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REVIEW ARTICLE

Optimising Inhaled Pharmacotherapy for Elderly Patients with Chronic Obstructive Pulmonary Disease: The Importance of Delivery Devices

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Abstract Chronic obstructive pulmonary disease (COPD) is common in older people. Inhaled medications are the mainstay of pharmacological treatment of COPD, and are typically administered by handheld inhalers, such as pressurised metered-dose inhalers and dry powder inhalers, or by nebulisers. For each of the three major categories of aerosol delivery devices, several new inhalers have recently been launched, each with their own particularities, advantages and disadvantages. Consequently, broader availability of new drug–device combinations will increase prescription opportunities. Despite this, however, there is limited guidance available in published guidelines on the choice of inhalers, and still less consideration is given to elderly patients with COPD. The aim of this article is to provide a guide for healthcare professionals on device selection and factors to be considered for effective inhaled drug delivery in elderly COPD patients, including device factors (device type and complexity of use), patient factors (inspiratory capabilities, manual dexterity and hand strength, cognitive ability, co-morbidities) and considerations for healthcare professionals (proper education of patients in device use).

Key Points

Chronic obstructive pulmonary disease (COPD) drug management relies on inhaled medications, and several inhaler types have been developed, each with their own characteristics, advantages and disadvantages.

Physical and cognitive impairment, which are common in elderly COPD patients, pose special challenges to the use of inhaler devices in the elderly.

In real-life care, factors to be considered when choosing an inhaler device for elderly COPD patients are availability and affordability of inhaled drugs and devices, the uniformity of inhaler devices when several drugs are to be inhaled, and the ability of patients to handle the selected device correctly.

1 Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health problem since its prevalence has risen sharply over recent decades, creating a large economic burden due to treatment costs [1]. In addition, at variance with heart disease and stroke, mortality rates for COPD increased steadily from 1950 to 2007, and in 2020 the disease is expected to be ranked as the third most common cause of death worldwide [2]. COPD is characterized by progressive, not fully reversible airflow limitation that is associated with an inflammatory response of the lung to noxious particles or gases [3]. A combination of small airway disease (obstructive bronchiolitis) and parenchymal

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destruction (emphysema) causes the airflow limitation, the relative components of these conditions varying between patients [4]. The cornerstone of pharmacological treatment of COPD is represented by bronchodilator and corticosteroid medications delivered to the airways using inhalation devices [3]. Currently, the main types of aerosol delivery devices are pressurised metered-dose inhalers (pMDIs) with or without a spacer, dry powder inhalers (DPIs) and nebulisers. Evidence suggests that any inhaler device category can be equally effective in treating patients if properly used [5]. However, each device exhibits distinct properties that warrant consideration in achieving successful medication delivery. In a large study performed on a primary care basis, Molimard and colleagues [6] found that 76 % of patients made errors with pMDIs and these errors were considered "critical" in 28 %. Depending on the device, at least one error was made with DPIs in 49–55 % of patients, which were considered critical in 11–32 % of patients [6]. Subsequent literature reviews confirmed the very high error rates in the use of pMDIs and DPIs [7, 8]. The problem of poor inhaler technique is not confined to primary care. Indeed, a significant proportion of patients with asthma or COPD attending chest clinics made "critical" errors when using inhaler devices [9]. Most importantly, these errors were often unrecognised, as patients did not demonstrate their inhaler technique to healthcare providers, and were associated with poor asthma control and COPD outcomes [9].

Over 10 % of the US population aged >75 years report having COPD [10]. Age-related physiologic changes (i.e. progressive reduction in chest wall compliance, reduction in the strength of respiratory muscles, anatomical changes of lung parenchyma and small airways) contribute to impaired pulmonary function and to the increased prevalence of COPD with age [11]. In addition, physical and cognitive impairment, which are common in older patients with COPD, pose special challenges to the use of inhalers. A study of cognitively impaired patients who were instructed on inhaler use showed that 50 % of patients with borderline cognitive impairment and virtually all patients with mild dementia do not operate pMDIs correctly just 1 day after training [12].

The present review article aims to provide a guide for healthcare professionals on device selection and implementation in elderly patients with COPD. We address the advantages and disadvantages of the currently available inhaler devices, examining features and co-morbidities of elderly COPD patients that may affect adherence to inhaled treatment. To achieve these aims, articles published from the date of inception up to November 2015 were identified through a search strategy run in the principal electronic databases (PubMed, ISI Web of Knowledge, EMBASE, Scopus). The following keywords were selected: "chronic obstructive pulmonary disease", "COPD", "device", "inhaler" and "elderly". No restriction was placed on study design and language of publication.

2 Overview of Currently Available Inhaler Devices

Inhaler devices used to deliver therapeutic agents as aerosols are based on one of the following three platforms: pMDIs, DPIs and nebulisers. The soft mist Respimat® inhaler (Boehringer Ingelheim, Ingelheim, Germany) is a new category of inhaler that falls within the definition of a nebuliser as it transforms aqueous liquid solution to aerosol droplets suitable for inhalation [13]. However, at variance with the traditional nebulisers, Respimat® is a handheld, multi-dose device that has the potential to compete with both pMDIs and DPIs in the portable inhaler market.

Due to several technological innovations obtained in the last two decades, all categories of inhaler devices have achieved a high delivery efficiency, with pulmonary deposition fractions of 50–60 % of the nominal dose compared with fractions of 10–15 % that were achieved in the past [14]. The increased efficiency obtained with innovations means that similar efficacy can be achieved with lower nominal drug doses [15]. However, at the present, the 'perfect' inhaler has yet to be designed. Empirically, it would be user-friendly, not require priming or coordination between triggering and inhalation, provide dose consistency independent of inhalation manoeuvres, have a dose counter that was based on actual inhalations rather than manipulations, and provide the patient feedback to confirm that a dose had been inhaled, that the technique used was correct and to provide a reminder about adherence. To date, none of the currently available inhalers can be considered as 'perfect' regarding all of these characteristics, and all inhalers need some training and regular checking of inhalation technique. Furthermore, all of the devices may have limitations particularly related to elderly COPD patients. Within the framework of the challenges that elderly patients with COPD face, the advantages and limitations of these devices for this specific population warrant careful clinical consideration when planning optimal COPD management. A description of each category of currently available inhaler devices is provided in Sects. 2.1–2.4, and a summary of advantages and disadvantages of each type with regards elderly patients with COPD is reported in Table 1.

2.1 Pressurized Metered-Dose Inhalers

Introduced in the 1950s, pMDIs were the first of the handheld delivery devices [5]. Technological developments in pMDIs have occurred over the past 60 years, but

Table 1 Advantages and disadvantages of aerosol delivery devices with regard to elderly patients with chronic obstructive pulmonary disease

Inhaler	Advantages	Disadvantages
pMDI	Portable and compact	Require hand–breath coordination, an issue for patients with low cognition
	Consistent dosing and rapid delivery not dependent on peak inspiratory flow	Require hand grip strength to actuate, an issue for patients with weak manual strength
	Multi-dose device	High oropharyngeal deposition (non-extrafine pMDI)
	Relatively cheap	Some pMDIs lack of dose counter
	Cannot contaminate contents	Contains propellants
	Available for most inhaled medications	
	Some pMDIs include a dose counter	
pMDI + spacer	Hand–breath coordination easier	Spacer assembly may be difficult in patients with impaired manual dexterity
	Tidal breathing inhalation technique possible	The added size of a spacer reduces pMDI portability and its immediate readiness for inhalation
	Large drug doses delivered more conveniently	Not breath-actuated
	Less oropharyngeal deposition	Plastic spacers may acquire static charge
	Higher lung deposition than a pMDI alone	Additional cost to pMDI
BA-pMDI	Portable and compact	Contains propellants
	Breath-actuated (no hand–breath coordination needed)	Few drugs available
	Require a low inspiratory flow to be triggered	
	Cannot contaminate contents	
sd-DPI	Portable and compact	sd-DPI needs to load and pierce the capsule, an issue for patients with impaired manual dexterity
md-DPI	Breath-actuated (no hand–breath coordination needed)	Require a variable, minimum inspiratory flow, an issue for patients with severe airway obstruction
	Some md-DPIs have feedbacks reassuring patients on correct drug intake	DPIs require different and sometimes high (up to 11) number of steps to be operated correctly, an issue for patients with low cognition or psychomotor deficits
	Does not contain propellants	Most types are moisture sensitive
	Dose counter included	
SMI (Respimat®)	Portable and compact	Require hand grip strength for loading the cartridge, an issue for patients with weak manual strength
	Multi-dose device	Require hand–breath coordination, an issue for patients with low cognition
	Higher lung deposition than non-extrafine pMDI	Not currently available in most countries
	Probably easier to use correctly than pMDI	Few drugs available
	Does not require propellants	Relatively expensive
Nebulisers	Minimal cognitive function needed	Require power source of battery pack
	No specific inhalation technique required	Long drug delivery time (Jet, ultrasonic), an issue that may affect patients adherence
	No hand strength needed	Require daily cleaning and maintenance
	Aerosol mist may reassure patients	Jet nebuliser cannot aerosolised large volumes of solution
	Vibrating mesh nebuliser are portable and do not require an outside energy source	Risk of bacterial contamination
	May dispense drugs not available with pMDIs or DPIs	Vibrating mesh are expensive

BA-pMDI breath-actuated pressurised metered-dose inhaler, *DPI* dry powder inhaler, *md-DPI* multi-dose DPI, *pMDI* pressurised metered-dose inhaler, *sd-DPI* single-dose DPI, *SMI* soft mist inhaler

the components of all pMDIs are essentially the same as those of the original 1950s pMDI: an aluminium canister, lodged in a plastic support, containing a pressurised suspension or solution of micronised drug particles dispersed in propellants, and a mouthpiece through which the aerosol is inhaled [16]. A surfactant is added to the formulation to reduce the particle agglomeration, and is responsible for the characteristic taste of specific inhaler brands. The key component of the pMDI is the metering valve, which delivers an accurately known volume of propellant containing the micronised drug at each valve actuation. The operation principle of the present pMDIs remains similar to

the original 1950s push-and-breath design: pressing the bottom of the canister into the actuator seating causes decompression of the formulation within the metering valve, resulting in an explosive generation of aerosol droplets that consist of drug particles contained within a shell of propellant. The change in propellants from chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA) has led to a low-velocity, low impact force and higher temperature spray, which improves the probability of the aerosol being inhaled into the lungs rather than colliding with the oropharyngeal mucosa [17]. Interestingly, some of the new HFA–pMDIs deliver droplets of smaller (<2 μ) size; this may increase peripheral lung deposition of drug particles [18, 19].

In terms of operational design, two generations of pMDI devices now exist in practice [20]. First-generation pMDIs are press-activated aerosols that require precise coordination between inhaler activation and inhalation by the patient. They are compact and portable, offer consistent dosing and rapid delivery, and sometimes include a dose counter. On the other hand, these pMDIs are difficult to operate correctly [6, 7, 9]. A meta-analysis [21] of 24 studies of pMDI use found that 77 % of patients make at least one error, with poor "hand–breath" coordination and overly rapid inspiration being the most frequent errors. Spacer devices or valved holding chambers (a spacer with a one-way valve at the mouthpiece end) reduce the need for hand–breath coordination, allowing time and distance for dispersion an aerosolised medication into a respirable size [22]. In addition, some spacers provide audible feedback to achieve the correct inspiratory flow, thus optimizing drug deposition in the lungs [22]. For these reasons, spacer devices should always be considered in elderly patients who demonstrate poor hand–breath coordination for both rescue and controller medications. However, spacers require cleaning between uses, are bulky and are inconvenient to carry, thus reducing the overall convenience inherent to the pMDI. In an observational study, Sadowski et al. [23] found that elderly COPD patients using pMDIs plus spacers demonstrated the poorest device acceptability compared with pMDI alone and DPI devices.

Second-generation pMDIs have been developed from the original press-and-breath pMDIs to overcome the problem of poor coordination between pMDI actuation and inhalation [20]. These pMDIs, named breath-actuated (BA)-pMDIs, require breath rather than press actuation to reduce the dependency on the patient's coordination of inhalation and actuation. The BA-pMDIs have a flow-triggered system driven by a spring that releases the dose during inhalation, so that firing and inhaling are automatically coordinated [20]. Some studies have shown improved deposition and increased patient confidence that a dose was successfully delivered associated with the use of BA-pMDI [24–26]. Errors when using BA-pMDI are less frequent than when using a standard pMDI [27]. Overall, incorporating BA-pMDIs into patients' regimens may improve overall disease outcomes and reduce healthcare costs associated with COPD compared with conventional pMDIs despite increased device cost and complexity.

2.2 Dry Powder Inhalers

DPIs are delivery devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route [6, 20]. DPIs rely on air drawn through the device to pick up powder from a container and carry it into the lungs within the same airstream [6, 20]. For this reason, DPIs are considered advantageous over pMDIs since they avoid the use of propellants and are instead actuated during the inhalation, thus allowing patient coordination issues to be overcome. Some DPIs are single-dose devices that require insertion and perforation of drug capsules designed to release all of the powdered content into the airstream. Other DPIs contain multiple doses taken from a reservoir or multiple prefilled blister/cartridges of drug powder [6, 20]; these do not require the user to carry packets of separate drug capsules, but function is otherwise similar to single-capsule devices. All DPIs require a variable number of essential consecutive steps to be prepared and correctly operated [20]. Notably, more recently introduced DPIs in the market (Ellipta®, GlaxoSmithKline, Brentford, Middlesex, UK; Nexthaler®, Chiesi, Parma, Italy; Spiromax®, Teva Pharmaceutical Industries, Petach Tikva, Israel) are characterised by a simple three-step operation procedure—open the cover, inhale from the mouthpiece and close the cover—which, taking into account typical human behaviour [28], increases the ease of use and reduces the possibility of errors with these inhalers.

The inhalation flow rate through the device is critical to the successful operation of all DPIs, and not using a forceful and deep inspiration from DPIs is a critical problem [29, 30]. The inspiratory effort required to deliver the drug to the lung varies depending on the resistance of the DPI (Fig. 1) [30–35]. It is the physical design of the DPI that establishes its specific resistance to airflow (measured as the square root of the pressure drop across the device divided by the flow rate through the device) with current designs having specific resistance values ranging from about 0.02 to 0.2 cm H_2O/L/min) [30]. To produce a fine powder aerosol with increased delivery to the lung, a DPI that is characterised as having a low resistance requires an inspiratory flow of >90 L/min, a medium-resistance DPI requires 50–60 L/min, and a high-resistance DPI requires <50 L/min [30]. Of note, DPIs with high resistance tend to produce greater lung deposition than those with a lower resistance [30].

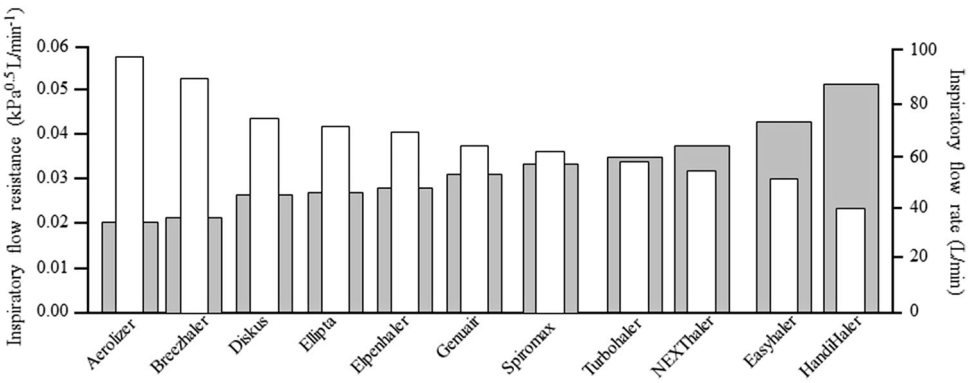

Fig. 1 Inspiratory flow resistance (*filled bars*) of various dry powder inhalers with respect to the inhalation flow (*white bars*) required to produce a pressure drop of 4 kPa [30–35]

Patients with COPD, especially during disease exacerbations, may use suboptimal inhalation flows from DPIs as they may not have the energy generated by their inspired breath to achieve the effective inhalation flows that are required for most DPI devices [30]. Unlike traditional pMDIs, which require the same inhalation manoeuvre, each DPI device is unique and requires its own 'bespoke' inhalation manoeuvre that should be correctly understood by both the patient and the healthcare professional. In this context, DPI devices such as the NextHaler® or the Genuair® (Almirall, Barcelona, Spain) include a dose protector that prevents release of the dose until a sufficient flow rate is achieved. The use of training devices to assess the patient's inhalation technique, with some mimicking the internal resistance of various inhalers, may also provide significant advantages [36]. These training devices can be used to confirm the adequacy of peak inspiratory flow either when first prescribing a new device in a patient or in their regular training and the monitoring of inhaler use [36].

The newest generation of DPIs are 'active', power-assisted devices that incorporate battery-driven impellers and vibrating piezoelectric crystals (e.g. MicroDose®, MicroDose Therapeutx, Monmouth Junction, NJ, USA) to disperse drug from the formulation, thus reducing the need for the patient to generate a high inspiratory flow rate, an advantage particularly for patients with impaired lung function [22, 37]. Due to the presence of an energy source, these devices enable dosing precision and reproducible aerosol production that is independent of the respiratory force. In vitro studies have shown that active DPIs produce a respirable aerosol fraction of 50–70 % of the nominal dose [22, 37]. On the negative side, active DPIs are obviously more sophisticated and expensive than passive DPIs.

2.3 Nebulisers

Various types of nebulisers are available on the market, and several studies have indicated that performance varies between manufacturers and also between nebulisers from the same manufacturers [38–41]. The traditional jet and ultrasonic nebulisers have recently been joined by a third type that use a vibrating membrane or mesh [42]. The jet (or pneumatic) nebulisers remain the most commonly used nebulisers in clinical practice; they generate aerosol particles as a result of the impact between a liquid and a jet of high-velocity gas (air or oxygen) in the nebuliser chamber. Treatment times with these devices are generally long, the air compressor are heavy and noisy, and mechanical shear forces can affect certain medications [38–40]. In addition, their efficiency is low with no more than 10–15 % of the delivered drug reaching the lungs [38–40]. The design of breath-enhanced jet nebulisers (e.g. PARI LC® Plus, PARI GmbH, Starnberg, Germany) is modified to allow for air entrainment during inspiration and to vent the expired air outside of the device [43, 44]. Their main advantage is to increase the output rate, which in turn will decrease the administration time [44]. BA nebulisers (e.g. AeroEclipse®, Monoghan Medical Corporation, Plattsburgh, NY, USA) emit aerosolised droplets only when the patient inhales. Therefore, no drug is wasted during exhalation as the case of regular jet nebulisers and dissemination of expensive or toxic drugs into the surrounding environment is avoided [44].

Ultrasonic nebulisers use a rapidly (>1 MHz) vibrating piezoelectric crystal to produce aerosol particles [38–40]. Although ultrasonic nebulisers operate silently and can nebulise solutions more quickly than jet nebulisers, they are not suitable for suspensions and their piezoelectric crystal can heat the liquid drug in the reservoir, making them inappropriate for thermal-labile medications [38–40].

Vibrating mesh nebulisers (e.g. the PARI eFlow®, PARI GmbH; MicroAir®, Omron Healthcare Europe BV, Hoofddorp, The Netherlands) are the newest type of nebuliser technology which overcome some of the disadvantages of both jet and ultrasonic nebulisers [42, 45]. These new-generation nebulisers have greater efficiency, precision and consistency of drug delivery, and are quiet and

generally portable [43, 46, 47]. However, they are also significantly more expensive than other types of nebuliser, and require careful instructions on use and hygiene to prevent build-up of deposits and blockage of the apertures, especially when suspensions are aerosolised, and to prevent colonisation by pathogens [42, 45].

Once set up, nebulisers are easier for patients to use than pMDIs or DPIs as they only require tidal respiration for effective drug delivery [38–40]. In addition, the visible aerosol produced by nebulisers may foster confidence in patients providing visual proof that they are receiving the medication [47]. Evidence indicates that elderly patients with COPD find nebulised bronchodilators to be more effective than therapy delivered via pMDIs [48]. In a survey of outpatients receiving nebuliser therapy, the majority reported that nebuliser use afforded improved symptom control, well-being and self-confidence [49]. Nebulisers offer a convenient way of delivering a higher dose to the airways, if necessary [50]: for this reason, most patients in the emergency department or intensive care unit are treated with a nebuliser. A consensus statement by the National Association for Medical Direction of Respiratory Care (NAMDRC) [51] indicated the following clinical situations in which home treatment with nebulisers is preferable to that with handheld inhalers: where the patient, despite appropriate instruction, is unable to use pMDIs or DPIs correctly due to locomotor, visual or cognitive impairments; and where the patient's lung mechanics are considered insufficient, i.e. a vital capacity less than 1.5 times the predicted tidal volume of 7 mL/kg body weight, an inspiratory flow rate less than 30 L/min or a breath-holding capacity less than 4 s. The same consensus statement also recommended nebuliser therapy for those patients with severe COPD who remain symptomatic despite inhalation of a high-dose of bronchodilator through correctly operated pMDIs or DPIs, and for COPD patients with mucus hypersecretion or mucus clearance problems, in whom the wetting action of the nebulised aerosol might facilitate mucus elimination [51].

2.4 Soft Mist Inhalers

The soft mist inhaler (SMI) was introduced in 2007 as the Respimat® Inhaler, and this is the only SMI currently marketed. It comprises design elements from the pMDI, but solves some disadvantages associated with pMDIs and DPIs [13]. The Respimat® device is a portable inhaler that slowly aerosolises propellant-free drug solutions as a soft mist (like nebulisers), thus decreasing the chance for oropharyngeal deposition [13]. Respimat® uses spring power (rather than a pressurised container) to generate a low-velocity vapour cloud into the mouth from a liquid formulation of the drug, which is pushed through a specially designed nozzle. The mist generation is sustained for approximately 1.5 s but still requires a degree of coordination of inhalation and actuation [13]. Lung deposition with Respimat® is higher and oropharyngeal deposition is lower than with conventional pMDIs [13]. Respimat® also has the benefit of a dose indicator that provides the user with an estimate of doses remaining in the cartridge. Administration of half of the cumulative dose of ipratropium bromide and fenoterol hydrobromide by Respimat® achieved the same therapeutic outcome as that of the full dose administered by pMDI to COPD patients [52].

3 Adherence to Inhaled Therapy

Exacerbations are a major cause of morbidity and mortality of COPD and therefore their prevention is a major goal of treatment [3]. Clinical trials have shown that effective management of COPD reduces the rate of exacerbations, thereby improving outcomes and health-related quality of life [3]. However, real-world studies indicate that the results of clinical trials do not translate into benefits in clinical practice, often because of poor patient adherence to treatment [53]. A recent Cochrane review highlighted the prevalence and clinical consequences of poor adherence to treatment and the lack of effective interventions, citing poor methodology for assessing adherence and the need to improve the design of interventions so that they lead to practical sustainable clinically relevant outcomes [54]. Treatment guidelines recommend that physicians discuss adherence issues with their patients and encourage compliance with prescribed medication regimens [3]. However, adherence to long-term therapy is poor in COPD patients, with up to 60 % of patients being non-adherent to prescribed treatments [55, 56]; this may result in negative impacts on health outcomes and quality of life and associated increased healthcare costs.

Adherence is not a simple binary issue of whether an individual has or has not taken their medication. In contrast, it is a much more complex issue related to each phase of medication use [57]. Patients may not fill their prescription or, once started, may only intermittently use their treatment due to forgetfulness or poor inhaler technique [57]. Patients may also stop using the inhaler earlier than suggested [57]. Information about the factors driving adherence in COPD are relatively under-researched. In a landmark paper, Vestbo et al. [58] reported that poor adherence to placebo among patients in a clinical trial was independently associated with a poorer prognosis than for patients adherent to placebo. These data suggest that poor adherence has another dimension beyond medical therapy that includes the physical and psychological aspects of the

individual, vulnerabilities that may hinder their motivation adhere to healthcare advice. A recent systematic review of the psychology of human behaviour [59] identified three domains of behaviour (capability, opportunity and motivation) that may be relevant in COPD, particularly in the elderly. For example, capability, defined as the individual's psychological and physical capacity to engage in the activity concerned [59], may be impeded by normal variations in cognitive capacity, such as the strength of an individual's prospective memory. Opportunity, defined as all of the factors that lie outside the individual that make the behaviour possible or prompt it [59], may be impeded due to poor healthcare professional knowledge of inhaler handling, leading to poor instruction. Motivation, defined as all those brain processes that energise and direct behaviour, not just goals and conscious decision-making [59], can be affected by patient beliefs about medicine and illness, depression or social isolation. While motivation for self-management has not been widely studied in COPD [60], it is recognised as being low in COPD and this is likely to impact adherence significantly [61].

Adherence to treatment is difficult to monitor without bias, as patients tend to over-estimate their adherence when using self-reporting questionnaires [62]. Furthermore, integral dose counters and pill counters do not provide precise information about when the doses were taken [62]. The advent of electronic monitoring devices may allow for potentially accurate and reliable assessment of adherence to inhaler devices [63]. These electronic devices provide adherence feedback to the patient through dosing prompts, while recording and charting adherence patterns that are uploaded to a website or mobile phone for viewing [64]. Internet-based patient management services have also been developed [65]; these web services are tele-health-based platforms, which monitor behaviour and provide caregivers with an alert when deviations from expected patterns of treatment taking occur. As such, these systems offer an opportunity to utilise adherence information and limit the risk of medication errors [65]. I-neb Insight Online (Respironics Respiratory Drug Delivery (UK) Ltd, Chichester, West Sussex, UK) is an example of a tele-health-based management system that facilitates the presentation and analysis of both adherence to treatment and competence regarding nebuliser use [65]. It consists of software running on a patient's home computer and an internet-accessed server utilised with the patient's system-specific nebuliser. This system provides detailed analysis of device usage by the patient and nebuliser performance data that are accessible to the patient, clinician and support programme personnel [65]. Several mobile phone medical applications are also available to monitor patients' adherence to treatment, as well as to support clinician engagement with patients, particularly for long-distance caregivers [66, 67]. Of note, the US Food and Drug Administration (FDA) has already cleared a handful of mobile medical apps that are either an accessory to an FDA-regulated medical device or transform a mobile platform into a regulated medical device [67]. Although the use of these electronic monitoring devices has significantly improved patients' adherence to treatments and inhaler use in clinical trials, their effect on clinical outcomes and healthcare costs in real-life elderly patients remains to be established.

4 Inhaler Device Selection: Special Challenges in Elderly Patients

Inhaler devices, which may seem simple to use to healthcare providers, frequently present challenges for elderly patients with COPD. The combined effects of co-morbidities, the complexity of the accompanying medication regimens, as well as age- and disease-related lung function decline may add to the complexity of using different inhalers (Table 2). Optimal management of the older COPD patient must consider all of their medical issues. Reductions in lung function due to severe airflow limitation and/or hyperinflation can leave patients unable to adequately inhale medication or to achieve the inspiratory flow needed for optimal drug delivery. Wieshammer and Dreyhaupt [68] investigated handling errors with DPIs in 67 outpatients with COPD. They found that the overall rate of ineffective inhalation was 31 %, and the error rate increased with increasing severity of COPD and with no prior instruction in inhaler technique. In addition, besides the severity of disease, age critically determined the frequency of handling errors [68]. Thus, while the error rate was 20 % for patients younger than age 60 years, it doubled to 41.6 % for those older than 60 years and even quadrupled to over 80 % for those older than 80 years. Training by the healthcare provider more than halved the overall error rate from 53 to 23 %, but ineffective use of inhalers in older patients remained high despite prior instructions [68].

Age-related conditions, such as dementia, depression and neuromuscular (e.g. Parkinson's disease) and cerebrovascular (e.g. stroke) diseases, have a negative impact on cognitive abilities, reducing patients' attentional functions and their capacity to concentrate on and take in complex instructions and information [69]. Research brain imaging studies have shown significant white matter pathology in the fronto-striatal regions of COPD patients, areas that impact planning, problem solving, and prospective memory capacity [70]. Patients with poor executive functioning often display a 'knowing–doing discrepancy'. While they can report specific instructions, they cannot translate these into specific behavioural and motor plans

Table 2 Potential issues that may prevent older COPD patients from using inhaler devices correctly

Factors	Mechanism
Cognitive function	Cognitive function determines the ability to acquire and retain techniques needed for competent use of inhalers. Cognitive impairment is often related to worsening of hypoxia and/or hypercapnia, as well as to co-morbidities such as Alzheimer's disease, Parkinson's disease, cerebrovascular diseases
Tremors	Intention tremors or tremors due to overuse of β-adrenergic agonists or Parkinson's disease can make proper inhaler loading or twisting the inhaler difficult or even impossible
Hand–eye coordination	Some older patients may have difficulties in locating their mouth for delivering the spray from a pMDI
Dexterity and hand strength	Inhaler manipulation requires manual dexterity and strength, which may be affected by osteoarthritis, joint pain and neurological conditions such as Parkinson's disease. Impairment in manual dexterity may affect preparation of capsule-based DPIs, which require loading, puncturing and inserting the capsule into a small holding chamber. Inadequate hand strength may lead to an inability to press the pMDI canister for releasing the dose
Vision	Visual deficits may affect the patient's ability to see the dose counter, leading some patients to believe the device still holds medications when it is empty. Visual deficits may affect proper loading of the inhaler, particularly for capsule-based DPIs
Hearing	Poor hearing may prevent patients from hearing the 'click' indicating readiness to inhale some DPIs or the discharge from a pMDI into a spacer
Chest wall and respiratory muscle strength	Stiffening of the thoracic cage from calcification of the rib cage and age-related kyphosis from osteoporosis may reduce the ability of the thoracic cage to expand during inspiration and places the diaphragm at a mechanical disadvantage to generate effective contraction. Respiratory muscle strength decreases with age due to muscle atrophy and age-related decrease in fast twitch fibres. All these age-related structural changes may reduce the patient's ability to generate the minimum flow and volume needed to correctly operate some inhaler devices

DPI dry powder inhaler, *pMDI* pressurised metered-dose inhaler

and activity [71]. Hence, abnormalities in executive function and the memory domain may influence adherence through poor recall of inhaler technique and remembering to use their inhaler. In COPD patients aged 76–94 years, Allen [12] demonstrated that cognitive impairments ranging from borderline to mild dementia correlated with incompetent use of a pMDI. Chronic hypercapnia and hypoxia, which are common in end-stage COPD, negatively affect cognitive function, especially in patients who already demonstrate mild cognitive dysfunction [72]. Hypoxia and hypercapnia seem to affect executive function more than orientation or memory [73].

The presence of rheumatologic diseases such as arthritis or joint pain as well as a reduction in physical strength may also contribute to an inability to use inhaler devices correctly [69]. Physical limitations may lead to an inability to prime and actuate a pMDI, thus compromising hand–breath coordination technique. Similarly, reductions in manual dexterity may negatively affect the preparation of some DPIs, mainly capsule-based DPIs requiring single doses to be individually loaded into the inhaler immediately before use. Inadequate hand strength for inhaler device manipulation may be evident in up to one-third of elderly patients [74]. Gray et al. [75] found that reduced hand strength was a significant predictor of incorrect use of pMDIs in a group of elderly (mean age 69.7 years) COPD patients.

4.1 Choosing an Inhaler Device for Elderly COPD Patients

There is increasing recognition that a successful clinical outcome is determined as much by the choice of an appropriate inhaler device as by the drugs that go in them [7, 8, 50]. However, the current literature seems to lack a unified consensus on the criteria for choosing and prescribing inhalation devices [76]. In contrast, healthcare professionals are usually comfortable treating patients based on the pharmacological properties of the drug molecule. However, although in clinical practice the selection of a class of medications is the first step followed by the specific substance [3] and, possibly, the inhalation device (if a choice is available), we believe that selection of the inhaler warrants greater priority [77, 78].

The key issues to consider when choosing an inhaler is the device with which the patient is already familiar or already using, the patient's preference, their ability to use the device correctly, the availability of devices that can deliver the desired drug, the convenience and portability of available devices, and the familiarity of the physician with potential devices [78]. Drug delivery from all inhaler devices depends on how the patient prepares the device and then inhales from it. The relative difficulties in completing these two steps correctly can be shown on a visual scale, with the pMDI being the easiest to prepare and the hardest

to inhale from correctly at one extreme and the nebuliser being the hardest to prepare and easiest to inhale from at the opposite end (Fig. 2). The opposing inhalation techniques needed to use pMDIs and DPIs correctly means that their concurrent use has obvious disadvantages and is discouraged [79]. In practice, however, the use of short-acting β_2-adrenergic agonists given via pMDIs is so common that many patients do use both types of device concurrently. In 2005 a joint committee of the American College of Chest Physicians and the American College of Asthma, Allergy, and Immunology published evidence-based guidelines provided recommendations on inhaler device selection and assessed the outcomes of aerosol therapy [5]. The authors found no significant difference between devices for any efficacy outcome in any clinical setting of patients investigated, while adverse effects were minimal and primarily related to a higher delivered drug dose [5]. The findings of this document should not be interpreted to mean that the device choice for a specific patient does not matter. Rather, the document states that each of the devices studied can work equally well in patients who can use them correctly. However, this evidence-based systematic review provides little information about who is likely to use one device or another properly, and nor does it address many other considerations that are important for choosing a delivery device, such as the age of the patients or the degree of severity of the disease. More recently, a position paper produced by a joint task force of the European Respiratory Society and the International Society of Aerosol Medicine provided indications for choosing the best inhaler device based on the patient's disease, level of inspiratory flow, population, clinical setting and inhalation technique [20]. Dekhuijzen et al. [78] proposed an algorithm that can be of assistance to help physicians make the most appropriate choice of inhaler device (Fig. 3). This algorithm is based on the patient's physical abilities, considering whether the patient is capable of inhaling consciously, reliably generating and controlling sufficient inspiratory flow, and coordinating inhaler activation with inspiration [78].

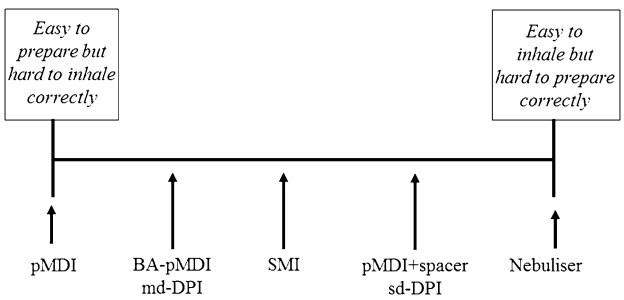

Fig. 2 Visual representation contrasting ease of use with ease of preparation. *BA-pMDI* breath-actuated pMDI, *md-DPI* multi-dose dry powder inhaler, *pMDI* pressured metered-dose inhaler, *sd-DPI* single-dose dry powder inhaler, *SMI* soft mist inhaler

Patient preference for a particular device is another important issue to consider when choosing an inhaler device for a particular patient [80]. Indeed, patient participation in treatment choices and patient satisfaction regarding their inhaler are both strongly associated with increased adherence [29] and, possibly, better outcomes [81]. Interestingly, patient preference might be indicative of ease of use at an individual level [82]. Several attributes of inhalers determine patients' preferences and satisfaction with their device. Their ranking of importance does not fit perfectly with that of doctors [83], underlining the need to personalise device choice by taking into account patients' input as part of a shared decision process.

The selection of an inhaler device for an elderly patient with COPD should be preceded by a careful evaluation of the cognitive competency of the patient, as well as of his/her co-morbidities. These constraints may easily be detected upon patient demonstration of each device. Such restrictions may be more evident in advanced stages of the disease and may warrant assisted administration of aerosolised medication through use of nebulisers by trained individuals. In patients aged 63–85 years, the rate of correct use almost doubled from 36 % for a pMDI to 64 % using a BA-pMDI [84]. When prescribing a pMDI in elderly patients, either a BA-pMDI or a press-and-breath pMDI in combination with a spacer should be prescribed [85]. Comparing these two alternatives in 423 patients aged over 70 years but with intact cognitive function, the pMDI with a large-volume spacer was correctly used more frequently than a breath-actuated inhaler [85]. Although symptom relief was somewhat slower than with administration of bronchodilator therapy with a nebuliser [86], dyspnoea and lung function improved to similar extents when using a pMDI plus spacer in elderly patients aged 60 years and over during an acute exacerbation of COPD [87]. Patients with COPD appear to make fewer device-handling errors when using a DPI than with a pMDI [88]. Similarly, elderly patients aged 75–101 years used the Turbohaler® DPI more correctly than a pMDI, even in combination with a large-volume spacer [89]. However, it should be noted that in this study [89] the main reason that the pMDI plus spacer combination performed less well was that patients had difficulties assembling the pMDI with the spacer. For the same reason, this study also found that patients used a BA-pMDI (the Easi-Breathe®) correctly more often than the pMDI plus spacer combination, in direct contradiction to Ho et al.'s [85] findings.

Therefore, when choosing between inhaler devices in elderly COPD patients with intact cognitive function, priority should be given to either a multi-dose DPI, a BA-pMDI or, if correct assembling can be assured, a pMDI

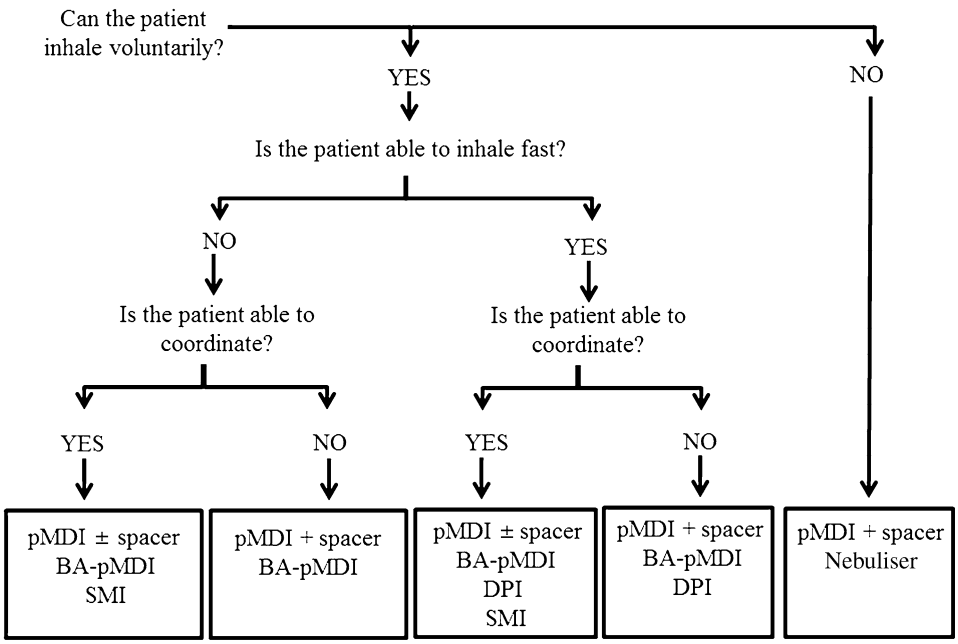

Fig. 3 Personalising inhalation therapy: a possible algorithm. The order of devices does not imply order of preference (modified from Dekhuijzen et al. [78]). *BA-pMDI* breath-actuated pMDI, *DPI* dry powder inhaler, *pMDI* pressurised metered-dose inhaler, *SMI* soft mist inhaler

plus spacer. Certainly, a press-and-breath pMDI should be the last choice when these alternatives are available.

5 Training Patients, a Major Role of Healthcare Professionals

Management of chronic airway disease is 10 % medication and 90 % education [90]. Given the high rate of inhaler misuse by patients and the lack of a 'perfect' inhaler that may reduce the need for patient education, repeated cycles of instruction on the correct use of inhalers and reassessment of patients' inhaler technique until they display mastery of device technique is of crucial importance. Patient education has repeatedly been shown to improve inhaler technique [90, 91], which in turn decreases symptoms and the hospitalisation rate, thus improving quality of life [92]. However, the positive effects of education tend to decrease with time [93], underlining the need to check inhaler technique regularly and provide retraining when necessary.

The cornerstone of education is knowledgeable healthcare providers. Failure of patients to use inhaler devices effectively can be largely attributed to deficiencies in clinicians' knowledge of inhaler technique. Studies assessing the knowledge of inhaler technique by healthcare professionals often found disappointing results [94]. In a study performed in 1999 involving 746 patients, 466 nurses and 428 physicians, only 9 % of patients, 15 % of nurses and 28 % of physicians showed correct inhalation technique with pMDIs [94]. Later on, although some improvement was found, only a minority (6–36 % depending on the device) were able to provide a fully correct demonstration of inhaler technique for pMDIs alone, pMDIs plus spacer, BA-pMDIs or DPIs [95]. Other studies of pharmacists' skills found similarly worrying results: for instance, among 266 pharmacists in Turkey, the mean number of correct steps was only about four to five out of ten for MDIs, Turbuhaler®, Diskus® and Aerolizer® [96]. General practitioners and nurses have also demonstrated insufficient scores [97]. In many cases, even hospital nurses caring for acute respiratory patients do not seem to have the required skills [98]. Respiratory therapists have been found to be more efficient at providing inhaler training [99], but they are not universally available.

These data underline the need to develop training programmes aiming at empowering healthcare professionals to teach and check inhalation technique. Such programmes have been shown to be efficient at improving both skills [100] and real-life practice [101] in both training and practicing caregivers.

6 Conclusion

Treatment of COPD with inhaled therapy should be customised to each older patient, since selection of an inhaler device for these patients is influenced by their cognitive, physical and educational abilities. pMDIs in conjunction with spacer devices, BA-pMDIs and multi-dose DPIs are the most practical way of delivering medications. These inhalers can be considered to be the first choice for elderly

patients able to follow and remember instructions. However, for those elderly patients with cognitive impairment and/or hand arthritis or neurological conditions causing frailty, nebulisers represent a valuable alternative. Once selected, patients should receive appropriate training in inhaler use and undergo regular assessment of inhalation technique during follow-up visits, a challenge for clinicians with busy schedules. Although patient education and involvement in treatment decisions can improve adherence [92–94], the multidimensional nature of adherence means that no single intervention or strategy per se can enhance it. All those involved in the process (government authorities, patient organisations, scientific societies, stakeholders) must cooperate to develop a combined action plan based on the individual needs of the patients.

Compliance with Ethical Standards

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Conflict of interest FL has received speaker honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla and Teva; GAF has received speaker honoraria from Edmond Pharma, Dompè, Menarini Farmaceutici and Mundipharma. CM and EC declare that they have no conflicts of interest.

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