

REVIEW

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The importance of inhaler devices in the treatment of COPD

Matteo Bonini¹ and Omar S. Usmani^{2,3*}

Abstract

Chronic obstructive pulmonary disease (COPD) represents a socio-economic burden and requires regular and ongoing treatment. Inhalation therapy is recommended at all stages of the disease and allows the delivery of active molecules directly to the target site of action, whilst minimising adverse side-effects. Inhalers therefore play a crucial role in the effective management of patients with COPD and their choice is as important as that of the drug. The three most important factors that influence inhaled drug deposition within the airways are the patient's inhalation flow, the aerosol velocity, and the inhaled drug particle size. These ultimately impact on the amount of drug reaching the target site and therefore the functional and clinical responses of the patient. Furthermore, patients' training and education in the use of inhalers have been shown to be directly related to the efficacy of the therapy. However, in daily clinical practice, too little consideration is given to the features of the different inhalers and to the ability of patients to properly handle the device, and precise recommendations are greatly needed to help healthcare professionals to advise and prescribe the most 'appropriate' inhaled drug/device product. The present review aims to provide the latest evidence on the importance of the inhaler device in the management of patients with COPD.

Keywords: Chronic obstructive pulmonary disease, Inhaler, Aerosol, Metered dose inhaler, Dry powder inhaler, Nebuliser, Treatment, Therapy, Adherence, Compliance

Introduction

Chronic obstructive pulmonary disease (COPD) represents a major global concern for national healthcare systems, being ranked as the fourth leading cause of death in the world and significantly affecting the quality of life of patients [1, 2]. COPD is characterised by persistent airway inflammation and bronchial obstruction and requires regular and ongoing treatment. Inhalation therapy is the mainstay of treatment in patients with COPD, where bronchodilators (beta-2 agonists, anti-muscarinic agents) and anti-inflammatory drugs (corticosteroids) are recommended by international strategy documents at any stage of the disease [3]. In contrast, oral treatments such as theophylline, phosphodiesterase-4 inhibitors and corticosteroids are only occasionally used. Indeed, inhaled treatment has several advantages over

oral therapy as inhalation allows the delivery of active molecules directly to the target site of action, whilst minimising adverse side-effects. Furthermore, a lower drug dose is needed to achieve the therapeutic effect via the inhaled route and the onset of action is more rapid, in contrast with oral administration [4].

Inhalers, therefore, play a crucial role in the management of patients with COPD and it is being recognised that the choice of the inhalation device appears to be as important as that of the drug molecule [5]. Indeed in daily clinical practice, pulmonologists usually focus on the pharmacological properties of the various respiratory drugs in selecting the best possible therapeutic option, but little consideration is given to the features of the different inhalers and to the ability of the patient to use the device, which are topical issues [6]. In fact it is often underappreciated that incorrect inhalation technique by the patient is directly associated with increased healthcare resource utilisation [7–9].

Furthermore, with increasingly constrained societal healthcare budgets and expiring patent protection for

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many branded medications, there is emphasis on the development of generic inhaled drugs that are therapeutically equivalent to the original registered products, but may differ in their formulation and the design of the inhalation device. This growing scenario poses practical clinical questions about the potential impact of switching from branded to generic inhaler products in managing patients with COPD [10]. Indeed, the estimated 10 new drug product launches in COPD over the next 2 years [11, 12] will lead to even more confusion, and apathy, in respiratory prescribing, as there are currently more than 250 inhaler products in pharmaceutical formularies [13] and direction is greatly needed to help healthcare professionals advise and prescribe the 'appropriate' inhaled drug/device product for patients.

The present review article aims to provide the latest evidence on the importance of the inhaler device in the management and treatment of patients with COPD, and specifically to collect data to support decisions on the appropriate choice of device by healthcare professionals. It also addresses and contrasts the advantages and limitations of different available inhalation device options.

Review

Methodology

Papers were identified through a search strategy run in the principal electronic database (Pubmed, ISI Web of Knowledge, CENTRAL) from the date of inception up to 10th March 2015. The following key-words were selected: "chronic obstructive pulmonary disease", "COPD", "device" and "inhaler". No restriction was placed on study design and language of publication.

Choosing an inhaler device

The goal of therapy in managing patients with COPD is to obtain full control of their symptoms and prevent disease exacerbations, by delivering the optimal inhaled drug dose to the target site of action in the lungs, with minimal or no adverse side-effects [3]. Despite the clinical importance of inhaled therapy in treating patients with COPD, current literature seems to lack a unified consensus on the standards for choosing and prescribing inhalation devices, whereas in contrast healthcare professionals are usually comfortable in treating patients based on the pharmacological properties of the drug molecule. In 2005, Dolovich and colleagues, on behalf of the American College of Chest Physicians (ACCP) and of the American College of Asthma, Allergy, and Immunology (ACAAI) published evidence-based guidelines to provide recommendations on inhaler device selection and assessed the outcomes of aerosol therapy [14]. Their systematic review and meta-analysis of randomized controlled trials (RCT's) showed no significant difference between devices for any efficacy outcome in any clinical

setting of patients investigated, while adverse side-effects were minimal and were primarily related to a higher delivered drug dose. The authors suggested that when selecting an aerosol delivery device, the choice should be based on several parameters, such as drug availability and administration time, patient age and ability to use the device correctly, convenience in both outpatient and inpatient settings, costs, as well as physician and patient preference. More recently, a position paper produced by a joint task force of the European Respiratory Society (ERS) and the International Society for Aerosols in Medicine (ISAM) provided indications for choosing the best inhaler device based on the patients' disease, level of inspiratory flow, population, clinical setting and inhalation technique [15]. However, less than 2 % of the Global Initiative for Obstructive Lung Disease (GOLD) strategy document for patients with COPD focusses on device-related issues [16]. In contrast the new GINA strategy document for asthma now places the assessment of the patient's inhalation technique and prescription of the appropriate device as a key component in their treatment algorithms [17].

The three most important factors that influence inhaled drug deposition within the airways is the patient's inhalation flow, the aerosol velocity, and the inhaled drug particle size; these factors ultimately impact on the amount of drug reaching the airways and therefore, the functional and clinical responses of the patient [18]. The choice of an inhalation device in patients with COPD should therefore be mainly driven by these parameters.

Inhalation flow and aerosol velocity

Achieving the correct inhalation flow from any inhalation device is critical in order for the patient to achieve therapeutic benefit from the inhaled drug. However, many patients use inhalers incorrectly and their suboptimal use directly affects clinical efficacy. The key concern in this scenario is that healthcare professionals often attribute lack of clinical efficacy with the pharmacological properties of the drug, rather than the inability of the patient to use the inhalation device properly. Consequently, doctors increase the drug dose delivered to the patient, leading to the potential for greater toxicity and adverse side-effects, which could have been avoided by attending to the patient-device interaction. With pressurised metered dose inhalers (pMDIs), the failure to inhale slowly and deeply is often a greater problem than poor coordination [19]; indeed, patients inhale too fast from pMDIs potentially leading to greater impaction of the aerosolised drug in the back of the throat and less drug reaching the lungs [20]. In contrast, dry powder inhalers (DPIs) require much higher inhalation flows than pMDIs, and not using a forceful and deep inspiration from DPIs is a critical problem [21]. Certainly

most DPIs are highly dependent on the patient's inhalation flow (flow-dependency) and sometimes inhalation flows ≥ 60 l/min are required to de-aggregate and disperse the drug powder. Patients with COPD use sub-optimal 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 [22]. It will therefore be appreciated that each DPI device is unique and each requires its own 'bespoke' inhalation manoeuvre that should be correctly understood by both the patient and the healthcare professional. In contrast, all pMDIs only require the same 'generic' inhalation manoeuvre from each device. The concerning scenario for the patient is when they are given a pMDI as a reliever medication, a DPI to deliver their maintenance treatment, and a nebuliser to give them added bronchodilation; that is, a prescription of three different devices each requiring different inhalation manoeuvres – no wonder patients don't know how to use devices effectively and are confused! In clinical practice we should try to stratify devices so that the reliever treatment and maintenance therapy are given by the same type of device in order to allow the same inhalation manoeuvre for both; that is, either two similar device types (both pMDIs or both DPIs) or, in the case of patients with asthma, the option of the use of two drugs delivered from one device using the maintenance and reliever therapy approach [23]. Certainly in asthma, it has been shown that patients prescribed the same type of device are more likely to achieve better disease control than those prescribed mixed inhalation device types [24]. The use of devices to assess the patient's inhalation technique (AIM, In-Check dial, 2-Tone trainer), with some mimicking the internal resistance of various inhalers, may also provide significant advantages. These can be used to confirm adequacy of peak inspiratory flow (PIF) either when first prescribing a new device in a patient, or in their regular training and monitoring of inhaler use [25, 26].

Particle size and fine particle fraction

The characteristics of the aerosol particle size distribution emitted from inhalation devices are important in directing the inhaled drug to the target site of action in the lungs. With this regards, the small airways have been extensively reported to be significantly involved in the onset and progression of COPD and a target site of action for inhaled therapy. However, due to their localization deep in the lungs and their anatomical structure, they may not be easily reached by all drug/device products [27, 28],

Drug deposition in the bronchial tree is achieved through different modalities [29]. Turbulence and inertial impaction occur when larger particles deposit in proximal airways, where the velocity of airflow is

maximal. Sedimentation allows suspended particles to deposit through the force of gravity, rather than being exhaled. Diffusion through Brownian motion is responsible for the deposition of the submicron particles within the airways. A drug particle size of between 2 to 5 microns has been shown to have the greatest potential to be deposited throughout the bronchial tree [30]. In fact, particles < 2 micron deposit in the central airways but also deeper into the acinar compartment, while particles > 5 micron tend to deposit proximally in the central airways or the oropharynx, where they produce no clinical effect and give rise to the potential for the drug to be swallowed and contribute to oral bioavailability and adverse side-effects through gastrointestinal absorption. Two indices commonly used to characterise the particle size distribution emitted from aerosols are: the mass median aerodynamic diameter (MMAD), which is the droplet size at which half of the mass of the aerosol is contained in smaller droplets and half in larger droplets [31], and the fine particle fraction (FPF), meaning the proportion of particles < 5 microns in diameter [32]. Both these indices can affect not only the total amount of drug reaching the lungs (total lung deposition), but also the amount of drug that is distributed between the central and distal lung regions.

In a scientific study in patients with asthma involving inhaled salbutamol aerosol particles of 1.5-, 3.0- and 6.0-MMAD, it was observed that the smaller 1.5 micron particles achieved better total lung deposition and better distal airways penetration compared to the larger particles [33, 34]. In clinical practice, commercial drug delivery devices with smaller MMADs have now been developed that have been shown to achieve greater levels of total lung deposition (> 40 %) compared to conventional larger drug particle devices (< 20 %) [35–38]. Specifically in patients with COPD, small particle (~ 1.5 microns) drug formulations have been shown to achieve as good levels of total lung deposition (~ 33 %) in severely diseased patients (FEV_1 43.6 ± 7.2 % of predicted) compared to healthy subjects with normal levels of lung function [39]. Inhalation devices have also been designed to have an emitted aerosol with a higher FPF [40], which have also been shown to achieve more distal airways deposition [41, 42].

The velocity at which an aerosol exits the device is also an important determinant of the regional distribution of drug reaching the lungs. It has been shown that a slow-moving velocity aerosol, coupled with a smaller drug particle size, achieves effective (> 50 %) total deposition in the lungs and also penetration into the distal airway tree [38, 43].

Inhaler training and education

Patient training and education in inhaler use and inhalation therapy is often overlooked in busy clinics, yet

critically the correct use of an inhaler by a patient is directly related to the efficacy of therapy. In other words, misuse of inhalers is directly linked to poor disease control [7–9]. Healthcare providers should not assume that the correct use of a device is intuitive or obvious from the accompanying drug patient information leaflet and instructions. Indeed, professionals should also not rely on only verbal communication either, but rather provide a comprehensive approach with a “step by step” practical hands-on demonstration on the use of the inhalation devices [44]. And this is, in itself, not enough since a retrospective study showed that almost 54 % of patients stopped their medications periodically over a period of 3 months [45]. International strategy documents [3] therefore recommend that inhaler re-education and re-training should be repeated at each visit with a healthcare professional, and that patients should be encouraged to bring their inhalers to demonstrate their inhalation technique. Education should also focus on the rationale why the patient needs the inhaler and on the importance of its regular and pertinent use [46].

Incorrect inhaler technique is a critical factor preventing patients with COPD from receiving the optimal benefits of their prescribed medications (up to 90 % of patients in clinical studies) [47], and particularly in the elderly population and in the late stages of the disease. It has in fact been shown that error rates related to device handling increase with age and with the degree of air-flow obstruction [48–50]. COPD itself is a disease of ageing and elderly patients may suffer from cognitive impairments, hearing and visual problems, or other physical disabilities that potentially all contribute to affect their ability to understand and follow treatment regimens [51]. In addition, aged and severely ill patients are often affected by multiple chronic comorbidities requiring multiple medications through different routes of administration, and treatment complexity is a well-recognized risk factor for poor adherence [52]. A poor device technique is also potentially responsible for relevant economic consequences, considering that of an estimated \$25 billion spent for inhalers annually, \$5–7 billion is wasted because of inhaler misuse [53].

Most importantly, education needs to be directed at healthcare professionals; if they do not know how to use inhaler devices properly, how are they going to teach their patients? In a study by Hanania and colleagues, performed over 20 years ago, respiratory physicians were the most uncertain in the correct use of a range of inhalation devices (pMDIs, DPIs and spacers) in contrast to respiratory nurses or physiotherapists [54]. The authors concluded that medical doctors in particular need additional instruction in inhaler usage during their training. However, the passage of time has not improved matters.

In a recent study, only 14 % of over 1500 physicians surveyed had adequate knowledge of inhaled therapy and of these, less than 50 % knew the correct inhalation manoeuvre required from a DPI device and only ~25 % checked the inhalation technique of the patient before prescribing a new device/drug combination [55].

Once treatment is initiated, adherence to the recommended therapeutic regimen is critical for achieving clinical benefits, particularly for long-term use therapies, and must be distinguished from compliance: the difference being in the patient's willingness to accept therapy. The non-compliant patient merely ignores prescriptions, while the non-adherent one fails to properly follow them despite the willingness to assume therapies [56]. Importantly, patients should be engaged in the decision of inhaler device prescription and the patient's preference should not be ignored [57], as it may significantly affect the effectiveness of inhalation therapy. An inhaler device should not be changed without consulting the patient and in the study by Doyle and colleagues, they showed that switching a patient's inhaler without their consent could diminish the self-control associated with good asthma management, leave the doctor-patient relationship damaged, and increase resource utilisation and waste medication [58]. Healthcare providers should therefore very carefully evaluate which device is appropriate to the clinical needs and wishes of the patient [57]. Taken together, the above observations emphasize the central role played by devices in clinical practice and support the importance of an adequate inhaler choice for optimal control of the disease.

Inhaler devices for treating COPD patients

Aerosols are either solutions containing the medication or, solid drug particles suspended in a gas or in a dry powder. Aerosols can be delivered from different pMDIs, DPIs and nebulisers. In recent years, several technological innovations in device engineering and formulation science have significantly improved the performance of all existing categories of inhalation devices, and some highly effective delivery systems have been developed (Table 1). The new ‘generation’ of inhalers have pulmonary deposition fractions of 40–50 % of the nominal dose, which are considerably higher compared with the 10–15 % that inhalers currently used in clinical practice achieve [59].

From the 19th century until the 1950's, compressed-air nebulizers were the main device in clinical use for the administration of inhaled aerosolised drugs to respiratory patients. The first commercial pMDI was developed by Riker Laboratories in 1956 as a portable, multi-dose delivery system for bronchodilator drugs. Since then, the pMDI has become the most commonly prescribed inhaler device for drug delivery to the bronchial tree [60]. The relatively low cost and the wide

Table 1 Principal features of available inhalers

Device	Type	Advantages	Disadvantages
Pressurised metered-dose inhalers (pMDI's)	• CFC driven (obsolete)	Portable and compact	Ozone-depleting properties (CFC driven)
		Independent of inspiratory flow	Better perform with spacers (CFC driven)
	• HFA driven	Reproducible dosing	Need to be shaken prior use (CFC driven)
		No contamination risk	Require coordination between actuation and inspiration (CFC and HFA driven)
		Quick and easy to use	High oropharyngeal deposition
• Breath-actuated	Wide variety of drugs available	Cold Freon effect	
	Low cost		
Dry powder inhalers (DPI's)	• Single-dose	Portable and compact	Inspiratory flow dependent
	• Multi-dose	Do not require coordination	Poor dose reproducibility
	• Power-assisted	Quick and easy to use	Affected by environmental factors (i.e. humidity)
		No spacer required	
Soft-mist inhaler		Portable	Dose loading into device
		Slow velocity aerosol	
		Long plume duration	
		Does not require coordination	
		No propellant	
		No spacer required	
Nebulisers	• Jet	Propellant free	Bulky equipment
	• Vibrating mesh	High patient's adherence	More complex use
	• Ultrasonic	Slow velocity aerosol	Power source
			Requires frequent cleaning

variety of medications available in the pMDI device have contributed to the popularity of this delivery system. However, the correct use of pMDIs requires a slow and deep inhalation and a certain degree of coordination between inhalation and device actuation. Too fast inhalation through a pMDI device and lack of coordination can both contribute to ineffective drug delivery to the lungs with excess deposition in the oropharynx [7]. To circumvent these issues, the combined use of a pMDI plus spacer is often recommended, especially for elderly patients who may have problems with dexterity and coordination. However, spacers were developed primarily to be used with the old chlorofluorocarbon (CFC) propellant pMDIs (which are now obsolete) mainly to achieve three key outcomes; (i) to create a 'space' for the fast aerosol plume to slow down and achieve a slow velocity prior to inhalation at the mouth, in order to decrease oropharyngeal deposition, (ii) to provide a distance in order for the CFC-propellant to evaporate and produce smaller drug particles prior to inhalation and thereby achieve more effective lung deposition and, (iii) to allow patients to comfortably inhale the drug from a 'holding chamber', thereby decreasing the need for coordination on actuation. However, the need for

spacers with the newer generation of hydrofluoroalkane (HFA) pMDIs, and particularly HFA-solution pMDIs, may be far less, as these devices have slower velocity aerosols with a smaller drug particle size or fine particle fraction. In addition, some of the newer pMDIs are less flow dependent; that is, there is consistency of dose delivery to the lungs irrespective of the inhalation flow of the patient [40].

The first generation of pMDIs consisted of aluminium canisters, containing a pressurised suspension of micronized drug particles dispersed in chlorofluorocarbon (CFC) propellants. In suspension formulations, the active drug is not soluble in the propellant and remains as a solid powder within the container. Consequently, the inhaler must be shaken prior use to ensure uniform distribution of the particles and a constant emitted dose at each use. Failure to shake the device has been shown to reduce the delivery of both beta-2 agonists and corticosteroids by up to 50 % [61]. Furthermore, studies report that not shaking the device between successive dosages can also reduce drug delivery [62]. Much of the innovation in pMDI development arose from the Montreal Protocol declaration banning the use of CFCs, and the pharmaceutical industries

developed HFA propellants for the new pMDIs that did not have ozone-depleting properties [63]. The transition from CFC to HFA propellants has allowed the opportunity for formulation scientists to develop pMDI solution formulations, and particularly HFA- solution pMDI aerosols in which the drug is uniformly distributed in the canister, which therefore doesn't need to be shaken prior to use [63].

Breath-activated pMDI (BA-pMDI) devices have been available for a good few years, and have been shown to be helpful in patients with poor coordination issues associated with conventional pMDIs [64]. BA-pMDI's contain a conventional pressurised canister, with a flow-triggered system driven by a spring, which releases the drug dose during inhalation, so that firing and inhaling are automatically coordinated. BA-pMDIs can be actuated at a low patient inhalation flow which is readily achievable by most patients. However, data report drug deposition in the lungs of patients using BA-pMDI's is not that different to patients with good coordination using a press-and-breathe pMDI of the same formulation, but only significantly higher compared to those patients with a poor coordination [64, 65]. More recent studies have shown improved drug deposition and increased patient confidence related to successful dosing with the use of BA-pMDI's [66, 67]. Prescribing BA-pMDI's to COPD patients may therefore improve disease control reducing health care costs, in spite of the increased device costs, but the greatest limiting factor is the availability of a variety of drug molecules in this particular device. Further advances continue in pMDI technology, and are represented by innovative devices which incorporate small microprocessors. These 'intelligent' inhalers allow the patient's inhalation to be controlled and their adherence to be monitored [64]. These developments may offer significant improvements to conventional pMDI's, but still require careful analyses to estimate patients' clinical benefits and justification for additional expenses.

In 1971, Bell and colleagues introduced the first DPI to deliver therapy to patients with COPD [68]. Since then, a diverse number of DPI devices are currently available to treat patients with COPD, each with its own different handling instructions and each with its own 'bespoke' inhalation manoeuvre. Based on their design, DPIs can be classified into three different categories: the first generation, single-dose DPIs; the second generation, multiple-dose DPIs, and the third generation DPIs, 'active' or power-assisted DPIs. The major advantage of DPIs is that they do not require coordinated activation. However, in a similar manner to pMDIs, there are marked differences between the lung deposition from different DPI devices. DPI devices can be flow-dependent leading to variability in drug delivery

to the lungs based on the inhalation flow of the patient through the device [62, 69]. In addition, most conventional DPIs are inherently dependent on the energy in the patient's breath during inhalation to de-aggregate and disperse the dry powder contained within the device, and these factors may lead to low levels of drug deposition (~20 %) to the lungs at low patient inhalation flows [70, 71]. However, recent innovations in DPI engineering and chemistry have advanced this device category with a newer generation of inhalers that are activated at low (and not high) patient inhalation flows (~30 l/min or less) and achieve far better levels of lung deposition (>40 %) [72]. DPIs have been also developed with small particle dry-powder formulations inhaled at low inhalation flows achieving high (>40 %) levels of lung deposition [42].

There are a variety of nebulisers - such as jet, vibrating mesh and ultrasonic - available on the market that are used mainly with bronchodilator agents in patients with COPD, and each has a variable performance based on the specific model [73, 74]. A newer generation of nebulisers have been developed that aim to decrease the inefficiency, waste, and variability of nebulized drug delivery. Some vibrating mesh disk nebulisers, powered by a compressor and containing a microchip, control drug delivery to the patient and have an adaptive aerosol system that is able to pulse the inhaled drug during the inhalation phase therefore leading to less dose wastage, as well as to provide detailed feedback on each treatment, and have been shown to improve the patient's adherence [75]. A smart nebuliser system has been developed that contains an electronic smart-card unit with an air compressor, which is coupled to either jet or vibrating mesh nebulisers and operates to accurately dose and target aerosol delivery, and studies have shown better efficacy compared to standard nebulisers and are an excellent driver for patients' adherence [76, 77]. New hand-held multi-dose nebuliser devices have also been developed that have the potential to compete with both pMDIs and DPIs on the portable inhaler market [75].

A unique device that has the attributes of a nebuliser (being propellant free), but also that of a pMDI (hand-held and portable), and that of a spacer (allowing a slow exit velocity aerosol) was developed over a decade ago and has been categorised as a 'soft-mist' inhaler [78]. This device atomises the drug solution using mechanical energy imparted by a spring, producing a fine, slow-moving mist, where aerosol spray duration is considerably longer (approximately 1.2 s) compared to that for pMDI's (0.15-0.35 s) and these features lead to low levels of drug deposition in the oropharynx and effectively high total lung deposition (>50 %) [79]. Indeed this device has additional

technological advances with a small drug particle size (an average MMAD of 2 microns), together with a high FPF (~75 %) which both contribute to effective distal airway lung deposition to target the site of disease in patients with COPD [38].

Conclusions

Inhalation therapy is the mainstay of treatment in patients with COPD. Collected data show that in the last years, several innovative and significant developments have been achieved in the field of device engineering and formulations. Physicians can count on a broad variety of device categories with features all providing effective aerosol delivery for COPD treatment. Indeed, it seems a perfect inhaler does not exist and each has its advantages and limitations. In fact, ensuring effective inhalation and drug delivery to the target site depends on many factors, which ultimately impact on patients' response to treatment. In daily practice, an appropriate inhaler choice should therefore carefully take into consideration not only device related aspects such as aerosol velocity and drug particle size, but also patients' pulmonary function (inhalation flow), skills (dexterity, cognition) and preferences. Unfortunately, however little has been done to sensitize the healthcare provider community to the relevance of these aspects. Furthermore, despite a good amount of reliable evidence in literature, few and vague recommendations are provided by international strategy documents and respiratory scientific societies. This situation results in a reduced efficacy of inhalation therapy and in a waste of financial resources. Efforts are therefore critically needed to improve healthcare provider knowledge and education of inhalation devices in order to optimise clinical benefits for their patients and positively influence both doctor-patient satisfaction with aerosol therapy.

Competing interests

MB declares no competing interests. OSU has received academic institutional grants in the last three years from AstraZeneca, Chiesi, GlaxoSmithKline, Prosonix, and Takeda; and has received speaker honoraria from Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, and Takeda.

Authors' contributions

MB run the search strategy and identified suitable papers to be included in the review. Both MB and OS equally contributed to manuscript preparation. Both authors read and approved the final manuscript.

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References

- Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095–128.
- Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2163–96.
- The 2015 Global Strategy for Diagnosis, Management, and Prevention of COPD. <http://www.goldcopd.org/> Accessed on March 7, 2015
- Dolovich MB, Dhand R. Aerosol drug delivery: developments in device design and clinical use. *Lancet*. 2011;377:1032–45.
- Lavorini F, Usmani OS. Correct inhalation technique is critical in achieving good asthma control. *Prim Care Respir J*. 2013;22(4):385–6. doi:10.4104/pcrj.2013.00097.
- Smaldone G, Berkland C, Gonda I, Mitchell J, Usmani OS, Clark A. Ask the experts: the benefits and challenges of pulmonary drug delivery. *Ther Deliv*. 2013;4(8):905–13.
- Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J*. 2002;19(2):246–51.
- Melani AS. Inhalatory therapy training: a priority challenge for the physician. *Acta Biomed*. 2007;78(3):233–45.
- Molimard M, Colthorpe P. Inhaler devices for chronic obstructive pulmonary disease: insights from patients and healthcare practitioners. *J Aerosol Med Pulm Drug Deliv*. 2014. [Epub ahead of print].
- Lavorini F, Ninane V, Haughney J, Bjermer L, Molimard M, Dekhuijzen RP. Switching from branded to generic inhaled medications: potential impact on asthma and COPD. *Expert Opin Drug Deliv*. 2013;10(12):1597–602.
- Cazzola M, Matera MG. Bronchodilators: current and future. *Clin Chest Med*. 2014;35(1):191–201.
- Matera MG, Calzetta L, Segreti A, Cazzola M. Emerging drugs for chronic obstructive pulmonary disease. *Expert Opin Emerg Drugs*. 2012;17(1):61–82.
- Capstick TG, Clifton IJ. Inhaler technique and training in people with chronic obstructive pulmonary disease and asthma. *Expert Rev Respir Med*. 2012;6(1):91–101.
- Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest*. 2005;127(1):335–71.
- Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P, et al. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J*. 2011;37:1308e31.
- Dekhuijzen PN, Bjermer L, Lavorini F, Ninane V, Molimard M, Haughney J. Guidance on handheld inhalers in asthma and COPD guidelines. *Respir Med*. 2014;108(5):694–700.
- The 2014 Global Initiative on Asthma. <http://www.ginasthma.org/> Accessed on March 7, 2015.
- Labiris NR, Dolovich MB. Pulmonary drug delivery. Part I: physiological factors affecting therapeutic effectiveness of aerosolized medications. *Br J Clin Pharmacol*. 2003;56(6):588–99.
- Al-Showair RA, Tarsin WY, Assi KH, Pearson SB, Chrystyn H. Can all patients with COPD use the correct inhalation flow with all inhalers and does training help? *Respir Med*. 2007;101(11):2395–401.
- Hardwell A, Barber V, Hargadon T, McKnight E, Holmes J, Levy ML. Technique training does not improve the ability of most patients to use pressurised metered-dose inhalers (pMDIs). *Prim Care Respir J*. 2011;20(1):92–6. doi:10.4104/pcrj.2010.00088.
- Chrystyn H, Small M, Milligan G, Higgins V, Gil EG, Estruch J. Impact of patients' satisfaction with their inhalers on treatment compliance and health status in COPD. *Respir Med*. 2014;108(2):358–65.
- Azouz W, Chetcuti P, Hosker HS, Saralaya D, Stephenson J, Chrystyn H. The inhalation characteristics of patients when they use different dry powder inhalers. *J Aerosol Med Pulm Drug Deliv*. 2015;28(1):35–42.
- Papi A, Corradi M, Pigeon-Francisco C, Baronio R, Siergiejko Z, Petruzzelli S, et al. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. *Lancet Respir Med*. 2013;1(1):23–31.

24. Price D, Chrystyn H, Kaplan A, Haughney J, Román-Rodríguez M, Burden A, et al. Effectiveness of same versus mixed asthma inhaler devices: a retrospective observational study in primary care. *Allergy Asthma Immunol Res.* 2012;4(4):184–91. doi:10.4168/air.2012.4.4.184.
25. Amirav I, Newhouse MT, Mansour Y. Measurement of peak inspiratory flow with in-check dial device to simulate low-resistance (Diskus) and high-resistance (Turbohaler) dry powder inhalers in children with asthma. *Pediatr Pulmonol.* 2005;39(5):447–51.
26. van der Palen J. Peak inspiratory flow through diskus and turbuhaler, measured by means of a peak inspiratory flow meter (In-Check DIAL). *Respir Med.* 2003;97(3):285–9.
27. Usmani OS. Treating the small airways. *Respiration.* 2012;84(6):441–53.
28. Bonini M, Usmani OS. The role of the small airways in the pathophysiology of asthma and COPD. *Therapeutic Advances in Respiratory Disease.* 2015. in press.
29. Tsuda A, Henry FS, Butler JP. Particle transport and deposition: basic physics of particle kinetics. *Compr Physiol.* 2013;3(4):1437–71.
30. Chrystyn H. Anatomy and physiology in delivery: can we define our targets? *Allergy.* 1999;54 Suppl 49:82e7.
31. Scichilone N, Benfante A, Bocchino M, Braido F, Paggiaro P, Papi A, et al. Which factors affect the choice of the inhaler in chronic obstructive respiratory diseases? *Pulm Pharmacol Ther.* 2015. [Epub ahead of print].
32. Friebel C, Steckel H, Müller BW. Rational design of a dry powder inhaler: device design and optimisation. *J Pharm Pharmacol.* 2012;64(9):1303–15.
33. Usmani OS, Biddiscombe MF, Nightingale JA, Underwood SR, Barnes PJ. Effects of bronchodilator particle size in asthmatic patients using monodisperse aerosols. *J Appl Physiol* (1985). 2003;95(5):2106–12.
34. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of beta2-agonist particle size. *Am J Respir Crit Care Med.* 2005;172(12):1497–504.
35. Newman S, Salmon A, Nave R, Drollmann A. High lung deposition of 99mTc-labeled ciclesonide administered via HFA-MDI to patients with asthma. *Respir Med.* 2006;100(3):375–84.
36. Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ. Lung deposition of hydrofluoroalkane-134a beclomethasone is greater than that of chlorofluorocarbon fluticasone and chlorofluorocarbon beclomethasone: a cross-over study in healthy volunteers. *Chest.* 2002;122(2):510–6.
37. Warren S, Taylor G, Smith J, Buck H, Parry-Billings M. Gamma scintigraphic evaluation of a novel budesonide dry powder inhaler using a validated radiolabeling technique. *J Aerosol Med.* 2002;15(1):15–25.
38. Brand P, Hederer B, Austen G, Dewberry H, Meyer T. Higher lung deposition with Respimat Soft Mist inhaler than HFA-MDI in COPD patients with poor technique. *Int J Chron Obstruct Pulmon Dis.* 2008;3(4):763–70.
39. De Backer W, Devolder A, Poli G, Acerbi D, Monno R, Herpich C, et al. Lung deposition of BDP/formoterol HFA pMDI in healthy volunteers, asthmatic, and COPD patients. *J Aerosol Med Pulm Drug Deliv.* 2010;23(3):137–48.
40. Johal B, Howald M, Fischer M, et al. Fine particle profile of fluticasone propionate/formoterol fumarate versus other combination products: the DIFFUSE study. *Comb Prod Ther.* 2013;3:39–51.
41. Tahir BA, Swift AJ, Marshall H, Parra-Robles J, Hatton MQ, Hartley R, et al. A method for quantitative analysis of regional lung ventilation using deformable image registration of CT and hybrid hyperpolarized gas/1H MRI. *Phys Med Biol.* 2014;59(23):7267–77.
42. Corradi M, Chrystyn H, Cosio BG, Pirozynski M, Loukides S, Louis R, et al. NEXThaler, an innovative dry powder inhaler delivering an extrafine fixed combination of beclomethasone and formoterol to treat large and small airways in asthma. *Expert Opin Drug Deliv.* 2014;11(9):1497–506.
43. Zierenberg B. Optimizing the in vitro performance of Respimat. *J Aerosol Med.* 1999;12 Suppl 1:S19–24.
44. Lavorini F, Levy ML, Corrigan C, Crompton G, ADMIT Working Group. The ADMIT series— issues in inhalation therapy. Training tools for inhalation devices. *Prim Care Respir J.* 2010;19:335–41.
45. Dolce JJ, Crisp C, Manzella B, et al. Medication adherence patterns in chronic obstructive pulmonary disease. *Chest.* 1991;99:837–41.
46. Press VG, Pincavage AT, Pappalardo AA. The Chicago Breathe Project: a regional approach to improving education on asthma inhalers for resident physicians and minority patients. *J Natl Med Assoc.* 2010;102:548–55.
47. Aggarwal B, Gogtay J. Use of pressurized metered dose inhalers in patients with chronic obstructive pulmonary disease: review of evidence. *Expert Rev Respir Med.* 2014;8(3):349–56.
48. Wieshammer S, Dreyhaupt J. Dry powder inhalers: which factors determine the frequency of handling errors? *Respiration.* 2008;75(1):18–25.
49. Rees J. Methods of delivering drugs. *BMJ.* 2005;331(7515):504–6.
50. Brennan VK, Osman LM, Graham H, et al. True device compliance: the need to consider both competence and contrivance. *Respir Med.* 2005;99(1):97–102.
51. Jarvis S, Ind PW, Shiner RJ. Inhaled therapy in elderly COPD patients; time for re-evaluation? *Age Ageing.* 2007;36(2):213–8.
52. Thomas M, Price D, Chrystyn H, Lloyd A, Williams AE, von Ziegenweid J. Inhaled corticosteroids for asthma: impact of practice level device switching on asthma control. *BMC Pulm Med.* 2009;9:1.
53. Fink JB, Rubin BK. Problems with inhaler use: a call for improved clinician and patient education. *Respir Care.* 2005;50:1360–74.
54. Hanania NA, Wittman R, Kesten S, Chapman KR. Medical personnel's knowledge of and ability to use inhaling devices. Metered-dose inhalers, spacing chambers, and breath-actuated dry powder inhalers. *Chest.* 1994;105(1):111–6.
55. Plaza V, Sanchis J, Roura P, Molina J, Calle M, Quirce S, et al. Physicians' knowledge of inhaler devices and inhalation techniques remains poor in Spain. *J Aerosol Med Pulm Drug Deliv.* 2012;25(1):16–22.
56. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353(5):487e97.
57. Hodder R, Price D. Patient preferences for inhaler devices in chronic obstructive pulmonary disease: experience with Respimat Soft Mist inhaler. *Int J Chron Obstruct Pulmon Dis.* 2009;4:381–90.
58. Doyle S, Lloyd A, Williams A, Chrystyn H, Moffat M, Thomas M, et al. What happens to patients who have their asthma device switched without their consent? *Prim Care Respir J.* 2010;19(2):131–9.
59. Heyder J. Deposition of inhaled particles in the human respiratory tract and consequences for regional targeting in respiratory drug delivery. *Proc Am Thorac Soc.* 2004;1:315–20.
60. Lavorini F, Corrigan CJ, Barnes PJ, et al. Retail sales of inhalation devices in European countries: so much for a global policy. *Respir Med.* 2011;105:1099–113.
61. Byron PR. Performance characteristics of pressurized metered dose inhalers in vitro. *J Aerosol Med.* 1997;10 Suppl 1:S3–6.
62. Thorsson L, Edsbacker S. Lung deposition of budesonide from a pressurized metered-dose inhaler attached to a spacer. *Eur Respir J.* 1998;12(6):1340–5.
63. Hendeles L, Colice GL, Meyer RJ. Withdrawal of albuterol inhalers containing chlorofluorocarbon propellants. *N Engl J Med.* 2007;356:1344–51.
64. Newman SP, Weisz A, Talaei N, Clarke S. Improvement of drug delivery with a breath actuated pressurised aerosol for patients with poor inhaler technique. *Thorax.* 1991;46:712–6.
65. Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ. Influence of particle size and patient dosing technique on lung deposition of HFA beclomethasone from a metered dose inhaler. *J Aerosol Med.* 2005;18:379–85.
66. Price DB, Pearce L, Powell SR, Shirley J, Sayers MK. Handling and acceptability of the East-Breathe device compared with a conventional metered dose inhaler by patients and practice nurses. *Int J Clin Pract.* 1999;53:31–6.
67. Hampson NB, Mueller MP. Reduction in patient timing errors using a breath-activated metered dose inhaler. *Chest.* 1994;106:462–5.
68. Bell JH, Hartley PS, Cox JSG. Dry powder aerosols: I. A new powder inhalation device. *J Pharm Sci.* 1971;60:1559–64.
69. Thorsson L, Edsbäcker S, Källén A, Löfdahl CG. Pharmacokinetics and systemic activity of fluticasone via Diskus and pMDI, and of budesonide via Turbuhaler. *Br J Clin Pharmacol.* 2001;52(5):529e38.
70. Palander A. In vitro comparison of three salbutamol-containing multidose dry powder inhalers. *Clin Drug Invest.* 2000;20:25–33.
71. Weuthen T, Roeder S, Brand P, Müllinger B, Scheuch G. In vitro testing of two formoterol dry powder inhalers at different flow rates. *J Aerosol Med.* 2002;15(3):297–303.
72. Colthorpe P, Voshaar T, Kieckbusch T, Cuoghi E, Jauernig J. Delivery characteristics of a low-resistance dry-powder inhaler used to deliver the longacting muscarinic antagonist glycopyrronium. *J Drug Assess.* 2013;2:11e6.
73. Hess DR. Nebulizers: principles and performance. *Respir Care.* 2000;45:609–22.
74. Boe J, Dennis JH, O'Driscoll BR, et al. European Respiratory Society Guidelines on the use of nebulizers. *Eur Respir J.* 2001;18:228–42.
75. Lavorini F, Fontana GA, Usmani OS. New inhaler devices - the good, the bad and the ugly. *Respiration.* 2014;88(1):3–15.
76. Vogelmeier C, Kardos P, Hofmann T, Canisius S, Scheuch G, Muellinger B, et al. Nebulised budesonide using a novel device in patients with oral steroid-dependent asthma. *Eur Respir J.* 2014. [Epub ahead of print].

77. Hofmann T. Optimized steroid delivery in severe and pediatric asthma: improved compliance and efficacy (abstract). Congress of the International Society for Aerosols in Medicine: Chapel Hill; 2013.
78. Dhand R. Aerosol plumes: slow and steady wins the race. *J Aerosol Med.* 2005;18(3):261–3.
79. Dalby RN, Eicher J, Zierenberg B. Development of respimat soft mist inhaler and its clinical utility in respiratory disorders. *Med Devices Auckl.* 2011;4:145e55.

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