

The Evolution of Pressurized Metered-Dose Inhalers from Early to Modern Devices

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Abstract

Pressurized metered-dose inhalers (pMDIs) are sometimes viewed as old-fashioned and as having been superseded by dry powder inhalers (DPIs). Here, we review the technological advances that characterize modern pMDIs, and consider how they can influence the effectiveness of drug delivery for patients with asthma and chronic obstructive pulmonary disease. Compared with old chlorofluorocarbon (CFC)-based inhalers, many hydrofluoroalkane (HFA)-driven pMDIs have more favorable plume characteristics such as a reduced velocity and a higher fine particle fraction; together, these advances have resulted in the development of pMDIs with reduced oropharyngeal deposition and increased lung deposition. In addition, the plume from many HFA-pMDIs is warmer, which may facilitate their use by patients; moreover, devices are equipped with dose counters, which improves their reliability. As well as reviewing the technological advances of pMDIs, we also discuss the importance of individualizing inhaler therapies to each patient by accounting for their personal preferences and natural breathing patterns. Because pMDIs and DPIs differ considerably in their handling characteristics, matching the right inhaler to the right patient is key to ensuring effective therapy and good compliance. Finally, the majority of patients can be trained successfully in the correct use of their pMDI; training and regular monitoring of inhalation technique are essential prerequisites for effective therapy. While the ‘ideal inhaler’ may not exist, pMDIs are an effective device option suitable for many patients. pMDIs, together with other types of devices, offer opportunities for the effective individualization of treatments.

Key words: aerosol distribution, inhaled therapy, metered dose inhaler, modeling

Introduction

THE FIRST GENERATION OF PRESSURIZED metered-dose inhalers (pMDIs), which used chlorofluorocarbon (CFC) propellants, were an innovation in inhalation therapy. Although the devices had some drawbacks, many of these have now been overcome, and modern pMDIs are more convenient and effective than their predecessors.⁽¹⁾ Despite this, pMDIs are still viewed by some as old-fashioned inhalers that have been superseded by dry powder inhalers (DPIs).

Technical challenges of early CFC-pMDIs included a high spray velocity and low plume temperature, which many patients, particularly children, found unpleasant (the ‘cold Freon’ effect).^(1,2) Furthermore, the large droplet size and high spray velocity favored deposition in the mouth and throat, limiting drug delivery to the lungs.^(1,2) Coordinating inspiration with inhaler actuation proved difficult for some

patients. Early devices also lacked a dose counter, making it difficult to tell how much medication was left;⁽¹⁾ thus, pMDIs gained a reputation for having poor efficiency and being difficult to use.

Despite this view, modern pMDIs remain a part of everyday life for large numbers of patients. Data from 16 European countries showed that overall, pMDIs accounted for almost half of all retail pharmacy sales of inhaled medications between 2002 and 2008.⁽³⁾ pMDIs were the most frequently prescribed short-acting bronchodilator devices, accounting for ~55% of overall sales, compared with ~25% for DPIs; pMDIs were also used more commonly than DPIs for inhaled corticosteroid (ICS) therapy.⁽³⁾

However, large variations were observed between countries: overall, pMDIs accounted for approximately 70% of retail pharmacy inhaler sales in the UK, compared with less than 20% in Sweden, Denmark, and Finland.⁽³⁾ More recently,

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pMDIs contributed up to 56% of retail sales of inhalers (some 25.4 million units) in the five largest European countries (France, Germany, Italy, Spain, and the UK) during the last quarter of 2011, compared with 26% and 15% for non-refillable and refillable DPIs, respectively, and 3% for breath-actuated MDIs.⁽⁴⁾

This clinically focused article provides an overview of the technological advances that characterize modern pMDIs, and discusses how these developments can improve the effectiveness of drug delivery for the treatment of patients with asthma and chronic obstructive pulmonary disease (COPD). It considers the different plume characteristics of the newer pMDIs and the implications for drug deposition compared with CFC-based devices; the review also discusses how factors such as education, training, and patient preference can play a key role in the effectiveness of, and compliance with, inhaler treatment.

History of Inhalation Therapy and Early Devices

Back to basics: The early history of inhalation therapy

Although the practice of inhalation therapy can be traced back thousands of years, it was the nineteenth century that saw the first advances in the development of inhalers, primarily for the treatment of patients with tuberculosis.⁽⁵⁾ Initially, inhalers relied on either heat to volatilize the medi-

cation, or vapor to aerosolize it.⁽⁵⁾ This changed with the first known pressurized inhaler, presented at the Medical Academy in Paris, France in 1858, in which the liquid medication was atomized using a pressure pump (Fig. 1).^(5,6) This early nebulizer was followed by the invention of Siegle's steam spray inhaler in Germany during the 1860s, which used steam rather than compressed air to disperse the liquid medication.^(5,7) In 1864, a patent was filed in London, UK for the first dry powder inhaler (DPI), which required the powder to be pulverized and kept dry—principles that still apply in today's DPIs.⁽⁵⁾

The early twentieth century saw many advances in inhaler design. Following the recognition that adrenal extract could act as a bronchodilator, reports of its use to treat asthma, and its delivery as an aerosol, soon followed.^(5,7) Nebulizer devices were developed, powered by electrical compression (such as the Pneumostat manufactured by Weil, Frankfurt, Germany in the early 1930s) or by hand (for example, the Glaseptic made by Parke, Davis & Company, London, UK).^(5,7) In the 1930s, adrenalin chloride solution was supplied as a bronchodilator in both glass-bulb and plastic-bulb, hand-powered nebulizers.⁽⁷⁾

Introduction of pMDIs and DPIs

The pace of technological development accelerated in the 1950s, resulting in the refinement of delivery devices with

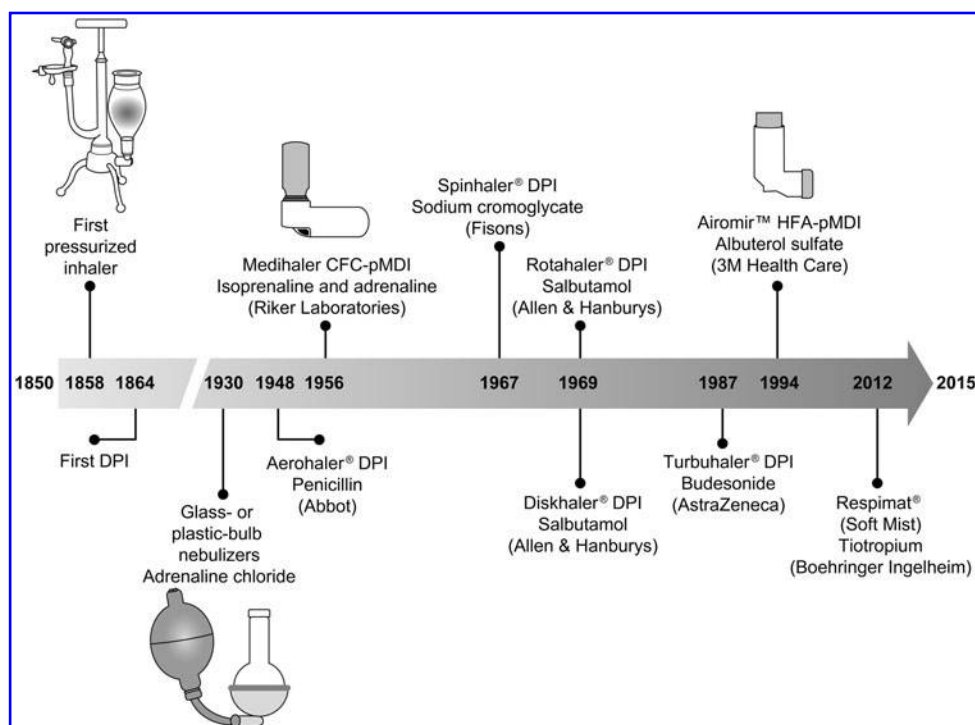


FIG. 1. Important milestones in the development of inhaler therapy. CFC, chloro-fluorocarbon; DPI, dry powder inhaler; HFA, hydrofluoroalkane; pMDI, pressurized metered-dose inhaler.

Aerohaler: trademark now registered by Boehringer Ingelheim Pharma GmbH & Co. KG (Ingelheim am Rhein, Germany); Spinhaler: Fisons Limited (West Mallings, UK); Ventolin Rotahaler now registered by Glaxo Group Limited (Brentford, UK); Airomir: 3M Health Care (St. Paul, MN, USA); Respimat: Boehringer Ingelheim Pharma GmbH & Co. KG, (Ingelheim am Rhein, Germany); Diskhaler: Glaxo Group Limited (Brentford, UK); Turbuhaler: AstraZeneca AB (Södertälje, Sweden).

two fundamentally different designs: pMDIs and DPIs. In pMDIs, drugs (either in solution or in suspension) are actively expelled from a pressurized storage container by a propellant. By contrast, DPIs have a passive mechanism that relies on the inspiratory force generated by the patient, first to extract the powdered drug from a reservoir or blister, and then to disaggregate the powder into respirable particles.⁽¹⁾

The introduction of the first aerosol-driven pMDI by Riker Laboratories (now 3M Health Care, St. Paul, MN, USA) in 1956 was a significant milestone (Fig. 1).^(5,8) The inhaler, which contained the nonselective β -agonists isoprenaline or adrenaline, was marketed as Medihaler-Iso and Medihaler-Epi, and was increasingly used by patients with asthma.⁽⁸⁾

The DPI first appeared in 1948, when Abbott (Maidenhead, UK) launched the Aerohaler[®] for the inhalation of penicillin, using a lactose-based formulation (Fig. 1).⁽⁵⁾ In the 1960s, new DPIs were developed by Fisons (Spinhaler[®]) and Allen & Hanbury's (Rotahaler[®]). Both were single-dose devices that needed to be reloaded before every actuation. The Turbuhaler[®], introduced by AstraZeneca (Södertälje, Sweden) in 1987, was the first DPI to feature a multi-dose reservoir with a self-metering mechanism.⁽¹⁾ Many other types of DPI followed, using powder reservoirs, multiple individual blisters, or disposable capsules.

The turn of the twenty-first century has also seen the development of alternatives to pMDIs and DPIs, including the Soft Mist inhaler (Respimat[®]) and breath-actuated pMDIs.^(1,9)

Evolution of the Modern pMDI

pMDIs using CFC propellants

Propellants are volatile substances that form liquids when cooled or compressed but are gaseous at ambient temperature and pressure, so they evaporate rapidly once ejected from a pressurized storage container. In pMDIs that used CFC propellants (CFC-pMDIs), the propellant was typically a combination of highly volatile dichlorodifluoromethane (CFC-12) with less volatile trichlorofluoromethane (CFC-11) and/or dichlorotetrafluoroethane (CFC-114).⁽¹⁾ Other compounds were also added to the drug-propellant mix to improve the performance of pMDIs. Surfactants such as oleic acid are used in inhalers containing drug suspensions to reduce the aggregation of drug particles, thereby stabilizing the suspension, and to lubricate the valve. In solution inhalers, co-solvents such as ethanol may be added to increase drug solubility.⁽¹⁾

Although the first CFC-pMDIs represented a real step forward in inhaler design, challenges remained in terms of device handling and drug delivery. CFC-pMDIs produced a rapid spray with a short duration. Owing to technical factors such as actuator nozzle size, the spray contained relatively large droplets and drug particles.⁽¹⁾ For many patients, coordinating device actuation with inhalation proved difficult with pMDIs, impeding drug deposition in the lungs and therefore reducing effectiveness.

The fairly large droplets produced by CFC-pMDIs increased oropharyngeal deposition;⁽¹⁾ this was compounded by the high spray velocity that further increased impaction on the back of the throat. Furthermore, some patients found the sensation of the high-velocity cold plume produced by the CFC propellant unpleasant, and this contributed to poor inhaler technique.⁽¹⁾ A study in 215 patients showed that

24% stopped inhaling upon release of aerosol into the mouth from a CFC-pMDI.⁽¹⁰⁾ This 'cold-Freon' effect also induced cough and even paradoxical bronchospasm in some patients.

Hence, although the introduction of pMDIs provided patients with a convenient inhaler with many practical advantages, devices using CFC propellants were associated with particle deposition in the mouth and throat and therefore with suboptimal lung deposition (only 10%–20%), as well as adverse effects in the upper respiratory tract, such as hoarseness and thrush with ICS.⁽²⁾

Introduction of the modern pMDI

Owing to environmental concerns about CFCs, other propellants were sought for use in pMDIs. Two hydrofluoroalkanes (HFAs) were identified as suitable alternatives, namely HFA-134a (tetrafluoroethane) and HFA-227 (heptafluoropropane). Inhalers using HFA rather than CFC propellants were developed, and the first HFA-pMDI (Air-omir[™], 3M Health Care) was launched in 1994 (Fig. 1).⁽¹⁾

However, the development of HFA-pMDIs was far from straightforward, presenting a number of technical challenges. Apart from the propellant, some of the other compounds and components used in CFC inhalers, such as surfactants and seals, were not suitable for use with HFAs, so alternatives had to be found. Other issues, such as valve design to improve emptying and reduce the need for priming, adhesion of the formulation to the canister walls, and the possibility of delivering higher drug doses per shot also needed to be considered.⁽¹⁾ Additional clinical trials were required to investigate the efficacy and safety of these new formulations.^(1, 2)

The switch to HFA propellants, however, provided the opportunity to address some of the drawbacks associated with CFC-pMDIs. While some HFA-pMDIs retained similar plume characteristics to CFC-based devices, many HFA-pMDIs were designed to deliver smaller particles, at a lower spray velocity and warmer temperature.^(1, 2) The following sections examine how changes in the particle size and plume characteristics seen with HFA-pMDIs have created the potential for improvements in drug delivery for patients, and consider the impact that device handling can have on treatment effectiveness.

Particle size and fine particle fraction

The effect of particle size on therapeutic response to inhaled drugs has been recognized for many years.^(11–13) Assuming a flow of 0.5–1 L/sec on aerosol inhalation, particles with an aerodynamic particle diameter of more than 5 μ m tend to be retained in the oropharynx, where they may cause local side effects. In contrast, particles with a diameter of 1–5 μ m are increasingly likely to be deposited in the bronchial and pulmonary regions of the respiratory tract.^(11,14,15)

The proportion of particles <5 μ m diameter in an emitted aerosol (the fine particle fraction [FPF]) correlates with lung deposition, and can be influenced by device characteristics such as nozzle diameter, the volume of the metered dose, and the aerosol formulation.⁽¹⁾ HFA-pMDIs have been developed that can deliver a smaller particle size and a higher FPF than the earlier CFC-pMDIs. This was illustrated by the comparison of beclometasone delivery between a beclometasone/formoterol HFA-pMDI (Foster[®]), which uses an

extra-fine formulation, and a CFC-pMDI.^(16,17) Compared with the CFC-pMDI, the HFA-pMDI achieved a much larger FPF (35% vs. 18%) and a smaller particle size (mass median aerodynamic diameter [MMAD]: 1.3 μm vs. 4.3 μm).^(16,17) Note that the differences in particle size are marked, as particle volume is related to the cube of the diameter. This change in profile led to a reduction of more than 50% in the dosing strength of beclometasone.^(17,18)

Particle size and FPF depend not only on the inhaler, but also on the inhalation technique of the patient. With DPIs, the FPF is affected by the inhalation flow velocity of the user.^(19,20) This is because the deagglomeration of dry-powder formulations into respirable drug particles depends on the inspiratory force generated during inhalation.^(19–21) In pMDIs, drug particles become aerosolized upon actuation of the device, so low inhalation flow velocities have less of an impact on the FPF.⁽²²⁾

In vitro data indicate that the FPFs of ICS and long-acting β_2 agonist (LABA) components of asthma combination therapies can vary not only between DPIs and pMDIs, but also between different products within each device category, and in different usage conditions.^(22–24) In an *in vitro* study using an Andersen cascade impactor, at a flow rate of 28.3 L/min, ICS FPFs were low with a budesonide/formoterol DPI (Symbicort® Turbuhaler: FPF: 8.2%; MMAD: 3.8 μm) and a fluticasone propionate/salmeterol DPI (Seretide® Accuhaler®; FPF: 12.5%; MMAD: 4.7 μm), and higher with a fluticasone propionate/formoterol pMDI (Flutiform®; FPF: 41.2%; MMAD: 3.5 μm) (Fig. 2).⁽²²⁾ Similar trends were observed for the FPF of the LABA component. FPF was also measured at a higher flow rate of 60.0 L/min, and was most consistent at the different flow rates for fluticasone propionate/formoterol (Fig. 2).

In a separate study that used a next-generation impactor, the ICS FPF of the beclometasone/formoterol pMDI (Foster®) at a flow rate of 30 L/min was reported as 34% (MMAD: 1.1 μm).⁽²³⁾ This study also reported the ICS FPF and fine particle dose (FPD) at flow rates of 30 and 60 L/min for beclometasone/formoterol pMDI (Foster®: 40% and 54% [FPF], and 34 μg and 47 μg [FPD], respectively) and fluticasone propionate/formoterol pMDI (Flutiform®: 37% and 34% [FPF], and 39 μg and 39 μg [FPD], respectively).⁽²³⁾ This showed that FPF and FPD were more consistent for Flutiform® than for Foster® at the different flow rates.⁽²⁵⁾

In addition, DPIs are susceptible to humidity, unlike pMDIs. Dry-powder formulations are hygroscopic and tend to congeal in humid conditions, which can lead to a marked and permanent decrease in FPF although the overall dose is not affected.⁽²⁶⁾ Furthermore, this could lead to increased impaction in the upper respiratory tract, owing to the high respiratory flows needed to deaggregate these larger particles. An *in vitro* study assessing the dispersion performance of a DPI showed that throat deposition increased with increasing device flow rate.⁽²⁷⁾

Finally, it is worth mentioning that the FPF generated by HFA-pMDIs is less dependent on ambient temperature than those generated by CFC-pMDIs. One study reported a marked drop in fine particle mass with a CFC-pMDI as ambient temperature was reduced from +20°C to –10°C; there was almost no change with the HFA-pMDI over this temperature range, although this may not be the case for all HFA-pMDIs.⁽¹⁾

Plume characteristics of pMDIs

Plume characteristics, such as velocity, force, shape, and temperature all affect lung deposition. The shift from CFC to HFA propellants resulted in devices with qualitatively improved plume characteristics, and reduced levels of throat deposition.^(1,28,29)

Many modern HFA-pMDIs have softer plumes than CFC-pMDIs. The plume impact force of many (but not all) HFA-pMDIs is typically about 4-fold lower than that of CFC-pMDIs,^(28,29) resulting primarily from the use of narrower actuator nozzles in HFA-pMDIs.⁽¹⁾ Accordingly, a study comparing four CFC-pMDIs and five HFA-pMDIs reported a tendency towards lower spray velocities with HFA propellants. Spray velocities of the four CFC-pMDIs tested were approximately 3-fold faster compared with three of the HFA-pMDIs.⁽³⁰⁾

In addition, plumes from HFA-pMDIs tend to be warmer than those from CFC-pMDIs: minimum plume temperatures may be up to 8°C with HFA-pMDIs, compared with approximately –30°C for many CFC-pMDIs.^(28,29) It is worth highlighting that not all currently available pMDIs share the same plume characteristics; indeed, while most CFC-pMDI sprays are very similar, HFA-pMDI sprays vary much more from product to product.⁽¹⁾

In the above-mentioned study, two of the HFA-pMDIs had spray velocities that were faster than those of the other HFA-pMDIs, and similar to those the CFC-pMDIs.⁽³⁰⁾ In another *in vitro* study, mean minimum plume temperature varied considerably between ten commercially available pMDIs, and was influenced by factors such as orifice diameter, metering volume, and choice of co-solvents. For example, an ethanol–HFA-134a formulation delivered through a fine actuator orifice was warmer than one using a 100% HFA-134a vehicle delivered through a coarse orifice.⁽³¹⁾ Similarly, in the *in vitro* study cited above, the plume impaction temperature of fluticasone propionate/salmeterol was –38°C at a distance of 25 mm from the mouthpiece, considerably colder than that of fluticasone propionate/formoterol (+6°C), possibly because of the use of different types of HFA propellant with different boiling points, or different excipients in each formulation.⁽²⁵⁾

The same study also demonstrated that the plume of fluticasone propionate/formoterol had a slower maximum velocity and a ~50% longer duration than that of fluticasone propionate/salmeterol.⁽³²⁾ As would be expected for a pMDI with a slower plume, fluticasone propionate/formoterol also had an approximately 50% lower impaction force than fluticasone propionate/salmeterol.⁽²⁵⁾

Lung deposition

In parallel with the changes in FPF, particle size, and plume characteristics, the technical advances in pMDIs have also resulted in increased lung deposition. Scintigraphy data have shown that HFA–beclometasone achieves higher rates of lung deposition than CFC–beclometasone and CFC–fluticasone propionate, which were both associated with higher oropharyngeal deposition (Table 1).⁽³³⁾ Lung deposition can also be modeled using functional respiratory imaging (FRI), which provides comparable estimates to scintigraphy.^(34,35) Recent FRI studies have reported total lung deposition of pMDIs of 44% (fluticasone propionate/

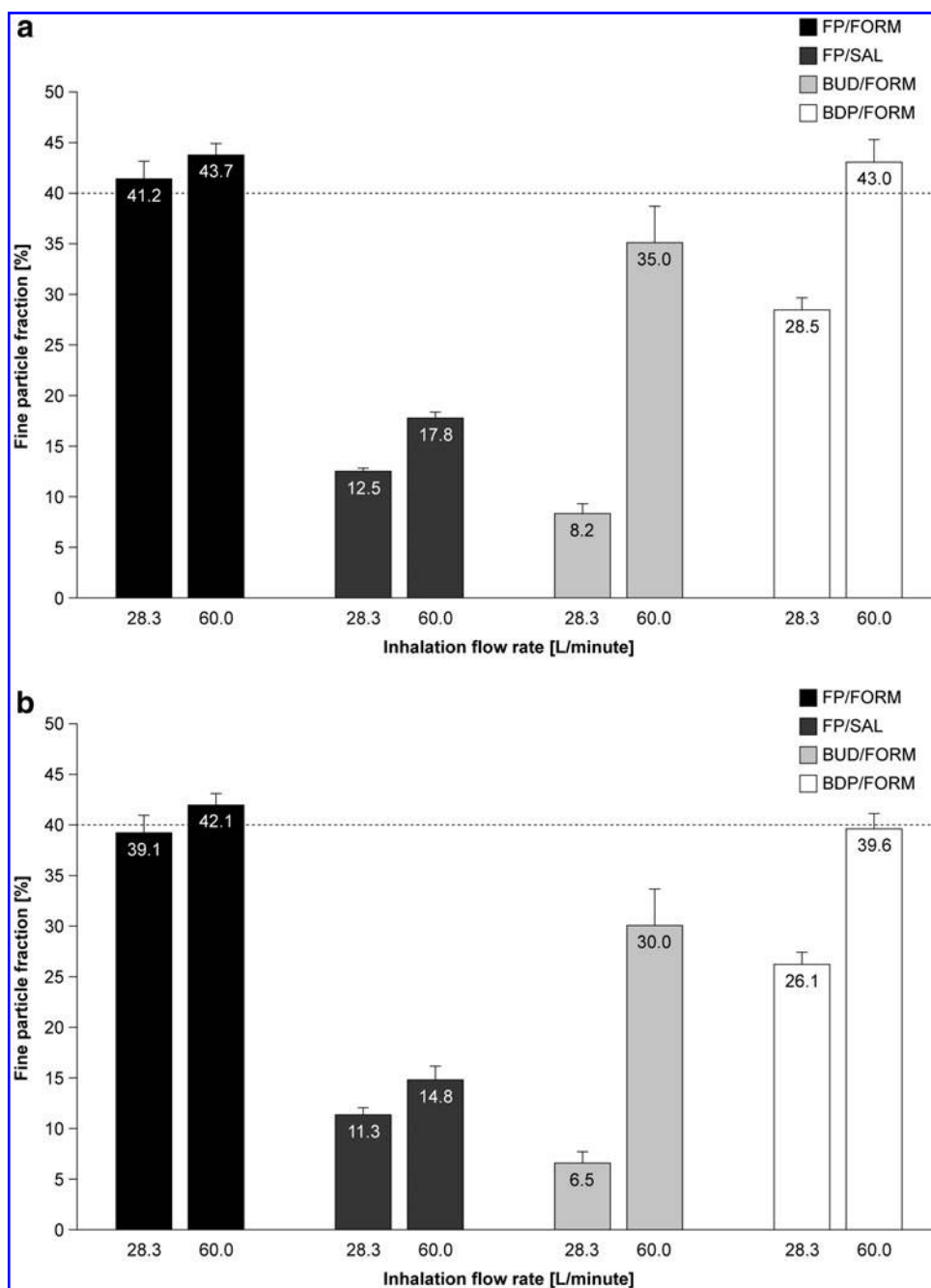


FIG. 2. Fine particle fractions and their flow dependency of the (a) ICS and (b) LABA components of ICS/LABA combination therapies, showing variations between different inhalers at different flow rates.

BDP/FORM, beclometasone/formoterol HFA-pMDI (Foster[®], Chiesi Farmaceutici S.p.A., Parma, Italy); BUD/FORM, budesonide/formoterol DPI (Symbicort[®] Turbohaler[®], AstraZeneca AB, Södertälje, Sweden); DPI, dry powder inhaler; FP/FORM, fluticasone propionate/formoterol HFA-pMDI (flutiform[®], Jagotec AG, Muttens, Switzerland); FP/SAL, fluticasone propionate/salmeterol DPI (Seretide[®] Accuhaler[®], Glaxo Operations UK Ltd, Hertfordshire, UK); HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; pMDI, pressurized metered-dose inhaler.

With kind permission from Springer Science+Business Media: *Combination Products in Therapy*, Fine particle profile of fluticasone propionate/formoterol fumarate versus other combination products: the DIFFUSE study, volume 3, 2013, pages 39–51, Johal B, Howald M, Fischer M, *et al.*, Figure 1.⁽²²⁾

TABLE 1. LUNG DEPOSITION DATA FOR DIFFERENT pMDIs FROM *IN VIVO* STUDIES AND FUNCTIONAL RESPIRATORY IMAGING-BASED MODELING STUDIES

Study	Participants	Inhaler type	Medication	Lung deposition [%]	MMAD [μ m]
<i>In vivo studies</i>					
Leach et al., 2002 ⁽³³⁾	Healthy adult volunteers (n=9)	HFA-pMDI	BDP	53	0.9
		CFC-pMDI	FP	12–13	2.0
		CFC-pMDI	BDP	4	3.5
De Backer et al., 2010 ⁽³⁵⁾	Healthy adult volunteers (n=8)	HFA-pMDI	BDP/FORM	34.1	1.30/1.30 ^a
	Patients with persistent asthma (n=8)			30.9	
	Patients with COPD (n=8)			33.1	
<i>FRI-based computer modeling studies</i>					
Vinchurkar et al., 2012 ⁽³⁴⁾	3D airway models from high resolution CT scans of patients with asthma (n=5)	HFA-pMDI	BDP/FORM	30	–
Van Holsbeke et al., 2014 ⁽³⁶⁾	3D airway models from CT scans of patients with asthma (n=6)	HFA-pMDI	FP/FORM	44.0/42.4 ^b	3.52/3.52 ^c
De Backer et al., 2014 ⁽³⁷⁾	3D airway models from CT scans of patients with stable asthma (n=16)	HFA-pMDI ^d HFA-pMDI ^f	FP/SAL FP/SAL	18.4/18.7 ^e 18.2/18.6 ^e	–

^aFor unlabeled BDP and FORM, respectively; ^bAt flow rates of 30 L/min and 60 L/min, respectively; ^cFor FP and FORM, respectively (at a flow rate of 30 L/min); ^dSeretide® Evohaler® (GlaxoSmithKline, UK); ^eFor FP and SAL, respectively; ^fSeroflo® (Cipla Ltd, Mumbai, India). Lung deposition data were reported as percentage of ex-actuator dose,⁽³³⁾ percentage of nominal dose,^(34, 35) or percentage of labeled dose.⁽³⁶⁾ Lung deposition data were not further defined by De Backer et al., 2014.⁽³⁷⁾

3D, three-dimensional; BDP, beclometasone dipropionate; CFC, chlorofluorocarbon; COPD, chronic obstructive pulmonary disease; CT, computed tomography; FORM, formoterol; FP, fluticasone propionate; FRI, functional respiratory imaging; HFA, hydrofluoroalkane; MMAD, mass median aerodynamic diameter; pMDI, pressurized metered-dose inhaler; SAL, salmeterol.

formoterol), 30% (beclometasone/formoterol), and ~18% (fluticasone propionate/salmeterol Evohaler® and Seroflo®) (Table 1).^(34,36,37)

Device handling and usability

Treatment guidelines for respiratory diseases such as asthma recommend that inhaled therapy is individualized for each patient, taking into consideration the patient's preferences and natural breathing patterns, their need for inhaler training, and the need for regular monitoring of inhaler technique.^(38,39)

Unsurprisingly, poor inhaler technique is linked to poor treatment outcomes. A large study involving more than 4000 patients with asthma found that individuals with inadequate pMDI technique had significantly less stable disease than those with good technique.⁽⁴⁰⁾ Correct inhaler usage is thus an important prerequisite for achieving asthma control, and increasing the dose or adding another treatment is not a substitute for adequate technique.⁽³⁹⁾ It is therefore concerning that outside the carefully controlled environment of clinical studies, many patients often use their inhalers incorrectly (regardless of whether they are prescribed a pMDI or a DPI), and adherence rates for inhaler use have been estimated to range from 20% to 73%.^(39,41,42)

Handling errors with inhalers (whether a pMDI or a DPI) can be regarded as either 'critical', which can lead to treatment failure, or as 'noncritical', which may be associated with a risk of decreased efficacy or increased side ef-

fects. Studies evaluating inhaler technique show a wide variation in the proportion of patients committing critical errors. Two large surveys, involving over 1600 and almost 4000 patients, reported that 12%⁽⁴³⁾ and 28.1%,⁽⁴⁴⁾ respectively, of patients made at least one critical error in inhaler use with pMDIs, whereas a value of 81% was reported in a smaller study in 156 patients.⁽⁴⁵⁾ The corresponding values for patients using DPIs in the three studies were 34.5–43.5%, 7.4–37.1%, and 15–45%, respectively. The most common critical errors with pMDIs were related to inhalation technique and its coordination with inhaler actuation. Studies reported that approximately 10%–30% of patients did not continue inhaling after actuation.^(43,45–47) There were, however, some differences between the studies in what was considered a critical error, making comparisons difficult. For example, failure to actuate the inhaler at the start of inhalation was considered a critical error in some studies,^(45–47) but surprisingly not in others.⁽⁴³⁾

With pMDIs, another common error is an inhalation that is insufficiently slow and deep.^(39,48) Many patients also experience difficulty coordinating actuation with inhalation, especially when inhaling too rapidly.^(39,49) Respiratory experts, including the European Respiratory Society/International Society for Aerosols in Medicine (ERS/ISAM) Task Force and the International Primary Care Respiratory Group, therefore emphasize that pMDIs should be used with a slow and deep inhalation over 4–5 seconds, beginning at the same time as device actuation.⁽¹⁴⁾ Inhaling the same volume over a longer time period reduces the flow rate.

Indeed, FRI data show that a 5-second inhalation duration with fluticasone propionate/formoterol can achieve a total lung deposition of 42%, a relative improvement of 15% compared with a 3-second inhalation duration.⁽⁵⁰⁾ Specifying a duration of inhalation, rather than simply using subjective terms such as ‘slowly’, should make it easier for patients to follow and remember instructions on inhaler technique.

A slow inhalation not only reduces the flow rate, but also gives patients more time to coordinate actuation and inhalation, thereby enhancing delivery to the lungs.^(14,49) However, modern pMDIs may deliver efficacious doses even without optimal coordination. Data from a pharmacological study indicate that ‘split-second’ coordination of actuation and inhalation is not essential, as long as patients have already started to inhale when they actuate their device.⁽⁵¹⁾ Consistent with this, a relatively late actuation in the second half of inspiration is not necessarily considered a ‘critical’ error, even though devices should ideally be actuated in the first half of inspiration.^(43,52) In patients with obstructive

airways disease, later actuation reduced lung deposition compared with early actuation when followed by shorter breath-holding, but had no significant effect on deposition with longer breath-holding (Fig. 3).⁽⁵²⁾ Interestingly, the deleterious effects of too rapid an inhalation on lung deposition are less evident with particles of 1.5 μm or 3 μm than with larger particles (6 μm), underlining the importance of a high FPF (Fig. 4).⁽⁵³⁾

Other Device Types

DPIs

Owing to their fundamentally different design, DPIs require a different inhalation technique from pMDIs. The ERS/ISAM Task Force guidelines advise patients to inhale forcefully from the beginning, rather than building up the speed of inhalation gradually.⁽¹⁴⁾ A forceful inhalation is essential because each DPI device has a minimum threshold energy below which deagglomeration of the drug particles is inefficient.⁽¹⁴⁾ An insufficient inhalation flow rate is likely to

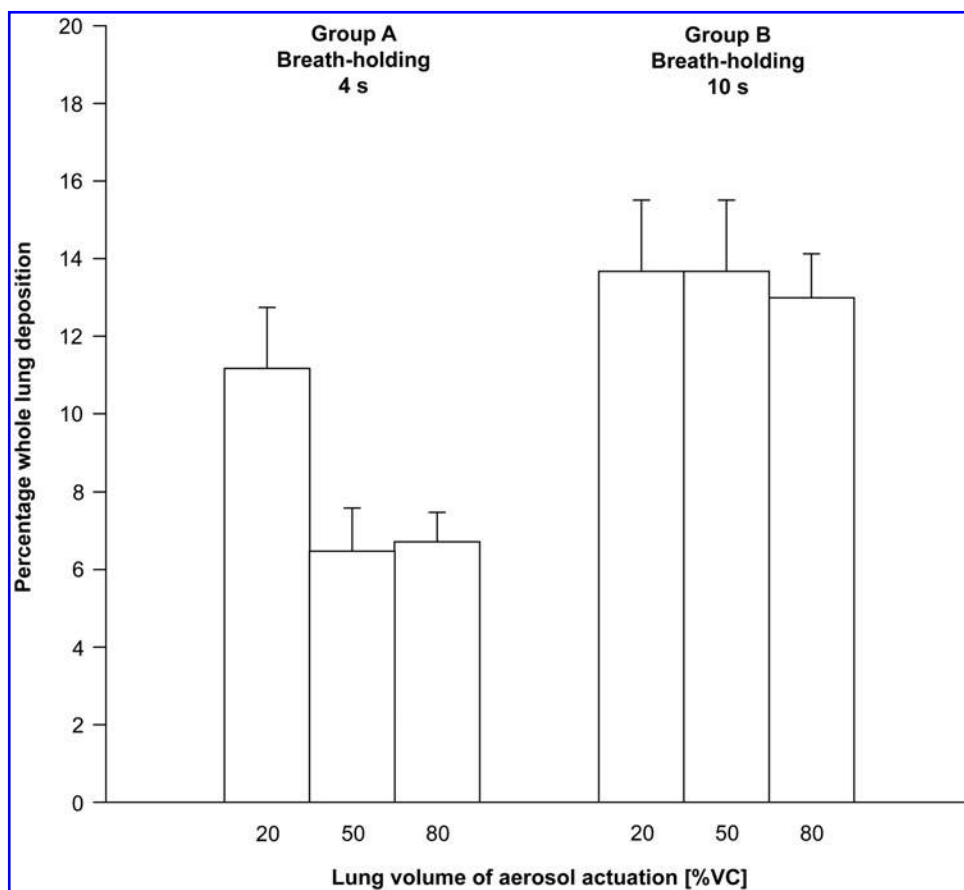


FIG. 3. Effect of actuation timing and breath-holding on whole lung deposition. Mean $\pm$ SEM percentage whole lung deposition in patients in group A (slow inhalation flow rate with 4 seconds' breath-holding) and group B (slow inhalation flow rate with 10 seconds' breath-holding). Each patient took part in three studies, with the aerosol actuated at three different lung volumes (20% of VC, 50% of VC, and 80% of VC). SEM, standard error of the mean; VC, vital capacity.

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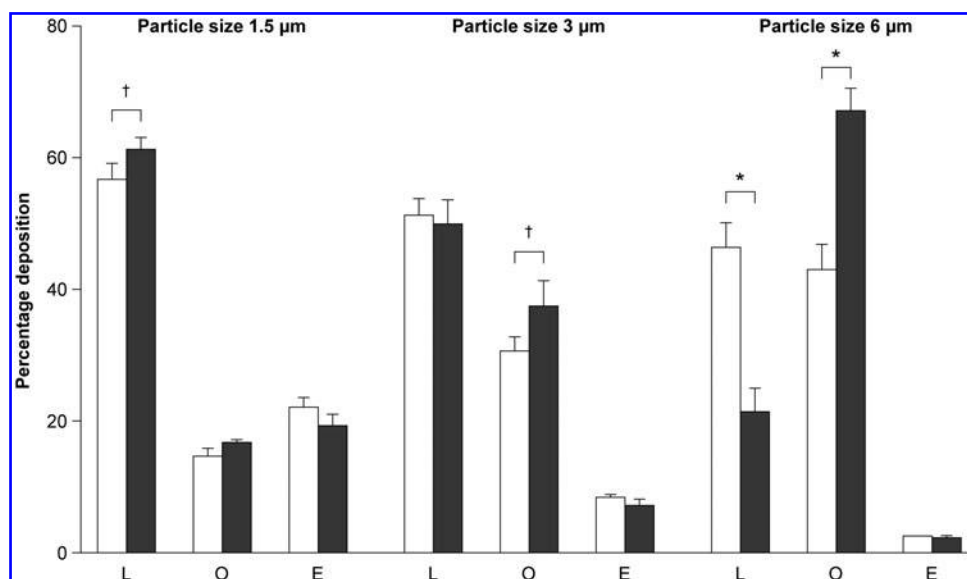


FIG. 4. Effect of inhalation flow rate and particle size on deposition. Effect of rapid inhalation (*shaded bars*) compared with slow inhalation (*white bars*) on deposition in lung (L), oropharynx (O), and exhaled fraction (E) for each particle size. Data are shown for 30 µg albuterol doses. * $p < 0.001$; † $p < 0.05$. All other flow-rate comparisons not significant.

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result in a reduced therapeutic effect, and remains one of the most common critical errors made with DPIs in practice.⁽¹⁴⁾

The need for different handling techniques and inhalation rates with pMDIs and DPIs is a potential source of confusion for patients who use more than one type of inhaler (such as a DPI for controller medication and pMDI for reliever medication). A study showed that the proportion of patients performing all of the critical steps of inhaler use correctly was lower for patients using a DPI and a pMDI than for those using the same type of inhaler (a combination of DPIs).⁽⁵⁴⁾ Using the same type of device is probably easier to teach to and learn for patients.⁽⁵⁵⁾

Breath-actuated pMDIs

Breath-actuated pMDIs have been developed in order to overcome the problem of coordinating actuation with inhalation that some patients experience with pMDIs. These devices contain an automatic trigger mechanism that senses the patient's inhalation, automatically releasing the dose.^(29,56) Breath-actuated pMDI provided significantly higher lung deposition compared with a conventional pMDI among patients with asthma who had poor coordination, and similar lung deposition in patients with good coordination.⁽⁵⁷⁾

Studies have reported that breath-actuated pMDI were easier to use than pMDIs, with more patients showing correct or good technique than with pMDIs or DPIs, and patient preference for the devices was high.⁽⁵⁶⁾ In one study, 11%–12% of patients using the breath-actuated inhaler made a critical inhalation error compared with 28% of patients using a pMDI.⁽⁵⁸⁾ However, another study reported that opti-

mal technique (correct execution of all preparation and inhalation steps) was similar with pMDIs and breath-actuated inhalers.⁽⁴⁶⁾ There are limited formulations currently available for breath-actuated pMDIs and initial costs are high.⁽⁵⁶⁾

Soft Mist Inhaler

The Respimat[®] Soft Mist inhaler (SMI) offers an alternative to DPIs and pMDIs, although the number of medications currently available with this type of inhaler is limited. In this device, mechanical energy is used to force the drug solution through nozzles to produce two fine jets of liquid that collide, generating a fine aerosol of relatively slow velocity and long duration.⁽⁹⁾ A study showed that mean plume velocity with the SMI was less than half that of the slowest HFA-pMDI and seven to eight times slower than for CFC-pMDIs.⁽³⁰⁾ Mean spray duration was also longer with the SMI (1.5 seconds) than with HFA-pMDIs or CFC-pMDIs (0.15–0.36 seconds). The long spray duration offers potential benefits in terms of coordinating device actuation and inhalation, while the low plume velocity reduces the risk of oropharyngeal deposition. Scintigraphy studies showed that whole lung deposition was approximately 40%–50% of metered dose with the SMI.^(59,60) At present, only bronchodilators are available in this type of device.

Getting the Best Out of pMDIs

In parallel with improvements in pMDI technology, other factors can contribute to significant improvements in asthma management. Training and educating patients and

healthcare professionals (HCPs), including physicians, nurses, pharmacists, and respiratory technologists, can play a key role in improving inhaler technique and compliance, and therefore ultimately improve the overall effectiveness of inhaled therapies.^(49,61)

In a study of 46 adolescents and adults with severe asthma, the proportion of patients who used their devices correctly increased from 37% at baseline to 80% at 3–4 months' follow-up after training by a pulmonary nurse specialist ($p=0.003$); overall median asthma control scores also improved significantly at follow-up (2.7 vs. 2.0; $p=0.002$).⁽⁶²⁾ Of those patients using a pMDI ($n=28$), 83% demonstrated correct technique at follow-up compared with 37% at baseline. With the Turbuhaler and DISKUS® DPIs, the proportion of patients with correct technique increased from 12% to 62% ($n=24$) and from 40% to 80% ($n=8$), respectively.⁽⁶²⁾

Another study in 727 patients with asthma (of whom 443 were receiving pMDI maintenance therapy) found that training by pharmacists resulted in optimal inhaler technique in 79% of participants.⁽⁴⁶⁾ One month after training, asthma control scores among patients who had achieved optimal technique at the end of training had improved from 1.8 to 1.4 ($p<0.001$). Importantly, in this study, compliance also improved with education.

A study in 307 patients with asthma or COPD showed that virtually all patients (99%) could be taught to use the fluticasone propionate/formoterol pMDI by a trained nurse within 15 minutes, accurately completing all eight steps involved in correct inhaler handling.⁽⁶³⁾ The study included a simple training instruction referred to as the '2-3-4' rule (2 seconds' exhalation; 3 seconds' inhalation; 4 seconds' breath-hold), which may have contributed to successful inhaler use by giving specific, nonsubjective instruction.

Taken together, these data suggest that, contrary to popular belief, the majority of patients can be successfully trained in correct pMDI technique. Moreover, such inhaler training can be effective with relatively short instruction sessions—an important factor in times of constrained healthcare budgets. However, the effect of training may decrease over time. It is therefore important that evaluation and reinforcement of correct inhaler technique occurs at each follow-up.

The training of HCPs who instruct patients in good inhaler technique is also important ('train the trainer'). In a randomized study involving 31 pharmacists, around 90% of participants initially demonstrated incorrect inhaler technique with a pMDI and a DPI. The pharmacists were then randomized to an inhaler training workshop ($n=16$) or received no intervention ($n=15$). After a 2-year follow-up, pharmacists who had received the support demonstrated significantly better inhaler technique than those in the control group ($p<0.05$). This showed that a single educational session can significantly improve HCPs' demonstration of inhaler technique over the long term.⁽⁶⁴⁾

To facilitate effective education sessions for both patients and HCPs, a wide range of inhaler training aids are now available.⁽⁶⁵⁾ The 2Tone® Metered Dose Inhaler Trainer mimics the inhalation through a pMDI, and provides audible feedback on the speed of the inhalation flow. A pair of sensitive reeds vibrates as air flows through. Above a pre-determined speed, a single tone is produced to signal an

optimal inhalation rate of 30–60 L/min; if the rate is too fast (>60 L/min), there are two tones; and no sound is produced if the rate is too slow.⁽⁶⁵⁾ Other tools to measure inspiratory flow include the In-Check DIAL® and the Vitalograph AIM™ (Aerosol Inhalation Monitor).⁽⁶⁵⁾

Matching Devices to Patients' Preferences

Even the best training programs may not be effective if the use of a device is not intuitive to the patient. Here we discuss the importance of matching inhaler choice with patients' preferences, considering factors of device design, familiarity, and versatility. Choosing the right inhaler for each patient increases the likelihood that it will be used correctly, reducing the amount of retraining required.

Devices differ in their handling characteristics, so it is important to recognize and respond to patient preferences when prescribing a particular inhaler, as this can affect compliance.⁽⁴⁸⁾ In a real-world survey of 1443 patients with COPD, patients' overall satisfaction with their maintenance inhaler showed a significant association with treatment compliance, and also with a reduction in COPD exacerbations.⁽⁶⁶⁾ Factors relating to durability, ergonomics, and ease of use were all important in influencing patient satisfaction.

Several studies have assessed patients' preferences for inhalers, with variations between types of device, and between individual devices of the same type, across studies (Table 2).^(67–71) In some studies, more patients preferred the pMDI than the DPI, while other investigations reported the opposite finding; in some reports, patients expressed no clear preference for either pMDIs or DPIs. For example, in one study comparing salbutamol inhalers in 419 patients with asthma or COPD, the overall appeal was similar for the HFA-pMDI and the DPI, and significantly greater than for the CFC-pMDI, although more patients ranked the DPI over the HFA-pMDI as their preferred choice (Table 2).⁽⁶⁷⁾ In another study of 307 patients with asthma or COPD, approximately half of patients preferred fluticasone propionate/formoterol pMDI to fluticasone propionate/salmeterol DPI and to budesonide/formoterol DPI (Table 2).⁽⁷²⁾

Many studies on patient preferences are of relatively short duration, so it is not clear how opinions and preferences might change with prolonged use, and how this could relate to longer-term outcomes. Interestingly, an observational retrospective database study comparing asthma outcomes at 1 year among 3134 patients initiating fluticasone propionate/salmeterol therapy showed that the odds of achieving asthma control were significantly greater for patients using a pMDI than for those using a DPI (odds ratio [OR]: 1.19; 95% confidence interval [CI]: 1.01–1.40).⁽⁷³⁾ The odds of treatment success (defined as no exacerbations and no change in asthma therapy) were also significantly higher with pMDI than with DPI use (OR: 1.23; 95% CI: 1.07–1.42), while the rate of asthma exacerbations was lower in the pMDI group, although the difference between groups was not statistically significant (Fig. 5).⁽⁷³⁾ The reasons for these differences in outcomes between inhaler types are unclear, but may possibly relate to real-world preference, improved compliance, and/or better inhaler handling with pMDIs over DPIs. In addition, the smaller particle size with pMDIs may result in better delivery of aerosol to peripheral airways, especially in small

TABLE 2. STUDIES COMPARING PATIENT PREFERENCES FOR pMDIs AND DPIs

<i>Study</i>	<i>Patients</i>	<i>Study design</i>	<i>Devices</i>	<i>pMDI/DPI preference and appeal</i>
Bryant et al. 2013 ⁽⁴⁷⁾	Asthma or COPD (N=103)	Questionnaire survey	pMDI pMDI with spacer DPI (Turbuhaler® or Accuhaler®)	Among patients using more than one inhaler type (n=21): 62% preferred a pMDI 33% preferred DPI 5% preferred pMDI with a spacer
Lindsay et al. 1994 ⁽⁶⁸⁾	Asthma (N=47)	Randomized, open-label, cross-over study	Terbutaline DPI (Turbuhaler) Salbutamol pMDI	Similar numbers of patients expressed a preference for the DPI and the pMDI: 20 individuals preferred the DPI 18 individuals preferred the pMDI
Bunnag et al. 2007 ⁽⁶⁷⁾	Asthma or COPD (N=419)	Comparative, randomized cross-over study	Salbutamol MDIs (CFC- and HFA-based) One salbutamol DPI	Overall appeal was similar for the HFA-pMDI and the DPI, and significantly greater than for the CFC-pMDI More patients ranked the DPI above the HFA-pMDI (47.5% vs 32.5%) as a preferred choice
Bell et al. 2015 ⁽⁷²⁾	Asthma or COPD (N=307)	Open-label, two-period, two-sequence, cross-over study	pMDIs (fluticasone propionate/formoterol or fluticasone propionate/salmeterol [Evohaler®]) DPIs (Accuhaler or Turbuhaler)	Overall, approximately half of patients preferred the fluticasone propionate/formoterol pMDI to the DPIs: 48.6% preferred the pMDI to the Accuhaler (n=35) 46.0% preferred the pMDI to the Turbuhaler (n=126)
Chorao et al. 2014 ⁽⁷¹⁾	Asthma or COPD (N=301)	Cross-sectional observational study	Wide range of devices (of those most commonly available in Portugal)	Patient satisfaction with their current inhaler was similarly high for pMDIs and for the different DPIs
Welch et al. 2004 ⁽⁶⁹⁾	Asthma (N=114)	Randomized, open-label, crossover study	Three pMDIs One DPI (Turbuhaler)	Significantly more patients preferred the DPI than preferred the pMDI: 74% preferred DPI 15% preferred pMDI Patients rated the DPI as significantly better for ease of use and overall satisfaction
Sheth et al. 2003 ⁽⁷⁰⁾	Asthma (N=154)	Randomized, open-label crossover study	pMDI DPI (Diskus)	Significantly more patients preferred the Diskus DPI than preferred the pMDI (60% vs 40%), and more individuals found the DPI easier to use (Diskus DPI, 59%; pMDI, 41%)

CFC, chlorofluorocarbon; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; HFA, hydrofluoroalkane; pMDI, pressurized metered-dose inhaler.

Accuhaler, Diskus and Evohaler: Glaxo Group Limited, Brentford, UK; Turbuhaler: AstraZeneca AB (Södertälje, Sweden).

children with narrower airways. Overall, the study suggests that pMDIs are at least as effective as DPIs in real-world situations.

Most patients use pMDIs for their rescue medication and so should be familiar with the technique for this type of

inhaler. Familiarity and experience with a particular type of inhaler may play a role in ensuring treatment effectiveness. Studies have suggested that using different device types for both their maintenance therapy and reliever inhaler may be associated with worse asthma outcomes than using the same

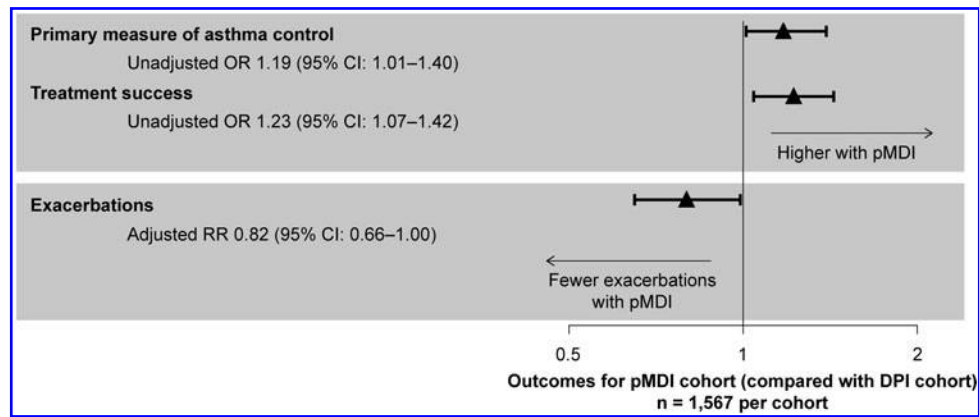


FIG. 5. Improved outcomes for patients with asthma receiving fixed-dose combination fluticasone propionate/salmeterol administered via a pMDI compared with a DPI. Data are shown for end of outcome year for patients initiating fixed-dose fluticasone propionate/salmeterol combination therapy. Asthma control was a composite measure comprising no recorded hospital attendance for asthma, oral corticosteroids, or antibiotics for lower respiratory tract infection. Exacerbations were defined as an unscheduled hospitalization or an emergency department visit for asthma or use of oral steroids. Treatment success was defined as no exacerbations and no change in asthma therapy. CI, confidence interval; DPI, dry powder inhaler; OR, odds ratio; pMDI, pressurized metered-dose inhaler; RR, rate ratio.

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type.⁽⁵⁵⁾ In a retrospective, primary care database analysis, patients who were prescribed the same inhaler for ICS controller and salbutamol reliever medication were significantly more likely to achieve asthma control (adjusted OR: 1.15; 95% CI: 1.02–1.28) and had a significantly lower rate of severe exacerbations (adjusted rate ratio: 0.79; 95% CI: 0.68–0.93) over 1 year than those prescribed mixed inhaler types.⁽⁵⁵⁾ Taken together, the variation shown in these studies clearly demonstrates that there is no ‘one size fits all’ approach, but that patients’ individual preferences need to be considered when selecting an inhaler.

Device design and spacers

The design and ‘feel’ of a device can affect its acceptance and use by patients. pMDIs are often used with spacers or valved holding chambers (VHCs) that attach to the mouthpiece of the inhaler to aid inhalation and reduce adverse effects caused by ICSs depositing in the upper respiratory tract.^(74, 75) Spacers consist of a simple open tube, while VHCs have a one-way inhalation valve in the mouthpiece.^(29, 75)

These devices can make pMDIs easier to use, as they dispense with the need to coordinate actuation and inhalation.⁽⁷⁴⁾ Patients actuate the pMDI into the spacer or VHC, then inhale the contents. With a VHC, patients can also use tidal breathing to inhale the aerosol, slowly breathing in and out of the spacer three or four times.⁽⁷⁵⁾ Closure of the inhalation valve during expiration prevents drug dispersal. Indeed a study in 82 children with asthma aged 5–15 years using a pMDI and a VHC, showed that an inhalation maneuver of five tidal breaths provides similar bronchodilator efficacy to a single deep inhalation followed by a breath-

hold.⁽⁷⁶⁾ Spacers and VHCs also help to decelerate the plume, which limits impaction and deposition in the throat, and increases delivery to lungs.⁽⁷⁴⁾ In addition, larger particles are retained in the device, reducing oropharyngeal deposition.⁽⁷⁴⁾

Slow inhalation is still recommended in order to reduce oropharyngeal deposition, and some spacers emit an audible warning if inhalation is too fast.⁽⁷⁵⁾ Some studies have suggested that using a pMDI with a spacer or VHC provides improved bronchodilation compared with a pMDI alone, although other studies have reported no difference.⁽⁷⁵⁾ Such improvements may reflect the inclusion of patients with poor inhalation technique in these studies. However, enhanced bronchodilation with a pMDI plus a spacer or a VHC compared with a pMDI alone has also been observed in patients with good technique.⁽⁷⁷⁾

A disadvantage with spacers and VHCs is that they can be bulky and awkward to carry around, and are unpopular with some patients, which may result in the pMDI being used without the device, or not being used at all.^(14,48) The proportion of patients using spacers varies considerably, despite their potential benefits. In a survey of patients with asthma in Canada, 46% used their pMDI with a spacer or VHC,⁽⁷⁸⁾ while a previous survey in the UK reported that approximately 10% of patients with asthma used a spacer device.⁽⁷⁹⁾ In a study of patients visiting a community pharmacy in New Zealand, over 40% of patients with COPD but only approximately 15% of patients with asthma used a pMDI with a spacer.⁽⁴⁷⁾ It is therefore important that pMDIs perform similarly when used either with or without a spacer or VHC. With some devices, there is also a risk of drug ‘capture’ by the electrostatically charged spacer walls, especially

if they have recently been cleaned with a dry cloth. This results in a considerably reduced dose to the lungs.⁽⁸⁰⁾

For the fluticasone propionate/salmeterol pMDI, single-dose pharmacokinetic data have shown that up to 2-fold increases in systemic exposure to fluticasone propionate and salmeterol may occur when the device is used with different spacer devices. In addition, in children, the use of a fluticasone propionate/salmeterol pMDI device with a spacer may result in up to 4-fold higher systemic exposure to fluticasone propionate compared with using no spacer.⁽⁸¹⁾ Relative lung bioavailability of fluticasone propionate and salmeterol also showed marked increases when the inhaler was used with a VHC compared with using no VHC.⁽⁸²⁾ By contrast, fluticasone propionate/formoterol showed similar efficacy and tolerability when used with or without a VHC in patients with asthma.⁽⁸³⁾ Furthermore, studies of fluticasone propionate/formoterol showed little change ($\leq 35\%$) in mean systemic bioavailability of fluticasone propionate in healthy volunteers when administered via the pMDI with a VHC compared with the pMDI alone.⁽⁸⁴⁾ It must be noted that most of the data described above were collected in individuals who had been trained to use the device properly. Thus, it is difficult to determine how these results can be extrapolated to patients in real life.

The combination of pMDI and VHC is important for treating pediatric patients, particularly young children and infants. Younger children have problems producing the forceful inhalation required to activate DPIs, so these are not recommended for children younger than 5–6 years of age.^(38,85) The combination of pMDI and VHC offers a cheaper and more convenient alternative to the use of a small volume nebulizer (SVN) for these patients.⁽²⁹⁾ One study in a pediatric hospital showed that the change from use of a SVN for albuterol administration to use of a pMDI plus VHC in children with asthma and bronchiolitis was associated with a 21% reduction in total albuterol administration costs.⁽⁸⁶⁾

For infants and children aged 4 years and under, who cannot reliably breathe through a mouthpiece, a facemask is attached to the VHC. In recent years much attention has been paid to the impact of facemask fit and design on treatment effectiveness.⁽⁸⁷⁾ Studies have shown that a good seal between the mask and the face is critical for effective drug delivery. Better fitting masks, with less leakage, improved aerosol delivery in infants and children.⁽⁸⁷⁾ The flexibility of the mask and its shape (contour) where it contacts the face are important in attaining a good fit. Reducing the volume of dead-space in the mask and valve system should also help to improve drug delivery. This dead-space effectively adds to the size of the VHC, so reducing its volume should increase the amount of drug inhaled with each breath, and increase the speed of VHC emptying.⁽⁸⁷⁾

The cooperation of the child or infant during treatment is another key factor for effective drug delivery; thus factors that improve the comfort and fit of the facemask should help them to accept its use, and so improve aerosol delivery.⁽⁸⁷⁾ The recently developed SootherMask incorporates the infant's or toddler's own pacifier, and has been shown to facilitate the administration of aerosol therapy (via a VHC and Soft Mist inhaler) to sleeping infants, with good lung deposition (as determined by scintigraphy).⁽⁸⁸⁾

The combination of a VHC and pMDI is useful for cognitively impaired and elderly patients when used in conjunction with a large (adult) mask. This set-up can also be used to speed the recovery from acute, severe asthma in the ambulance and in the emergency department using multiple (10–20) bronchodilator puffs, offering an effective alternative to treatment using a SVN, which is more costly and may take longer to initiate (although the difference is likely to be small with trained professionals).^(74,75) A study in adult asthma patients treated in a large emergency department showed greater improvement in peak flow rates, reduced time spent in the emergency department, and lower total treatment dose when albuterol was administered using a pMDI and VHC than with a nebulizer.⁽⁸⁹⁾ pMDIs can also be used as an alternative to SVNs to deliver aerosol therapy (via specific spacer devices) to patients on assisted ventilation and in tracheotomized patients, where DPIs would not be relevant.⁽⁷⁴⁾

Until recently, patients using pMDIs had difficulty assessing how many doses remained in their inhaler.⁽¹⁾ Opaque drug canisters meant that patients had to monitor how often they had actuated their inhaler to estimate the number of doses remaining and to ensure that they did not use the inhaler more than the recommended number of times.^(1,90) In one survey of patients with asthma, 74% of patients did not know how many actuations their inhaler contained, and patients replaced the canister either when they could no longer hear a sound when it was actuated (72%), or when it was 'old'.⁽⁹⁰⁾ Without a dose counter, patients may continue to use their pMDI long after the active drug has been depleted, as the presence of propellant in the device suggests that it is still providing medication.

The presence of a dose counter is considered by patients among the most important features of an ideal inhaler,⁽⁹¹⁾ and difficulty assessing the number of remaining doses has been reported to adversely affect patient satisfaction with pMDIs.^(69,70) Integrated dose counters in newer pMDIs are therefore an important development that can improve device handling for patients. Studies have shown that most patients were satisfied with the ease of use and convenience of a pMDI with an integrated dose counter after using it for about 1 month, and most thought that it would help them keep track of their medication use.^(92,93) The proportion of patients who were satisfied with the device also increased by 43% compared with previous pMDIs without a dose counter; two-thirds of patients also agreed that the dose counter relieved anxiety about running out of medication or taking a sub-therapeutic dose.^(92,93)

Device choice and treatment decisions

Improved matching of devices to patients' preferences and characteristics (e.g., their abilities and natural inhalation profiles) could reduce the misuse of inhalers, increase adherence, and therefore improve treatment outcomes. When treating patients with asthma or COPD, HCPs are faced with a wide range of bronchodilator and ICS therapy options, and a variety of different devices for delivering them. In selecting the most appropriate treatment, HCPs have to consider not only which medication but also which inhaler device is suitable for a particular patient. Indeed, patients' preferences and their ability to use their inhaler are key

TABLE 3. ISSUES TO CONSIDER IF ASTHMA IS NOT UNDER CONTROL

A	Is it really Asthma?	Consider other diagnoses (e.g., hyperventilation, vocal cord dysfunction, Churg–Strauss syndrome, carcinoid)
B	Are all Bronchial triggers known?	Exposure to unknown triggers at work, hobby, rhino-sinusitis, gastroesophageal reflux (GERD), intolerance to medications
C	Is Compliance optimal?	Does the patient use the medication at the prescribed dosages?
D	Can the patient handle the Device?	Is the patient able to use the device correctly?
E	Is Every small airway reached?	Does the anti-inflammatory medication reach the peripheral compartment of the lung?

Reproduced from Dekhuijzen R, Magnan A, Kneussl M, The ADMIT series—Issues in inhalation therapy 1) The goals of asthma treatment: can they be achieved? *Prim Care Respir J* 2007;16:341–348, and Dekhuijzen R. Inhaler therapy for adults with obstructive lung diseases: Powder or aerosol? *Ned Tijdschr Geneesk* 1998;142:1369–1374.^(94,96)

factors to consider when their asthma is not controlled (Table 3),⁽⁹⁴⁾ and should depend on patients' abilities to handle the device, generate an adequate inspiratory flow, and coordinate actuation with inspiration.

HCPs may be able to improve patient–inhaler matching by considering four key factors: patient characteristics ('Who'), the type of medication ('What'), the target regions in the lung ('Where'), and 'How' this can best be achieved by a given device in a specific patient (the '3W–H'

approach).⁽⁴¹⁾ Using this proposed approach, HCPs can determine the types of inhaler appropriate for a particular adult patient based on a few key characteristics (Fig. 6). For example, any available DPI or pMDI would be suitable for patients showing good coordination and an adequate inspiratory flow (block A), whereas a DPI would not be appropriate for patients with an inadequate inspiratory flow (blocks C and D).⁽⁴¹⁾ For infants and young children, the GINA report recommends the use of a pMDI plus dedicated spacer with face mask for those aged 0–3 years and pMDI plus dedicated spacer with mouthpiece for those aged 4–5 years.⁽⁹⁵⁾

Conclusions

pMDIs have always been compact, portable, robust, convenient, unobtrusive, and affordable; however, early models achieved suboptimal levels of lung deposition. Since the introduction of the first HFA-pMDI two decades ago, pMDIs have evolved markedly from early CFC devices. Many modern HFA-pMDIs produce plumes with a higher FPF and a lower force and velocity than their CFC-based predecessors, with the potential to reduce oropharyngeal deposition and improve lung delivery. The warmer and softer plumes may also be more attractive to patients, while the introduction of dose counters has helped to increase patients' confidence and decrease the risk of relying on an empty device.

DPIs and pMDIs differ fundamentally in their underlying designs, so each type will suit some patients better than others; compared with DPIs, HFA-pMDI drug delivery is less dependent on inhalation effort. HFA-pMDIs are also familiar to patients, as they are widely used for reliever medication. There is no such thing as the 'ideal inhaler', but pMDIs offer an attractive device option in many cases, and should be considered when choosing an inhaler device to prescribe.

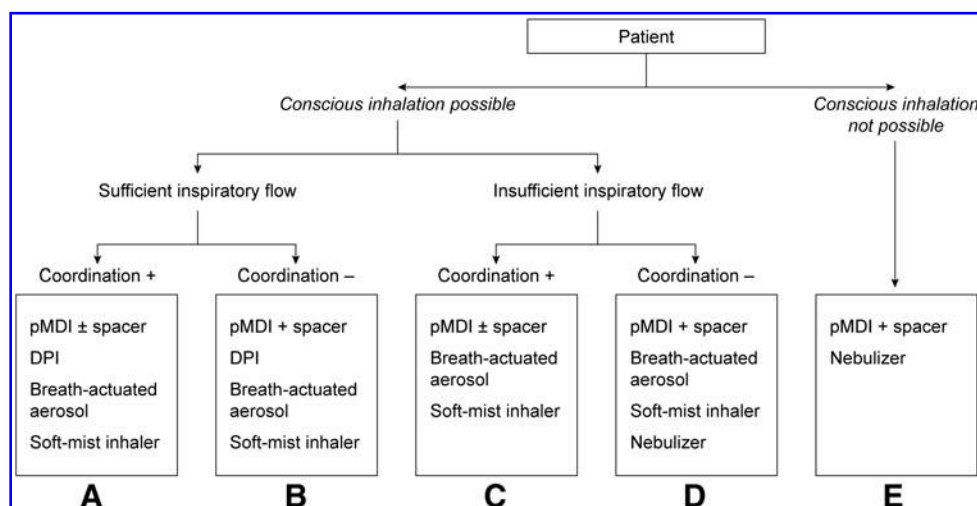


FIG. 6. Choosing an inhaler for adult patients: the ABCDE (3H-W) decision algorithm. DPI, dry powder inhaler; pMDI, pressurized metered-dose inhaler. Reprinted from *Respir Med*, 107;12:1817–1821. Dekhuijzen PNR, Vincken W, Virchow JC, et al., Prescription of inhalers in asthma and COPD: towards a rational, rapid and effective approach. Copyright (2013), with permission from Elsevier.⁽⁴¹⁾

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Author Disclosure Statement

Nicolas Roche has, over the past 3 years, received (i) fees for speaking, organizing education, participating in advisory boards or consulting from Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, MSD-Chibret, Mundipharma, Novartis, Pfizer, Sandoz, Sanofi-Aventis, Stallergenes, Teva; (ii) research grants from Novartis, Boehringer Ingelheim and Pfizer.

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References

- Bell J, and Newman S: The rejuvenated pressurised metered dose inhaler. *Expert Opin Drug Deliv*. 2007;4:215–234.
- Leach CL: The CFC to HFA transition and its impact on pulmonary drug development. *Respir Care*. 2005;50:1201–1208.
- Lavorini F, Corrigan CJ, Barnes PJ, Dekhuijzen PR, Levy ML, Pedersen S, Roche N, Vincken W, and Crompton GK: Retail sales of inhalation devices in European countries: So much for a global policy. *Respir Med*. 2011;105:1099–1103.
- Price D, Marshall J, and Turner R: Inhaler use in five European countries: Analysis of sales data from Q4 2005 to Q4 2011. *Value Health*. 2012;15:A361 (Abstract PMD392).
- Sanders M: Inhalation therapy: An historical review. *Prim Care Respir J*. 2007;16:71–81.
- Sales-Girons J: Étude médicale et historique des eaux minérales sulfureuses d'Enghien-Les-Bains: Application des eaux sulfureuses pulvérisées au traitement des malades de poitrine. Paris: Delahaye, 1864:1–190. Available at: <https://ia600800.us.archive.org/30/items/39002086471225.med.yale.edu/39002086471225.med.yale.edu.pdf>; Accessed April 3, 2015).
- Anderson PJ: History of aerosol therapy: Liquid nebulization to MDIs to DPIs. *Respir Care*. 2005;50:1139–1150.
- Crompton G: A brief history of inhaled asthma therapy over the last fifty years. *Prim Care Respir J*. 2006;15:326–331.
- Dalby RN, Eicher J, and Zierenberg B: Development of Respimat[®] Soft Mist Inhaler and its clinical utility in respiratory disorders. *Med Devices (Auckl)*. 2011;4:145–155.
- Crompton GK: Problems patients have using pressurized aerosol inhalers. *Eur J Respir Dis Suppl*. 1982;119:101–104.
- Leach CL: Improved delivery of inhaled steroids to the large and small airways. *Respir Med*. 1998;92(Suppl A):3–8.
- 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;1:315–320.
- Newman SP, and Chan HK: In vitro/in vivo comparisons in pulmonary drug delivery. *J Aerosol Med Pulm Drug Deliv*. 2008;21:77–84.
- Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P, Everard ML, Horvath I, Navalesi P, Voshaar T, and Chrystyn H: What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J*. 2011;37:1308–1417.
- Pritchard JN: The influence of lung deposition on clinical response. *J Aerosol Med*. 2001;14(Suppl 1):S19–26.
- Bousquet J, Poli G, Acerbi D, Monno R, Ramael S, and Nolleaux F: Systemic exposure and implications for lung deposition with an extra-fine hydrofluoroalkane beclomethasone dipropionate/formoterol fixed combination. *Clin Pharmacokinet*. 2009;48:347–358.
- Paggiaro P, Nicolini G, and Papi A: Extrafine beclomethasone dipropionate/formoterol hydrofluoroalkane-propelled inhaler in asthma. *Expert Rev Respir Med*. 2008;2:161–166.
- Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burt J, Donnell D, Hannon S, and Colice GL: Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol*. 1999;104:1215–1222.
- Taylor A, and Gustafsson P: Do all dry powder inhalers show the same pharmaceutical performance? *Int J Clin Pract Suppl*. 2005:7–12.
- Hill LS, and Slater AL: A comparison of the performance of two modern multidose dry powder asthma inhalers. *Respir Med*. 1998;92:105–110.
- Telko MJ, and Hickey AJ: Dry powder inhaler formulation. *Respir Care*. 2005;50:1209–1227.
- Johal B, Howald M, Fischer M, Marshall J, and Venthoye G: Fine particle profile of fluticasone propionate/formoterol fumarate versus other combination products: The DIFFUSE Study. *Comb Prod Ther*. 2013;3:39–51.
- De Maria R, Zagnoni I, Bodria A, Bonelli S, Alberi MD, Lewis DA, Johnson R, and O'Shea H: Foster: A high-efficiency combination metered-dose inhaler with consistent particle size distribution at alternative flow rates. *Comb Prod Ther*. 2014;4:1–5.
- Johal B, Howald M, Fischer M, Marshall J, and Venthoye G: Letter in response to the review by De Maria et al. 2014. *Comb Prod Ther*. 2014;4:doi: 10.1007/s13556-13014-10007-13550.
- Johal B, Tuohy J, and Marshall J: Plume temperature and force of fluticasone propionate/formoterol pMDI compared with fluticasone propionate/salmeterol pMDI. *Eur Respir J*. 2014;44 (Suppl 58):Abstract P955.
- Atkins PJ: Dry powder inhalers: An overview. *Respir Care*. 2005;50:1304–1312.

27. Coates MS, Chan HK, Fletcher DF, and Raper JA: Influence of air flow on the performance of a dry powder inhaler using computational and experimental analyses. *Pharm Res.* 2005;22:1445–1453.
28. Gabrio BJ, Stein SW, and Velasquez DJ: A new method to evaluate plume characteristics of hydrofluoroalkane and chlorofluorocarbon metered dose inhalers. *Int J Pharm.* 1999;186:3–12.
29. Lavorini F: The challenge of delivering therapeutic aerosols to asthma patients. *ISRN Allergy.* 2013;2013:102418.
30. Hochrainer D, Holz H, Kreher C, Scaffidi L, Spallek M, and Wachtel H: Comparison of the aerosol velocity and spray duration of Respimat Soft Mist inhaler and pressurized metered dose inhalers. *J Aerosol Med.* 2005;18:273–282.
31. Brambilla G, Church T, Lewis D, and Meakin B: Plume temperature emitted from metered dose inhalers. *Int J Pharm.* 2011;405:9–15.
32. Johal B, Murphy S, and Marshall J: Plume characteristics of fluticasone propionate/formoterol pMDI compared with fluticasone propionate/salmeterol pMDI. Presented at the European Respiratory Society Annual Congress, Barcelona, Spain, 7–11 September 2013.
33. Leach CL, Davidson PJ, Hasselquist BE, and 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;122:510–516.
34. Vinchurkar S, Backer LD, Vos W, Holsbeke CV, Backer JD, and Backer WD: A case series on lung deposition analysis of inhaled medication using functional imaging based computational fluid dynamics in asthmatic patients: Effect of upper airway morphology and comparison with in vivo data. *Inhal Toxicol.* 2012;24:81–88.
35. De Backer W, Devolder A, Poli G, Acerbi D, Monno R, Herpich C, Sommerer K, Meyer T, and Mariotti F: Lung deposition of BDP/formoterol HFA pMDI in healthy volunteers, asthmatic, and COPD patients. *J Aerosol Med Pulm Drug Deliv.* 2010;23:137–148.
36. Van Holsbeke C, Marshall J, De Backer J, and Vos W: In vitro lung deposition of fluticasone propionate/formoterol (FP/FORM) pressurized metered dose inhaler (pMDI) with different inhalation profiles. Presented at the European Respiratory Society Annual Congress 2014.
37. De Backer J, Van Holsbeke C, Vos W, Vinchurkar S, Rebello J, Mangale M, and De Backer W: Lung deposition analysis of two formulations of fluticasone/salmeterol HFA pMDI in stable asthma patients. Presented at the European Respiratory Society Annual Congress, Munich, Germany, 2014.
38. Global Initiative for Asthma: Global strategy for asthma management and prevention 2014. Available at: <http://www.ginasthma.org/>. Accessed April 3, 2015.
39. Haughney J, Price D, Barnes NC, Virchow JC, Roche N, and Chrystyn H: Choosing inhaler devices for people with asthma: Current knowledge and outstanding research needs. *Respir Med.* 2010;104:1237–1245.
40. Giraud V, and Roche N: Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J.* 2002;19:246–251.
41. Dekhuijzen PN, Vincken W, Virchow JC, Roche N, Agusti A, Lavorini F, van Aalderen WM, and Price D: Prescription of inhalers in asthma and COPD: Towards a rational, rapid and effective approach. *Respir Med.* 2013;107:1817–1821.
42. Lavorini F, Levy ML, Dekhuijzen PN, and Crompton GK: Inhaler choice and inhalation technique: Key factors for asthma control. *Prim Care Respir J.* 2009;18:241–242.
43. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, Serra M, Scichilone N, Sestini P, Aliani M, and Neri M: Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med.* 2011;105:930–938.
44. Molimard M, and Le Gros V: Impact of patient-related factors on asthma control. *J Asthma.* 2008;45:109–113.
45. Rootmensen GN, van Keimpema AR, Jansen HM, and de Haan RJ: Predictors of incorrect inhalation technique in patients with asthma or COPD: A study using a validated videotaped scoring method. *J Aerosol Med Pulm Drug Deliv.* 2010;23:323–328.
46. Giraud V, Allaert FA, and Roche N: Inhaler technique and asthma: Feasibility and acceptability of training by pharmacists. *Respir Med.* 2011;105:1815–1822.
47. Bryant L, Bang C, Chew C, Baik SH, and Wiseman D: Adequacy of inhaler technique used by people with asthma or chronic obstructive pulmonary disease. *J Prim Health Care.* 2013;5:191–198.
48. Chrystyn H, and Price D: Not all asthma inhalers are the same: Factors to consider when prescribing an inhaler. *Prim Care Respir J.* 2009;18:243–249.
49. Papi A, Haughney J, Virchow JC, Roche N, Palkonen S, and Price D: Inhaler devices for asthma: A call for action in a neglected field. *Eur Respir J.* 2011;37:982–985.
50. Van Holsbeke C, Marshall J, De Backer J, and Vos W: The effect of inhalation duration on lung deposition with a pressurized metered-dose inhaler (pMDI). Presented at the European Respiratory Society Annual Congress 2014.
51. Tomlinson HS, Corlett SA, Allen MB, and Chrystyn H: Assessment of different methods of inhalation from salbutamol metered dose inhalers by urinary drug excretion and methacholine challenge. *Br J Clin Pharmacol.* 2005;60:605–610.
52. Newman SP, Pavia D, Garland N, and Clarke SW: Effects of various inhalation modes on the deposition of radioactive pressurized aerosols. *Eur J Respir Dis Suppl.* 1982;119:57–65.
53. Usmani OS, Biddiscombe MF, and Barnes PJ: Regional lung deposition and bronchodilator response as a function of beta₂-agonist particle size. *Am J Respir Crit Care Med.* 2005;172:1497–1504.
54. van der Palen J, Klein JJ, van Herwaarden CL, Zielhuis GA, and Seydel ER: Multiple inhalers confuse asthma patients. *Eur Respir J.* 1999;14:1034–1037.
55. Price D, Chrystyn H, Kaplan A, Haughney J, Roman-Rodriguez M, Burden A, Chisholm A, Hillyer EV, von Ziegenweid J, Ali M, and van der Molen T: Effectiveness of same versus mixed asthma inhaler devices: A retrospective observational study in primary care. *Allergy Asthma Immunol Res.* 2012;4:184–191.
56. Salvi S, Gogtay J, and Aggarwal B: Use of breath-actuated inhalers in patients with asthma and COPD. An advance in inhalational therapy: A systematic review. *Expert Rev Respir Med.* 2014;8:89–99.
57. Newman SP, Weisz AW, Talaei N, and Clarke SW: Improvement of drug delivery with a breath actuated pressurised aerosol for patients with poor inhaler technique. *Thorax.* 1991;46:712–716.
58. Molimard M, Raherison C, Lignot S, Depont F, Abouelfath A, and Moore N: Assessment of handling of inhaler devices

- in real life: An observational study in 3811 patients in primary care. *J Aerosol Med.* 2003;16:249–254.
59. Newman SP, Brown J, Steed KP, Reader SJ, and Kladders H: Lung deposition of fenoterol and flunisolide delivered using a novel device for inhaled medicines: Comparison of RESPIMAT with conventional metered-dose inhalers with and without spacer devices. *Chest.* 1998;113:957–963.
 60. Pitcairn G, Reader S, Pavia D, and Newman S: Deposition of corticosteroid aerosol in the human lung by Respimat Soft Mist inhaler compared to deposition by metered dose inhaler or by Turbuhaler dry powder inhaler. *J Aerosol Med.* 2005;18:264–272.
 61. Melani AS: Inhalatory therapy training: A priority challenge for the physician. *Acta Biomed.* 2007;78:233–245.
 62. Harnett C, Hunt E, Bowen B, O'Connell O, Edgeworth D, Mitchell P, Eustace J, Henry M, Kennedy M, Plant B, and Murphy D: A study to assess inhaler technique and its potential impact on asthma control in patients attending an asthma clinic. *J Asthma.* 2014;51:440–445.
 63. Bell D, Mansfield L, Lomax M, and Dissanayake S: Patient handling study of fluticasone propionate/formoterol fumarate pressurized metered-dose inhaler. *Respirology.* 2014; 19(Suppl 3):1–62 Abstract O-A-016.
 64. Basheti IA, Armour CL, Reddel HK, and Bosnic-Anticevich SZ: Long-term maintenance of pharmacists' inhaler technique demonstration skills. *Am J Pharm Educ.* 2009;73:32.
 65. Lavorini F, Levy ML, Corrigan C, and Crompton G: The ADMIT series—issues in inhalation therapy. 6) Training tools for inhalation devices. *Prim Care Respir J.* 2010; 19:335–341.
 66. Chrystyn H, Small M, Milligan G, Higgins V, Gil EG, and Estruch J: Impact of patients' satisfaction with their inhalers on treatment compliance and health status in COPD. *Respir Med.* 2014;108:358–365.
 67. Bunnag C, Fuangtong R, Pothirat C, and Punyaratabandhu P: A comparative study of patients' preferences and sensory perceptions of three forms of inhalers among Thai asthma and COPD patients. *Asian Pac J Allergy Immunol.* 2007;25:99–109.
 68. Lindsay DA, Russell NL, Thompson JE, Warnock TH, Shellshear ID, and Buchanan PR: A multicentre comparison of the efficacy of terbutaline Turbuhaler and salbutamol pressurized metered dose inhaler in hot, humid regions. *Eur Respir J.* 1994;7:342–345.
 69. Welch MJ, Nelson HS, Shapiro G, Bensch GW, Sokol WN, Smith JA, and Parasuraman BM: Comparison of patient preference and ease of teaching inhaler technique for Pulmicort Turbuhaler versus pressurized metered-dose inhalers. *J Aerosol Med.* 2004;17:129–139.
 70. Sheth K, Bernstein JA, Lincourt WR, Merchant KK, Edwards LD, Crim CC, and Dorinsky PM: Patient perceptions of an inhaled asthma medication administered as an inhalation powder via the Diskus or as an inhalation aerosol via a metered-dose inhaler. *Ann Allergy Asthma Immunol.* 2003;91:55–60.
 71. Choroa P, Pereira AM, and Fonseca JA: Inhaler devices in asthma and COPD—An assessment of inhaler technique and patient preferences. *Respir Med.* 2014;108:968–975.
 72. Bell D, Mansfield L, Lomax M, and Dissanayake S: Fluticasone/formoterol pressurized metered-dose inhaler: An assessment of patient preference and usability in adolescent and adult patients with obstructive lung disease. *RDD Europe* 2015. 2015;2:239–244.
 73. Price D, Roche N, Christian Virchow J, Burden A, Ali M, Chisholm A, Lee AJ, Hillyer EV, and von Ziegenweidt J: Device type and real-world effectiveness of asthma combination therapy: An observational study. *Respir Med.* 2011;105:1457–1466.
 74. Terzano C: Pressurized metered dose inhalers and add-on devices. *Pulm Pharmacol Ther.* 2001;14:351–366.
 75. Lavorini F, and Fontana GA: Targeting drugs to the airways: The role of spacer devices. *Expert Opin Drug Deliv.* 2009;6:91–102.
 76. Stephen D, Vatsa M, Lodha R, and Kabra SK: A randomized controlled trial of 2 inhalation methods when using a pressurized metered dose inhaler with valved holding chamber. *Respir Care.* 2015;60:1743–1748.
 77. Fontana GA, Lavorini F, Chiostri M, Castellani W, Boddi V, and Pistolesi M: Large and small airway responses to procaterol hydrochloride administered through different extension devices in asthmatic patients. *J Aerosol Med.* 1999;12:177–185.
 78. Fitzgerald JM, Chan CK, Holroyde MC, and Boulet LP: The CASE survey: Patient and physician perceptions regarding asthma medication use and associated oropharyngeal symptoms. *Can Respir J.* 2008;15:27–32.
 79. Hilton S: An audit of inhaler technique among asthma patients of 34 general practitioners. *Br J Gen Pract.* 1990;40:505–506.
 80. O'Callaghan C, Lynch J, Cant M, and Robertson C: Improvement in sodium cromoglycate delivery from a spacer device by use of an antistatic lining, immediate inhalation, and avoiding multiple actuations of drug. *Thorax.* 1993;48:603–606.
 81. Seretide Evohaler Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/medicine/2914; Accessed April 3, 2015.
 82. Nair A, McKinlay L, Williamson P, Short P, Burns P, and Lipworth BJ: Comparative lung bioavailability of fluticasone/salmeterol via a breath-actuated spacer and conventional plastic spacers. *Eur J Clin Pharmacol.* 2011;67:355–363.
 83. Price D, Papi A, Kaiser K, Grothe B, and Lomax M: Fluticasone propionate/formoterol fumarate combination therapy is equally effective and well-tolerated when administered with or without a spacer device to patients with asthma. *Eur Respir J* 2011;38:726s.
 84. Flutiform Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/medicine/26954; Accessed April 3, 2015.
 85. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, Smaildone GC, and Guyatt G: Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest.* 2005;127:335–371.
 86. Salyer JW, DiBlasi RM, Crotwell DN, Cowan CA, and Carter ER: The conversion to metered-dose inhaler with valved holding chamber to administer inhaled albuterol: A pediatric hospital experience. *Respir Care.* 2008;53:338–345.
 87. Amirav I, and Newhouse MT: Review of optimal characteristics of face-masks for valved-holding chambers (VHCs). *Pediatr Pulmonol.* 2008;43:268–274.
 88. Amirav I, Newhouse MT, Luder A, Halamish A, Omar H, and Gorenberg M: Feasibility of aerosol drug delivery to sleeping infants: A prospective observational study. *BMJ Open.* 2014;4:e004124.

89. Newman KB, Milne S, Hamilton C, and Hall K: A comparison of albuterol administered by metered-dose inhaler and spacer with albuterol by nebulizer in adults presenting to an urban emergency department with acute asthma. *Chest*. 2002;121:1036–1041.
90. Rubin BK, and Durotoye L: How do patients determine that their metered-dose inhaler is empty? *Chest*. 2004;126: 1134–1137.
91. Liam CK, Lim KH, and Wong CM: Acceptance of the Accuhaler, a multi-dose powder inhaler, among asthmatic patients: A comparison with the pressurized metered-dose inhaler. *Asian Pac J Allergy Immunol*. 2000;18:135–140.
92. LaForce C, Weinstein C, Nathan RA, Weinstein SF, Staudinger H, and Meltzer EO: Patient satisfaction with a pressurized metered-dose inhaler with an integrated dose counter containing a fixed-dose mometasone furoate/formoterol combination. *J Asthma*. 2011;48:625–631.
93. Sheth K, Wasserman RL, Lincourt WR, Locantore NW, Carranza-Rosenzweig J, and Crim C: Fluticasone propionate/salmeterol hydrofluoroalkane via metered-dose inhaler with integrated dose counter: Performance and patient satisfaction. *Int J Clin Pract*. 2006;60:1218–1224.
94. Dekhuijzen PN, Magnan A, and Kneussl M: The ADMIT series—Issues in inhalation therapy. 1) The goals of asthma treatment: can they be achieved? *Prim Care Respir J*. 2007;16:341–348.
95. Global Initiative for Asthma (GINA): GINA Report, Global Strategy for Asthma Management and Prevention. http://www.ginasthma.org/local/uploads/files/GINA_Report_2015_Aug11.pdf; accessed September 2015.
96. Dekhuijzen PN: Inhaler therapy for adults with obstructive lung diseases: Powder or aerosol? *Ned Tijdschr Geneesk*. 1998;142:1369–1374.

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