed the inclusion criteria of clinical trials (Phases II–III) performed on recently marketed medicines and concluded that these studies involved a very low proportion of older adults. Age-related exclusion criteria (comorbidity, concomitant medications, etc.) were used particularly in large clinical trials [15]. Surprisingly, an upper age limit was also applied in Parkinson disease trials, even if Parkinson's disease is predominantly a geriatric disorder [18]. The representation of older adults remained relatively poor also in clinical trials studying treatment strategies for solid tumors and hematologic malignancies [19]. For example, trials in type 2 diabetes mellitus used an arbitrary upper age limit for participants in 65.7% of cases, even if this disorder is prevalent particularly in older age [20].

This underrepresentation of seniors in clinical trials has serious consequences for the safe and effective use of medicines in older patients. The problem has been recognized by the International Council for Harmonization (ICH) guideline ICH E7 in 1993, and amended by the European Medicines Agency (EMA) in 2010 [21], which requires the participation of a desirable proportion of older adults (> 65 years of age) in clinical trials. This guideline states that "it would be usually appropriate to include more than 100 geriatric patients in the Phase 2 and 3 databases and include patients over the entire spectrum of the geriatric patient population" [21]. However, adherence to these guidelines is still insufficient [22] and, considering the heterogeneity of the older population, the requested size of at least 100 patients is still highly underestimated for relevant pharmacoepidemiologic research.

The main reasons for the under-enrollment of older people in clinical trials are the difficulties in recruiting or retaining older patients, particularly those with chronic disorders and several health problems, or ethical problems when investigators and physicians are reluctant to expose older patients (mostly with comorbid illnesses and/or advanced disorders) to experimental, more risky therapies [17, 22]. The enrolment of older adults in clinical trials, and barriers to their participation, has gained interest in recent years; for example, the ROAR program - "Recruiting Older Adults into Research" (the US program) seeks to raise research awareness and engagement among older adults for participation in clinical trials for Alzheimer's disease, and also for other disease conditions [23]. Moreover, the "Interventions on Frailty Working Group" developed recommendations on how to screen, recruit, evaluate, and retain frail older people in clinical trials [24, 25].

Underrepresentation of older adults in RCTs contribute to clinical and ethical dilemmas when prescribing approved "standard dosing/drug therapies" (tested on substantially healthier subjects) to geriatric patients [26]. However, with increasing utilization of e-health records and medication claims data, the role of observational research is becoming crucial in order to obtain appropriate answers on the real-life effectiveness, efficacy, and safety of medications in geriatric patients, as well as on utilization patterns and new signals of drug risks [27, 28]. Observational studies, cohort, case–control, cross-sectional, and outcome studies [29] utilizing different data sources (e.g., supplements to registration RCTs, data from practical clinical trials, patient registries, administrative claims databases, health surveys, and medical records) [30] help to answer these questions using real-world data from real geriatric patients in real conditions [28]. However, the important role of confounders in observational studies must be taken

into consideration, including uncontrolled conditions of medication use by patients [27] (see also Table 1 [27, 31]).

Several examples can be stated from observational studies on geriatric patients of how risks of medicines or their inefficacy can be determined. For example, a recent study with a sample of more than 110,000 older Medicare beneficiaries conducted by Graham and colleagues published in JAMA in 2016 confirmed that the risk of intracranial bleeding and extracranial bleeding, including major gastrointestinal bleeding, was significantly higher after rivaroxaban 20 mg daily compared to dabigatran 150 mg twice daily [32]. Japanese matched-pair analyses confirmed that, most probably, the safest of these new oral anticoagulants (NOACs) when considering the risk of major bleeding and any bleeding and comparative efficacy to warfarin was apixaban 5/2.5 mg BID, while dabigatran 150/110 mg BID and rivaroxaban 15/10 mg QD were associated with significantly fewer events of major bleeding, but not any bleeding compared with warfarin [33].

The observational research and e-health systems open large possibilities to define the real therapeutic value of drugs in clinical practice in different subgroups of older patients in different settings of care with the use of huge study datasets [34]. In Europe nowadays, the main large medical datasets are THIN and CPRD (The Health Improvement Network and Clinical Practice Research Datalink, United Kingdom), the HSD-CSD-LPD database in Italy (Health Search Database-Cegedim-Strategic Data-Longitudinal Patient Database), the IPCI and PHARMO databases in the Netherlands (Integrated Primary Care Information and PHARMO Database Network), the Spanish database for pharmacoepidemiological research in primary care (BIFAP) or Information System for the Development of Primary Care Research (SIDIAP) in Spain, and the Pharmacoepidemiological Research Database (GePaRD) in Germany [34]. Some of these datasets are also linked with other data sources (e.g., socioeconomic data of patients) [27]. However, for future geriatric observational research, of high importance are mainly datasets implementing information on comprehensive geriatric assessment and frailty measures, e.g., geriatric datasets of GIFA (Italian Group for Pharmacoepidemiology) [35], interRAI acute care datasets (University of Brisbane, Queensland, Australia) [36], and interRAI integrated geriatric care datasets in Canada (e.g., CIHI, Canadian Institute for Health Information, Ontario, Canada) [37].

Insufficient consideration of the impact of age-related changes and geriatric frailty on the therapeutic value of drugs in daily clinical practice

It is well known that chronological age (65 years and older) cannot be considered a cut-off point for geriatric age because chronological aging does not correspond with physiological aging. There is an extensive inter-individual heterogeneity among older adults of the same age group in biological age and this, of course, contributes to substantial heterogeneity in therapeutic responses and outcomes among older patients [38]. It is very important to adjust the selection of medications and dosages with respect to biological age and age-related changes in drug pharmacokinetics and pharmacodynamics, of which the most known changes are listed in Table 1 [11–13]. Until now, the highest emphasis has been put on adjustments of dosing in relation to renal and hepatic functions, but, in the future, a more complex approach in drug selection and dosing with respect to all individual pharmacological and physiological changes in geriatric patients is necessary. Even if many age-related changes are known for decades, specific clinical tests enabling their identification are mostly missing in everyday clinical practice. Thus, they cannot be identified in advance and preventive measures are very limited (see Table 2 [11–13]). Because the majority of healthcare professionals care and will care in the future particularly for older patients in different settings of care, knowledge of pharmacological changes accompanying aging and associated drug risks are crucial for all healthcare professionals [39].

Besides age-related pharmacological changes, geriatric frailty further increases the heterogeneity in patients' drug response in the same age cohort [40] and the concept of "frailty" has emerged as another measure of "biological age"

Table 1 Major characteristics of randomized controlled trials and observational studies [27, 31]

Randomized controlled trials	Observational studies
Strong internal validity and poor generalizability (narrow eligibility criteria)	Limited internal validity (confounding and causal inference), but strong external validity and strong generalizability
"Ideal setting" (population with single disease, experienced providers, centers of excellence)	Real-world setting, provide information on "real-world" use and practice, inform clinical practice
Smaller sample	Larger sample
Defined period of time	Longer follow-up
Limited ability to detect rare and delayed adverse drug reactions	Can detect signals about the benefits and risks of drugs, rare and delayed adverse drug reactions, help formulate hypotheses to be tested in subsequent studies

Table 2 Major age-related changes in drug pharmacokinetics and pharmacodynamics in older patients, clinical consequences (examples), and availability of diagnostic tests to identify these age-related changes [11–13]

	Age-related anatomical changes	Age-related functional changes	Clinical consequences for the therapeutic value of drugs in older patients (examples of PIMs)	Diagnostic tests available in daily clinical practice to identify the age-related change
Central nervous system	Neuronal losses in different areas of the brain, about 10–50% (the highest loss of neurones is usually detected in gyrus temporalis without significant impact on functional status). In the seventh decade of life, the weight of the brain is 10% less than in the third decade.	Decreased central dopaminergic (DA) transmission, decreased number of DA neurons in substantial nigra, and decreased capacity of D2-receptor sites and dopamine in the old age. Concentrations of monoaminooxidase (enzyme-degrading DA) are increased.	Higher risk of drug-related pseudoparkinsonism and extrapyramidal side effects after anti-DA drugs (e.g., typical antipsychotics, high doses of atypical antipsychotics, cinnarizine, flunarizine, etc.)	No specific tests available to detect sensitivity to anti-DA drugs in daily clinical practice. Monitoring of short- and long-term drug response is necessary.
	Decrease in brain perfusion is often associated with pathological changes (mainly cardiovascular disorders). Less robust is the hematoencephalic barrier and central side effects of drugs are more pronounced (e.g., drug-related deliria in users of polypharmacy).	Decrease in peripheral and central cholinergic activity (so-called "age-related cholinergic deficit"), decrease in the number of cholinergic neurons, lower activity of acetylcholine, and lower production of acetylcholine transferase (enzyme responsible for the synthesis of acetylcholine).	Anticholinergic (ACH) drugs/drug combinations frequently cause central ACH side effects (cognitive impairment, deliria, depression) and/or peripheral ACH side effects (dry mouth, tachycardias, constipation, retention of urine, worsening of narrow-angle glaucoma, etc.). ACH medications must be indicated, if possible, at the lowest dose for the shortest period of treatment. Non-ACH drug alternatives should be preferred.	No specific tests available to detect sensitivity to ACH drugs in daily clinical practice. Monitoring of short- and long-term drug response is necessary.
		Increased response to central sedative effects of drugs. In the eighth decade of life, twice as high sedative response compared to middle age (third decade of life) was documented.	Risk of sedation after application of sedative drugs (sedative antidepressants, benzodiazepines, hypnotics, sedative antihistamines, typical antipsychotics, etc.). If needed, low-dose (half-dose) regimens of these medications should be applied.	No specific tests available to detect sensitivity to sedative drugs in daily clinical practice. Monitoring of short- and long-term drug response is necessary.
		Decreased response of central adrenoreceptor sites to sympathomimetics, increased activity of monoaminooxidase (enzyme-degrading catecholamines).	Risk of drug-related depression after application of centrally acting sympatholytic drugs (e.g., higher doses of metoprolol, other highly lipophilic beta-blockers, methyldopa, etc.).	No specific tests available to detect sensitivity to sympatholytic drugs in daily clinical practice. Monitoring of short- and long-term drug response is necessary.
Cardiovascular system	Increased accumulation of fat, collagen, elastin, and lipofuscin in myocardial tissue; electrical, mechanical, and biometrical parameters of the heart are changed; aterosclerotic processes in the vessel wall are increased and the elasticity of vessels is decreased.	In some seniors, left ventricular ejection fraction (EF) is decreased. In healthy older individuals (due to compensatory mechanisms), EF may stay unchanged even by the age of 80 years. Minute heart output is usually decreased because of pathological changes (e.g., heart failure). The vessel resistence increases, as well as	Risk of orthostatic hypotension and falls, with subsequent risk of injuries, fractures, and immobilization can be substantially increased by negative chronotropic drugs, sedative and vasodilating drugs, diuretics, etc. Drugs having negative chronotropic effect (beta-blockers, verapamil, some fluorochinolones, etc.)	Blood pressure and pulse monitoring (including measures after verticalization to estimate the risk of orthostasis). Other specific cardiological tests (e.g., decrease in EF, atherosclerotic changes of coronary vessels, etc).

Table 2 (continued)

	Age-related anatomical changes	Age-related functional changes	Clinical consequences for the therapeutic value of drugs in older patients (examples of PIMs)	Diagnostic tests available in daily clinical practice to identify the age-related change
		diastolic blood pressure. The sensitivity of baroreceptor sites is significantly decreased (in both normotensive and hypotensive patients). This contributes to the higher risk and prevalence of orthostatic hypotension in older age (usually together with other aggravating factors, e.g., dehydration, lower renal concentration ability, lower ability of vessels to vasoconstriction, etc.).	may also increase the risk of drug-related sick sinus syndrome, severe bradycardias, and syncopes.	
		Changes in the balance of local factors having pro-constrictive/pro--aggregative effect and vasodilating/antiplatelet effect in vessel walls. Higher risk of vasoconstriction and thrombosis in older patients.	Some vasodilating agents (e.g., ergot alkaloids) can paradoxically cause vasoconstriction of changed coronary vessels. Therapeutic response to direct vasodilating agents is decreased (e.g., to pentoxifylline, nootropic agents, etc.). If they are recommended, then usually for short term and in higher, effective doses.	No specific tests available for daily clinical practice to detect responsiveness of vessel walls to drug treatment.
Gastrointestinal system	Atrophy of gastrointestinal tract and decreased permeability of intestinal barrier (that mostly does not significantly influence drug absorption).	Decrease in intestinal active transport.	Decrease in absorption of vitamin D and, partially, Ca2+, Fe2+, and other ions.	No specific tests available for daily clinical practice. Monitoring of lower plasmatic levels of Fe, vitamin D, Ca, etc. may be an indirect test of some deficits (however, decreased active intestinal transport can be only one of the possible causes of such deficits).
		Decreased production of acetylcholine, cholecystokinin, and other prokinetic gastrointestinal hormones, slowed gastric emptying and intestinal motility, susceptibility to constipation.	Prolonged onset of several drugs (mainly acidic drugs, e.g., NSAIDs, sulfonamides, sulfonylureas, and others), ACH medications may worsen or aggravate constipation.	No specific tests available for daily clinical practice (consideration of digestive problems, present constipation).
		Decreased intestinal blood flow.	Decreased absorption of drugs dependent on the magnitude of intestinal blood flow (e.g., furosemide).	No specific tests available for daily clinical practice.
		Decreased gastric acid secretion and increased levels of gastrin with increased risk of gastritis and gastric ulcer. In the group of 60-year-old persons, basal achlorhydria was detected in 43% of men and 36% of women.	Higher age is considered to be a separate risk factor of gastropathies. Preventive therapy (PPI) is indicated when at least one more gastrotoxic factor is present, e.g., use of gastrotoxic drugs (NSAIDs, methotrexate, and	No specific tests available for daily clinical practice, only specific invasive gastroenterological tests (e.g., endoscopy).

Table 2 (continued)

	Age-related anatomical changes	Age-related functional changes	Clinical consequences for the therapeutic value of drugs in older patients (examples of PIMs)	Diagnostic tests available in daily clinical practice to identify the age-related change
			other antirheumatic drugs, corticosteroids, etc.).	
Urogenital tract and renal functions	Glomerular atrophy, reduced number of glomeruli, tubular and vascular changes; men: prone to development of benign prostatic hypertrophia; women: pelvic relaxation, higher risk of urine incontinence and urine infections.	Progressive decline in renal functions (about 7%/decade) is documented since the fifth decade of life. By the age of 70 years, renal function has reduced by approximately 40% compared to younger subjects at the age of 30 years. Glomerular filtration rate decreases physiologically by 1 mL/min/ year (even in the absence of cardiovascular, renal, and acute disorders). Plasmatic concentration of albumin stays relatively stable (with respect to decreased proportion of muscle tissue and lower production of creatinine).	Higher risk of side effects and clinically significant drug interactions when administering drugs that are highly eliminated renally (> 80%, e.g., dabigatran).	Renal function tests available (only estimations), e.g., CKD-epi, MDRD, and Cockroft–Gault formulas.
		Ability to concentrate urine is decreased, as well as Na+ retention (probably due to lower excretion of renin).	Higher risk of drug-related hyponatremia or SIADH (syndrome of impaired secretion of antidiuretic hormone) when administering risky drugs (e.g., selective serotonin reuptake inhibitors [SSRIs], mirtazapine, carbamazepine, etc.). Higher risk of hyperkalemia.	Plasma ion concentrations (natremia, kalemia). Antidiuretic hormone (ADH) plasmatic concentrations.
		Higher concentration of Na+ in renal tubules, higher excretion of water.	Decease in total body water by 15–20% when compared to younger patients (aged 20–30 years), higher risk of dehydration. Diuretics should not be administered as monotherapy in patients without volume-dependent edemas, as they can cause or worsen urinary incontinence (mainly loop diuretic)/	Plasma ion concentrations (Na+, Cl−, osmotic blood pressure), daily balance of water (daily intake of water and excretion of urine).
		Kidneys have lower ability to sustain blood volume and proportion of body fluids. There is a higher risk of hemodynamic instability in older patients. For sufficient blood flow in kidneys and for ensuring intraglomerular filtration pressure, the autoregulatory activity of renal prostaglandins are important.	Drugs decreasing intraglomerular filtration pressure (ACE-Is, ARBs, NSAIDs, direct vasodilators, e.g., urapidil, etc.) may lead (particularly in combinations) to hemodynamic instability and renal insufficiency. ACE-Is and ARBs decrease intraglomerular filtration pressure, NSAIDs cause vasoconstriction of vas efferens. In sensitive seniors, their combination may	No specific tests available for daily clinical practice to measure renal blood flow.

Table 2 (continued)

	Age-related anatomical changes	Age-related functional changes	Clinical consequences for the therapeutic value of drugs in older patients (examples of PIMs)	Diagnostic tests available in daily clinical practice to identify the age-related change
			aggravate drug-related renal failure.	
Hepatic functions	Hepatic atrophy begins in the 5th–6th decades of life, but does not significantly influence the hepatic functions. The decreased hepatic perfusion and lower metabolic capacity of some hepatic enzymes have the highest impact on drug efficacy and safety in older patients.	Decreased hepatic blood flow (caused by decreased minute heart output), significant decrease in the first-pass effect of many drugs (by 25–40%).	Drugs having the high first-pass effect (e.g., verapamil, metoprolol, morphine, etc.) may substantially increase plasmatic concentrations. Their first-pass inactivation is significantly decreased (by average in 20–40%). Drugs eliminated mostly by demethylation are considered inappropriate in older patients.	No specific tests available for daily clinical practice; decrease in EF may help to estimate possible risk.
		Decreased activity of demethylation enzymes.	Drugs eliminated by demethylation (imipramine, amitriptyline, diazepam, etc.) significantly prolongs elimination half-life with significant increase of the risk of cumulation and toxicity.	No specific tests available for daily clinical practice.
		Mild decrease in activity of CYP3A4 in older women (most probably due to decrease in estrogen production).	More than 60% of commonly prescribed drugs are eliminated by CYP3A4 isoenzymes. Adverse drug events and drug interactions are more significant in older patients than in younger adults.	No specific tests available for daily clinical practice (awareness necessary in drugs significantly eliminated by CYP3A4 enzymes).
		Decreased synthesis of coagulation factors.	Higher risk of bleeding when anticoagulation therapy is indicated, risky drug combinations (low-dose aspirin, other NSAIDs, anticoagulation therapy, etc.).	Thorough consideration of all factors and estimated risk/benefit of the treatment. Anticoagulation tests (e.g., INR, anti-Xa assay, APPT test).
Endocrine system	Decreased production of many endocrine glands (since the fifth decade of life).	Decreased production of sexual hormones (in women, rapid decrease in menopause; in men, stable decrease with aging).	Higher sensitivity to drugs antagonizing receptors for sexual hormones, risk of gynecomastia (e.g., digoxin, spironolactone).	No specific tests available for daily clinical practice.
		Decreased secretion of pancreatic hormones (mainly after repeated stimulation by food).	Impaired digestion, decreased tolerance to fatty foods and sweet foods.	No specific tests used in daily clinical practice.
		Decreased production of thyroid hormones.	Slowed metabolism, higher risk of hypothyroidism (e.g., after application of thyrostatic agents).	Thyroid gland function tests.
		Decreased secretion of adrenocortical hormones, decreased secretion of insulin in some patients, and/or decreased glucose tolerance.	Higher risk of diabetes mellitus (DM), higher risk of DM after diabetogenic drugs (e.g., corticosteroids, thiazide diuretics, etc.), impaired glucose tolerance.	Tests of DM or impaired glucose tolerance.
Immune system	Involutional decline in the function of thymus (crucial	Decreased function of T-lymphocytes and decreased	Higher risk for infections and cancers.	No specific tests used in daily clinical practice.

Table 2 (continued)

	Age-related anatomical changes	Age-related functional changes	Clinical consequences for the therapeutic value of drugs in older patients (examples of PIMs)	Diagnostic tests available in daily clinical practice to identify the age-related change
	for the maturation of T-lymphocytes), usually starting in the fifth decade of life.	cell immunity. No decrease in the number of B-lymphocytes; most probably, their function is altered also.		
Musculoskeletal system	Decrease in proportion of muscle tissue, by 20% at the age of 80 years when compared to the age of 20 years.	Decreased muscle strength, walking speed (one of the important markers of geriatric frailty).	Risk of instability and falls, higher risk of frailty. Risk of myositis and rhabdomyolysis during treatment with higher doses of statins, higher toxicity of digoxin. Low-dose regimens are recommended.	Speed walking test, grip strength tests. Frailty assessments and scales.
	Decreased bone mineral density	Increased activity of osteoclasts and decreased activity of osteoblasts, increased osteoresorption (rapid decline in older women after menopause).	Higher risk of increased osteoresorption, osteopenia, or osteoporosis after indication of several drugs (corticosteroids, thyroid hormones, antiepileptics, high-dose antacids, etc.). Low-dose regimens and preventive application of calcium and vitamin D is recommended.	Tests and clinical assessments of osteoporosis/osteopenia.
	Increase in the proportion of fatty tissue (in up to 30%).	Accumulation of highly lipophilic drugs in fatty tissue.	Significantly prolonged elimination half-life of highly lipophilic drugs, later onset of steady-state concentrations in these medications, accumulation. The risk of toxicity during the periods of substantial weight loss.	No specific tests used in daily clinical practice.

ACE-Is angiotensin-converting enzyme inhibitors; *ACH* anticholinergic; *ADH* antidiuretic hormone; *anti-Xa assay* anti-factor Xa assay; *APPT test* activated partial thromboplastin time test; *ARBs* angiotensin II receptor blockers; *CKD-epi* Chronic Kidney Disease Epidemiology Collaboration equation; *DA* dopamine, dopaminergic; *INR* International Normalized Ratio; *MDRD* Modification of Diet in Renal Disease Study equation; *NSAIDs* nonsteroidal anti-inflammatory drugs; *SIADH* syndrome of impaired secretion of antidiuretic hormone; *SSRIs* selective serotonin reuptake inhibitors

and, probably, a better prognostic factor of possible poor health outcomes. Frail older people are more vulnerable to adverse drug events/outcomes [40] and the identification of geriatric frailty is an important predictive factor of possible adverse drug reactions and events [41].

Frailty is, in general, a term widely used to denote a multidimensional syndrome of loss of reserves (energy, physical ability, mobility, cognition, and health) that gives rise to an increased vulnerability of older persons to stressors (e.g., concomitant acute illnesses, hospitalizations, medical procedures) [42]. Although the biological mechanisms underlying physical frailty are still scarcely understood, common signs include fatigue, weight loss, muscle weakness, and progressive decline in physiological functions [43]. Operational criteria to define physical frailty are based on impairment in several physiological domains, including mobility, balance, muscle strength, motor processing, cognition, nutrition (often identified as nutritional status or weight loss), endurance (including feelings of fatigue and exhaustion), and physical activity [24]. Assessment of frailty significantly varies among different tools, which include: (1) frailty phenotype, based on the presence of 3 out of 5 risk factors (weight loss, exhaustion, low physical activity, muscle weakness, and slow gait) [40]; (2) the "Rothman" instrument, which is a modification of the frailty phenotype including cognition parameters [43]; (3) frailty scales and indicators, e.g., Clinical Frailty Scale (CFS); Tilburg Frailty Indicator (TFI); Groningen Frailty Indicator (GFI); and (4) frailty indexes including the number of health deficits (e.g., symptoms, signs, disabilities, laboratory, radiographic test), such as the FRAIL index (the Fatigue,

Resistance, Ambulation, Illnesses and Loss of weight index) and others [44, 45]. The EMA recommends the Short Physical Performance Battery (SPPB) as an instrument to assess physical frailty in clinical trials, and gait speed as an alternative instrument [46]. As claims databases and electronic health records became important sources for observational studies, several tools have recently been developed to measure geriatric frailty in these datasets, e.g., Medicare claims-based algorithm of frailty [47], claims-based frailty index [48], claims-based frailty indicator [49], electronic frailty index [50], etc. In observational studies, these tools may help to improve the validity and reduce confounding when adverse drug outcomes are tested.

Frailty measures have also been utilized in first observational studies providing information on the efficacy and safety of drug therapies particularly in frail older patients. An observational study by Pilotto and colleagues showed that statins reduced the 3-year mortality rate even in frail older persons with cardiovascular disorders [51]. Martinez and colleagues compared, in an observational study, apixaban, dabigatran, and rivaroxaban versus warfarin in frail older patients with nonvalvular atrial fibrillation, and concluded (in contradiction to findings in the previous section) that only rivaroxaban was associated with reduced risk of stroke or systemic embolism and there were no significant differences in the risk of major bleeding for NOACs when compared to warfarin [52]. In another study using frailty tools, Droz and colleagues evaluated the efficacy and tolerability of taxane therapy in senior adults with chemonaïve metastatic castration-resistant prostate cancer and found that frail patients experienced more toxicity events but still gained significant clinical benefit from taxane therapy [53]. In another study, antidepressant use in not frail older women was associated with increased risk of incident frailty after 3 years [54].

It has also been described that the use of PIMs in older patients may contribute to a decline in physical performance and functional autonomy. Many of these PIMs cause frequent peripheral and central side effects [55–57] and may aggravate or worsen geriatric symptoms and syndromes (e.g., depression, cognitive impairment, urinary incontinence, weight loss, malnutrition, etc.) [55–59]. Interaction between the processes and exposure to PIMs may speed up the manifestation of geriatric frailty [58–60]. Some geriatric studies confirm that PIMs are often prescribed to frail older adults and frailty has also been documented as a specific risk factor or predictor of PIM use [59, 60].

Comprehensive geriatric assessment and care management including the assessment of geriatric frailty has already shown a benefit by reducing suboptimal prescribing in frail older inpatients and outpatients, and by reducing serious adverse drug reactions [61]. However, we still know little about how to individualize drugs with respect to the degree of geriatric frailty, and geriatric teaching books still mostly recommend "higher cautiousness" and the "start low-go slow" approach [62].

Frequent use of high-risk medications in older patients in different settings of care

Many explicit criteria of PIMs in older patients have been developed in the past 25 years, e.g., Beers criteria 2015 [55], STOPP/START criteria [56], Australian medication use and prescribing indicators [63], NORGEP criteria [64], PRISCUS and FORTA criteria [65], and others, to assist prescribers in the identification of high-risk medications in older patients and to help them reduce the excessive and unnecessary prescribing of such medications. Also, drugs having poor efficacy in older age (mostly due to processes of aging) are included on the lists of PIMs [55, 56, 63–65].

Despite the first explicit criteria of PIMs being published more than 20 years ago and updated many times since (at the last time in the year 2015) [55] and despite the development of national variations of these criteria in many countries [56, 63–65], epidemiological findings still confirm the highly prevalent use of PIMs in older adults in different settings of care, in up to 84.5% in acute care [60], up to 62.4% in noninstitutionalized seniors in the community (using five or more medications) [66], or up to 70% in older residents in nursing homes [67]. According to two systematic reviews, the weighted prevalence of the use of PIMs in Europe was 22.6% in community-dwelling older adults and 49.0% in institutionalized older people, with substantial variations across study sites and countries [68, 69]. Two larger studies using claims databases examined the trends of the use of PIMs in the outpatient setting in Ireland and in the USA (1997–2012), and showed that the prevalence of PIMs slightly increased in Ireland from 32.6% to 37.3% and decreased in the USA from 64.9% to 56.6% [70, 71]. Many of the adverse drug reactions of PIMs mimic geriatric syndromes (e.g., impaired cognition, instability and falls, malnutrition, etc.) or may cause or aggravate various geriatric problems (e.g., renal insufficiency, short memory impairment, severe bradycardias, sedation, and others) [55, 56, 60]. Despite contradictory findings, exposure to PIMs led, in some studies, to higher occurrence of geriatric symptoms, syndromes, and geriatric frailty, increased hospitalizations, healthcare costs, and decreased quality of life [57–59, 72–74].

Some publications show that PIMs are more likely to be prescribed in disadvantaged older patients or in older patients at higher risk of adverse drug events/outcomes. Older adults using polypharmacy, psychotropic drugs, or geriatric patients suffering from polymorbidity are more likely to be exposed to PIMs [75–77]. Factors associated with socioeconomic problems or lower socioeconomic status (e.g., having poor economic situation, not having informal carer, etc.) [76] were also significantly associated with PIM use, as well as signs of inadequate care management or care risks (e.g., having more than one prescriber [78], frequent physician visits [77], longer stay in nursing homes

[68, 79], longer hospital stay [80], etc.). Based on findings of our European multicentric project ADHOC ("AgeD in Home Care"), the odds of being prescribed at least one PIM increased exponentially with increasing number of risk factors for adverse drug events [76].

Deprescribing, defined as the "process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes", can be used to reduce exposure to PIMs and to improve older patients' safety and health outcomes [81]. Various tools of deprescribing have been published to date, e.g., specific guidelines for deprescribing, different risk scores and clinical prediction tools helping to estimate individual risk of adverse drug events, scales enabling to identify individual anticholinergic and sedative medications burden, and implicit and explicit criteria of inappropriate prescribing [82]. Fifteen deprescribing tools have been already specifically developed for frail older patients or for older adults with limited life expectancy (e.g., Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy, STOPPFrail) [83] [84]. However, a systematic review and meta-analysis of studies published by Page et al. in 2016 showed conflicting results on the impact of deprescribing on older patients' mortality. While the mortality of older adults has been reduced in nonrandomized studies, no reduction was found in RCTs (except for a subgroup of RCTs analyzing non-educational patient-specific deprescribing interventions) [85].

Frequent underuse of some beneficial nonpharmacological strategies (e.g., physical exercise) in contrast to high prevalence of polypharmacy and PIM use

Even if the primary goal of this article was to emphasize issues related to inappropriate drug prescribing with respect to aspects of ageism, this short subsection is devoted to the underuse of some highly beneficial nonpharmacological strategies (e.g., physical exercise) in contrast to the frequent overuse of PIMs and polypharmacy. This subsection does not focus on all nonpharmacological interventions (e.g., other physiotherapeutic methods, occupational therapy, speech, language therapy, and nutritional therapy), as this was not a primary goal of this article [86], neither does it consider patient medication adherence and persistence, which are the other biggest issues of rational drug treatment [87].

There is clear, strong epidemiological evidence indicating that some nonpharmacological approaches, e.g., regular physical activity, have an important preventive effect associated with reduced rates of all-cause mortality and morbidity [88]. Regular aerobic exercise is one of the most potent strategies to preserve vascular functions with advancing age; other pharmaceutical and nutraceutical strategies can only help to further delay, minimize, or prevent arterial aging [89]. Increase in exercise capacity (increase in each one metabolic equivalent during the exercise) is associated with a 16% mean reduction in all-cause and CVS mortality in older adults [90]. These results correspond favorably with the survival benefit reached by the secondary prevention of myocardial infarction with the use of low-dose aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors [91].

Particularly, physiological functions can be preserved or improved by regular exercise and the prevalence of several disorders is significantly reduced, e.g., hypertension, stroke, metabolic syndrome, type 2 diabetes, breast and colon cancer, depression, the risk of falling, etc. [88]. A systematic review by Lozano-Montoya and colleagues showed that exercise interventions alone or with nutritional supplementation may improve physical performance in community-dwelling older patients with physical frailty and sarcopenia, but further well-designed studies are needed on this topic to also confirm the effectiveness of such interventions [92]. An RCT published by Martínez-Velilla and colleagues also showed that exercise can reverse functional decline in hospitalized older patients [93].

Moreover, polypharmacy and some medications may negatively influence functional capacity and physical activity (e.g., benzodiazepines, Z-drugs, other hypnosedatives, older generations of antidepressants, antipsychotics, etc. that are also stated on the lists of PIMs). According to the study of Heseltine and colleagues, every additional medication prescribed (OR 1.069, CI 1.016–1.124) increased the likelihood of being categorized as sedentary [94]. The results of walking speed and grip strength tests were also inversely associated with polypharmacy [95].

Contradictory are findings of studies testing the impact of physical exercise on cognitive functioning. Two systematic reviews published showed no evidence of the benefit of exercise on cognitive performance in older patients without cognitive impairment and with dementia [96, 97]. The only benefit in older patients having dementia was the improvement in the ability to perform activities of daily living, although the quality of this evidence was low [96]. A review of studies summarized by Santos-Lozano and colleagues described that regular physical activity may prevent the development of Alzheimer's disease in older persons, but further rigorous research is needed [98].

In Table 3, we summarized, as an example, the effectiveness of some nonpharmacological, pharmacological, and combined interventions in preventing falls in older people in different settings of care. The findings are based on two Cochrane systematic reviews [99, 100] that confirmed the predominant positive role of exercise and, partially, also vitamin D supplementation.

Among available therapeutic strategies, regular physical activity is a potent "healthy clinical strategy for healthy aging", particularly in community-residing older adults. In

Table 3 Examples of the effectiveness of some nonpharmacological, pharmacological, and combined interventions in preventing falls in older patients [99, 100]

	Community		Care facilities		Hospitals	
	Rate	Risk	Rate	Risk	Rate	Risk
Exercise	Significantly reduced (group exercise classes and exercises individually delivered at home)	Significantly reduced (group exercise classes, exercises individually delivered at home, and tai chi)	Uncertain effect	Little or no difference	Uncertain effect	Uncertain effect
Vitamin D*	Does not appear to reduce, but may be effective in people who have lower vitamin D levels before treatment	Does not appear to reduce, but may be effective in people who have lower vitamin D levels before treatment	Probably reduces	Little or no difference	Uncertain effect	Uncertain effect
Multifactorial	Effective	Not effective	Uncertain effect	Little or no difference	May reduce, although this is more likely in a subacute setting	Uncertain effect
Multiple	Few were effective	Few were effective	Uncertain effect	Uncertain effect	Lack of evidence	Lack of evidence
Medication review	Not effective	Not effective	Little or no difference	Little or no difference	Uncertain effect	Uncertain effect

Multifactorial intervention is a multiple-component intervention with individual assessment of risk

Multiple intervention is a multiple-component intervention without individual assessment of risk

*Vitamin D may be considered not only as pharmacological intervention, but also as nutritional intervention

real clinical practice, the important role of this nonpharmacological strategy is highly underestimated and not always recommended by prescribing physicians. Appropriate exercise is available at low cost and relatively free of adverse effects [101]. It decreases the rapidity of aging, all-cause morbidity, and mortality. On the other hand, strategies helping to reduce the burden of polypharmacy and, particularly, long-term exposition to PIMs may also help to increase the physical activity in older patients.

Limitations

The first limitation of our article is that, in our narrative literature review, we focused only on a general overview of newer research findings for four particular areas listed in the Methodology section. Secondly, as the narrative literature review method was selected, we did not follow any strict guidelines for conducting systematic literature reviews. This approach introduces bias, as well as the fact that we mainly focused on newer RCTs, observational studies, and literature reviews published after the year 2000. Thirdly, even if works on specific subsections have been conducted and reviewed by experts in particular professional areas, specific selection of articles might lead to another bias. Lastly, while the aim of our article was to emphasize important problems of safe medication prescribing in older adults directly or indirectly linked to aspects of ageism, ageism is not a frequently used key word in the study databases, so we also selected articles using other key words related to safe and effective medication use in older adults.

Conclusion

Rational prescribing in older patients is accompanied by many clinical and ethical dilemmas and problems that directly or indirectly result from or in ageist practices. Clinical guidelines are often non-geriatric and evidence from recent studies do not yet provide clear answers on how to specifically individualize drug treatment (dosing, drug combinations, etc.) with respect to all age-related pharmacological and physiological changes and different stages of geriatric frailty. Clinical tests that may help to identify important age-related changes are mostly non-specific or missing in daily clinical practice and cannot support enough highly individualized drug treatment. Moreover, new rigorous geriatric evidence is necessary not only from randomized controlled trials (RCTs), but also from geriatric observational studies. Aging of the population creates a new challenge for research and clinical practice that should focus more on effective and safe pharmacological and nonpharmacological interventions in specific cohorts of geriatric patients. Moreover, e-health and information technologies, data sharing between different settings of care, and already higher emphasis on individualized drug treatment in

older patients will speed up the process of geriatrization of medicine and pharmacy.

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Compliance with ethical standards

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