Do We Need Different Treatments for Very Elderly COPD Patients?

S. Valente^a G. Pasciuto^a R. Bernabei^b G.M. Corbo^a

^aU.O.C. Pneumologia e Fisiopatologia Respiratoria, Dipartimento di Medicina Interna e Scienze Specialistiche,
e ^bCentro Medicina dell'Invecchiamento, Dipartimento di Scienze Gerontologiche, Geriatriche e Fisiatriche,
Università Cattolica S. Cuore, Roma, Italia

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Abstract

Population ageing is a new challenge for physicians because of the clinical complexity of the elderly. Although geriatric pharmacology is an emerging issue, very little is known and the choice of different treatments for the very elderly is still an important question. Chronic obstructive pulmonary disease is one of the most common chronic diseases throughout the world affecting prevalently older people. Despite the increasing burden of chronic obstructive pulmonary disease in older people, underdiagnosis and undertreatment in this age group are still common problems. Some patients are frail as they have impaired homeostatic mechanisms, deteriorated physiological systems, and limited functional reserve. Pharmacotherapeutic decisions should be combined with a careful assessment of comorbidity, polypharmacy, and age-related changes in pharmacokinetics and pharmacodynamics in order to minimize adverse drug events, drug-drug or drug-disease interactions, and nonadherence to

treatment. There are few studies that specifically examine age as a factor influencing the pharmacokinetics and pharmacodynamics of inhaled therapies, the cornerstone of treatment for chronic obstructive pulmonary disease. This review provides a summary of age-related physiological changes and their impact on pharmacokinetics and pharmacodynamics, with particular regard to the drugs implicated in chronic obstructive pulmonary disease treatment, in order to optimize drug therapy.

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Introduction

The number of older people continues to grow rapidly worldwide, especially in developing countries, and coping with the rising costs of health and social care de-

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mands increased efforts. Population ageing is one of the new challenges of humanity in the 21st century. Around the world, a 'demographic revolution' is underway. Globally, the number of persons aged 60 years or over is expected to almost triple, increasing from 737 million in 2009 to 2 billion by 2050. The proportion of older people is growing faster than that of any other age group. The number of patients aged over 80 years is currently rising and it is projected to increase almost 4-fold. By 2050, it is expected that this segment of the population will reach 395 million or 4.3% of the world population. By 2050, the number of centenarians (about 180,000 in 2000) is expected to increase too, and they are estimated to number 3.2 million, which represents about an 18-fold increase.

Particularly rapid increases in this segment of the population are expected in the less-developed regions where the oldest old are projected to increase from 52 million in 2010 to 274 million in 2050, implying an average annual rate of 4.14%. By 2050, 69% of all persons aged 80 years or over are expected to reside in developing countries [1].

Ageing involves a reduction in homeostatic mechanisms, the loss of functional reserve [2], and the deterioration of almost all of the human physiological systems. Hence, advanced age is associated with an increased prevalence of diseases, comorbidity, poorer quality of life, hospitalization, disability, and mortality [3].

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic diseases throughout the world prevalently affecting older people. It is associated with significant morbidity and mortality and is currently the fourth leading cause of death in the world. By 2020, the disease is expected to be the third leading cause of death worldwide [4]. Despite the increasing burden of COPD in older people, underdiagnosis and undertreatment in this age group is still a common problem.

This review provides a summary of age-related physiological changes and their impact on pharmacokinetics and pharmacodynamics, with particular regard to the drugs implicated in COPD treatment, in order to optimize drug therapy.

The Effect of Ageing on the Respiratory System

Ageing involves structural changes to the thoracic cage leading to a reduced chest wall compliance. In kyphosis, a reduced height of the thoracic vertebrae and calcification of the rib cartilage stiffen the thoracic cage impairing the expansion of the chest wall, the action of the diaphragm, and the emptying of the lungs. Diaphragmat-

ic strength is reduced by 25% in healthy older people compared to young adults [5]. The ageing process involves the degeneration of the elastic fibers around the alveolar duct resulting in air trapping and senile hyperinflation [6].

Age is inversely related to extremity muscle strength, respiratory muscle strength, and pulmonary function [7]. The decline in maximum inspiratory pressure can cause poor ventilation and can impair the clearance of airway secretions. There is no correlation between age and total lung capacity (TLC), while functional residual capacity (FRC) and residual volume (RV) increase with age. Lastly, small airway caliber declines progressively with age (table 1). For all these reasons, COPD is more prevalent in very elderly populations [8].

COPD is characterized by the progressive impairment of airflow. It progresses slowly over a period of years so that its symptoms are not usually exhibited until the age of 55 years and mortality often does not occur until the patients are 65 years of age or older. The FEV₁/FVC ratio declines with age and controversies exist regarding the use of a fixed FEV₁/FVC ratio of 0.7 as the threshold for identifying airway obstruction in the elderly. COPD progression in the oldest age group may be correlated to increased comorbidity, a compromised immune system, and an age-related decrease in lung function leading to high rates of mortality. Old age and comorbidity are partly responsible for the misdiagnosis and undertreatment of COPD in older adults. There is a disparity between practice guidelines and their implementation in older people with COPD resulting in a few subjects receiving spirometry examinations annually, blood gas analysis, the influenza vaccination annually, respiratory medications, and ventilatory support [9, 10].

Older adults with COPD generally have a poor health status because of more chronic comorbidities and limitations in activities of daily living.

Prescribing for Older People

Because of the high susceptibility of older people to disease, the use of medication is extensive and the number of drugs per patient rises progressively with age. Prescribing for older people, however, is a complex issue as the behavior and the effects of medications can vary in the elderly according to the health of the patient, the route of metabolism or elimination of the drug, and the intrinsic safety of the drug. Five key steps have been identified in prescribing: determine the evidence of efficacy in old-

Table 1. Changes in the respiratory system due to age

Feature	Change	Effect
Lung structures	Degeneration of elastic fibers Destruction of lung parenchyma Reduction in supporting tissue and stiffening of the thoracic cage Loss of strength of the inspiratory muscles Decline in the sensitivity of respiratory centers	Decreased lung elastic recoil Reduced chest wall compliance Senile hyperinflation Poor ventilation Reduction in the ventilatory response to hypoxia and hypercapnia
Pulmonary function	Increase in RV and FRC Reduction in VC Decline in FEV ₁ Decline in DLCO corrected for alveolar volume Decline in maximum oxygen consumption Reduction in PaO ₂ Increase in D(A-a)O ₂	Reduced respiratory reserve capacity Reduced exercise capacity
Pulmonary receptors	Reduction in high-affinity β_2 -adrenoreceptors Reduction in high-affinity muscarinic receptors	Reduced sensitivity to the effect of anticholinergic and β_2 -agonists

er subjects; assess the likelihood of adverse drug events; discuss the harm/benefit analysis with the patient; decide on the dose, formulation, and delivery of the drugs, and monitor the patient very carefully [11]. The process of ageing influences the pharmacodynamic responses and can affect all pharmacokinetic stages (absorption, distribution, metabolism, and excretion of drugs) differently.

Thus, prescribing for geriatric patients requires a careful and peculiar assessment of the following specific elements: pharmacokinetics, pharmacodynamics, polypharmacy, comorbidity, adverse drug reactions, drug interactions, the delivery system, and the social and economic factors that affect nutrition and medication adherence. All of these factors can have an impact on the outcomes.

Age-Related Changes in Pharmacokinetics

Oral absorption depends on the physicochemical properties of the drug and on physiological aspects of the gastrointestinal tract. Age results in a decline in gastric acid secretion, delayed gastric emptying, decreased splanchnic blood flow, a decrease in the height of the villi in the small bowel and reduced surface area available for absorption, decreased peristalsis, a slowed colonic transit, and reduced active transport [12–18]. Although all of these age-related physiological changes might affect drug absorption, they appear to have no clinical significance.

Inhalation is the preferred mode of delivery for many drugs for the treatment of airway diseases, especially asthma and COPD. The advantage of this route is the delivery of drugs to the site where they are needed. As a result, it allows the administration of reduced doses which are effective with a much lower risk of side effects [19]. Therapeutic efficacy depends on adequate airway drug deposition, which is influenced by particle size and inhalation techniques. Inhaled drugs can be delivered by nebulizers, metered-dose inhalers, and dry-powder inhalers. Of critical importance is the potential inability to produce an adequate peak inspiratory flow. Both physiological age-related changes and airway diseases can lead to weak inspiratory maneuvers. The previously described age-related reduction in thoracic compliance and in diaphragmatic strength associated with the COPD-related decline in inspiratory muscle function due to lung hyperinflation can impair the generation of an adequate peak inspiratory flow. Older people have further difficulties with the delivery devices because of visual limitations, cognitive deterioration, poor coordination, and arthritis which can impair device handling. Problems have been found with all of the devices, as well as with spacer chambers. An ideal device for all patients does not exist and it makes the choice of the device in older adults a complex one [20].

The size and physical properties of the particles are of crucial importance in determining the deposition site, the drug dissolution, and the pulmonary residence time. The optimum size is 2–5 μm .

Very little of the total drug delivered reaches the periciliary fluid of the bronchi. Regardless of the device used, only 5–10% reaches the thoracic airways. The remaining significant fraction of the delivered dose impacts the oropharynx, is swallowed, and can thus reach the systemic circulation from the gastrointestinal tract. It is absorbed into the blood stream and metabolized like an oral formulation. The portion of the drug that reaches the airway is absorbed from the lumen and can act locally. Drugs can also be absorbed into bronchial vessels, subsequently reaching the systemic circulation. A fraction of drug could also be removed by mucociliary clearance and be swallowed.

To achieve the intended pharmacologic effects, drugs should reach effective concentrations at their sites of action. Once drugs have been absorbed, the concentration depends on the distribution, metabolism, and excretion.

The process of ageing involves several physiological changes that affect drug distribution. Weight and lean body mass progressively decrease with age [21], and in the elderly a reduction in body size, a decrease in total body water, and a significant increase in the proportion of body fat [22] have been shown. As a result of the altered body composition, the volumes of distribution of lipophilic drugs increase and the concentration of water-soluble drugs increases. These changes should always be considered when deciding on the dose regimen of medications in order to optimize drug therapy in older adults. In the elderly, serum albumin concentrations decrease [23] and there is an increase in α_1 -acid glycoprotein [24]. Consequently, the unbound fraction of the drugs changes. Changes in binding plasma proteins occur in the elderly but do not have a relevant clinical significance [25].

The metabolism of medications in the liver is influenced by hepatic blood flow, intrinsic clearance (the mass and activity of drug metabolizing enzymes), and protein binding. Limitations in hepatic blood flow or in intrinsic clearance lead, respectively, to a flow-limited metabolism or to a capacity-limited clearance. Several changes in the physiological features of the liver occur with aging. The size of the liver decreases after the age of 50 years from roughly 2.5% of the total body mass to a nadir of just more than 1.5%, with a decrease in hepatic volume of 20–30% [26]. Interestingly, although the total number of hepatocytes in an aged liver is decreased, there is an increase in the mean cell volume [3]. The increase in the hepatic extracellular space and pseudocapillarization impair the hepatic uptake of substrates from sinusoidal blood [26]. Alterations in blood flow occur parallel to a decrease in liver mass of approximately 40%. The activity of micro-

somal cytochrome P_{450} enzymes involved in the phase I hepatic metabolism is not correlated with age. Phase II or conjugation reactions are not modified in the elderly [27]. However, most drugs metabolized by cytochrome P_{450} or phase I reactions have an impaired clearance in older people, irrespective of which cytochrome P_{450} enzyme is involved [28]. This decreased metabolic clearance might be due to the reductions in hepatic blood flow and liver size [29].

After the age of 50 years, the weight of the kidneys decreases with a reduction in renal mass of 20–30%, principally due to cortical tissue loss which is related to glomerulosclerosis [30]. After the age of 40 years, renal blood flow declines by approximately 1% per year and the glomerular filtration rate declines by 0.75 ml/min/year [31]. In addition, tubular senescence is seen in the elderly population. Although the decline in the glomerular filtration rate is the most important pharmacokinetic change in the elderly, it is only minimally affected by old age. It is related to several diseases, the prevalence of which increases with age. Hypertension, diabetes mellitus, vascular disease, atherosclerosis, and nicotine accelerate the process of glomerulonephrosis [32]. The age-related decline in renal function has an important effect on the clearance of drugs that are secreted or filtered by the kidney, and dose adjustment might be necessary in older people in order to avoid adverse drug reactions [33]. Age-dependent changes in renal function are responsible for changes in pharmacokinetics and pharmacodynamics, including nephrotoxicity. In many cases the kidneys are the target organ of adverse drug reactions as well [34].

Pharmacokinetic Properties of Bronchodilators and Inhaled Steroids

Bronchodilators and anti-inflammatory drugs are the mainstay of the pharmacology of COPD. Bronchodilators currently used in the regular treatment of COPD and recommended in the GOLD guidelines [4] include 1 long-acting anticholinergic, i.e. tiotropium, and 2 long-acting β -agonists, i.e. salmeterol and formoterol. Several inhaled corticosteroids are available, including fluticasone propionate, budesonide, beclomethasone dipropionate, flunisolide, triamcinolone, and mometasone.

Tiotropium

Tiotropium is a long-acting antagonist of the muscarinic receptors. Its quaternary ammonium structure, derived from ipratropium, results in minimal absorption,

low bioavailability, and prevents the penetration of the blood-brain barrier. The bioavailability is 19.5% following dry-powder inhalation in healthy volunteers [35]. Tiotropium is delivered via a HandiHaler. A new device, the Respimat Soft Mist Inhaler, has been proposed as an alternative tool with a delivery system which is independent of the patient's inspiratory effort. It has been found to be effective and well tolerated [36].

The peak plasma concentration (6 pg/ml) is reached within 5 min and declines rapidly within 1 h to very low levels (2 pg/ml) which could occupy <5% of the muscarinic receptors even at high doses [37]. Mean steady-state concentrations (16 ng/ml) were achieved after 2–3 weeks of once-daily inhaled tiotropium 18 µg, with a mean plasma elimination half-life of 5–6 days. Seventy-two percent of the drug is bound to plasma proteins.

The metabolism of tiotropium is minimal as 74% of an intravenous dose is excreted unchanged by the kidneys. A portion of the drug is nonenzymatically cleaved to 2 inactive compounds, and a fraction of the dose is metabolized by cytochrome P450 2D6 and 3A4 isozymes and then further metabolized via glutathione conjugation to many phase II metabolites. After inhalation, 14% of the dose is excreted unchanged in the urine, undergoing active tubular secretion as well, and the remaining nonabsorbed drug is eliminated in feces. The renal clearance and urinary excretion of tiotropium decrease in patients with renal impairment and in patients with advanced age, which is likely a result of reduced renal function [35].

In the literature no studies have been found on the effect of age and severe renal or hepatic impairment on tiotropium pharmacokinetics.

β₂-Agonists

Inhaled β₂-agonists have a chemical structure derived from the catecholamines and they exist as stereoisomers. They are lipophilic and diffuse into the cell membrane, thus having a longer duration of action. Inhaled β₂-agonists have low oral bioavailability because of a high first-pass metabolism.

Salmeterol is characterized by a long aliphatic chain. It is a lipophilic compound which rapidly passes the airway epithelium and is retained in the airway tissue. Its long duration of action of 12 h is likely due to receptor binding that anchors the drug within the receptor-binding cleft. After inhalation, most of the dose is swallowed through the oropharynx.

When salmeterol is inhaled, plasma concentrations are 0.1–0.2 and 1–2 µg/l 5 and 10 min after the administration of a single dose of 50 and 400 µg, respectively.

After regular inhalation of salmeterol 50 µg twice a day for 10 months, a second peak concentration of 0.07–0.2 µg/l is achieved 45–90 min after administration, probably due to gastrointestinal absorption of the swallowed drug. Salmeterol is 94–98% bound to plasma proteins. The oral administration of 1 mg of radiolabelled [¹⁴C] salmeterol had a half-life of 5.5 h in 1 healthy subject. Salmeterol is predominantly metabolized by hydroxylation in the liver. Cytochrome P450 isozyme 3A4 is responsible for its aliphatic oxidation. The metabolites formed by the liver are excreted predominantly in feces [38].

Formoterol has a high lipophilicity which keeps the drug within the membrane close to the receptor.

About 90% of the inhaled dose is swallowed. Following inhalation, the absorption of inhaled formoterol is rapid and reaches C_{max} at 10 min. Its systemic bioavailability is approximately 61% of the delivered dose. It reaches very low plasma concentrations even with high doses of the drug. Formoterol is metabolized by glucuronidation in the liver and the metabolites are completely excreted. After oral administration approximately 67% of the drug is excreted in urine and the 33% in feces. After inhalation, 6.9% of the administered dose is excreted, unchanged, in urine. Formoterol has a half-life of 5 h [39].

Pharmacokinetic studies of formoterol and salmeterol have been limited by the low and sometimes undetectable plasma concentrations after inhalation.

Salmeterol and formoterol pharmacokinetics have not been studied in older patients with COPD or hepatic disorder. It could be interesting to evaluate if the pulmonary distribution and absorption of the inhaled drugs change in older patients with COPD because of the airway impairment.

Inhaled Corticosteroids

Inhaled corticosteroids are widely used in COPD as they allow the delivery of steroids to the lung, reducing systemic side effects. They are highly lipophilic drugs which readily pass the airway epithelium reaching the glucocorticoid receptors. Most of the inhaled dose is deposited in the oropharynx and is then swallowed. Subsequently, the drug is absorbed from the gastrointestinal tract and, via enterohepatic circulation, is subjected to first-pass metabolism in the liver. A much smaller fraction of the delivered dose reaches the airways and, if not removed by mucociliary clearance, will eventually be available in the systemic circulation. There is a varying degree of oral bioavailability: 41% for 17-beclomethasone monopropionate, <1% for beclomethasone dipropionate

as an unchanged compound, 12% for budesonide, 7% for flunisolide, 23% for triamcinolone, and $\leq 1\%$ for fluticasone; this last value is due to low absorption from the gastrointestinal tract and a high hepatic first-pass metabolism. As a result, systemic bioavailability depends on the lung component of absorption for those compounds which have a low oral bioavailability, such as fluticasone. It has been found that the systemic availability of inhaled fluticasone propionate is lower in patients with asthma compared to healthy individuals [40]. Pharmacokinetic differences have also been observed between healthy controls and COPD patients. As no differences were indeed found between these 2 groups after intravenous administration, it is likely that the pharmacokinetic changes of inhaled fluticasone propionate in the COPD group are due to alterations in absorption and/or deposition from the lung [41].

Protein-bound corticosteroids are inactive. Once absorbed, inhaled corticosteroids are metabolized by the liver where they are transformed into inactive metabolites.

Fluticasone propionate has a half-life of 14 h and 87–100% is excreted in feces [42].

Budesonide reaches the maximum plasma concentration at 17–30 min. It has a high degree of hepatic first-pass metabolism (90%) and is metabolized by hydroxylation via cytochrome P450 isozyme 3A4. Significant increases in budesonide plasma levels were observed in late-stage primary biliary cirrhosis and were associated with serious side effects [43]. Its half-life is 2.8 h. Compared to fluticasone, budesonide reaches the peak plasma concentration earlier and this concentration is also higher. These differences are explained by the high pulmonary deposition of budesonide, its higher oral bioavailability, greater water solubility, and a lower volume of distribution [44]. The systemic bioavailability of inhaled budesonide was found not to differ significantly between healthy and asthmatic individuals [45].

Beclomethasone dipropionate is administered as a prodrug and is activated in the lung by esterase activity. There is a transformation to metabolites that are active (17-beclomethasone monopropionate) and inactive (21-beclomethasone monopropionate). Its half-life is 6.5 h.

Flunisolide is rapidly absorbed and metabolized into an inactive metabolite so that its systemic activity is minimal. It has a half-life of 1.6 h.

In the literature there are no studies on age-related changes in inhaled steroids pharmacokinetics.

Age-Related Pharmacodynamic Changes

Pharmacodynamics are affected by some patient-specific factors including age, sex, ethnicity, genetics, disease processes, and prior and present drug exposure [46]. Important changes in pharmacodynamics occur in the elderly and consist of alterations in the number and/or affinity of receptors in the target organ, the response of the cells to the drug-receptor interaction, and homeostatic mechanisms [47]. Pharmacodynamic changes related to ageing may result in an increased or reduced sensitivity to the effect of some drugs for any given plasma concentration.

Most of the studies on age-related changes in pharmacodynamics have evaluated the cardiovascular and central nervous systems. Very little is known about the respiratory system.

Tiotropium is a nonselective inhibitor of muscarinic receptors. It has an affinity which is 6- to 20-fold greater than that of ipratropium and a dissociation time which is 100 times slower than that of ipratropium. Moreover, its dissociation from M_1 and M_3 receptors is 3.5 and 8 times slower, respectively, than its dissociation from M_2 receptors. This kinetic selectivity for M_1 and M_3 receptors together with the great affinity result in a more potent effect and a prolonged duration of action. It produces a bronchodilator effect and does not retard mucus clearance from the lung [48]. Tiotropium has an onset of action within 30 min of administration and its peak effect is achieved within 3–4 h. The duration of action extends up to 32 h after a single inhaled dose with a half-life of 540 min.

A significant reduction in high-affinity binding sites in old tissues compared with young tissues was observed in guinea pigs. There was a change in the muscarinic receptor subtypes and receptor coupling to G proteins with senescence [49]. Lee et al. [50] found that the airway smooth muscle in young rats was more sensitive to cholinergic stimulation *in vivo* and *in vitro* compared to older rats, likely due to a higher expression of M_2 and M_3 muscarinic receptors in airway smooth muscle. Data on the effects of tiotropium in human older adults are not available.

The pharmacodynamic effect of β_2 -agonists depends on their local tissue concentration. They produce bronchodilation by directly stimulating β_2 -receptors in airway smooth muscle. This results in the activation of stimulatory G protein and, consequently, in the activation of adenylyl cyclase. This increases intracellular cAMP, leading to the relaxation of airway smooth muscle via several processes.

Salmeterol and formoterol have a high affinity to β_2 -adrenergic receptors. Salmeterol has an onset of 20 min and a duration of 12 h. Formoterol has an onset of 15 min and a duration of 12 h [51].

The β -adrenergic response to β_2 -agonists decreases with increasing age. There are changes in the β -adrenergic system in older people. Aging is associated with the downregulation of β -adrenergic receptors, elevated plasma noradrenaline levels, and a reduced cAMP response to β -adrenergic stimulation [52, 53]. A downregulation of β_2 -adrenergic receptors may also explain the higher concentration of drug needed with increasing age to reach the desired effect. In a study of the bronchodilator response to inhaled albuterol after methacholine-induced bronchoconstriction, older subjects had reduced and delayed responses to albuterol [54]. It has been found that the response to salbutamol also declines significantly with age [55].

The pharmacodynamic effects of inhaled corticosteroids are influenced by the local concentration within the airways. Fluticasone propionate has the greatest degree of topical potency followed by budesonide, beclomethasone dipropionate, triamcinolone, and flunisolide [56–58]. The degree of topical activity is also related to the affinity for glucocorticoid receptor binding [59].

Corticosteroids, once they have entered target cells, bind to glucocorticoid receptors in the cytoplasm and this complex is transported to the nucleus and interacts with gene transcription. It increases the transcription of anti-inflammatory genes and inhibits the transcription of inflammatory genes.

Combination therapy consisting of an inhaled corticosteroid with β_2 -agonists can offer more benefits than either component alone. This could be due to interactions between the 2 compounds. Inhaled corticosteroids can increase β_2 -receptor synthesis, and long-acting β_2 -agonists appear to enhance glucocorticoid-steroid complex nuclear translocation.

No study evaluating the effects of inhaled steroids in a very elderly population has been found.

Polypharmacy, Compliance, and Drug Averse Events in the Elderly

Pharmacotherapy in the elderly requires knowledge of the age-dependent changes in pharmacokinetics and pharmacodynamics, as well as an assessment of comorbidity and concurrent drug therapy to reduce adverse effects. Older people are the major consumers of drugs due

to the increasing incidence of chronic disease with advancing age. The 35 million people over the age of 65 years in the USA currently constitute about 12% of the population but consume 25% of the prescribed medications [60]. A large study in Europe enrolling 2,707 patients with a mean age of 82 years found that more than 95% of patients received at least 1 medication, and polypharmacy (defined as the use of ≥ 6 medications) was documented in 51% of patients [61]. Other studies documented that elderly people take, on average, 2–9 prescription medications [62–66].

In the elderly, factors predisposing to polypharmacy are poorer health, multiple chronic diseases, multiple prescribing physicians, therapeutic advances, the expectations of the patient, education, an increasing demand for health care, supplemental insurance, and a reluctance to discontinue old medications. Polypharmacy increases the risk of inappropriate medications [61, 67–69], nonadherence to treatments [46], morbidity, mortality and adverse drug reactions [70].

Inappropriate prescribing in the elderly population is an emerging health issue and comprises: the inappropriate dose, formulation, duration, and delivery of drugs; the use of unnecessary drugs; the omission of necessary medicines, and the risks of drug interactions and adverse drug events. A population-based cohort study found that 20% of ambulatory older adults received at least 1 inappropriate drug prescription per year [68]. A large study enrolling 5,734 hospitalized patients with a mean age of 79 years reported that polypharmacy increased the risk of inappropriate medications as defined by the Beers criteria [69]. Errors in prescribing and in the omission of medicines are highly prevalent among medically stable older people in primary care as well [71].

Currently, inappropriate medications are detected according to screening tools for the assessment of the quality and safety of prescriptions; these tools are: the Beers criteria [72, 73], the Inappropriate Prescribing in the Elderly Tool (IPET) [74], the Medication Appropriateness Index [75], and the latest STOPP (Screening Tool of Older Persons' potentially inappropriate Prescription) and START (Screening Tool to Alert doctors to the Right Treatment) criteria [76]. The Beers criteria are one of the most used tools to assess the inappropriateness of prescriptions. They include 2 lists of medications to be avoided in older people regardless of the diagnosis and considering the diagnosis. They were published in 1991, revised in 1997, and updated in 2002. The updated 2002 version was designed for all older people and not just for nursing home residents (as were the 2 previous ones). Respiratory

Table 2. Inappropriate prescription in respiratory pharmacology: START and STOPP criteria

STOPP	START
Drug prescriptions potentially inappropriate in persons aged ≥ 65 years	Medications to be considered for people aged ≥ 65 years with the following conditions when no contraindication to prescription exists
1 Theophylline as monotherapy for COPD	1 Regular inhaled β_2 -agonist or anticholinergic agent for mild-to-moderate asthma or COPD
2 Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-to-severe COPD	2 Regular inhaled corticosteroid for moderate-to-severe asthma or COPD when the predicted FEV ₁ <50%
3 Nebulized ipratropium with glaucoma	3 Continuous oxygen at home with documented chronic type 1 respiratory failure (pO ₂ <8.0 kPa and pCO ₂ <6.5 kPa) or type 2 respiratory failure (pO ₂ <8.0 kPa and pCO ₂ >6.5 kPa)

pharmacology is underrepresented in the 2002 Beers criteria. They identify the use of propranolol and of long-acting benzodiazepines (chlordiazepoxide, chlordiazepoxide-amitriptyline, clidinium-chlordiazepoxide, diazepam, quazepam, halazepam, and chlorazepato) as inappropriate prescriptions for older adults with COPD. They do not sufficiently address other drug-disease interactions, the misuse of drugs, and under- or overprescribing.

The IPET consists of a list of 37 agents contraindicated or with a high risk of drug-drug or drug-disease interactions and a list of the 14 most prevalent inappropriate prescriptions. This screening tool is mainly addressed to cardiovascular, psychotropic, and nonsteroidal anti-inflammatory agents. It classifies the use of β -blockers in COPD as an inappropriate prescription. The revised Beers criteria appear to identify more inappropriate prescriptions than the IPET [77].

The STOPP and START criteria are able to detect inappropriate medications (drug calls duplication and drug-drug and drug-disease interactions) and the omission (or underprescription) of indicated drugs, respectively. They have shown better sensitivity than the Beers

criteria in identifying prescription problems and in identifying patients requiring hospitalization as a result of inappropriate prescription-related adverse events [78]. START criteria can help to consider the benefit of starting new drugs in selected clinical situations (table 2).

All these screening tools can help prevent inappropriate prescriptions in late life and improve appropriate prescribing with a reduction in adverse drug events, costs, nonadherence, and polypharmacy.

Because of polypharmacy the compliance with a drug regimen becomes difficult. Nonadherence to treatments can be influenced by several factors such as the complexity of the dosing schedule, frequent changes in medication, multiple medications, side effects, the cost of drugs, difficult routes of administration, difficult-to-open containers, cognitive impairment, visual impairment, inadequate patient education or understanding, and the impairment of physical function [79]. The problem of the different delivery devices in COPD has been previously discussed.

In the elderly the use of numerous medications associated with pharmacokinetic and pharmacodynamic changes can lead to adverse drug reactions, defined as any injury resulting from drug therapy [80]. The occurrence of these events is further made easier by the impairment of homeostatic mechanisms, by comorbidity, and by the possibility of several types of interactions which comprise drug-drug interactions, drug-disease interactions, drug-food interactions, and drug-herb interactions [81]. As a result, older people are more prone to adverse drug reactions and, generally, these are more severe [82, 83]. Prescribing the lowest effective doses of medication to older patients can help avoid adverse drug reactions, minimize side effects, and increase rates of compliance [84]. Adverse drug reactions are a leading cause of hospitalization [85–87], mortality [88], falls [89], fractures, and hypoglycemia. Up to 30% of hospital admissions [90] in older people are related to adverse drug events and 20% of readmissions to hospital in a geriatric population of 706 patients were drug-related [91].

An interesting challenge in pulmonary pharmacology is the coexistence of chronic heart failure or ischemic heart disease and COPD because of the potential deleterious effects of β -blockers in patients with COPD and of β_2 -agonists in patients with cardiovascular problems. Recent studies demonstrated that the use of β -blockers in patients with COPD, both in those undergoing vascular surgery and in those admitted for acute exacerbations of COPD, was safe and associated with reduced in-hospital

mortality [92, 93]. There is evidence that cardioselective β -blockers should not be routinely withheld from patients with COPD.

The most common adverse events reported with increasing age and tiotropium were dry mouth, constipation, headache, pharyngitis, and urinary tract infection. A small increase in the risk for cardiovascular events has been found with inhaled anticholinergics [94, 95]. Tiotropium has no inhibitory effect on cytochrome P450 isozymes and no clinically significant interactions have been reported [35].

Notwithstanding the low oral bioavailability, inhaled β_2 -agonists have the potential to cause systemic adverse effects such as tremor, tachycardia, palpitations, and changes in blood glucose and plasma potassium concentrations. No interaction between salmeterol and other pharmaceutical agents that are metabolized by CYP3A was found.

Adverse systemic effects of inhaled corticosteroids include loss of glycemic control [96], cataracts [97], skin bruising [98], adrenal suppression [99], and osteoporosis [100]. Inhaled corticosteroids are also associated with an increased risk of pneumonia [101, 102].

Severe adverse drug events can occur with theophylline, especially in the elderly. It is a third-line bronchodilator which is absorbed rapidly after oral administration and reaches the peak plasma concentration after 1.5–2 h. It is cleared by hepatic cytochrome P450 (85–90%) and urinary excretion (10–15%). Its half-life is approximately 4–8 h in young adults. Theophylline has a narrow therapeutic range of 10–20 $\mu\text{g/ml}$. It is a nonspecific inhibitor of all phosphodiesterase enzyme subsets, and it explains the wide range of toxic effects. Toxicity is dose-related and problems include: arrhythmias, convulsions, hypokalemia, hyperglycemia, hypercalcemia, hypophosphatemia, acidosis, nausea, vomiting, headache, insomnia, and nausea. One study showed reduced clearance and an increased half-life of theophylline with advancing age [103], in contrast with other studies [104, 105] which found no significant correlation between patient age and theophylline clearance. Older adults have a higher risk of toxicity when taking theophylline because of concomitant diseases, especially cardiovascular disease, reduced drug clearance, and polypharmacy, with consequent potential drug-drug interactions.

Some studies [106, 107] have shown that pharmacists can help to assess and prevent potential drug-related problems, but further data are necessary.

The increased risk of adverse drug reactions, polypharmacy, concomitant disease states, and age-associated

Table 3. Appropriate prescriptions: what to consider

O	Obtain detailed information on medications, diseases, and diets
L	Limit polypharmacy
D	Detect inappropriate medications (taking into account screening tools as well)
E	Evaluate the need for drugs, stopping drugs which are not indicated
R	Review the dose, duration, delivery, and formulation according to age-related changes in pharmacokinetics and pharmacodynamics
P	Prescribe necessary drugs that are indicated (start omitted medicines)
E	Educate and enhance people's compliance to treatments
O	Organize a careful monitoring of patients and of new prescriptions
P	Plan a simplified treatment regimen
L	Limit adverse drug reactions, drug-drug interactions, and drug-disease interactions
E	Elucidate the risk/benefit ratio for the therapeutic schedule

ed changes in pharmacokinetics and pharmacodynamics demand a detailed evaluation of risk/benefit ratios before prescribing. Despite the complexity of geriatric pharmacology and despite older people being the major recipients of drugs, the elderly are poorly represented in clinical trials. The reasons why they are excluded from studies are the unawareness of the need for and the importance of clinical data representing older adults, anxiety regarding the occurrence of adverse drug events and poor adherence, ethical issues, and difficulties related to confounding comorbidities and to the identification of outcomes. The direct extrapolation of clinical trial results from those obtained from younger patients or healthy older people may not be possible [108]. The lack of an evidence base for prescribing to the elderly makes pharmacotherapeutic decisions more complex (table 3).

Conclusions

Because of population ageing there is a pressing need to develop and validate guidelines and diagnostic and therapeutic criteria addressed to the very elderly. This age group could largely benefit from appropriate and adequate therapy.

There are few studies that specifically examine age as a factor influencing the pharmacokinetics and pharmacodynamics of inhaled therapies. This gap of information should prompt clinical researchers to investigate the effects of traditional drugs in older people in order to ad-

minister a more rational therapy, eventually adjusting doses, preventing potential adverse events, and optimizing benefits. To this effect, collaboration between experts in respiratory medicine and geriatric pharmacologists should be welcome and valuable.

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