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Aerosol Devices and Asthma Therapy

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Abstract: Aerosol delivery of asthma medications maximizes local effects in the lung and minimizes systemic effects compared with oral therapy. Both corticosteroids and bronchodilators are available in a variety of delivery devices for the treatment of asthma. The 1987 Montreal protocol requiring the phasing out of the chlorofluorocarbon (CFC) propellant in commonly used pressurized metered-dose inhalers (pMDIs) provided an impetus for the development of new technologies for the delivery of inhaled asthma medications. For pMDIs, CFC has been replaced with hydrofluoroalkane (HFA) propellant. New types of dry powder inhalers (DPIs) and nebulizers, aerosol delivery devices that do not use propellants, also have been introduced. Drug delivery varies based on the device type, the product formulation and patient-related factors. Thus, drug delivery can differ when the same medication is delivered via an HFA pMDI, a CFC pMDI, a DPI or a nebulizer. Even among the same type of device (eg. DPIs, pMDIs), inhaler designs and drug formulations differ. Drug and device selection should be based on consideration of the patient's ability to use the device properly, the availability of a desired drug or drugs (ie. maintenance and rescue) in a particular inhaler device and patient preference. This review describes key characteristics for each device type, explains differences in markers of lung deposition, lists potential advantages and disadvantages of the different devices and discusses how these and other factors need to be considered when selecting an inhaler device that meets the individual needs of a patient.

Keywords: aerosol devices, asthma therapy, pMDI, MDI, HFA, nebulizers.

INTRODUCTION

Inhaled therapy, the most important component of asthma therapy, allows for the selective delivery of drug to the lung tissue while minimizing systemic side effects [1-3]. Because drug is delivered straight to the diseased tissue, relatively low doses can be used and the therapeutic effect is observed more rapidly compared with systemic treatment. However, there also are disadvantages associated with aerosolized therapy; for example, drug is delivered to an organ that is specialized in excluding foreign material. Furthermore, there are a number of devices available on the market at this time, each unique in its own way, often making therapeutic choice difficult.

Modern inhalation therapy for the treatment of asthma dates back to the 1950s, when the Aerohaler® was used to administer norisodrine powder [4]. A revolutionary advance, the development of pressurized metered-dose inhalers (pMDIs) came about in the mid-1950s, when the teenaged daughter of the Riker Laboratories president suggested that asthma medications would be more convenient if delivered similarly to the way perfume was delivered in a spray device [3-5]. Based on this suggestion, the Medihaler-Epi® (epinephrine; 3M-Riker) was introduced in 1956 [5, 6].

Since the introduction of the pMDI more than 50 years ago, there have been numerous advances in device technology and inhaled drug formulations [4]. For example, challenges posed by improper inhalation technique, poor coordination, high oropharyngeal deposition and the need to replace chlorofluorocarbon (CFC) propellants as a result of the 1987 Montreal protocol, which banned substances that deplete the ozone layer, led to the evolution of the pMDI device [3, 4, 7, 8]. In addition, numerous accessory devices (eg. spacers), breath-actuated devices and dry powder inhalers (DPIs) have become available. Furthermore, specialized nebulizers have been introduced and feature breath-enhanced, breath-actuated and vibrating-mesh technology [9].

The efficient delivery of aerosol formulations has become increasingly important as the growing sophistication of available devices and formulations has translated into a complexity of offerings. Therefore, it has become even more important that the prescribing clinician gain a basic understanding of the device differences to facilitate selection of the most appropriate device, customized for each patient. It is important that clinicians individualize the choice of asthma device according to what works best for the patient in a particular setting, taking numerous variables into consideration [2, 10, 11]. The purpose of this article is to review current asthma medication delivery devices to guide the clinician in identifying the most appropriate device and to teach the effective use of each device.

KEY CHARACTERISTICS OF DEVICE TYPES

At this time, aerosol delivery of asthma medication can be administered using a pMDI, a breath-actuated MDI, a DPI or a nebulizer [12]. Within each device classification, further differentiation can be made based on metering, means of dispersion or design [13]. For example, in contrast to pMDIs

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or DPIs, nebulizers deliver an aerosol generated from a polar liquid, typically water, in which the drug is dissolved or suspended. While the nebulizer is one delivery device option, it is larger and less portable than the pMDI and DPI devices, which are handheld. In contrast to drug delivery from a nebulizer, pMDIs and DPIs deliver bolus doses of drug in either a particulate suspension or solution via a non-polar volatile propellant or, in the case of a DPI, in a dry powder mix that is dispersed upon inhalation [13, 14]. Potential advantages and disadvantages of each device are summarized in Table **1**.

One potential disadvantage of pMDIs is that the patient is required to coordinate actuation with inhalation, which may lead to variable and sometimes low drug delivery. However, this can be overcome through the use of a spacer device. In addition, pMDIs are economical, small and highly portable. DPIs are an alternative to pMDIs that do not require coordination of actuation with inhalation; however, optimal performance of a DPI is based on the patient's ability to inhale forcefully and deeply [2]. Incorporation of dose counters in newer designs of DPIs eliminates uncertainty about the number of doses remaining in the device throughout the product's life cycle. The dose counter also will be incorporated into new pMDIs in accordance with a new Food and Drug Administration (FDA) guidance issued to prevent the premature discard of pMDI or the continued use of pMDI beyond the recommended number of doses [21]. Nebulizers are advantageous because they require less patient coordination than pMDIs and DPIs and offer the ability to administer multiple medications that may not be available in a combined product simultaneously, as well as modify doses of medications. These devices, however, are not easily portable, require a longer treatment time compared with pMDIs and DPIs and drug delivery may vary depending on the choice of nebulizer [22]. Controller and rescue medications for asthma are available in several device types and are summarized in Table **2** [23, 24].

pMDIs

Many parts of a pMDI, including the container, the actuator, the metering valve, the propellants and the formulation, influence drug delivery from the device (Fig. **1**) [14, 25].

Drug formulation characteristics, including the use of solutions versus suspensions, the use of surfactants to reduce particle aggregation and to lubricate the valve mechanism, the presence of excipients to solubilize surfactants or the drug itself and the drug concentration, also may affect the delivered dose of drug [14, 25]. For example, high vapor pressure, small drug particle size, or low drug concentration in suspension drug formulations may reduce the aerosol particle size [14, 25]. Other critical components of the pMDI include the metering valve and the actuator. Improvements in metering valve design have mostly eliminated problems associated with erratic dosing after storage of the device valve-down or after use of the device when the canister is almost empty [14]. The actuator, which is critical for aerosol formation, is partly responsible for determining the aerosol size and is based on the diameter of the nozzle; although aerosol particle size has been described to increase in a step-wise fashion directly with the nozzle size, a nozzle that is too narrow can emit a wide, spray-cone angled mist that results in a large amount of drug being deposited on the mouthpiece of the actuator [14, 26].

Suitable propellants for pMDIs must be nontoxic, nonflammable and compatible with the selected drug formulations and have appropriate boiling points and densities [27]. Traditional pMDIs were formed with the CFC propellant CFC-12. Due to the international agreement to phase out the use of CFC propellants, pMDIs are now available using an hydrofluoroalkane (HFA) propellant [7, 20]. Many significant advances were made during the movement to eliminate the CFC propellant from pMDIs (although some CFC pMDIs are still available, the FDA has called for the removal of all CFC albuterol pMDIs from the market by 2008) [8, 28]. Reformulation of the CFC pMDIs with HFA presented an opportunity to improve the pMDI device. For example the first CFC-free MDI, HFA albuterol sulfate (Airomir® in Europe, 3M Health Care Ltd, Loughborough, United Kingdom; Proventil® HFA in the United States, 3M Pharmaceuticals, St Paul, Minnesota), has the same emitted dose and particle size distribution as the CFC-containing device, but emits a warmer spray that reduces the 'cold Freon effect,' which causes the patient to stop inhaling. Other advantages of this HFA albuterol device include maintained dose in cold climates, less dose variability when the canister is almost empty and no loss of dose when the device is stored inverted [8, 20].

The change from CFC to HFA formulations also presented an opportunity to engineer average aerosol particle sizes of 0.9-1.2 μm to reach the entire respiratory tract (large and small airways), which is particularly important when treating with inhaled corticosteroids (ICSs) [8, 29, 30]. The ICS dose required for equivalent lung deposition may vary between the older CFC pMDI versus the reformulated HFA pMDI device. For example, lung deposition is greater for beclomethasone solution formulation delivered via an HFA pMDI (55 to 60% of the drug) than a suspension formulation CFC pMDI (4 to 7% of the drug), and the distribution of drug in the lung is improved (ie. more drug deposited in the peripheral airways) using the HFA formulation [29]. Furthermore, it has been reported that similar efficacy (eg. change from baseline in percentage predicted FEV_1) is achieved with half the dose of beclomethasone HFA pMDI compared with beclomethasone CFC pMDI [31, 32]. In a similar manner, a study of HFA pMDI beclomethasone extrafine aerosol 800 μg/day demonstrated a similar systemic safety profile and an improved efficacy compared with CFC pMDI beclomethasone 1500 μg [33]. Noninferiority studies of children or adults with mild to moderate persistent asthma have demonstrated that budesonide CFC and HFA pMDI devices provide clinical compatibility regarding efficacy and safety when administered at microgram-equivalent dosages [34, 35]. Although these studies support clinical efficacy between the CFC and HFA devices, it is important to consider the limitations of some comparator trials that evaluate clinical efficacy using high, fixed doses of ICS in relatively stable patients [33, 34].

Because some patients may have difficulty coordinating inhalation and device actuation, breath-actuated MDIs were developed (eg. pirbuterol acetate inhalation aerosol, Maxair™

Table 1. Potential Advantages and Disadvantages of Each Type of Asthma Aerosol Device[a]

Device Type	Population[b]	Advantages	Disadvantages
pMDI	• Aged ≥ 5 years (< 5, spacer or valved holding chamber) • Slow inhalation and coordination of actuation during inhalation may be difficult, particularly in young children and elderly	• Portable and compact • Can be used quickly • Often the least expensive device • No preparation of drug required • No contamination of contents • Some of the newer HFA solutions have a very high lung deposition fraction (≥ 50%)	• Need to coordinate actuation and inhalation • High pharyngeal deposition • Upper limit to unit dose content • Difficult to determine remaining doses/no dose counters
Breath-actuated MDI	• Aged ≥ 5 years • May be particularly useful for patients unable to coordinate inhalation and actuation or for elderly patients	• Indicated for patients unable to coordinate inhalation and actuation • May be particularly useful in the elderly • Less variation in emitted dose due to reproducible actuation	• Patients may incorrectly stop inhalation at actuation • Cannot be used with available spacer/valved-holding chamber devices
DPI	• Aged ≥ 4 years • Most children aged < 4 years may not generate sufficient inspiratory flow	• Breath actuated • Less patient coordination required compared with a pMDI device • No need for propellant • Portable and compact • Can be used quickly • No preparation of drug required • Dose counters in newer designs	• Some units are single dose • Loss of dose if patient exhales through the device • Can result in high pharyngeal deposition • Upper limit to unit dose content
Spacer/holding chamber	• Aged ≥ 4 years (< 4 years old, valved holding chamber with face mask) • Indicated for patients who have difficulty performing adequate MDI technique	• Reduced need for coordination • Reduced pharyngeal deposition	• Complexity of inhalation may be increased for some patients • Increases expense and decreases portability compared with MDI alone • Development of static charge on the inner walls can attract aerosol particles to the walls and reduce lung delivery • Integral actuator devices may alter aerosol properties compared with native actuator
Nebulizers	• Patients of any age who cannot use a metered-dose inhaler with a valved holding chamber and a face mask	• Patient coordination not required • Effective with tidal breathing • May be able to administer multiple medications • Dose modification is possible • May be used at any age	• Lack of portability (jet nebulizers) • Lengthy treatment times • Device cleaning required and contamination possible • Lack of availability of some medications in a preparation that can be nebulized • Suspensions not aerosolized well (ultrasonic nebulizers) • Variability of performance efficiency among different nebulizers • Less efficient than other devices (waste) • Expensive (ultrasonic nebulizers) • More effective if triggering the device is coordinated with inspiration • Face mask must fit appropriately

pMDI, pressurized metered-dose inhaler; HFA, hydrofluoroalkane; CFC, chlorofluorocarbon; DPI, dry powder inhaler.

[a] See references [10, 14-20].

[b] Population recommendations are based on Figure 3-24 of the 2007 National Asthma Education and Prevention Program. Expert Panel Report 3; however, patient coordination, preference, and ability should all be taken into consideration when prescribing the appropriate delivery device.

Adapted from Dolovich *et al.* 2000 [18] with permission of the *Respiratory Care* journal.

Table 2. Aerosolized Rescue and Controller Medication Commonly Used in the United States[a] and the United Kingdom[b] for the Treatment of Asthma

United States

Drug Class	Device Type	Generic Name	Trade Name
SABA			
	pMDI	Metaproterenol	Alupent® Inhalation (Boehringer Ingelheim, Ridgefield, CT)*
	HFA pMDI	Albuterol	Proventil® HFA (Key Pharmaceuticals, Inc., Kenilworth, NJ) Ventolin® HFA (GlaxoSmithKline, Research Triangle Park, NC) ProAir® HFA(Teva Specialty Pharmaceuticals, LLP, Horsham, PA)
		Levalbuterol	Xopenex HFA® (Sepracor Inc., Marlborough, MA)
	Breath-activated pMDI	Pirbuterol	Maxair™ Autohaler™ (Graceway Pharmaceuticals, Bristol, TN)*
	Nebulizer	Metaproterenol	Alupent® Inhalation Solution (Boehringer Ingelheim, Ridgefield, CT)
		Albuterol	AccuNeb™ (DEY®, Napa, CA)
		Levalbuterol	Xopenex® Inhalation Solution (Sepracor Inc., Marlborough, MA)
LABA			
	DPI	Formoterol	Foradil® Aerolizer® (Schering Corporation, Kenilworth, NJ)
		Salmeterol	Serevent® Diskus® (GlaxoSmithKline, Research Triangle Park, NC)
ICS			
	pMDI	Flunisolide	Aerobid® (Forest Laboratories, Inc., St. Louis, MO)* Aerobid®-M (Forest Laboratories, Inc., St. Louis, MO)*
		Triamcinolone	Azmacort® (Kos Pharmaceuticals, Inc., Cranbury, NJ)*
	HFA pMDI	Beclomethasone	QVAR® Inhalation Aerosol (3M Pharmaceuticals, Northridge, CA)
		Fluticasone	Flovent® HFA (GlaxoSmithKline, Research Triangle Park, NC)
	DPI	Budesonide	Pulmicort Turbuhaler® (AstraZeneca LP, Wilmington, DE)
		Mometasone	Asmanex® Twisthaler® (Schering Corporation, Kenilworth, NJ)
	Nebulizer	Budesonide	Pulmicort Respules® (AstraZeneca LP, Wilmington, DE)
ICS/LABA			
	HFA pMDI	Salmeterol/fluticasone	Advair® HFA (GlaxoSmithKline, Research Triangle Park, NC)
		Budesonide/formoterol	Symbicort® Inhalation Suspension (AstraZeneca LP, Wilmington, DE)
	DPI	Salmeterol/fluticasone	Advair Diskus® (GlaxoSmithKline, Research Triangle Park, NC)

United Kingdom

Drug Class	Device Type	Generic Name	Trade Name
SABA			
	HFA pMDI	Salbutamol	Airomir® Inhaler (3M Health Care Limited, Loughborough, UK) Salbulin® (3M Health Care Limited, Loughborough, UK) Salamol® (Norton Healthcare Limited, Chesire, UK) Ventolin™ Evohaler™ (Allen & Hanburys, Middlesex, UK)

(Table 2) contd….

Drug Class	Device Type	Generic Name	Trade Name
	Breath-activated pMDI	Salbutamol	Airomir® Autohaler (3M Health Care Limited, Loughborough, UK) Salamol® EasiBreathe® (Norton Healthcare Limited, Chesire, UK)
	Nebulizer	Salbutamol	Salamol Steri-Neb® (Norton Healthcare Limited, Chesire, UK) Ventolin™ Nebules™ (Allen & Hanburys, Middlesex, UK)
		Terbutaline	Bricanyl Respules® (AstraZeneca UK Limited, Luton, UK)
	DPI	Salbutamol	Asmasal® Clickhaler (UCB Pharma Limited, Berkshire, UK) Pulvinal™ Inhaler (Trinity-Chiesi Pharmaceuticals Limited, Cheadle, UK) Ventodisks™ (Allen & Hanburys, Middlesex, UK) Ventolin™ Accuhaler™ (Allen & Hanburys, Middlesex, UK)
		Terbutaline	Bricanyl® Turbohaler (AstraZeneca UK Limited, Luton, UK)
LABA			
	pMDI	Salmeterol	Serevent™ Inhaler (GlaxoSmithKline, Middlesex, UK)* Serevent™ Evohaler™ (GlaxoSmithKline, Middlesex, UK)
		Formoterol	Atimos® Modulite® (Trinity-Chiesi Pharmaceuticals Limited, Cheadle, UK)
	DPI	Formoterol	Foradil® (Schering Corporation, Kenilworth, NJ) Oxis® Turbohaler (AstraZeneca UK Limited, Luton, UK)
		Salmeterol	Serevent™ Diskhaler™ (GlaxoSmithKline, Middlesex, UK) Serevent™ Accuhaler (GlaxoSmithKline, Middlesex, UK)
ICS			
	pMDI	Beclomethasone	Becloforte™ (Allen & Hanburys, Middlesex, UK)* Becotide™ Inhaler (Allen & Hanburys, Middlesex, UK)*
	HFA pMDI	Beclomethasone	Clenil® Modulite® (Trinity-Chiesi Pharmaceuticals Limited, Cheadle, UK) QVAR® (3M Health Care Limited, Loughborough, UK) QVAR® Autohaler (3M Health Care Limited, Loughborough, UK)
		Budesonide	Pulmicort® pMDI (AstraZeneca UK Limited, Luton, UK)
		Ciclesonide	Alvesco® (ALTANA Pharma AG, a Nycomed Company, Roskilde, Denmark)
		Fluticasone	Flixotide™ Evohaler™ (Allen & Hanburys, Middlesex, UK)
	DPI	Beclomethasone	Asmabec® Clickhaler (UCB Pharma Limited, Berkshire, UK) Becodisks™ (Allen & Hanburys, Middlesex, UK) Pulvinal™ Inhaler (Trinity-Chiesi Pharmaceuticals Limited, Cheadle, UK)
		Budesonide	Pulmicort® Turbohaler® (AstraZeneca UK Limited, Luton, UK)
		Fluticasone	Flixotide™ Accuhaler™ (Allen & Hanburys, Middlesex, UK) Flixotide™ Diskhaler™ (Allen & Hanburys, Middlesex, UK)
		Mometasone	Asmanex® Twisthaler® (Schering Corporation, Kenilworth, NJ)

(Table 2) contd….

Drug Class	Device Type	Generic Name	Trade Name
	Nebulizer	Budesonide	Pulmicort Respules® (AstraZeneca UK Limited, Luton, UK)
		Fluticasone	Flixotide™ Nebules™ (Allen & Hanburys, Middlesex, UK)
ICS/LABA			
	DPI	Salmeterol/fluticasone	Seretide® Accuhaler® (GlaxoSmithKline, Middlesex, UK)
		Budesonide/formoterol	Symbicort® Turbuhaler® (AstraZeneca UK Limited, Luton, UK)

*Contains chlorofluorocarbons.
[a] See reference [23].
[b] See reference [24].
Manufacturing information is current as of June 19, 2007.
SABA, short-acting β_2-adrenergic antagonist; pMDI, pressurized metered-dose inhaler; HFA, hydrofluoroalkane; LABA, long-acting β_2-adrenergic antagonist; DPI, dry powder inhaler; ICS, inhaled corticosteroid.

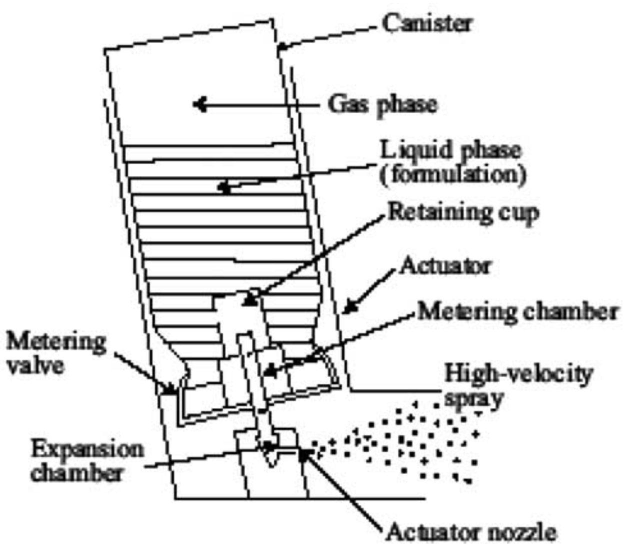

Fig. (1). Schematic of a typical pressurized metered-dose inhaler. Reproduced from Newman *et al.* 2005 [14] with permission of Lippincott Williams & Wilkins.

Autohaler™ (3M Pharmaceuticals, Northridge, CA, USA). Breath-actuated devices are composed of a conventional pressurized canister that is triggered by a spring when the patient inhales slowly through the mouthpiece [36]. Results from a small study (n = 18) that compared albuterol delivery via a breath-actuated MDI with a conventional pMDI indicate that the breath-actuated device was helpful in increasing lung dose in patients with poor inhalation technique, but not in those with good technique [36].

Spacer Systems

The use of various spacers (eg. InspirEase™, Allergy Asthma/Technology, Ltd., Morton Grove, IL, USA; Aerochamber™, Allergy Asthma/Technology, Ltd., Morton Grove, IL, USA), which attach directly to the pMDI device, is one method of addressing the difficulties some patients have when using pMDIs [37]. The purpose of spacers is to slow the velocity of the aerosol spray, allowing time for the propellants to evaporate and large drug particles to settle, thereby decreasing oropharyngeal deposition while increasing lung deposition [12, 38, 39]. In addition, spacers decrease the need for coordination of inhalation and actuation [38, 39]. Spacers may be categorized into 3 basic types: tube spacers, which are simple extensions to the inhaler mouthpiece; holding chambers, which usually contain a one-way valve in the mouthpiece and often are designed to match the shape of the expanding spray plume; and reverse-flow devices, which allow the spray to be fired away from the patient into the bag or chamber from which the patient inhales [37]. The volume of spacer devices varies widely, from < 50 ml (selected tube spacers) to 750 ml (selected holding chambers) [37].

The advantages of using a spacer include improved ease of use of pMDIs, improved pulmonary drug delivery and use in conjunction with a face mask to deliver drug to young children [37, 40]. Because spacers increase the bulk of a pMDI and may be inconvenient, they should only be considered for use in patients who cannot use a pMDI correctly [37]. It has been suggested that spacers be routinely used in preschool-aged children, for the delivery of ICS with a low first-pass metabolism in all age groups and in all patients who cannot use pMDIs or DPIs correctly [39, 40]. Furthermore, spacers may be appropriate for delivering high doses of corticosteroids in an effort to lower needed doses of maintenance therapy and reduce oral deposition [37, 39].

Of note, in studies of patients with good or poor inhaler technique, the use of a spacer enhanced bronchodilator response only in patients with poor technique [41, 42]. A review of studies that compared the use of pMDIs with or without add-on devices demonstrated that although the use of spacers did not always increase lung deposition, they always reduced oropharyngeal deposition [43]. Although spacers may increase lung delivery, factors including incorrect use and electrostatic charge may potentially cause drug delivery to decrease when using a spacer device [9, 11, 37].

The type of spacer and method of its use can markedly affect the delivery of asthma medication [40]. Reduced drug delivery has been associated with multiple actuations into the spacer before inhalation, delay of inhalation after actuation, ill-fitting face masks (when used with spacer device) and accumulation of static electricity [39, 40]. Because spacer size may affect drug delivery, it is recommended that only spacers evaluated for use with a particular pMDI be used in combination [40].

DPIs

Most of the currently available DPIs use the same principles of operation: micronized drug is blended with large carrier particles to prevent aggregation and improve flow. A static powder bed is used to conduct the dispersion of the dry powder upon inspiration. When the patient inhales, shear and turbulence are created by airflow through the device, and air is introduced into the powder bed. Upon fluidization of the static powder, drug enters the patient's airway [13]. Thus, DPIs do not use propellants; rather, drug delivery depends on the patient's peak inspiratory flow (PIF) [44].

There are several types of DPIs that can be classified according to how the dose of drug is stored within the device: a single-dose system where the drug is stored in single prefilled capsules, or a multidose system using disks or using a multidose reservoir inhaler where a dosing disk meters the dose [44-46]. Although DPIs obviate the need for coordination of actuation and inhalation, essentially making them breath-actuated, the PIF required for effective deaggregation of the powder varies among DPI devices because of difference in inhaler resistance [44, 46, 47].

In general, a patient's inspiratory force influences drug delivery from a low-resistance DPI but less from a high-resistance DPI. High-resistance DPIs include Pulvinal® (Trinity-Chiesi Pharmaceuticals Limited, Cheadle, UK) and the Inhalator® (Boehringer Ingelheim, Ingelheim, Germany). The Pulmicort Turbuhaler® (AstraZeneca LP, Wilmington DE, USA) has been categorized as an intermediate/high-resistance device and the Diskus® (GlaxoSmithKline, Research Triangle Park, NC, USA) as a medium resistance device. The Rotahaler® (GlaxoSmithKline, Research Triangle Park, NC, USA) and Aerolizer® (Novartis Pharma AG, Basle, Switzerland) have been described as low-resistance devices [48-52]. In general, patients, including children, are able to obtain the necessary PIF required for adequate drug delivery [11, 53]. In fact, Agertoft and Pedersen demonstrated that after instruction and training, the majority of children aged 4 to 5 years can generate a sufficient PIF from the Turbuhaler DPI [54].

Several single-dose DPIs as well as multiple-dose DPIs are currently available for the delivery of asthma medications in the United States or abroad (Table **2**) [23, 24]. In addition to differences in the character of the particulate system, other key differences are intrinsic to the device; among the multiple-dose DPIs, these differences include dose counters, ability to reload the device, ease of cleaning and device resistance (Table **3**) [51, 52, 55]. Furthermore,

Table 3. Comparison of Selected Multiple-Dose Dry Powder Inhaler Devices[a]

Variable	Turbuhaler*	Diskus/Accuhaler†	Twisthaler‡	Diskhaler†§	Clickhaler§||	Pulvinal®§¶	Easyhaler§#
Dose metering: blister pack (maximum)	NA	**√ (60)**	NA	**√ (8)**	NA	NA	NA
Reservoir (maximum)	**√ (200)**	NA	**√ (200)**	NA	**√ (200)**	**√ (100)**	**√ (200)**
Dose counter	X √†	√	√	√	√	X	√
Overdose-secure	√	√	√	√	√	√	√
Device lock out	X	√	√	X	√	X	X
Reloadable	X	X	X	√	X	X	X
Lactose carrier	X√**	√	√	√	√	√	√
Shape/handling resembles pMDI	X	X	X	X	√	X	√
Number of operating maneuvers	6	6	6	8	7	7	7
Easy to prime	++	+++	NA	+	+++	++	+++
Easy to clean	+++	++	+++	+	+++	+++	+++
Device resistance	+++	++	++	+	+++	++++	++++

*AstraZeneca LP, Wilmington, DE.
†GlaxoSmithKline, Middlesex, UK.
‡Schering Corporation, Kenilworth, NJ, USA.
§Not available in the United States for the administration of asthma medications.
||Innovata Biomed, St Albans, UK.
¶Trinity-Chiesi, Pharmaceuticals Limited, Cheadle, UK.
#Orion, Kuopio, Finland.
**Available in some products using the Turbuhaler® device.
[a] See references [51,52,55].
Manufacturing information is current as of June 19, 2007.
NA, not applicable.
Adapted from *Pulmonary Pharmacology & Therapeutics*, Vol 16, Smith I.J., Parry-Billings M., The inhalers of the future? A review of dry powder devices on the market today, Table **2**, pp 79-95, copyright 2003, with permission from Elsevier [51].

inhalation techniques vary according to the type of DPI being used [46].

The performance of a DPI also depends on the character of the particulate system. Characteristics of the particulate system include crystallinity, polymorphism, moisture content, hygroscopicity and particle size [13]. Of these, the single most important variable of a DPI formulation is particle size. Aerodynamic size is a method for determining particle size, and substantial evidence links aerodynamic size to the probability of lung deposition; particle size between 1 and 5 µm is ideal [13, 45].

Nebulizers

There are 2 basic types of nebulizers for the delivery of asthma medications, small-volume jet nebulizers (compressor-driven) and non–compressor-driven (ie. ultrasonic and vibrating mesh or plate) nebulizers. Variations in jet nebulizer design include open-vent nebulizers, breath-assisted open-vent nebulizers and adaptive aerosol delivery devices [3]. Open jet nebulizers incorporate an extra open vent into the system to generate greater airflow, resulting in a greater amount of particles generated leading to shorter nebulization times; however, these systems can be expensive [9]. Breath-assisted devices incorporate a valve that opens during inspiration and allows extra air to be drawn through the device to abrogate the loss of aerosol during exhalation. However, these devices depend on the patient's inspiratory flow. Adaptive aerosol delivery devices, which pulse drug during the inspiratory phase, are able to analyze the patient's breathing pattern and adapt the pulsed dose of aerosol throughout treatment. Ultrasonic devices use a high-frequency vibrating crystal to produce aerosol particles; although these devices deliver droplets with a slightly higher mass median aerodynamic diameter (MMAD) compared with jet nebulizers, treatment times are shorter, they operate silently and they produce a high mass output [9]. The most recent nebulizer technology utilizes a vibrating mesh or plate to generate a fine-particle, low-velocity mist. The vibrating mesh nebulizer offers portability, battery operation, efficient delivery of aerosols and suspensions and minimal residual drug volume in the device [11].

Like other asthma devices, factors that affect the delivery of aerosol from a nebulizer include inherent characteristics of the system and the physicochemical properties of the drug. Characteristics of the system that affect nebulizer delivery may include driving gas flow, residual volume of drug and volume fill [11]. Patient-related factors also may affect nebulized drug delivery and include breathing pattern, body size in children younger than 6 months, crying and the use of a face mask or mouthpiece [9]. Unfortunately, it is difficult to compare nebulizer systems because, in many cases, manufacturers provide insufficient detail on the differences among their systems [9].

Because nebulizers require neither the coordination of actuation with inhalation required with pMDIs nor the adequate inspiratory flow required with DPIs, a nebulizer device is a good delivery choice for infants, young children and others who cannot effectively use inhalers.

MARKERS OF LUNG DEPOSITION

The amount of drug deposited in the lungs varies according to delivery device; therefore, drug delivery is an important consideration for drug and device selection. Lung deposition may be evaluated by use of radiolabeled substances or by pharmacokinetic measurement [44]. Often, studies of lung deposition also include particle size measurements to determine the percentage of drug in the respirable range (< 5 µm in diameter) [56]. For example, a study of healthy volunteers who received radiolabeled CFC fluticasone (MMAD = 2.0 µm), HFA beclomethasone dipropionate (MMAD = 0.9 µm) and CFC beclomethasone dipropionate (MMAD = 3.5 µm) demonstrated that, as a percentage of the dose emitted from the actuator, lung deposition increased as particle size decreased (Fig. **2**) [30].

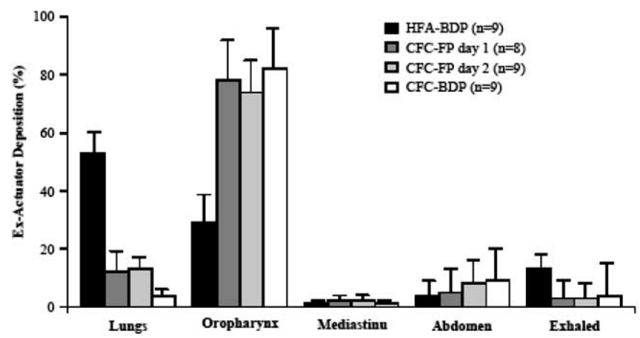

Fig. (2). Lung deposition to the oropharynx, lung and small airways is based on particle size. HFA, hydrofluoroalkane; BDP, beclomethasone dipropionate; CFC, chlorofluorocarbon; FP, fluticasone propionate.
Reproduced from Leach *et al.* 2002 [30] with permission of The American College of Chest Physicians.

In a review of DPI devices used for asthma therapy, Newman reported that lung deposition assessed by radionuclide imaging ranged from 13.1 to 34.3% of the metered dose [44, 57-62]. The wide range of delivered doses to the lungs among these studies probably reflects both the diverse patient populations and the different devices or their formulations.

As with DPIs, lung deposition from pMDIs also varies among devices and formulation types. In one review [56], whole lung deposition was as low as 3.2% for drug delivered (drug not specified) via a CFC pMDI [63] to 55% for an ICS delivered via an HFA pMDI [29]. The use of HFA propellants has reportedly increased lung deposition from pMDIs: particle size is reduced, enabling a larger part of the metered dose to reach the entire respiratory tract (Table **4**) [8]. For example, compared with the CFC-containing suspension of 200 µg budesonide, the non-CFC suspension of 200 µg budesonide pMDI has a fine particle dose that is nearly two-fold larger (86.2 µg versus 43.3 µg) and a MMAD of ~3.1 µm versus ~4.5 µm [20]. In addition, spacer devices generally increase the amount of drug deposited in the lungs by slowing aerosol velocity, which decreases oropharyngeal deposition [37, 39].

Table 4. Comparison of Particle Size for CFC and HFA Inhaled Corticosteroids[a]

Inhaled Corticosteroid	MMAD (µm)	Lung Deposition (%)
Fluticasone Rotadisk	> 4	15
Triamcinolone	4.5	14
CFC flunisolide	3.8	15–20
CFC beclomethasone	3.5	10–15
CFC fluticasone	2.5	20
HFA flunisolide	1.2	68
HFA beclomethasone	1.1	56
HFA ciclesonide	1.0	52

MMAD, mass median aerodynamic diameter; CFC, chlorofluorocarbon; HFA, hydrofluoroalkane.
[a] See reference [8].
Reproduced from Leach 2005 [8] with permission of the *Respiratory Care* journal.

When using a nebulizer, clinicians must consider how the design of the device will affect lung delivery. Conventional ultrasonic nebulizers do not efficiently deliver suspensions or viscous solutions because these types of formulations dampen the propagation of ultrasonic waves [17]. Furthermore, proteins and peptides can be denatured by the heating that occurs with these ultrasonic devices [64, 65]. With conventional jet nebulizers, lung deposition and the percentage of particles in the respirable range varies among nebulizer/compressor types [22]. In a study that evaluated delivery of budesonide inhalation suspension from 27 nebulizer/compressor combinations using a breathing pattern simulation for a 3-year-old child, the PARI LC®-Jet Plus nebulizer/PARI MASTER® Compressor (PARI Respiratory Inc., Midlothian, VA) system was one of the most efficient systems tested [22].

While thorough comparisons among devices indicate that no device has superior clinical efficacy [15, 56, 66-69], many trials designed to compare the efficacy between inhaled asthma medication delivered by different devices are flawed in their design or underpowered [56] and overlook variability among individual patients by averaging the results of the study population. Efficacy in asthma is not easy to measure and is often based on objective (spirometry) and subjective (symptom assessments) measures and should not be confused with efficiency [56]. In clinical trials, patients are often instructed on correct device use regularly, which may not occur in real life. In addition, clinical trials often do not consider patient preference, which may positively or negatively affect adherence to drug regimens. Some factors that affect patient preference include ease of use, ease of learning how to use the device, convenience, dose counter, comfort, size and time to administer dose [70-77]. Some studies indicate a preference for DPIs over pMDIs [70-75] and pMDIs plus spacers over nebulizers [76, 77]; however, it is important to note that the most efficacious device will be one that the patient will use correctly and consistently [11, 56]. Therefore, physicians should prescribe a device that best meets a patient's individual needs.

DRUG AND DEVICE SELECTION

Prescribing physicians should be cognizant that many patients are unable to master the necessary techniques needed for the administration of aerosolized asthma therapy by simply reading patient instructions. In addition, patients may not be aware of poor inhaler technique until they are asked to demonstrate the use of their inhalers [38]. Efficacy of available drugs or devices may be reduced because of poor inhaler technique. Periodic reinforcement of good inhalation technique is almost always useful, particularly in patients who only use inhaled medication occasionally (ie. quick-relief medications) [38]. Even patients who usually practice good technique may be inconsistent at times, thereby requiring reinforcement.

Device selection should be based on the patient's ability to properly use the device and availability of a desired drug or drugs (ie. maintenance and rescue). In choosing an inhalation therapy, consider the pharmacology of the drug, the aerosol characteristics and the complexity of the device [2]. With delivery of more than one drug in the same device (eg. ICS plus LABA in one inhaler), the physician should not assume that 2 drugs can be combined without altering their pharmacodynamics. Moreover, a combination of drugs delivered via one type of device, such as a DPI, may provide a different result if delivered via a pMDI. However, studies of the combination of budesonide and formoterol delivered via a DPI and pMDI indicate similar efficacy and safety [78, 79].

Other factors, such as the patient's breathing pattern and ability to use the device correctly, should also be considered when selecting the appropriate inhaler device [16, 80]. For optimal drug delivery, nebulizers do not require patient coordination but do require slow tidal breathing. In contrast, patient coordination and slow inhalation (30 l/min) is required for optimal drug delivery from a pMDI. DPIs require less patient coordination than a pMDI; however, the patient must be able to generate the necessary inhalation forces to disperse the drug. Proper device selection is particularly important in the young and elderly populations because of poor coordination skills and lack of hand strength and finger dexterity [38]. Therefore, evaluate patient variables, such as pathophysiology and severity of lung disease, as well as the age, size and skills of patients. Lastly, many patients with asthma use multiple inhalers. Clinicians should consider the entire array of devices that a patient uses and try to reduce the risk of confusion by using inhalers requiring similar techniques when possible.

CONCLUSIONS

There are many devices available for the delivery of inhaled asthma medication. The growing number of marketed devices and the complexity of their design pose a challenge to clinicians, who must choose which device is most suitable for the treatment of their patients. To accomplish this, one must first gain a thorough understanding of the advantages and disadvantages of these devices. Perhaps more importantly, patient characteristics, such as coordination, inhalation technique, successful past use of asthma devices and total number of device techniques to be used concomitantly, must be considered to customize device selection. Evidence-based literature consistently reports that the clinical of one device is not superior to another. Thus, the choice of therapy should be based on the availability of the desired formulation within a particular device, patient characteristics and their device preferences, ease of use, the patient's ability to use the device correctly and reimbursement issues or insurance coverage.

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LIST OF ABBREVIATIONS

CFC	=	Chlorofluorocarbon
DPI	=	Dry powder inhaler
FDA	=	Food and Drug Administration
FEV_1	=	Forced expiratory volume in 1 second
HFA	=	Hydrofluoroalkane
ICS	=	Inhaled corticosteroid
LABA	=	Long-acting β_2-adrenergic agonist
MMAD	=	Mass median aerodynamic diameter
PIF	=	Peak inspiratory flow
pMDI	=	Pressurized metered-dose inhaler
SABA	=	Short-acting β_2-adrenergic agonist

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