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REVIEW-THEMED SECTION

Prescribing medicines to older people—How to consider the impact of ageing on human organ and body functions

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Ageing is associated with several changes in human organs, which result in altered medication pharmacokinetics and pharmacodynamics. Ageing is also associated with changes in human body functions, such as impaired vision, hearing, swallowing, motor and cognitive functions, which can affect the adequate intake and administration of drugs. As a consequence, older people, and especially patients older than 75 years, are the main users of many drugs and they frequently use 5 drugs or more long-term (i.e. polypharmacy). All this increases the complexity of adequate drug intake, administration and adherence. However, there is a lack of evidence on the considerations that should be taken into account to ensure appropriate drug prescribing to older people. This review article summarizes the most clinically relevant changes in human organ and body functions and the consequential changes in pharmacokinetics and pharmacodynamics in older people, along with possible dosing consequences or alternatives for drugs frequently prescribed to this patient population. Recommendations are given on how ageing could be considered in clinical drug development, drug authorization and appropriate prescribing.

KEYWORDS
drug authorization, impaired organ function, older people, pharmacodynamics, pharmacokinetics, pharmacotherapy

1 | INTRODUCTION

1.1 | Ageing population

The world's population is ageing rapidly. In Europe, the number of people older than 65 years will grow from 17.4% of the population in 2010 to 29.5% in 2060.[1] In addition, there will be an increase in the percentage of people aged 80 years and older (the oldest-old) and by 2060 the number of people older than 80 years will nearly have tripled to 12%.[2] Many of the oldest-old are considered frail, which is a medical syndrome with multiple causes and contributors. It is characterized by diminished strength, endurance, walking speed and reduced physiological function. All this increases an individual's vulnerability for developing increased dependency and/or death.[3]

1.2 | Life expectancy

For the first time in history, most people can now expect to live into their 60s and beyond. In low- and middle-income countries, this is largely the result of reductions in mortality at younger age due to improved mother and child care, adequate food intake, hygiene, improved treatment of infectious diseases, and a politically safe environment. In the developed world, the further increase in life expectancy is mainly due to declining mortality amongst older people, which is the result of improved medical care such as the prevention and treatment of cardiovascular diseases and the development of anaesthesiology medicines and techniques.[1] In the developed world, all this has also resulted in a gradual epidemiological shift in the main causes of death. Whereas infectious diseases and acute illness used to

be the main cause of death, nowadays it is chronic diseases such as heart failure and degenerative illnesses.[4]

Ageing comes with an increase in disease burden, although in low- and middle-income countries older people generally carry a greater disease burden than those living in developed countries. The main causes of disability are sensory impairments (particularly in low- and lower-middle income countries), back and neck pain, chronic obstructive pulmonary disease (particularly in low- and lower-middle-income countries), depressive disorders, falls, diabetes, dementia and osteoarthritis. These diseases may not only have a significant impact on how to prescribe drugs, but they also require changes in the way societies are organized in order to implement prevention programmes, e.g. against diabetes or falls, and how societies foster adequate medical, pharmaceutical and assistive care against acceptable cost.[1] An increased life expectancy also implies that even drugs with a longer time until benefit can be beneficial to older people.

1.3 | Biological changes associated with ageing

The decline in human organ and body functions associated with (biological) ageing is caused by changes in multiple biological mechanisms. These changes are caused by increased oxidative stress, increased lipid peroxidation, telomere shortening, altered gene expression and upregulation of apoptosis, leading to damage to mitochondrial and nuclear DNA.[5] All this will also alter the pharmacokinetics and pharmacodynamics of many drugs, where pharmacokinetics relates to the movement of a drug into, through and out of the human body (absorption, bioavailability, distribution, metabolism and excretion), and pharmacodynamics to the biochemical and physiological effects of drugs on the body and their mechanism of action.[6]

Although ageing (biological) and chronological age are not strongly associated, chronological age is clearly associated with a gradual decline in human organ and body functions. This decline results in an increase in (co-)morbidities and an increasing number of older people on polypharmacy (chronic use of ≥5 drugs). Physicians experience difficulties in managing drug therapies in older people due to the altered pharmacokinetics and pharmacodynamics of the drug in combination with practical user problems, especially as there is a lack of evidence on which to base prescribing decisions i.e. evidence-based medicine.

This review article summarizes the most clinically relevant changes in human organ and body functions and the consequential pharmacokinetics and pharmacodynamics in older people, along with possible dosing consequences or alternatives for drugs frequently prescribed to this patient population. Recommendations are given on how ageing could be considered in clinical drug development, drug authorization and appropriate prescribing.

2 | HOW ALTERED HUMAN ORGAN FUNCTIONS AFFECT PHARMACOKINETICS

The absorption, distribution, metabolism and excretion of drugs are affected to a varying extent by the ageing process itself and by diseases commonly associated with ageing (Table 1).[14]

2.1 | Absorption

Absorption is the movement of a drug from the site of administration into the systemic circulation. For oral and partly also for rectal drugs, it takes place mainly via the small intestine. For other drugs, it may take place via e.g. the skin, muscle, subcutaneous layer or lungs. The bioavailability of a drug refers to the portion of an ingested dose that reaches the systemic circulation.[15]

There are several physiological changes in the gastrointestinal tract with advancing age that may affect the bioavailability of oral and rectal drugs. Examples include reduction in intestinal blood flow and gastric acid production, or decreased gut motility and delayed gastric emptying because of a loss of local neural control. Pharmacokinetic studies on the effect of ageing on drug absorption have yielded conflicting results. Several studies did not show any age-related differences in absorption rates for different drugs.[16] However, other studies have shown a reduced absorption of vitamin B_{12}, iron and calcium and an increased absorption of levodopa and other drugs.[17] For drugs absorbed by passive diffusion in the gut such as penicillins, diazepam and metronidazole, there do not seem to be any age-related changes.[18] Hypochlorhydria is more common in older adults, which may reduce the absorption of weakly basic drugs, such as ketoconazole.[18]

The absorption rate of subcutaneous or intramuscular drugs from their site of administration into the blood circulation can be reduced by decreased tissue blood perfusion and increased by reduced muscle mass (which mainly impacts drugs administered as depot preparations).[19] Reductions in chest wall compliance, ventilation–perfusion matching and alveolar surface area may decrease the absorption of drugs via the inhaled route.[20] Thus, in general drug absorption is affected by the ageing process; however, in most cases, it is of no clinical importance.

2.2 | First-pass metabolism and bioavailability

First-pass metabolism can be defined as the metabolism of a drug or other substance before it reaches the systemic circulation. It mainly occurs in the liver (e.g. for propranolol and lidocaine) by CYP3A4, the most important enzyme in first-pass metabolism. It can also occur in the gut (e.g. for benzylpenicillin, calcium antagonists and insulin), where CYP3A4 is also present.[21] The impact of first-pass metabolism decreases with advancing age, which is probably due to a reduction in liver mass and blood flow and also decreased CYP and other biotransformation enzyme activity, such as flavine monooxygenases and UDP glucuronosyl transferases. Therefore, the bioavailability of drugs undergoing extensive first-pass metabolism and consequently, having low bioavailability, such as opioids and metoclopramide, can be significantly increased. As a consequence, these drugs, and especially those with a narrow therapeutic index, should be initiated at a low dose. Alternatively, other routes of administration, such as intravenous, intramuscular, transdermal and sublingual can be considered. First-pass activation of several pro-drugs, such as the angiotensin-converting enzyme inhibitors enalapril and perindopril, may also be reduced

TABLE 1 Pharmacokinetic changes associated with ageing and possible dosing consequences

Pharmacokinetic parameter	Considerations in older people	Impact on drug pharmacokinetics	Potential effects	Example(s)	Possible dosing consequence	References
Absorption	Decreased gastric acid production	Impaired drug dissolution	Decreased bioavailability of drugs	Erythromycin ketoconazole	Effect not clinically relevant	7
	Decreased gastric motility Decreased small bowel surface area Decreased splanchnic blood flow	Decreased absorption of drugs	Standard dose may be inadequate	Vitamin B12 iron calcium	Effect not clinically relevant, possible increase of dose or other route of administration	7
	Reduced first-pass metabolism	Increased absorption of high-clearance drugs Decreased absorption of drugs from prodrugs	Increased plasma concentration	Morphine lidocaine verapamil propranolol nitroglycerine	Start low, go slow dosing is based on effect Consider transdermal administration	4,8
			Decreased plasma concentration	Hydroxyzine valaciclovir captopril prednisone clopidogrel	Effect not clinically relevant	
Distribution	Increased proportion of body fat	Increased distribution of lipid-soluble drugs	Prolonged lipid-soluble drug half-life	Macrolides benzodiazepines morphine amiodarone	Prolonged effect after discontinuation	7,9,10
	Decreased lean body mass; decreased total body water Increased α-l-acid glycoprotein levels	Decreased distribution of water-soluble drugs Decreased free concentration of basic drugs	Increased plasma concentration Standard dose may be inadequate	Digoxin lithium β-lactams gentamicin theophylline	Reduce loading dose Lower standard dose of drugs with narrow therapeutic index	7,9,10
	Malnutrition/proteinuria leading to hypoalbuminaemia	Increased concentration of free drug	Drug toxicity	Acenocoumarol	Dose based on effect (INR) Start low	4,8
Metabolism	Liver disease Normal physiological effects of ageing on the liver	Reduced hepatic blood flow and hepatic mass Decreased cytochrome P450 enzyme activity	Drugs with a high extraction ratio are associated with the largest reductions in hepatic clearance First pass effect of prodrugs is decreased	Opioids metoclopramide lidocaine pethidine propranolol	Start low Dose based on effect and side effects	7,11
				enalapril perindopril	Effect not clinically relevant	
	Polypharmacy	Competition for cytochrome P450 hepatic enzymes	Variable drug activity	Macrolides	Based on effect	4,7
Elimination	Decreased renal function Renal disease	Decreased renal blood flow Decreased glomerular filtration rate	Decreased drug removal Accumulation of drug in plasma increased risk of toxicity	Digoxin lithium gentamicin angiotensin-converting enzyme inhibitors	Start low Monitor serum plasma concentrations	7,12,13

with decreasing first-pass metabolism, possibly leading to lower systemic concentrations of the active drug substance.[22] This is, however, not a clinically relevant effect for drugs with a broad therapeutic index such as angiotensin-converting enzyme inhibitors.

For dermal products, the age-related reduction in the hydration and lipophilic content of the older skin may theoretically reduce the absorption of hydrophilic drugs. However, no significant differences in transdermal absorption between young and older people have been observed in clinical practice and so far, there does not seem a need to consider this aspect upon prescribing.[23]

2.3 | Distribution

The term volume of distribution relates to the ratio of the total amount of drug in the body to drug plasma concentration. It is determined by drug- and patient-related factors. Drug-related factors e.g. relate to the level of protein and tissue binding, acidity, lipophilicity, water solubility, charge and size.[4] Changes in the patient body composition, including a progressive reduction in the proportion of total body water and consequently a relative increase in body fat, may alter the volume of distribution of drugs in older people. Polar, mainly water-soluble, drugs will in contrast have smaller volumes of distribution resulting in higher plasma concentrations in older people (e.g. gentamicin, digoxin, lithium and theophylline). For these drugs, the dose should be reduced.[4] However, nonpolar drugs (e.g. benzodiazepines, morphine and amiodarone) are more lipid-soluble and so their volume of distribution increases with age. The main clinically relevant effect of an increased volume of distribution is a prolongation of the terminal elimination half-life, since more lipid-soluble drugs may form a deposit in the body fat. An increased volume of distribution and elimination half-life have been demonstrated for drugs such as diazepam, thiopental and lidocaine. Consequently, after discontinuation of treatment adverse effects continue for a longer period of time.[4]

The 2 primary drug binding proteins are α-1-acid glycoprotein and albumin. Acidic compounds (e.g. diazepam, phenytoin, naproxen, warfarin, acetylsalicylic acid) mainly bind to albumin whereas basic drugs (e.g. lidocaine, clozapine, propranolol) bind to α-1 acid glycoprotein. Although no substantial age-related changes in the concentrations of both proteins have been observed, albumin is commonly reduced in people with malnutrition, cachexia or acute illness whereas α-1 acid glycoprotein is increased during inflammatory disease and cancer. An increase in α-1 acid glycoprotein may therefore cause a decrease of the free fractions of lidocaine, clozapine, propranolol and other basic drugs. The main factor determining drug effect is the free (unbound) concentration of the drug. Although changes in plasma protein binding may theoretically contribute to changes in physiological effects of drugs that are highly protein-bound, its clinical relevance is limited for most of the drugs.[24]

P-glycoprotein (P-gp) is a membrane-associated protein located mainly in the gut-kidney and blood–brain barrier, whose primary function is as an efflux pump.[25] Changes in P-gp activity in older patients have not been extensively studied. One study involving the P-gp substrate verapamil, showed decreased P-gp activity in the blood–brain barriers of older people, which could indicate that the ageing brain is at higher risk for increased drug exposure, especially for drugs that are actively pumped out of the brain by P-gp, such as domperidone, loperamide, paclitaxel, ondansetron and cyclosporine A.[26,27]

2.4 | Metabolism

Metabolism refers to the breakdown of drugs by the body generally rendering more water-soluble substances that are more readily excreted from the body. The liver is the primary location for drug metabolism. Its enzymes transform lipid-soluble drugs into more water-soluble compounds before elimination from the body. These transformations occur as a result of phase I cytochrome P450 enzyme reactions, such as oxidation, reduction and hydrolysis, or phase II conjugation reactions, such as glucuronidation, sulfation or acetylation.[28] As mentioned before, the most important cytochrome P450 enzyme involved in (first-pass) metabolism is CYP3A4. The rate of drug metabolism in the liver depends on the capacity of the liver to remove the drug from the systemic circulation (i.e. hepatic extraction ratio), which is mainly dependent on the hepatic blood flow, but also on the uptake of the drug into hepatocytes, and the enzyme metabolic capacity. Factors that may contribute to potential alterations in hepatic clearance in older adults are reduction in liver volume, blood flow and metabolic capacity.[29]

2.4.1 | Liver volume

The reduction in liver volume which may be down to 30% in older people compared to younger adults, is known to have an impact on drug clearance.[30] Several studies have shown age-related reductions in the clearance of many drugs mainly metabolized by phase-1 pathways in the liver. Phase-2 pathways do not seem to be significantly affected.[30] Thus, although the reduction in hepatic metabolism is present, it is in general not of clinical relevance, except for drugs undergoing extensive first-pass metabolism such as opioids and metoclopramide. In these cases, the intended effect can be reached with lower drug doses, as the bioavailability will increase due to the reduced first-pass metabolism.

2.4.2 | Blood flow

Drugs are classified into 3 groups based on their extraction ratio (E): high (E > 0.7, such as lidocaine, pethidine and propranolol), intermediate (E 0.3–0.7, such as acetylsalicylic acid, codeine, morphine and triazolam), and low extraction ratio (E < 0.3, such as carbamazepine, diazepam, phenytoin, theophylline and warfarin). When E is high, the blood flow is the rate-limited step in excretion. In case of a low E, changes in blood flow have low impact on clearance. Consequently, the age-associated reduction in liver blood flow with approximately 1% per year from the age of 30 years affects mainly the clearance of drugs with a high extraction ratio. Labetalol, nifedipine and verapamil indeed showed increased plasma levels in older patients; however,

other high-extraction drugs showed no difference in bioavailability.[31] Nevertheless, it has been recommended that the dose of flow-limited drugs should be reduced by approximately 50% in older people, since a consistent decrease of 15–60% is seen in older people receiving flow-dependent drugs intravenously, and 50% or more of flow-dependent drugs given orally.[29]

2.4.3 | Metabolic capacity

Although no particularly strong effects of the combined effects of age and metabolic genotype on pharmacokinetics have been demonstrated, a moderate ~1.5-fold increase in systematic exposure of drugs is found and, in a few drugs, systemic exposure can rise 2-fold or even more. Examples include capecitabine (due to reduced activity of dihydropyrimidine-dehydrogenase), clomipramine (CYPD2D6/CYP2C19), codeine, ezetimibe, fluvoxamine, paroxetine, venlafaxine and zolpidem.[32]

For metabolic capacity-limited drugs with low protein binding, such as paracetamol and theophylline, there is evidence to suggest a decreased metabolic clearance of 30–50% in older people. For metabolic capacity-limited drugs with high protein binding, such as naproxen and valproic acid, total clearance is unreliable, as changes in protein binding may obscure the true intrinsic clearance. However, there is evidence of a decrease in free clearance of around 50% in older people.[29]

2.5 | Excretion

Excretion is the process by which metabolic waste is eliminated from the body via the urine, faeces, bile or lungs. The most important route is renal excretion. The kidney decreases in size by 20–30% between age 30 and 80 years, and microscopic analysis of the older kidney has shown increased fibrosis and tubular atrophy.[33] The age-related reduction in glomerular filtration rate affects the clearance of many drugs such as water-soluble antibiotics, diuretics, digoxin, water-soluble β-blockers, lithium, nonsteroidal anti-inflammatory drugs and newer anticoagulant drugs such as dabigatran and rivaroxaban. Much of this decline appears to be caused by morbidities commonly associated with age, such as hypertension, rather than the natural ageing process. The clinical importance of such reductions of renal excretion is dependent on the width of the therapeutic index and therefore the risk of toxicity. Drugs with a narrow therapeutic index such as aminoglycoside antibiotics, digoxin and lithium are known to have serious adverse effects if they accumulate only marginally more than intended. Because of diminished muscle mass in older patients, serum creatinine may be within the reference limits, while renal function is markedly diminished. Estimation of the glomerular filtration rate with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or Modification of Diet in Renal Disease (MDRD) formulas may be helpful. However, these formulas are not well validated in frail patients. Although in general the Cockcroft–Gault (CG), MDRD and CKD-EPI estimate the mean GFR of an older population well, in individual cases, all formulas may misestimate kidney function by up to 30 mL/min/1.73 m^2.[34-36] Unlike the CG formula, the MDRD equation does not require knowledge of the individual's weight. A major limitation of the MDRD formula is that it underestimates renal function at or above a GFR of 60 mL/min/1.73 m^2, leading to an overestimation of CKD prevalence.[37] By contrast, use of the CKD-EPI results in an increased prevalence of eGFR <60 mL/min/1.73 m^2 in older people.[38] Flamant *et al*. concluded in a review comparing the CG to MDRD and CKD-EPI that MDRD and CKD-EPI should be preferred in older people.[39] The 2012 KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease recommend the use of the CKD-EPI equation to estimate GFR instead of the MDRD due to better accuracy.[40] More recently, cystatin-C based equations have been developed, which may be more accurate; however, since cystatin-C is not yet generally available for daily use, use of these equations is not recommended by the KDIGO guideline.[41]

3 | HOW ALTERED HUMAN ORGAN FUNCTIONS AFFECT PHARMACODYNAMICS

As stated above, pharmacodynamics describe the effects of drugs on the body.[5] The degree of a drug's pharmacological effect depends on the number and the affinity of target receptors at the site of action, signal transduction, and regulation of homeostasis.[19] Pharmacodynamic changes in older people are more complicated to investigate and predict. Studies have reported altered pharmacodynamics with drugs acting on the central nervous system and cardiovascular drugs. For example, older people have a decreased sensitivity of their cardiac β-1 and β-2 adrenergic receptors and therefore a decreased response to β-agonists, such as dobutamine (β-1 agonist) and salbutamol (β-2 agonist).[18,42] The mechanisms of action for these changes are still largely unclear. Proposed mechanisms of action include changed concentrations of neurotransmitters and receptors, hormonal modifications, increased blood–brain-barrier permeability, decreased P-gp activity and impaired glucose metabolism.[43] Changes in homeostatic mechanisms, such as impaired reflex tachycardia and impaired regulation of temperature and electrolytes, may also result in an increased risk for adverse drug reactions.[44] Table 2 summarizes some important pharmacodynamic changes with ageing, along with dose recommendations.[4]

4 | HOW FRAILTY MAY ALTER PHARMACOKINETICS AND PHARMACODYNAMICS

Frailty, defined by the World Health Organization as “a clinically recognizable state in which the ability of older people to cope with everyday or acute stressors is compromised by an increased vulnerability brought by age-associated declines in physiological reserve and function across multiple organ systems”, may independently predict reduced clearance of drugs such as gentamicin.[45]

TABLE 2 Pharmacodynamic changes associated with ageing and possible dosing consequences[4,8]

Drug	Pharmacodynamic effect	Age-related change	Dose recommendation
Antipsychotics	Sedation Extrapyramidal symptoms	Increased	Decrease
Benzodiazepines	Sedation Postural sway Memory impairment	Increased	Decrease/re-evaluate necessity and, if necessary, preferably use short-term and select benzodiazepines that are glucoronidized (lorazepam lormetazepam, oxazepam and temazepam)
Beta-agonists	Bronchodilatation	Decreased	Increase slowly based on effect
Beta-blocking agents	Antihypertensive effects Vasoconstrictive effects (peripheral)	Decreased target tension	Increase slowly based on effect
Vitamin K antagonists	Anticoagulant effects	Increased	Decrease based on effect (INR)
Furosemide	Peak diuretic response	Decreased especially in decreased renal function	Increase based on effect
Morphine	Analgesic effect, sedation	Increased especially in decreased renal function	Decrease/switch
Propofol	Anaesthetic effect	Increased	Decrease
Verapamil	Antihypertensive effect Constipation	Increased	Decrease, add laxative

This reduction of clearance with frailty is plausible since frailty is associated with sarcopenia. Sarcopenia is defined as a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes, such as falls, fractures, physical disability and mortality.[46] Sarcopenia consequently has impact on the clearance of highly hydrophilic drugs such as gentamicin that are poorly distributed into muscle mass.[47] Another important aspect of frailty is unspecific systemic inflammation, partially due to dysregulation of the immune system. Systemic inflammation may result in downregulation of cytochrome P450 enzymes, increasing the risk of individual overdose in older people.[32]

5 | HOW DEMENTIA MAY ALTER PHARMACOKINETICS AND PHARMACODYNAMICS

People with dementia have an increased risk of anorexia and weight loss, which leads to a reduction in muscle mass and albumin, which leads to alterations in distribution, with water-soluble drugs having a reduced volume of distribution while lipophilic drugs will have increased volume of distribution. Furthermore, dementia is associated with an increased permeability of the blood–brain barrier and possible decreased P-gp activity, which is likely to increase access of drugs to the brain, increasing the risk of neurological adverse drug effects. The reduction in acetylcholine in people with dementia, coupled with increased permeability of the blood–brain barrier discussed earlier, leads to an increased risk of the central adverse effects of anticholinergic drugs.[18]

6 | HOW ALTERED HUMAN BODY FUNCTIONS INFLUENCE ADEQUATE DRUG INTAKE BY OLDER PEOPLE

Ageing is associated with the impairment of multiple human body functions, such as vision, hearing, swallowing, motor functions, hand–eye coordination, health literacy, cognition and difficulty with self-caring.[48] Furthermore, any possible assistance may be limited in older people, since they are often living alone, or with someone who is just as old and just as care-dependent. Previous studies have shown that older people encounter multiple practical problems with taking their drugs correctly, such as problems with reading and understanding the instructions for use, handling the outer packaging, handling the immediate packaging, completing preparation before use, or forgetting to take the drug.[49,50] As a consequence, patients and their prescribers may use their drugs other than instructed. For example, opening capsules and taking the contents with food or drink to ease swallowing, administering a dispersion of crushed tablets through feeding tubes in patients who are seriously ill or suffering from swallowing difficulties, or removing tablets from the primary package for storage in a multicompartment compliance aid to ease medication management.[51] Such alterations in the administration can alter the drug's safety and efficacy profile through e.g. the risk for degradation, dosing inaccuracies or altered bioavailability.[52] As any such coping strategies may not be reported by patients to their physicians, it is important that decisions in changes related to the dose, type of drug and decision to initiate or stop a remedy only take place once it has been confirmed that the lack of efficacy or an increase in side effects is not caused by incorrect medication use. Therefore, it is essential that discussion on any practical medication issues in older people are repeatedly initiated

TABLE 3 Information on drug registration needed for appropriate prescribing to older patients[61]

1	What is the number of patients included ≥65 y?
2	What is the number of patients included ≥75 y?
3	What is the number of patients included ≥85 y?
4	Are >100 persons included >75 y in diseases also present in older people?
5	Are the majority of persons in the database >75 y in diseases characteristically associated with ageing?
6	Are the patients included in the studies reasonably representative of the older population suffering from the disease/condition?
7	Are subjects excluded based on age? If so, what is the reason?
8	Are subjects excluded on base of comorbidities? If so, which comorbidities and what is the reason?
9	Are subjects excluded with comedication? If so, which comedication and what is the reason?
10	Is a postauthorization efficacy study in older patients planned?
11	Is a postauthorization safety study in older patients planned?
12	Is a single-dose pharmacokinetic study in subjects >65 y available?
13	Is a single-dose pharmacokinetic study in subjects >75 y available?
14	Is a multiple-dose pharmacokinetic study in subjects >65 y available?
15	Is a multiple-dose pharmacokinetic study in subjects >75 y available?
16	Is drug accumulation in long-term use to be expected and to what extent?
17	Is the pharmacokinetic studied in renal dysfunction?
18	Is the drug metabolized with a high extraction ratio?
19	Is the drug metabolized via CYP 450?
20	Is transportation of the drug depended of drug transporters such as P-glycoprotein?
21	Has the drug a narrow therapeutic dose range?
22	Are there clinically relevant drug–drug interactions?
23	Are there important drug-disease interactions?
24	Are there age-related differences in efficacy?
25	Are there age-related differences in dose–response?
26	Is the time-to benefit of the drug of importance? If so, is the time-to benefit calculated in the elderly?
27	Are there age-related differences in adverse effects?
28	Does the drug at therapeutic dose have anticholinergic effects? If so, to what extent?
29	Does this drug at therapeutic dose increase the risk of delirium? If so, to what extent?
30	Does this drug at therapeutic dose increase the risk of dizziness? If so, to what extent?
31	Does this drug at therapeutic dose increase the risk of falls? If so, to what extent?
32	Does the drug at therapeutic dose have sedative effects? If so, to what extent?
33	Does the drug at therapeutic dose have orthostatic effects? If so, to what extent?
34	Does the drug at therapeutic dose have effects on the locomotor system? If so, to what extent?
35	Does the drug at therapeutic dose have effects on haemostasis? If so, to what extent?
36	Does the drug at therapeutic dose have effects on food intake? If so, to what extent?
37	Are effects on quality of life studied in patients >75 y and, if so, to what extent?
38	Is the drug intake studied in older persons (i.e. user-friendliness, e.g. package, easy to swallow) and if so to what extent?
39	Are risks with respect to any medication errors, e.g. with respect to dose mistakes, studied and if so to what extent?
40	Are clear instructions for older persons present in the patient information leaflet and are they authorized by patients themselves?

by physicians or other health care providers as older people may quickly vary the way they handle their drugs.

7 | HOW AGEING SHOULD BE CONSIDERED IN CLINICAL DRUG DEVELOPMENT

Because of the age-associated impairments in human organ and body functions, it is essential that the special needs of older people are considered during the development, authorization and appropriate prescribing of medicines. Since older people frequently are excluded from clinical trials in the pre-authorization phase,[53-56] the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), a worldwide committee of the drug regulatory authorities and the pharmaceutical industry formerly from Europe, Japan and USA, and nowadays also including Brazil, Canada, China, Chinese Taipei, Korea, Singapore and Switzerland, already developed a guideline for studies involving older people in 1994. This ICH E7 guideline focuses on what investigations should be carried out in this population, and what information should be reported in the preauthorization file for the approval of a new drug (so excluding generics).[57] Although the guideline is not legally binding, applicants for marketing authorization have to provide the authorities with convincing arguments why they did not follow ICH recommendations.

In 2010, the ICH E7 guideline has been updated by the questions and answers document because experiences by all parties with the implementation of the guideline since its publication had resulted in the need for some clarification.[58] Questions answered by this document include: 'Why do we need an adequate representation of geriatric patients in the clinical database?'; and 'What should be taken into account when estimating an adequate representation of geriatric patients to be included in the clinical database?' The ICH E7 guideline, however, is almost 25 years old and might no longer reflect the current needs of healthcare professionals and their patients in clinical practice, especially not in developed countries. Clinicians specifically need information on patients older than 75 years because in this age group changes in pharmacokinetics and pharmacodynamics become clinically relevant. This information could be gathered as part of preauthorization trials. Furthermore information about time-until-benefit in older people, anticholinergic effects, drug–disease interactions and convenience of use is important.[59]

To more adequately contribute to the needs of the ageing European population, the European Medicines Agency's Committee for Medicinal Products for Human use has established a Geriatric Expert Group (GEG) to provide scientific advice on issues related to older people, and in 2011 the European Medicines Agency published a European Geriatric Medicine Strategy to better address the needs of older people within the existing legislative framework.[48,60] The GEG has discussed about information of crucial importance when considering the use of medicinal products in geriatric patients. Table 3 shows which information should be available in the preauthorization phase to provide prescribers information for appropriate prescribing to older patients. If the information is not present, it should be gathered as soon as possible in the postauthorization phase.

About the same time as the GEG was created, in the Netherlands, the Expertise Centre Pharmacotherapy in Old Persons (Ephor) was founded to improve effective and as safe as possible pharmacotherapy and appropriate prescribing to older patients.[62] Amongst others, Ephor has made several evidence-based medicines reports for the treatment of frail patients. It has also developed a polypharmacy module in the e-learning method Pscribe for teaching to medical students, physicians and pharmacists.[63] Furthermore, Ephor investigates, together with other centres in Europe, efficient methods for optimizing polypharmacy with the digital Systematic Tool to Reduce Inappropriate Prescribing assistant.[64,65]

For drug development and prescription to older people, it is necessary not only to consider the altered pharmacokinetics and pharmacodynamics, but also the altered human body functions and the risk for medication errors in a real-world practice. Examples of medication errors due to impaired body functions include lack of drug intake because of difficulties with opening blister packs, accidentally eating nonparenteral formulations, and overdosing due to multiple tablet strengths that are available with a similar appearance in terms of colour, size and shape.[49,66] Examples that are rather related to the product itself, but that require particular consideration in older people e.g. relate to drug degradation when drugs are stored outside their approved packaging to ease medication management. For example, the drug dabigatran cannot be stored in a medicines compliance aid for even 1 week.[67]

8 | CONCLUSION

Older people face multiple problems potentially influencing the beneficial and adverse effects of pharmacotherapy, of which the actual effects are not always easy to predict beforehand. Prescribing (selecting, informing patients, initiating, monitoring and continuation) of drugs to older people provides major challenges to many physicians. Next to changes in pharmacokinetics and pharmacodynamics upon ageing, changes in body functions, such as visual acuity, motor functions and cognition also pose a challenge for appropriate prescribing as they may affect the correct use of the drug. To adequately address the needs of older people and their prescribers, it is important that during the drug development process sufficient information is gathered about the possible changes in pharmacokinetics and pharmacodynamics in older people, especially in patients older than 75 years suffering from comorbidities, and that this aspect requires due consideration during drug authorization. Therefore, we recommend a revision of the ICH E7 criteria so that more data in people older than 75 years will be acquired. Furthermore, it is important during this process that any practical problems that older people may experience will be addressed by adjusting the product design.

8.1 | Nomenclature of target and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[68] and are permanently achieved in the Concise Guide to PHARMACOLOGY 2017/2018.[69]

COMPETING INTERESTS

There are no competing interests to declare.

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