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Altered pharmacology and toxicology during ageing: implications for lung disease

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Purpose of review
Drug use in elderly people is high compared to younger people. Simultaneously, elderly are at greater risk when exposed to environmental substances. It is puzzling therefore, that ageing, as a variable in pharmacological and toxicological processes is not investigated in more depth. Moreover, recent data suggest that molecular manifestations of the ageing process also hallmark the pathogenesis of chronic lung diseases, which may impact pharmacology and toxicology.

Recent findings
In particular, absorption, distribution, metabolism and excretion (ADME) processes of drugs and toxins alter because of ageing. Polypharmacy, which is quite usual with increasing age, increases the risk of drug–drug interactions. Individual differences in combination of drugs use in conjunction with individual variations in drug metabolizing enzymes can influence lung function.

Summary
Exploring exposure throughout life (i.e. during ageing) to potential triggers, including polypharmacy, may avoid lung disease or unexplained cases of lung damage. Understanding of the ageing process further unravels critical features of chronic lung disease and helps to define new protective targets and therapies. Optimizing resilience can be key in pharmacology and toxicology and helps in maintaining healthy lungs for a longer period.

Keywords
ageing, pharmacogenetics, pulmonary fibrosis, resilience, senolytics

INTRODUCTION

It is increasingly recognized that the value of large cohort studies is limited. The era of very successful blockbuster drugs, the profitable 'one-size-fits-all drugs' is clearly declining. The approach of introducing small molecular improvements in existing drugs, e.g. a new beta2 adrenoceptor agonist or a new muscarinic M3 antagonist with a longer residence time on the receptor to achieve duration has been fruitful, but currently large advances in pharmacotherapy rather seem to arise from more personalized or precision pharmacology [1].

The same holds for toxicology [2]. Epidemiological studies on the toxicity of pesticides for example are frequently based on limited data. Pulmonary toxicity is multifactorial and factors like dose, circumstances of exposure and genetic predisposition should be taken into account to better understand possible associations between exposure to pesticides and pulmonary effects [3]. It has been suggested that in susceptible people, exposure to man-made-mineral fibres might be related to sarcoidlike granulomas [4]. Examples of (rare) drug-induced toxicity are easily explained by more individualized research approaches. Recent examples include among others tamsulosin- [5] or simvastatin-associated lung damage [6]. Among the various factors that influence the elimination and effect of compounds like genes, sex [7] and environment, two

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KEY POINTS

- In general, drug development usually follows a 'one-size-fits-all' policy, which works well for the majority of the population. Accordingly, human toxicity of compounds is usually also studied at population level.
- A more personalized approach taking into account a patient's pharmacogenetic profile, together with history, environment, and lifestyle will optimize the efficacy of a drug and minimalize toxicity.
- Harmful ageing health effects are underestimated variables of influence in pharmacology and toxicology.
- Ageing hallmarks reflect lung disease. Senolytics, compounds that selectively clear senescent cells, could therefore be considered as new therapeutics for lung disease.
- The increased risk of polypharmacy accompanying ageing deserves much more attention.
- A dynamic conceptualization of health as 'the ability to adapt' changes the view on pharmacology and toxicology. Resilience optimization seems key in this respect.

aspects seem to receive less attention, i.e. lifestyle and ageing [8], as illustrated in Table 1.

THE AGEING PROCESS

Ageing converts healthy adults into frail ones [9]. The ageing process diminishes reserves in most physiological systems and exponentially increases vulnerability to most diseases and to death. There are several theories of ageing: programmed ageing as in Werner's syndrome also known as 'progeria' due to single gene mutations and wear and tear theories.

There are several programmed ageing theories. In apoptosis, a form of programmed cell death, dying cells do not swell and lyse, the cytoplasm shrinks, blebbing of plasma membranes occurs, nuclear chromatin condenses genomic DNA fragments and dying cells are engulfed by phagocytes without causing inflammation. Another programmed ageing theory is the finite cell division theory. At each cell cycle, a piece of the repetitive ends of chromosomes, so-called telomeres, is lost. A cell stops dividing when a critically shortened telomere length has been reached. Telomerases protect telomeres from attrition with each replication. Furthermore, certain neuroendocrine- and immunological theories have also been assumed to be included in programmed ageing theories.

In wear and tear theories of ageing a large number of genes are supposed to be responsible for a species' maximal life span and ageing is the result of random events. The 'free radical' theory of ageing proposes that in particular reactive oxygen species are involved in the ageing process [9]. This 'free radical' theory overarches other suggestions as the 'error catastrophe' theory in which free radicals may lead to random errors in gene transcription, which may lead to cumulating of nonfunctional proteins resulting in a catastrophe. Also the 'rate of living' theory is explained by free radical damage due to free radical generation due to higher mitochondrial activity. Also DNA damage or glycosylation of proteins as wear and tear processes might at least partly be the result of free radical involvement [2].

Table 1. PubMed hits in the last 10 years by search queries (pharmacology or toxicology) and either genes, environment, gender, lifestyle or ageing

Genes	151 192
Environment	190 818
Sex	77 843
Lifestyle	13 959
Ageing	48 944

AGEING LUNG

Applying the molecular manifestations of these theories of ageing to the lungs allows defining specific hallmarks for the pathogenesis of chronic obstructive pulmonary disease (COPD), lung cancer and idiopathic pulmonary fibrosis (IPF) [10,11]. Cellular protein damage, directly (through e.g. oxidation or glycosylation) or indirectly via damage to genomic DNA or via an effect on gene transcription affects the proteome. To maintain protein homeostasis, indicated as 'proteostasis', repair and degradation like the ubiquitin–proteasome system and the cytosolic autophagy play a role [12]. To repair DNA damage poly(ADP-ribose) polymerase-1 (PARP-1) activation is needed which leads to huge consumption of cellular ATP and thus an deprivation of energy. In fact, systemic poly(ADP-ribose) polymerase-1 activation has been observed in COPD patients [13]. Telomere attrition [14], epigenetic alterations, stem cell- and immune dysregulation as well as extracellular matrix dysfunction during ageing are related to COPD, interstitial lung disease like IPF and sarcoidosis and lung cancer [15–21].

DRUG USE

The prevalence of noncommunicable chronic lung diseases increases during ageing [10]. It is not

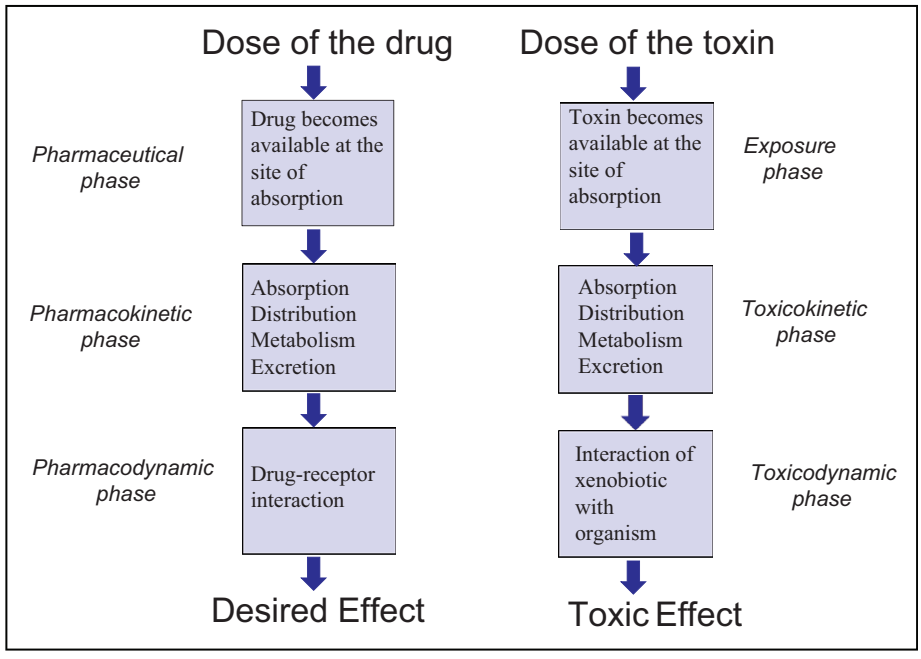

FIGURE 1. Three phases of the dose (of a drug or toxin) – pharmacological desired/toxic effect of a drug/xenobiotic: (i) the pharmaceutical/exposure phase; (ii) the pharmacokinetic/toxicokinetic phase; (iii) the pharmacodynamic/toxicodynamic phase.

surprising therefore that older adults are prescribed more drugs than other age groups. The journey of a drug through the body can be described in three phases: the pharmaceutical-, the pharmacokinetic- and the pharmacodynamic phase (Fig. 1). Similarly in toxicology three phases can be discerned: the exposure-, the toxicokinetic- and the toxicodynamic phase. Ageing affects all three phases, which impacts the desired effect (for drugs) and the toxic effect (for toxins).

PHARMACEUTICAL/EXPOSURE PHASE

For many years [22], it has been suggested that elderly are at greater risk when exposed to environmental substances. Adverse effects of long-term, low-level exposure will have longer time to be manifested with advancing years. More specifically, inhaled drug delivery, which is frequently used for dosing lung medication, may become more complicated in elderly patients depending on the type of device and complexity of use. Also age-dependent changes in patient characteristics like manual dexterity, hand strength, cognitive ability and comorbidities may influence inhaled dose administration [23].

PHARMACO- AND TOXICOKINETIC PHASE

It is not only the lung that is affected as a result of increasing frailty with age. Functions of other organs, like intestine, liver and kidney also gradually decline with age. These organs play a crucial role in the pharmacokinetic-/toxicokinetic phase (Fig. 1). The ADME, i.e. absorption, distribution, metabolism and excretion of xenobiotics (toxins and drugs) is affected by ageing and by diseases that may accompany ageing [24].

Absorption

Absorption from the gastrointestinal tract may alter during ageing [24]. The gastric pH increases, because of lower gastric acid production. Higher gastric pH may increase the absorption of weakly acid drugs or more commonly reduce the absorption of weakly basic drugs because drug dissolution in the stomach is affected by the pH. A higher pH may also cause early dissolution of enteric coated delayed-release dosage forms, e.g. enteric coated sulfasalazine, which may cause drug degradation and hence a reduced therapeutic effect [25]. These effects may further be influenced by medication that increases gastric pH such as proton pump inhibitors. These drugs also have been studied in patients with IPF [26]. The intestinal blood flow reduces and the number of absorbing cells decline with age. The clinical relevance of these phenomena on drug absorption is still not clear [24,27▪▪]. Gastrointestinal mobility decreases and gastric emptying is slower which may decrease the rate of absorption of actively transported iron, calcium and vitamin B_{12}.

Knowledge on age dependent changes in non-oral absorption routes via for example intramuscular, dermal, subcutaneous and pulmonary administration is very limited, but the clinical relevance of these changes seems to be low [24,27▪▪].

Distribution

The body composition changes in older adults. Body water content decreases by 20%, body fat content increases 30%, and muscle mass decreases approximately 30% [28]. This may result in an increased volume of distribution for lipophilic compounds like diazepam, morphine or amiodarone which may prolong the half-life of these agents and thus a prolonged effect after discontinuation. The decreased water content reduces the plasma volume and in this way the initial volume of distribution, which increases the plasma concentration shortly after administration. This is mainly important for compounds with a narrow therapeutic window as theophylline [27▪▪] for which the standard dose should be reduced in order to prevent toxicity [29]. Malnutrition or proteinuria in elderly may lead to hypoalbuminemia and in this way to an increased concentration of free drug, resulting in toxicity as with acenocoumarol [27▪▪]. On the other hand, α1-acid glycoprotein frequently increases with age in association with several inflammatory diseases. This may result in a decreased free fraction of basic compounds like lidocaine and clozapine.

Metabolism

Biotransformation of compounds primarily occurs in the liver. Other organs, like gastrointestinal wall, lungs, and kidneys also have metabolic capacity. Metabolism aims to transform lipid soluble compounds into more water-soluble metabolites to enable the body to excrete these metabolites via the kidneys into the urine [2]. A reduced hepatic blood flow for example caused by liver disease, will decrease the rate of metabolism of drugs with a high hepatic extraction ratio. For drugs with a low hepatic extraction ratio, not the blood flow but rather the metabolic capacity of the liver is rate limiting. This entails that the metabolism in particular oxidation of drugs catalysed by cytochrome P450 enzymes, so-called phase I metabolism is the limiting factor. During ageing, cytochrome P450 enzyme activity decreases [27▪▪]. Phase II metabolism, i.e. conjugation reactions as glucuronidation seem to be preserved in older persons. This is interesting because enzymatic glucuronidation activity is expressed just after birth, which can be visible in a lack of glucuronidation of bilirubin (jaundice in babies), but keeps active during ageing.

Excretion

Excretion predominantly occurs via the urine but could also occur via the bile, faeces or exhalation [2]. A decreased renal function with ageing may be the result of a declined renal blood flow or decreased glomerular filtration rate. This may hamper drug or drug metabolite removal and accumulation of drugs in plasma and increase the risk of toxicity [27▪▪].

PHARMACO- AND TOXICODYNAMICS

There are many examples of alterations in drug sensitivity associated with ageing [27▪▪,30]. This either may lead to alterations in the desired effect or may increase risk of drug use (Table 2).

In this article, we limit the examples to drugs which are of importance to pulmonary medicine. Drugs that are particularly of interest in pulmonology are β2 adrenoceptor agonists. An age related decrease in bronchodilatation has been reported. Apparently the β-receptor response decays during ageing, perhaps via its sensitivity to oxidative stress [31]. It is suggested to slowly increase the dose in these instances based on effect.

Beware that the response to benzodiazepines increases with ageing. The pharmacodynamic effects like sedation, postural sway and memory impairment increase. These drugs should therefore preferably be used short term. Benzodiazepines which are glucuronized, like lorazepam or oxazepam that have a short half live have preference. The response to opioid analgesics like morphine increases, particularly in decreased renal function. In discussions on safety concerns with regard to prescribing benzodiazepines and opioids in interstitial lung diseases [32], age should be taken into account too.

The anticoagulant effect of effect of vitamin K antagonists like warfarin is increased. The dose should be adapted based in effect (INR). This may be of particular importance in view of the report that coumarin users may experience periods of diffuse alveolar haemorrhage (DAH) which may trigger fibrosing interstitial pneumonias [33].

The anaesthetic effect of propofol increases with age [27▪▪], this might be important in discussing this drug as a risk factor for acute exacerbations of idiopathic interstitial pneumonia after surgery [34].

Loop diuretics have been associated with increased the incidence of respiratory-related morbidity and mortality among older adults with non-palliative COPD [35]. In that respect, it is intriguing

Table 2. Clinical consequences of altered pharmacology and toxicology associated with ageing

Drug	Altered pharmacology/toxicology	Clinical consequence
Simultaneous use of multiple drugs	Interaction between drugs in case of polypharmacy	1. In case of polypharmacy, adjust medication as much as possible 2. Check for polymorphisms of biotransformation enzymes 3. In case of abnormal metabolism adjust medication if necessary
Simultaneous use of multiple drugs	Anticholinergic burden due to accumulation of drugs with (unexpected) anticholinergic activity	1. Check anticholinergic burden scale 2. Adjust medication as much as possible
β2 Adrenoceptor agonists	Bronchodilation decrease with ageing	Increase dose slowly based on clinical effect
Benzodiazepines	Increased sedation and/or cognitive failure with ageing	1. Re-evaluate necessity or use benzodiazepines with short half live 2. In case of continuation, decrease dose
Opioid analgesics, such asmorphine	Increased response, in particular in case of decreased renal function with ageing	Decrease dose, or switch, if possible
Vitamin K antagonists	Increased anticoagulant effect with ageing	Decrease dose based on clinical effect
Propofol	Increased anaesthetic effect with ageing	Decrease dose
Furosemide	Decreased response with ageing in case of decreased renal function	Increase dose based on clinical effect

that the peak diuretic response of furosemide decreases with ageing, especially in association with decreased renal function. Accordingly, it is recommended to increase the dose to have the desired effect [27▪▪].

Glucocorticosteroids (GCs) are the mainstay of therapy in various inflammatory lung diseases but at the same time are associated with several substantial adverse effects like increased risk of infections, worsened glycaemic control, osteoporosis, high blood pressure and emotional instability [36]. Especially for elderly patients, which have less intense homeostatic control, balancing safety and efficacy for GCs in the treatment schedule will be important. Again, it should be emphasised that individual differences in ADME and efficacy may strongly influence the (side-) effects of GCs [37].

POLYPHARMACY

Elderly patients more often suffer from comorbidities, so polypharmacy is quite common with increasing age. This increases the risk of drug–drug interactions. All aspects of the ADME process can be affected by polypharmacy. Individual differences in combinations of drug use in conjunction with individual variations in drug metabolizing enzymes, the metabolic genotype, can unexpectedly influence lung function. Recent examples include simvastatin- [6] and tamsulosin-associated pulmonary toxicity [5]. Many compounds have anticholinergic adverse effects. The anticholinergic side effect of single compounds is often relatively mild. However, a mixture of drugs due to polypharmacy will aggravate this anticholinergic effect. Even food supplements may add to this drug-induced anticholinergic effect [38]. Risks of this so-called anticholinergic accumulation are often regarded as typical age-related symptoms like physical and cognitive impairment. Although common anticholinergic adverse effects like dry mouth, blurred vision and cardiac effects are well known, the anticholinergic load because of polypharmacy, leading to summed effects of multiple drugs, is less well known [39]. This phenomenon certainly deserves much more attention. This anticholinergic accumulation also leads to a dry mouth. Saliva plays a pivotal role in mouthfeel and taste [40]. Taste sensations decrease with age and less saliva will aggravate this. Moreover, some drugs, like the antifibrotic drugs pirfenidone and nintedanib, are known to lead to loss of appetite [41]. Even in paediatric populations, iatrogenic taste dysfunctions are known [42].

It should be realized that nutrient availability and sensing are important regulators to maintain cellular metabolic homeostasis. Appetite loss, taste disturbances or enteral feeding to administer nutrition depending whether a prepyloric or postpyloric tube is inserted, influence availability of nutrition. It is exactly this availability of nutrition, that attenuates hallmarks of biological ageing. The antihyperglycemic agent metformin reduces hepatic glucose

production via improved hepatic insulin sensitivity, which reduces fasting plasma glucose levels. But the actions of metformin are broader and attenuates hallmarks of ageing via mitigating genomic instability, augmenting autophagy thereby stabilizing proteostasis and reducing inflammation [43,44]. The biochemical molecular target for metformin is recognized as complex I of the mitochondrial respiratory chain. An increased ADP/ATP ratio in mitochondria leads to activation on AMPK. This leads to inhibition of mTORC1 (mammalian target of rapamycin complex 1), a protein complex that functions as a nutrient/energy/redox sensor and controls protein synthesis. For protein production, activation of mTORC1 is needed, but cells must have adequate energy, nutrients and oxygen available in order for mRNA to start. The mechanisms of the antifibrotic effect of metformin have been discussed in depth recently [45].

Compounds that selectively eliminate senescent cells are denominated senolytics. Dasatinib, which is an ATP-competitive protein kinase inhibitor and used for treatment of chronic myelogenous leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia in combination with the plant derived flavonoid quercetin have been clinically tested in patients with IPF. This open label pilot study gives some indications that senolytics may alleviate physical dysfunction in IPF [46]. The plant-derived flavonoid fisetin also seems capable to destroying senescent cells and is a promising senolytic agent [47]. It alleviates bleomycin-induced pulmonary fibrosis in mice and is suggested to be an interesting candidate for treating patients with IPF. Based on our own results it might even be suggested to combine the plant-derived compounds fisetin and quercetin in that respect [48,49].

HEALTH

In 1948, the World Health Organisation (WHO) defined 'health' as a state of complete physical, mental and social well being and not merely the absence of disease and infirmity. It is not surprising that this definition emerged after the Second World War, an era where a 100% risk-free situation was envisioned. The pursuit of 'health for all' was in line with this rather static, broad and unfortunately poorly quantifiable WHO definition of health. In the first decade of the 21st century, health was conceptualized in a more dynamic way as 'the ability to adapt' [50]. With this new view on health, the function of pharmaceuticals change and new modulating roles of nutrients emerge [50]. Nutrients seem very well suited to contribute to reset homeostasis to acquire or maintain optimal health. Even the classical view on toxicology needs adjustment. Stressors are not synonymous with toxicity but may rather increase human performance, endurance and resilience and thus the ability to adapt [51▪].

CONCLUSION

The effect of ageing in pharmacology and toxicology is still underestimated in clinical practice. We urge greater awareness of ageing in relation to lung disease presentation, course and prognosis. Furthermore, we would like to stress that thorough exploring exposure throughout life to potential triggers including polypharmacy in unexplained/idiopathic cases is warranted to avoid lung damage or taper down disease progression in the future. Understanding the ageing process may help to further unravel critical features of chronic lung diseases and to define new therapies targeting hallmarks of ageing [10]. Moreover, the realization that optimizing health, attained by increasing the aptitude to adapt during ageing, changes our view on pharmacology and toxicology. Pharmacology needs a more personalized policy instead of the usual one-size-fits-all approach and the field of toxicology broadens by judging a xenobiotic (within limits of exposure) as trigger for optimizing resilience.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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Stressful, subtoxic stimuli can trigger biological defence mechanisms. This can lead to protection, repair and enhancement of biological systems. This paper attempts to translate these biological phenomena into clinical recommendations and may transform future pharmacology and toxicology.