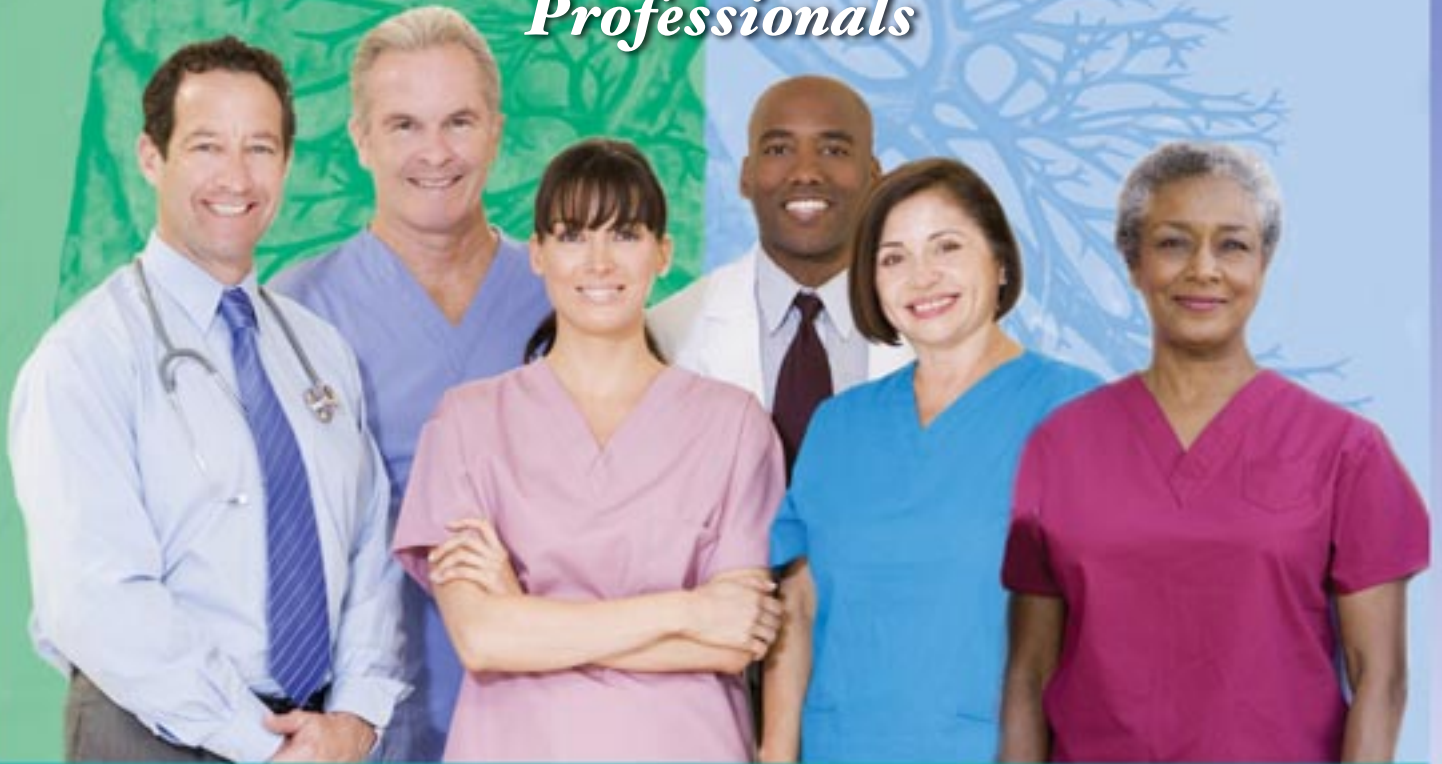


GUIDE TO ***Aerosol Delivery Devices*** *for Physicians, Nurses, Pharmacists, and Other Health Care Professionals*



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***Produced by the
American Association for Respiratory Care***

Supported by an educational grant from Philips Respironics

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DISCLOSURE:

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NOTE:

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FOREWORD

The American Association for Respiratory Care (AARC) is happy to release the second edition of “Guide to Aerosol Delivery Devices for Physicians, Nurses, Pharmacists, and Other Health Care Professionals.” This Guide should provide you with necessary information about currently available aerosol delivery devices in the U.S. market. Included are criteria for selecting the right device for each patient, infection control, educating the patients on the correct use of the device, as well as pediatric and neonatal aerosol delivery considerations. Additionally, an executive summary has been prepared that will allow you to get an overview of essential points that must be considered when deciding on the most appropriate device for your patient(s). Is it the right medication for the patient? Is the delivery device compatible for the patient given their possible limitations? What is the patient’s level of understanding and competency for a selected device? All are important as decisions are made for matching up the patient to the most appropriate device.

This Guide will provide you with step-by-step application on all available devices. Currently there are three basic types of delivery systems, which include nebulizers, metered-dose inhalers, and dry-powder inhalers. All three have their own specific characteristics and delivery capabilities. Adequate self-management and matching the correct device to the patient will increase your patients’ chances for better adherence over the long run.

The American Association for Respiratory Care has other resources available directed at patients to help them learn more about better self-management of lung disease. They are available at www.aarc.org or www.yourlunghealth.org. There you will find “Allergy and Asthma Health” (an online magazine), smoking-cessation information, and so much more. In addition to this, an aerosol guide written for patients can be downloaded at http://www.aarc.org/resources/aerosol_resources/aerosol_guide_patient.pdf. We hope that you find this Guide and our other materials useful.

Thomas Kallstrom, MBA, RRT, FAARC
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EXECUTIVE SUMMARY

Objectives

This guide provides an overview of the important information and considerations that must be addressed to ensure that patients who self-administer aerosol medications for chronic respiratory conditions achieve the intended clinical outcomes.

Background

The delivery of aerosolized medication directly to the airways is a mainstay in both the emergency treatment and long-term management of chronic obstructive pulmonary disease (COPD), asthma, and other chronic lung diseases in both the adult and pediatric populations. However, in light of the myriad of devices available, coupled with a lack of intuitive understanding by patients regarding the optimum technique required for each device, it is becoming increasingly important for health care professionals who treat patients with respiratory disorders to provide both initial and remedial training in proper device use. This is especially important given the high user-error rates observed with both metered-dose and dry-powder inhalers. Less than optimal delivery of aerosolized medications through improper technique or mismatched device can result in worsening of symptoms. This can often lead to the incorrect assumption that the disease state is deteriorating when, in fact, it is because insufficient amounts of prescribed medications are reaching the targeted lung fields.

To address this important challenge, the American Association for Respiratory Care (AARC) has prepared this resource guide to help those health care professionals treating respiratory patients to provide accurate information on the proper use of all aerosol delivery devices.

Basics of Aerosol Drug Delivery

Delivering medications by inhaling an aerosol has several significant advantages over systemic drug delivery, which include:

- Selective treatment of pulmonary conditions by direct deposition of medication to airway receptor sites, allowing for lower medication dosages to achieve the desired therapeutic effect
- Rapid onset of action of broncho-active medications for the reversal of acute episodes of bronchoconstriction
- Reduced incidence of side effects due to lower systemic bioavailability of medications administered via inhalation
- Relative ease and convenience of self-administration by patients, parents, and caregivers for long-term use.

Delivery Devices

There are 3 common types of aerosol generators used for inhaled drug delivery:

- A small-volume nebulizer (SVN)
- A pressurized metered-dose inhaler (pMDI)
- A dry-powder inhaler (DPI)

Under ideal conditions and when used correctly, the amount of actual drug delivered to the airways is comparable with all 3 types of devices. However, both the pMDI and the DPI, while more convenient (both are self-contained and can be carried in a purse or pocket), are more difficult to use since they both require that specific steps be followed, in precise order, to achieve optimal airway deposition and the desired therapeutic effect. For example, a pMDI requires coordination between actuation and inhalation. Further, the new HFA propellant

pMDIs require a slow, deep inhalation followed by a 5–10 second breath-hold. A valved holding chamber can help those patients unable to coordinate actuation with breathing. Patients should also be aware of the need to prime their pMDI to mix the medication and propellant and should consult the package insert on how to do so and at what frequency. Further, pMDIs require periodic rinsing of the boot to prevent “crusting,” which obstructs the delivery of medication. The following table identifies key concepts of the pMDI. (See Table A.)

Table A. Patient population, advantages, and disadvantages of a pressurized metered-dose inhaler

Intended Patients	Advantages	Disadvantages
< 3 yrs with spacer & face mask	Portable, light, and compact	Hand-breath coordination needed
> 3 yrs with spacer & mouthpiece	Combination drugs available	Patient actuation, breath-hold required
Adults with spacer & mouthpiece	Shorter treatment times	Drug dosing is fixed
Patients with good hand/eye coordination	Reproducible dosing	Foreign body can lodge inside the actuator boot
	No drug preparation needed	High oral-pharyngeal deposition
	Difficult to contaminate	Dose counter needed
NOTE: FACE MASK NEEDED WITH PHYSICAL OR COGNITIVE LIMITATIONS; CHILDREN REQUIRE ADULT ASSISTANCE FOR ACTUATION.		Canister nozzle can become obstructed if not periodically rinsed

DPIs have two different mechanisms for preparing the drug for delivery. With some types of DPI, the patient has to first load the medication dose into the device. This, however, is not true with all DPIs, as others come with a supply of medication already loaded. To dispense the medication from the DPI, the patient must first prepare the dose for inhalation per manufacturers instructions. When ready, the patient should inhale forcefully and quickly through the mouthpiece, followed by a 5–10 second breath-hold. To ensure effective drug delivery to the airways with a DPI, patients must be able to generate a minimum peak *inspiratory* flow rate of 30 L/min. For best drug delivery, achieving inspiratory flow rates of 60–90 L/min provides superior efficacy in delivery. On the other hand, while an SVN is the easiest to use, these devices are less convenient than inhalers. SVNs require an electrical or battery power source for a compressor that is connected to a jet nebulizer to convert liquid medication into an aerosol. The following tables identify key concepts for the DPI and SVN (see Tables B and C respectively).

Table B. Patient population, advantages, and disadvantages of a dry-powder inhaler

Intended Patients	Advantages	Disadvantages
> 5 yrs (w/o any physical or cognitive limitations)	Small and portable	Peak inspiratory flow > 30 L/min required
	Propellant free	Each DPI is designed differently
	Breath actuated	Vulnerable to humidity
	Built-in dose counter	Limited range of drugs available
	No drug preparation needed	Misuse = high oral drug deposition
	Difficult to contaminate	Difficult to use by very young and old
NOTE: ALL PATIENTS MUST BE CAPABLE OF GENERATING A MINIMUM PEAK INSPIRATORY FLOW RATE OF 30 L/MIN.		

Table C. Patient population, advantages, and disadvantages of a small-volume nebulizer

Intended Patients	Advantages	Disadvantages
< 3 yrs with face mask	Can nebulize a variety of drugs	Longer treatment times
> 3 yrs with mouthpiece or face mask	Can combine medications	Equipment used is larger
Adults with mouthpiece or face mask	Drug doses can be modified	Electrical/battery power source/gas source needed
Patients with physical/ cognitive limitations that preclude pMDI/DPI utilization	Minimal coordination required	Equipment varies
	Ease of use for all ages	Potential for contamination. Devices require periodic cleaning or disinfection.
	Normal breathing pattern	Inadvertent drug delivery to eyes with masks
NOTE: FACE MASK NEEDED WITH PHYSICAL OR COGNITIVE LIMITATIONS; CHILDREN REQUIRE ADULT SUPERVISION.		

Irrespective of which device is selected, patients and/or caregivers will need to be trained (and periodically retrained with every health care visit) in the proper technique required for optimum use and desired therapeutic effect. This is especially true for both the pMDI and DPI where user-error rates are most notable.

Device Recommendations

In determining which aerosol delivery device to prescribe or recommend, the following general guidelines are suggested:

Infants and small children:

- < 3 years of age: SVN or pMDI with valved holding chamber and properly fitting face mask.
- 3–5 years of age without any physical limitations: SVN or pMDI with valved holding chamber and mouthpiece; with physical limitations: SVN or pMDI with valved holding chamber and face mask.

- Children > 5 years of age without any physical limitations: SVN, pMDI, or DPI with mouthpiece; with physical limitations: SVN or pMDI with valved holding chamber and face mask.

Adolescents and adults:

- Without physical/psychological limitations: SVN, pMDI, or DPI with mouthpiece; with physical/psychological limitations: SVN with face mask.
- If unable to physically generate a minimum peak inspiratory flow rate > 30 L/min: SVN or pMDI with mouthpiece; with physical/psychological limitations: SVN with face mask.

Key Device Considerations

The ideal aerosol-generating device(s) will vary for each patient and will be dependent upon:

- The clinical objectives of therapy
- The medication to be administered and available formulations
- The age and physical/psychological capabilities of the user
- Third-party payer criteria for reimbursement.

To maximize the advantages of inhaled medications, the selected aerosol-generating device should:

- Deliver an effective dose of the desired medication to the airways
- Minimize oropharyngeal deposition with resultant swallowing and systemic side effects
- Be easy and convenient for the patient/caregiver to use
- Be cost effective.

Drug Deposition

Drug deposition within the lung is influenced by several factors, including the type of aerosol-generating device used, the size of the individual aerosol particles produced, properties of the medication to be delivered, disease state and severity, and the patient's breathing pattern and technique. Other factors that can influence drug deposition include patient preference for a particular device type and, perhaps most importantly, patient acceptance of the importance of continuing to self-administer aerosol medications as prescribed.

Drug Classifications

Common classes of medications suitable for aerosol delivery include: short-acting beta agonists (e.g., albuterol, levalbuterol), long-acting beta agonists (e.g., salmeterol, formoterol, arformoterol), short-acting anticholinergic antagonists (e.g., ipratropium), long-acting anti-cholinergic antagonists (e.g., tiotropium), and anti-inflammatory agents (e.g., budesonide, fluticasone, beclomethasone, ciclesonide, mometasone).

While each of the described medications are intended to be administered individually, there are also various combinations of these commercial drugs available when a synergistic effect is desired. However, such combinations are likely to be available only in a pMDI or DPI. Examples of popular combination formulations include: albuterol and ipratropium (pMDI, liquid solution), salmeterol and fluticasone (pMDI, DPI), and formoterol and budesonide (pMDI).

Short-acting beta agonists (SABAs) are indicated for the rapid relief of acute episodes of bronchospasm associated with both asthma and COPD. SABAs have a quick on-set of action (typically 3–5 minutes but may be longer) and can provide relief for up to 4–6 hours. SABAs are to be administered 3–4 times a day, although more frequent dosing may be temporarily required during very severe exacerbations. The addition of short-acting anticholinergics to a SABA may further enhance bronchodilation but is typically reserved for conditions of severe airway

obstruction. Current evidence-based treatment guidelines for both asthma and COPD suggest that the continuing need for more frequent administration or higher doses of a SABA (alone or in combination with ipratropium) is indicative of poor symptom control and possible disease deterioration.

Long-acting beta agonists (LABAs) are indicated for the sustained control of bronchospasm in patients with COPD. LABAs have a slightly longer onset of action (typically 15–60 minutes) but provide relief for up to 12 hours. LABAs are typically administered twice a day (morning and evening), and more frequent dosing is not recommended. Patients taking a LABA should use their SABA sparingly (only on an as-needed basis) and never combine 2 LABAs. LABAs are not indicated for the long-term monotherapy of asthma symptoms.

The long-acting anticholinergics are also indicated for the sustained control of bronchoconstriction in patients with COPD. Taken once a day, tiotropium blocks the muscarinic receptor subtype M3 on airway smooth muscle, preventing acetylcholine from activating the receptor. When tiotropium is combined with a LABA, which stimulates the beta-2 receptor on bronchial smooth muscle, the overall improvement in bronchodilation is greater than what is observed with each drug individually.

Inhaled corticosteroids (ICSs) are intended primarily for the prophylactic control of airway inflammation in patients with chronic pulmonary disease. The prescribed dose should be the lowest needed to maintain sustained control, which will be greatly determined by the degree of severity. When a moderate-to-high dose of an ICS alone fails to achieve sustained control of symptoms, the addition of a LABA is typically recommended.

Adverse Events

While rare, there are potential adverse events associated with aerosol drug delivery. The degree of any complication will vary with each drug, its dose, and dosing frequency as well as with the type of device being used. For example, excessive doses of both SABAs and LABAs can result in cardiac excitation, nervousness, tremors, and difficulty sleeping. Paradoxical bronchospasm has been reported in some patients after they receive a few doses of a SABA or LABA for the first time. Oropharyngeal deposition of an ICS, due to inadequate inhaler use or failure to rinse the mouth after administration, can result in Candidiasis (thrush) or dysphonia. Respiratory infections can also result if SVN parts are not properly cleaned after use and periodically disinfected.

Summary

When properly prescribed and administered, aerosol drug therapy is an efficient, effective, and economical way to deliver an array of medications to treat acute and chronic respiratory diseases. When trained in proper technique (based upon their age, plus physical and cognitive limitations), patients are capable of self-administration regardless of device type. This guide is provided as a resource for health care professionals treating patients with respiratory diseases so that optimum outcomes can be attained from this important therapeutic intervention.

The complete manual, “Guide to Aerosol Delivery Devices for Physicians, Nurses, Pharmacists, and Other Health Care Professionals” is available on the AARC website at http://www.aarc.org/resources/aerosol_resources/aerosol_guide_pro.pdf.

ADDITIONAL READING

National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. Updated 2007. NIH Publication No. 07-4051.

Global Initiative for Chronic Obstructive Lung Disease (GOLD) website. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [GOLD report]. Updated 2010. Available at www.goldcopd.org Accessed June 8, 2011

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1. AEROSOL DRUG DELIVERY

The delivery of aerosolized medication with small particles has become the mainstay for the management of many respiratory disorders, such as asthma and obstructive lung disease, in both the adult and pediatric population. Medication delivery by inhaled aerosols has significant advantages over systemic drug delivery and includes:

- Select treatment of the lungs through direct deposition of medication to airway receptor sites allowing for lower medication dosages to achieve the desired therapeutic effect
- Rapid onset of action of bronchodilating medication allowing for rapid reversal of acute bronchoconstriction
- Reduced incidence of systemic side effects related to lower bioavailability of systemic drugs.¹

For these reasons, the National Asthma Education and Prevention Program (NAEPP) guidelines and the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines currently emphasize inhalation therapy as the therapy of choice for the management of obstructive airway disease. As new macromolecular medications are developed, patients with non-respiratory disease may also benefit from aerosol delivery of drugs such as opiates and insulin.

The ideal aerosol delivery device will vary depending on the medication to be administered, clinical situation, and the patient. To maximize the advantages of inhaled medications, the device selected should:

- Deliver an adequate dose of medication to the lungs
- Minimize oropharyngeal deposition and systemic side effects
- Match the needs of the patient
- Be simple for the patient to use
- Be cost effective.¹

Factors Affecting Aerosol Drug Deposition

Drug deposition within the lung is influenced by several factors including particle size; properties of medication to be delivered; type of aerosol generator used; disease state and ventilatory patterns; as well as patient technique, preference, and acceptance of the aerosol delivery device.¹

Particle Size and Medication Properties

To realize therapeutic effect in the airways and lung, aerosolized medications must be deposited beyond the oropharyngeal region. Particle size plays an important role in this. For an aerosol particle to be considered within a respirable range or having the potential to reach the periphery of the lungs and airways, the particle must be between 1–5 microns in size. Particles that are 1–2 μm are optimal for deposition in the alveolar area.² As particle size increases above 3 μm , aerosol deposition shifts from the periphery of the lung to the conducting airways. Oropharyngeal deposition increases as particle size increases above 6 μm , while those particles less than 1 μm generally are exhaled. The greater percentage of drug that is within the 1–5 μm range, the greater the potential for effective aerosol therapy. See Figure 1.

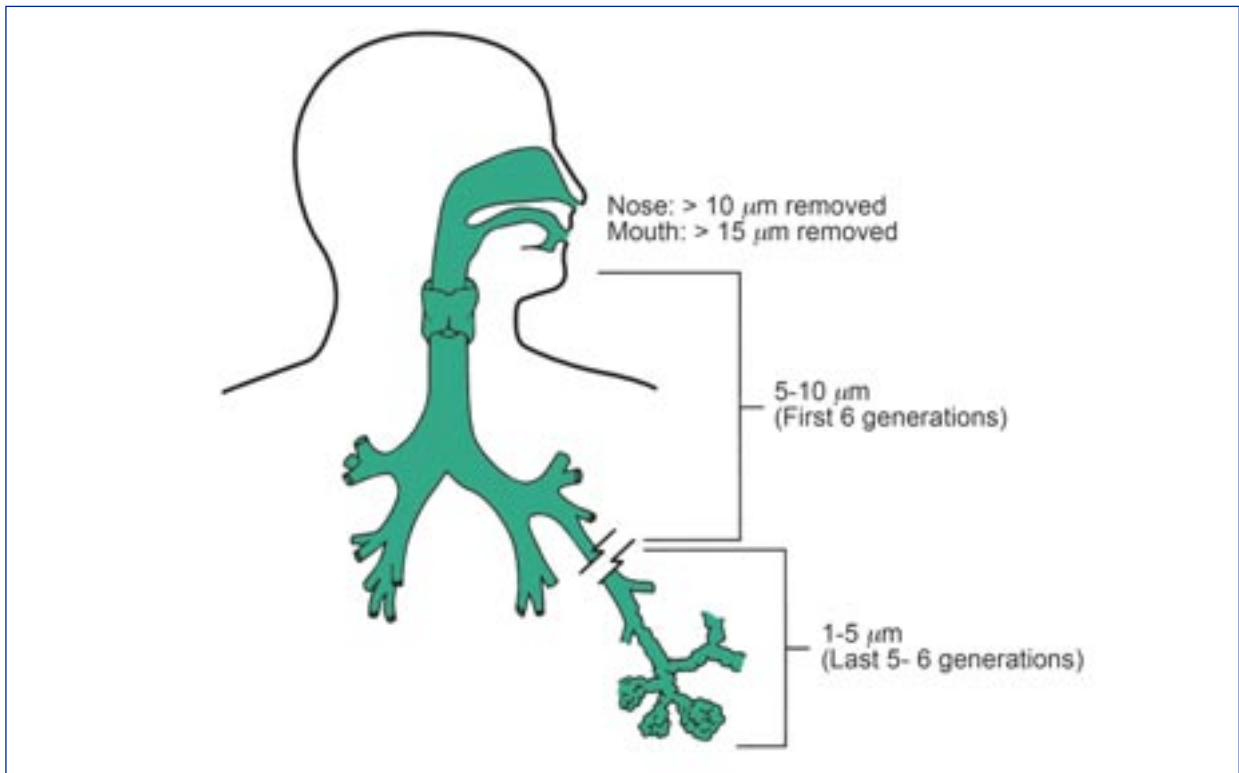


Figure 1. A simplified view of the effect of aerosol particle size on the site of preferential deposition in the airways (From Reference 3, with permission)

In order for inhaled drugs to reach their targeted receptors, they must penetrate the mucous layer and airway mucosa. Ultimately, the greatest effect of lung dose, the mass of drug delivered to the lung, is dependent on the rate of drug clearance from the airway and the medication site of action.

Disease State and Ventilatory Patterns

Respiratory disease state and anatomy can directly influence delivery of aerosolized drugs. Airway narrowing associated with bronchoconstriction may result in particle deposition to the central airways, as opposed to the lung periphery. Small airway obstruction associated with acute bronchiolitis in infants has been observed to reduce drug delivery with as little as 1.5% of aerosolized drug being deposited into the lung and 0.6% penetrating to the peripheral airways.

Effective distribution of particle depositions may also be compromised by mucous plugging or atelectasis seen in cystic fibrosis or other mucous-producing diseases. Finally, individual patient ventilatory patterns (e.g., tidal volume, breath-hold time, respiratory rate, and nose versus mouth breathing) can dramatically alter the deposition of aerosolized particles in the lungs.

Types of Aerosol Generators

Three common types of aerosol generators are used for inhaled drug delivery: the small-volume nebulizer (SVN), the pressurized metered-dose inhaler (pMDI), and the dry-powder inhaler (DPI). Device types are described briefly below, and specific information related to their use is discussed separately in subsequent sections.

- **Small-volume Nebulizer:** The SVN is an aerosol generator used to deliver liquid medications (e.g., bronchodilators) to the mid-to-lower airways. High velocity pressurized airflow is used to convert drug solutions into fine mists with particles that can then be inhaled using a facemask or mouthpiece. This conversion process requires the use of compressed

air, oxygen, a compressor, or an electrically or battery powered device and is not dependent on the manual dexterity or cognitive abilities of the patient. Most patients in the ambulatory setting will use a compressor as the power source for the SVN. The basic model is a stationary, countertop plug-in type that uses a standard AC outlet. Portable SVNs powered by a rechargeable battery or from the ancillary DC power outlet are available for individuals who travel or require treatments away from home.

- **Pressurized Metered-dose Inhaler:** The pMDI is a portable, hand-held drug delivery system that uses a pressurized propellant to create and deliver inhaled medications, including bronchodilators, anticholinergics, and glucocorticoids. Pressurized metered-dose inhaler canisters contain monotherapy or combination therapy (inhaled corticosteroid and long-acting beta agonist) medications and reliably deliver a specific amount of medication — a metered dose — with each actuation. Traditionally, the propellant has been a chlorofluorocarbon (CFC). Since the adoption of the Montreal Protocol, an international agreement designed to protect the ozone layer, CFCs have been phased out and new CFC-free propellants such as hydrofluoroalkane (HFA) 133a are now typically in use.

It is important for clinicians to instruct patients that medications delivered via a HFA pMDI have a softer plume than medications previously delivered with older CFC devices. While this may result in a different feel or taste, it does not interfere with the effectiveness of drug delivery when the device is used correctly.

All pMDIs are activated by the patient. Unlike the SVN, effectiveness of drug delivery with pMDIs is highly dependent upon the patient's ability to apply pressure to the base of the canister and simultaneously taking a slow, deep breath. Use of pMDIs may not be suitable for patients unable to take slow, deep breaths or for those patients with arthritis or upper extremity weakness.

Because of high medication loss in the oropharynx and hand-held coordination difficulty with pMDIs, valved holding chambers or spacers are often used together with the pMDI to improve medication delivery. These devices attach to the pMDI and temporarily hold the dispensed dose of medication, making the exact timing of device actuation with inhalation less critical. The chamber length increases the distance that drug particles travel from the pMDI mouthpiece to the patient's mouth. The extra distance allows the particles to slow, float within the device, and be optimized for inhalation without excess medication deposit to the tongue and throat.

There are several valved holding chambers and spacers on the market, with and without masks, and are available by prescription. Patients need to be aware that while the pMDI itself is often covered by insurance, spacers and holding chambers are often not covered.

- **Dry-powder Inhaler:** The DPI is an aerosol device that delivers drug in a fine, micronized powder form. There is no propellant in the DPI. Instead, these devices direct a patient's inhaled air through loose powder to create an aerosol. Dispersion of the powder into respirable particles is dependent on the creation of turbulent airflow within the device. The patient using the DPI provides the force to propel the medication from the device. The young, elderly, and those patients with neuromuscular weakness or altered mental status may not be able to generate sufficient inspiratory effort to benefit from their use. Also, if manual dexterity is compromised, patients may not be able to operate or load some devices.

These aerosol devices vary greatly in their ability to deliver particles to the lungs. Even with the optimal use of any aerosol delivery system, lung deposition may range from 10–15% of the total medication dose.³⁻⁷ For example, out of the 200 micrograms (μg) of albuterol released in two actuations or puffs from a pMDI, approximately 20–40 μg reach the lungs with optimal technique. Specifically, despite optimal inhalation technique, pMDIs rarely deliver more than 20% of the dose released during each actuation; and as little as 10% of the administered dose

may reach the lung periphery. This is because as much as 80% of the medication remains in the oropharynx and an additional 10% escapes into the atmosphere during exhalation or is deposited on the MDI actuator.⁴ Figure 2 describes the percentages of drug deposition for different aerosol systems, showing that oropharyngeal loss, device loss, and exhalation/ambient loss differs among aerosol device types, as do lung doses.

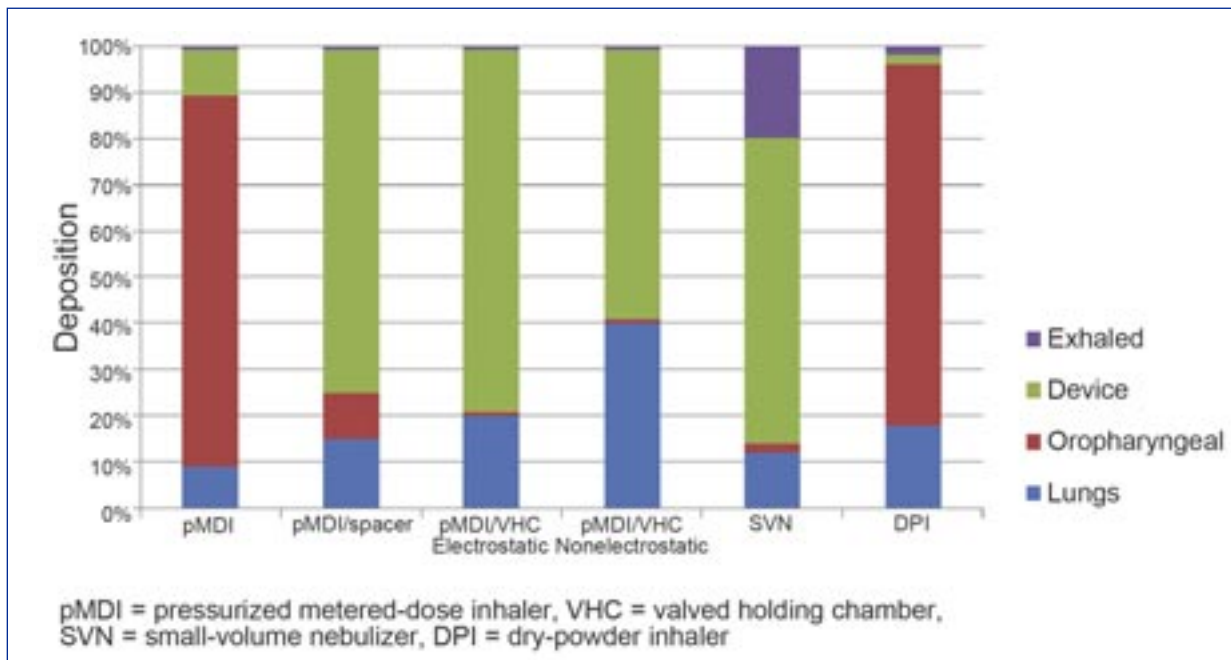


Figure 2. Drug deposition with common aerosol inhaler devices. Shown by color are the varying percentages of drug lung deposition and drug loss in the oropharynx, device, and exhaled breath.

(Modified, with permission, from Reference 5 and Reference 10)

It is important to realize that various types of aerosol devices deposit a different fraction of the total prescribed dose of a given drug (also termed “nominal” dose) in the lungs. In addition, different types of aerosol devices, such as nebulizers and pMDIs, do not have the same nominal dose. Using albuterol as an example, the typical pMDI nominal dose is two actuations, or about 200 µg, while the typical nebulizer nominal dose is 2.5 mg, or 12 times more drug. Table 1 lists both the pMDI and nebulizer nominal doses for several drugs, showing this difference.

Table 1. Differences in nominal (total) dose between a pMDI and an SVN for different drug formulations (Modified, with permission, from Reference 8)

Drug	pMDI Nominal Dose	SVN Nominal Dose
Albuterol	0.2 mg (200 µg)	2.5 mg
Ipratropium	0.04 mg (40 µg)	0.5 mg
Levalbuterol	0.045 mg – 0.09 mg	0.31 mg – 1.25 mg

Equivalence of Aerosol Device Types

Historically, nebulizers were thought to be more effective than pMDIs, especially for short-acting bronchodilators during an exacerbation of airflow obstruction. Contrarily, evidence has shown equivalent clinical results, whether a pMDI, a nebulizer, or a DPI is used, provided that the patient can use the device correctly.¹¹ For bronchodilators, the same clinical response is often achieved with the labeled dose from the pMDI, despite the higher nominal dose for the nebulizer. Because any of these aerosol generators, if used properly, can be effective with their label dose, dosage should be device specific and based on the label claim.

Newer aerosol devices and drug formulations are increasing the efficiency of lung deposition when compared to the traditional devices previously used. For example, lung deposition for HFA-beclomethasone dipropionate (QVAR™) is in the range of 40–50% of the nominal dose compared to using a pMDI formulation with hydrofluoroalkane propellant.¹² A new device, the Respimat® inhaler, has shown lung depositions as high as 40%.¹³ Although lung dose efficiency varies between devices, inhalers with relatively low lung deposition fraction have been clinically proven to achieve the desired therapeutic effect in the target audience.

Just as lung dose efficiency differs among devices, patient ability (both physically and cognitively) to use and understand the various delivery devices will likewise vary and is an important factor in drug deposition. Consideration of individual patient factors such as arthritis, weakness, and altered mental status will influence selection of specific delivery devices. Once selected, care must be taken to frequently reassess patient ability to use the device correctly, as poor understanding and improper technique may lead to therapeutic nonadherence, poor drug delivery, and suboptimal disease and symptom control. Patient preference and acceptance of an aerosol device can help ensure adherence to the prescribed medication regimen. Quality patient education and ongoing patient monitoring is key to the effective use of any aerosol delivery device.¹⁴

Advantages and Disadvantages of Aerosol Drug Delivery

As discussed earlier, there are a number of advantages to treating pulmonary disease with inhalation therapy. The primary advantage is the ability to target the lung directly using smaller doses, resulting in fewer systemic side effects than with oral delivery.¹⁵ As seen in Figure 3, inhalation of terbutaline (a short-acting beta-2 agonist) from a pMDI resulted in better airflow than with a much larger oral dose or even with a subcutaneous injection of drug.

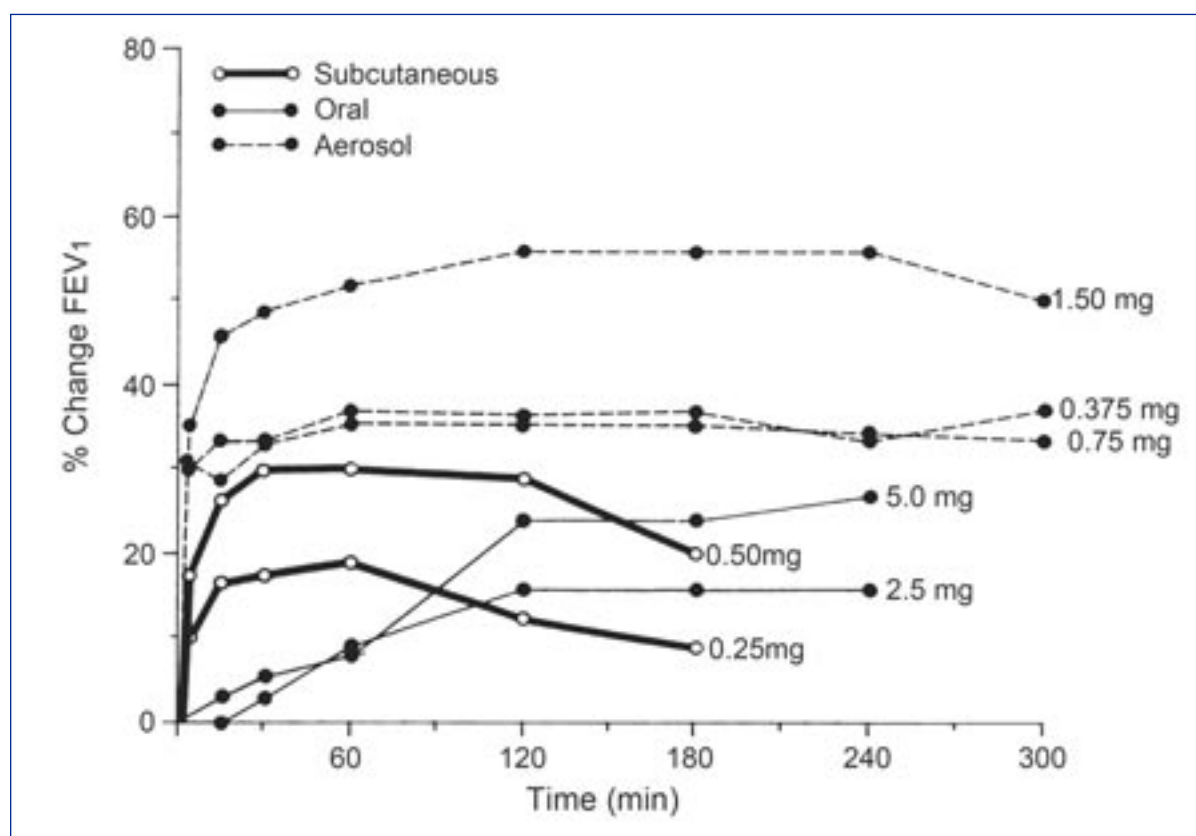


Figure 3. Changes in FEV₁ for 3 different routes of administration with terbutaline. Greater clinical effect was seen with drug delivered as inhaled aerosol from a pMDI, compared to similar or larger doses delivered orally or by subcutaneous injection. (From Reference 9, with permission)

Aerosolized drugs and delivery devices are not without shortcomings. Advantages and disadvantages associated with their use are summarized in Table 2 below.

Table 2. Advantages and disadvantages of the inhaled aerosolized drugs

(Modified, with permission, from Reference 5)

Advantages	Disadvantages
Aerosol doses are generally smaller than systemic doses.	Lung deposition is a relatively low fraction of the total dose.
Onset of effect with inhaled drugs is faster than with oral dosing.	A number of variables (correct breathing pattern, use of device) can affect lung deposition and dose reproducibility.
Drug is delivered directly to the lungs, with minimal systemic exposure.	The difficulty of coordinating hand action and inhalation with the pMDIs reduces effectiveness.
Systemic side effects are less frequent and severe with inhalation when compared to systemic delivery.	The lack of knowledge of correct or optimal use of aerosol devices by patients and clinicians decreases effectiveness.
Inhaled drug therapy is less painful than injection and is relatively comfortable.	The number and variability of device types confuses patients and clinicians.
	The lack of standardized technical information on inhalers for clinicians reduces effectiveness.

Hazards of Aerosol Therapy

Hazards associated with aerosol drug therapy may occur as a result of the type and dose of the inhaled medication, the aerosol generator being used, the aerosol administration technique, and the environment. Hazards of aerosol therapy can impact the patient receiving therapy, as well as care providers and bystanders.

Hazards for Patients

Adverse Reaction: Most hazards associated with aerosol therapy are attributed to adverse reactions to the drug being used. Therefore, inhaled medications should be administered with caution. Types of adverse reactions include headache, insomnia, and tachycardia and/or nervousness with adrenergic agents, local topical effects with anticholinergics, and systemic/local effects of corticosteroids.^{16,17} If any adverse reactions are seen during aerosol drug therapy, the treatment should be stopped. Patients should be advised to notify their health care provider should any of these reactions occur during home administration.

Paradoxical Bronchospasm: Administering a cold and high-density bronchodilator aerosol may induce bronchospasm in patients with asthma or other respiratory diseases.¹⁷⁻¹⁹ If bronchospasm occurs during aerosol therapy, then therapy should be stopped. If it persists, the health care provider should be notified.

Drug Concentration: In both jet and ultrasonic nebulizers, drug concentration may increase significantly during aerosol therapy.²⁰⁻²² An increase in drug concentration may be due to evaporation, heating, or the inability to nebulize suspensions efficiently.^{17,19,22,23} As a result of changes in drug concentration, the dose of the drug remaining in the nebulizer at the end of aerosol therapy is increased, and the patient is exposed to higher concentrations of inhaled medications.

Infection: It has been well documented that aerosol generators can be contaminated with bacteria and increase the risk of infection in patients with respiratory diseases.²⁴⁻²⁹ The risk of transmission of an infection is dependent upon duration of exposure to drugs with pathogens and the procedures taken by health care providers to avoid pathogen exposure. Proper practices of medication handling, device cleaning, and frequent disinfecting of nebulizer parts can greatly reduce this risk.

Eye Irritation: Inhaled medications delivered with a facemask may inadvertently deposit in the eyes and result in eye irritation. Improving the interface between the facemask and patient may eliminate this problem and increase the amount of drug delivered to the distal airways. Therefore, caution should be exercised when using a facemask during aerosol drug administration.

Hazards for Care Providers and Bystanders

Health care providers and bystanders have the potential risk of exposure to exhaled medications during routine monitoring and care of patients receiving aerosol therapy. There is also a risk of second-hand inhalation of pathogens during aerosol administration that could lead to infection, increase the risk of asthma-like symptoms, and cause occupational asthma.³⁰⁻³²

Currently Available Aerosol Drug Formulations

Some aerosol drugs are available in more than one formulation. Others (often newer drugs) are available only in a single formulation. As the CFC propellants used in pMDIs have been phased out, older aerosol drugs are being transitioned to the newer HFA-propelled pMDI formulations. New aerosol drugs are either formulated as an HFA-pMDI (e.g., pMDI-levalbuterol) or, more commonly, as DPIs (e.g., formoterol, tiotropium, mometasone). Table 3 provides currently available aerosol drug formulations, their brand names, and their FDA-approved aerosol delivery devices. Because costs are always subject to change, up-to-date pricing can be obtained by accessing www.drugstore.com.

Table 3. Currently available aerosol drug formulations with corresponding inhaler device type

Drug	Brand	Device
Short-acting Bronchodilator		
Albuterol Sulfate	AccuNeb [®]	SVN
	Albuterol Sulfate	SVN
	ProAir [®] HFA	pMDI
	Proventil [®] HFA	pMDI
	Ventolin [®] HFA	pMDI
Levalbuterol	Xopenex [®] Inhalation Solution	SVN
	Xopenex HFA [™]	pMDI
Ipratropium Bromide	Ipratropium Bromide	SVN
	Atrovent HFA [®]	pMDI
Ipratropium Bromide and Albuterol Sulfate	Ipratropium Bromide and Albuterol Sulfate	SVN
	DuoNeb [®]	SVN
Pirbuterol	Combivent [®]	pMDI
	Maxair [®]	DPI
Long-acting Bronchodilator		
Aclidinium Bromide	Tudorza [™] Pressair [™]	DPI
Arformoterol	Brovana [®]	SVN
Formoterol	Perforomist [®]	SVN
	Foradil [®] Aerolizer [®]	DPI
Salmeterol	Serevent [®]	DPI
Tiotropium	Spiriva [®]	DPI
Corticosteroids		
Beclomethasone	QVART [™] 40	pMDI
	QVAR 80	pMDI
Budesonide	Pulmicort	SVN
	Pulmicort [®] Flexihaler [®]	DPI
Ciclesonide	Alvesco [®]	pMDI
Fluticasone	Flovent [®] Diskus [®]	DPI
	Flovent HFA	pMDI
Indacaterol	Arcapta [™] Neohaler [™]	DPI
Mometasone	Asmanex [®] Twisthaler [®]	DPI
Combination Drugs		
Mometasone/Formoterol	Dulera [®]	pMDI
Fluticasone and Salmeterol	Advair HFA [®]	pMDI
	Advair Diskus [®]	DPI
Budesonide and Formoterol	Symbicort [®]	pMDI
Mucoactive Drugs		
Acetylcysteine	Mucomyst [®]	SVN
Dornase Alpha	Pulmozyme [®]	SVN
Other Drugs		
Aztreonam	Cayston [®]	SVN
Cromolyn Sodium	Cromolyn Sodium	SVN
Zanamivir	Relenza [®]	DPI
Tobramycin	TOBI [®]	SVN

2. AEROSOL DRUG DELIVERY: SMALL-VOLUME NEBULIZERS

As mentioned previously in this guide, SVN's are popular aerosol generators selected by clinicians and patients to convert liquid drug solutions or suspensions into aerosols that can be inhaled and delivered to the lower respiratory tract. Nebulizers have been the cornerstone of medical aerosol therapy in the acute and critical care setting. However, nebulizers are now widely used in clinic and outpatient settings as well as in the home environment. They remain the device frequently prescribed for infants, small children, and the elderly or those who are unable to operate, coordinate, or properly use either inhaler. This functionality offsets the issues of portability, weight, noise, cost, and time of administration associated with nebulizers. The time required to deliver a dose of aerosolized medication is an important determinant of patient adherence, especially in the outpatient and home settings.³³

Types of Small-volume Nebulizers

There are two main types of SVN's: pneumatic jet nebulizers and electronic nebulizers.

Pneumatic Jet Nebulizers

Pneumatic jet nebulizers (most commonly used in the hospital or clinic) are low-cost, mass-produced, single-patient-use (disposable) devices. Nebulizer systems may include a nebulizer, compressor or power pack, tubing, and accessories. The compressor or electronics are generally durable and long lasting, whereas nebulizer cups and accessories require frequent replacement.

Jet nebulizers use compressed air or oxygen to aerosolize liquid medications. Compressed gas is delivered as a jet through a small opening, generating a region of subambient pressure above a small capillary tube placed in the medication cup or reservoir. The solution to be aerosolized is pulled into the gas stream and then sheared into a liquid film. This film is unstable and rapidly breaks into droplets due to surface tension forces. As larger droplets impact the baffle placed in the aerosol stream, smaller particles form and become entrained in the gas stream inhaled by the patient. Any remaining large droplets fall back into the liquid reservoir for recycling.

Depicted in Figure 4 below are four different designs of the pneumatic jet nebulizer: jet nebulizer with reservoir tube, jet nebulizer with collection bag, breath-enhanced jet nebulizer, and breath-actuated jet nebulizer.

A. Jet Nebulizer with a Reservoir Tube: The T-piece jet nebulizer with the reservoir tube is the least expensive and most routinely used of the four designs. This nebulizer provides continuous aerosol during inhalation, exhalation, and during breath-holding, causing the release of aerosol to ambient air during exhalation and anytime when the patient is not breathing (Figure 4-A).^{34,35} Consequently, only 10–20% of the emitted aerosol is inhaled.

The T-piece nebulizer with a piece of large-bore corrugated tubing attached to the expiratory side of the nebulizer helps to decrease drug loss and increase inhaled drug mass. Inhaled drug delivery is enhanced since the piece of corrugated tubing acts as a reservoir by filling with aerosol during the patient's pre-inspiratory pause, allowing a large bolus of aerosol to be available at the very beginning of inhalation. Examples of jet nebulizers with a reservoir tube include the Sidestream[®] Nebulizers (Philips Respironics, Andover, MA) and the Micro Mist[®] (Teleflex Medical, Research Triangle Park, NC).

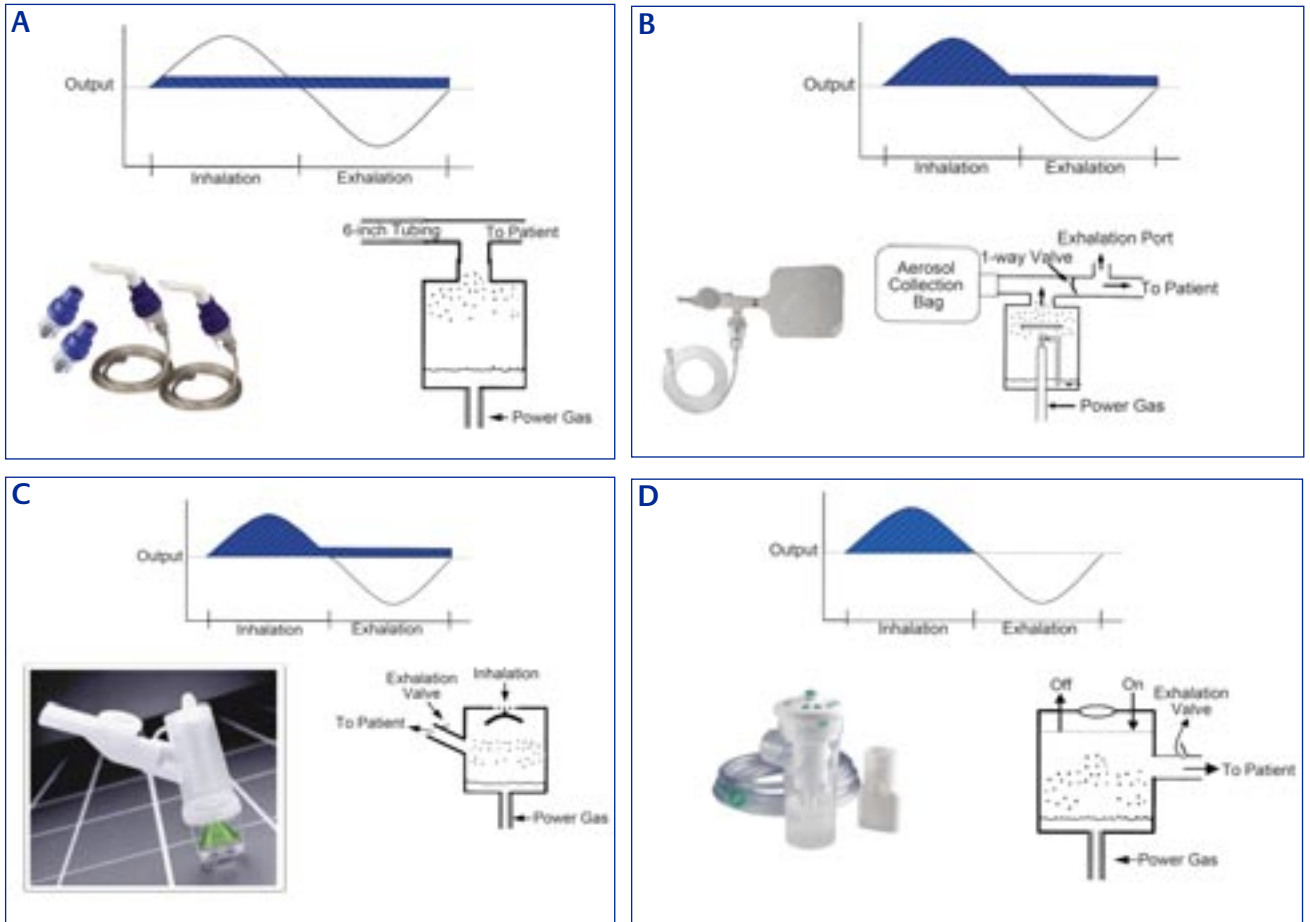


Figure 4. A. Standard T-piece jet nebulizer with reservoir tubing; B. Jet nebulizer with collection bag; C. Breath-enhanced jet nebulizer; D. Breath-actuated jet nebulizer. (From Reference 5, with permission)

Figure 5 shows a cut-away view of a jet nebulizer. The word “jet” is used because the pressurized gas is forced through a small narrow orifice (a jet) that is located proximal to an equally small capillary tube. As the pressurized gas leaves the jet, it mixes with the liquid medication in the capillary tube to create a mist.

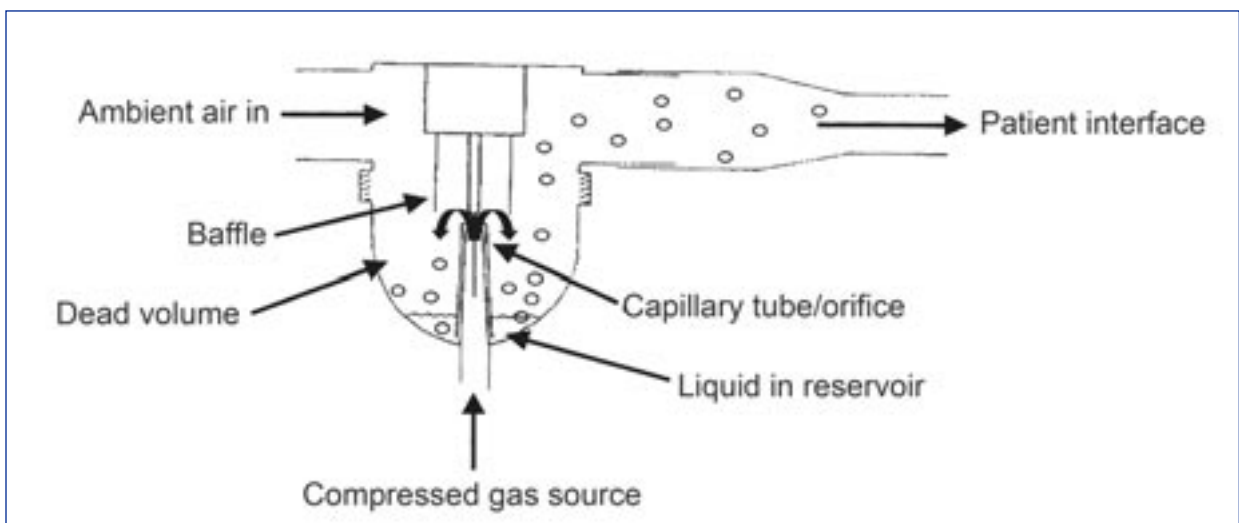


Figure 5. Labeled schematic illustration of the operation of a standard jet nebulizer

B. Jet Nebulizer with Collection Bag: These types of nebulizers generate aerosol by continuously filling a reservoir bag (Figure 4-B). The patient inhales aerosol from the reservoir through a one-way inspiratory valve and exhales to the atmosphere through an exhalation port between the one-way inspiratory valve and the mouthpiece.³⁶

C. Breath-enhanced Jet Nebulizer: Breath-enhanced nebulizers use 2 one-way valves to prevent the loss of aerosol to environment (Figure 4-C). The output rate is controlled by the patient's breathing. When the patient inhales, the inspiratory valve opens and gas vents through the nebulizer. Exhaled gas passes through an expiratory valve in the mouthpiece. Figure 6 illustrates the operation principle of the breath-enhanced nebulizer.

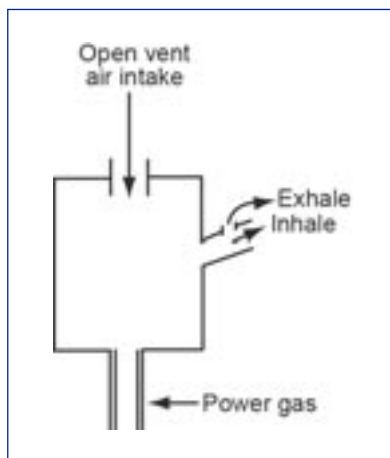


Figure 6. Schematic diagram of a breath-enhanced nebulizer

D. Breath-actuated Jet Nebulizer: Breath-actuated nebulizers are designed to increase aerosol drug delivery to patients by generating aerosol only during inspiration. Consequently, loss of medication during expiration is greatly reduced, as shown in Figure 4-D.³⁵ Moreover, since the newer, fully integrated breath-actuated nebulizers produce an aerosol with more than 70% of aerosol particles in the desirable $3\ \mu\text{m}$ range, drug delivery to the airways is increased by more than 3-fold over conventional jet nebulizers.

Electronic Nebulizers

Besides the standard jet nebulizer, there are several other types of hand-held portable SVN on the market. These other models are called electronic nebulizers and can be classified as either “ultrasonic” or “vibrating mesh.” Figure 7 shows an example of each type.



Figure 7. An ultrasonic nebulizer (left) and a vibrating mesh nebulizer (right)

The main difference is that these electronic nebulizers do not use a compressor and jet nebulizer. Instead, they use electrical energy to turn the liquid medication into a mist. Electronic nebulizers are small, quiet, and typically powered by standard size batteries.

Ultrasonic Nebulizers

Ultrasonic nebulizers use a transducer to convert electrical energy to high-frequency ultrasonic vibrations. These vibrations are transferred to the surface of the medication solution that is placed over the transducer, thereby generating an aerosol. Small-volume ultrasonic nebulizers are now commercially available for delivery of inhaled bronchodilators in aqueous form. However, ultrasonic nebulizers should not be used to nebulize suspensions such as budesonide.

Ultrasonic nebulizers consist of a power unit and transducer, with or without an electric fan. The power unit converts electrical energy to high-frequency ultrasonic waves. A transducer vibrates at the same frequency as the applied wave. Ultrasonic waves are transmitted to the surface of the solution to create an aerosol. A fan is used to deliver the aerosol to the patient, or the aerosol is evacuated from the nebulization chamber by the inspiratory flow of the patient. Figure 8 shows the operating principle of an ultrasonic nebulizer.

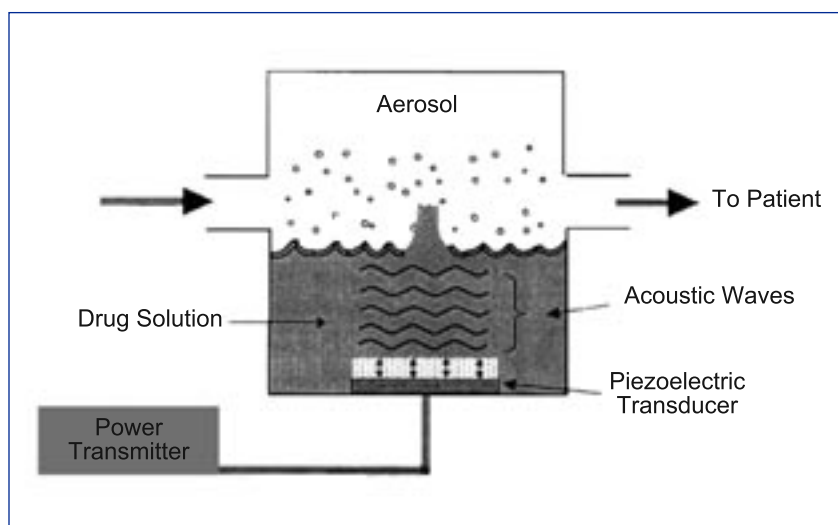


Figure 8. Components and operation principle of an ultrasonic nebulizer
(From Reference 5, with permission)

Small-volume ultrasonic nebulizers are commercially available for delivery of inhaled bronchodilators; large volume ultrasonic nebulizers are used for sputum induction. A potential issue with the use of ultrasonic nebulizers is drug inactivation by ultrasonic waves; however, to date, this has not been shown to occur with medications commonly delivered using this system. Of more immediate concern with ultrasonic nebulizers is fatty acid contamination of the drug solution by the user. Fatty acid contamination, caused by oils or lotions on the hands, alters the surface tension of the liquid and may impede nebulization.

Vibrating Mesh Nebulizers

Several manufacturers have developed aerosol devices that use a mesh with multiple, tiny openings to produce a liquid aerosol. In these devices, a solution is forced through a fine mesh to produce an aerosol. Mesh nebulizers have the ability to generate aerosols with a fine-particle fraction, which results in more efficient drug delivery compared to other types of nebulizers. The aerosol is generated as a fine mist, and no internal baffling system is required. These nebulizers are portable, battery-operated, and highly efficient.³³ They have minimal residual medication volume and some are breath-actuated. They are being developed in cooperation with pharmaceutical companies to deliver expensive formulations with which precise dosing is needed.

Adaptive Aerosol Delivery Nebulizer

This nebulizer incorporates mesh technology with new adaptive aerosol delivery (AAD) technology. An AAD device monitors the patient's breathing pattern and delivers the aerosol at the beginning of inhalation. This improves the likelihood of the aerosol penetrating deep into the respiratory tract. AAD nebulizers are desirable when the clinician prescribes a novel and/or expensive medication that requires precise dosing, such as iloprost, for the treatment of pulmonary arterial hypertension.

In summary, there are various types of SVN's available. One group is powered by compressed gas (pneumatic) and the other by electrical current (electronic). Table 4 below shows the pros and cons associated with SVN's, irrespective of type or model.

Table 4. Advantages and disadvantages of small-volume nebulizers

(Modified, with permission, from Reference 5).

Advantages	Disadvantages
Ability to aerosolize many drug solutions	Treatment times may range from 5–25 minutes.
Ability to aerosolize drug mixtures (>1 drug) if drugs are compatible	Equipment required may be large and cumbersome.
Minimal patient cooperation or coordination needed.	Need for power source (electricity, battery, or compressed gas)
Useful in very young, very old, debilitated or distressed patients	Potential for drug delivery into the eyes with face mask delivery
Drug concentrations and dose can be modified.	Variability in performance characteristics among different types, brands, and models
Normal breathing pattern can be used and an inspiratory pause (breath-hold) is not required for efficacy.	Assembly and cleaning are required. Contamination is possible with improper handling of drug and inadequate cleaning.

Factors Affecting Jet Nebulizer Performance and Drug Delivery

There are many factors for health care providers to keep in mind during aerosol therapy. Nebulizer design determines the size of particle and output performance produced, which results in the ultimate efficiency of medication according to the factors discussed below. Various types of nebulizers are available on the market, and several studies have indicated that performance varies among manufacturers and also between nebulizers from the same manufacturer.^{5,37,38}

Gas Flow and Pressure: Jet nebulizers are designed to operate by means of varied levels of compressed gas flow and pressure. Each model of jet nebulizer is designed to work best at a flow rate up to 6-8 L/min, which should be listed on the device label. Operating any jet nebulizer at a lower flow or pressure will increase particle size. For example, a jet nebulizer designed to operate at 6–8 L/min at 50 psi will produce larger particles if driven by a compressor producing 13 psi. Consequently, jet nebulizers should be matched with a compressor or gas source that matches their intended design. Gas flow is also inversely related to nebulization time. Using a higher gas flow rate in aerosol therapy will decrease the amount of treatment time needed to deliver the set amount of drug.

Fill and Dead Volumes: Optimizing the fill volume is another factor that increases the efficiency of jet nebulizers. These nebulizers do not function well with small fill volumes like 2 mL or less. It is recommended to use a fill volume of 4–5 mL unless the nebulizer is specifically designed for a smaller fill volume.^{5,38} This precaution dilutes the medication, allowing for a greater proportion to be nebulized, though it increases the treatment time. The amount of medication remaining in the jet nebulizer at the end of a treatment can range from 0.5 to 2.0 mL. The greater the amount of dead volume, the less drug nebulized.

Gas Density: The density of gas used to run a jet nebulizer (oxygen/air or heliox) can impact aerosol deposition by affecting aerosol output and particle size.

Humidity and Temperature: Humidity and temperature can also affect particle size and medication remaining in the nebulizer cup after therapy. Specifically, water evaporation during aerosol therapy can reduce the temperature of an aerosol, which results in an increase in solution viscosity and a decrease in the nebulizer output of drug.

Breathing Pattern: Breathing pattern influences aerosol deposition in the lower respiratory tract. The patient should be instructed to do normal breathing with periodic deep breaths during aerosol therapy.

Device Interface: Therapeutic aerosols can be administered using either a mouthpiece or a facemask. Ideally, a mouthpiece should be used. The nose tends to filter more aerosol than the mouth, so use of a mouthpiece should be encouraged when appropriate. Mouthpieces cannot be used for infants and small children. In addition, the use of a mouthpiece may be uncomfortable for longer aerosol therapy administration. Use of a mask increases the potential amount of aerosol deposited on the face, in the eyes, and into the nose. Whether a mouthpiece or a facemask is used, it is important to instruct the patient to inhale through the mouth during aerosol therapy. Proper mask fit and design can optimize the inhaled dose and reduce deposition to the eyes. Health care providers must keep all of these factors in mind when delivering therapy.

Nebulizers for Specific Applications

There are nebulizers for specific applications, such as for ribavirin or pentamidine administration. These nebulizers have specific characteristics such as valves that prevent exposure of secondhand pentamidine aerosol and contamination of the room air with exhaled aerosol.

Continuous Aerosol Therapy

Continuous aerosol drug administration of beta-agonists is a treatment modality that is sometimes used to treat patients suffering an acute asthma attack that is refractory to intermittent treatments. Commercial nebulizers used in continuous nebulization commonly have luer lock ports designed for use with infusion pumps. The nebulization is most commonly administered using standard aerosol masks. Due to the potential for overdosing, the use of continuous aerosol administration should be restricted to the acute care setting where continuous patient monitoring is available.

Drug-delivery Technique

Because different types of nebulizers are available on the market, the health care provider needs to be aware of the operation instructions prior to giving aerosol therapy and certainly prior to instructing patients in at-home use. Proper technique is provided in Technique Box 1.

Technique Box 1. Steps for Correct Use of Nebulizers

Technique for Jet Nebulizers: When a jet nebulizer is used, the patient should:

1. Wash hands with soap and warm water and dry thoroughly.
2. Assemble tubing, nebulizer cup, and mouthpiece (or mask).
3. Put medicine into the nebulizer cup.
4. Sit in an upright position.
5. Connect the nebulizer to a power source.
6. Breathe normally with occasional deep breaths until sputter occurs or until the end of nebulization.
7. Keep the nebulizer vertical during treatment.
8. Rinse the nebulizer with sterile or distilled water and allow to air dry.

Technique for Mesh and Ultrasonic Nebulizers:

When a mesh or ultrasonic nebulizer is used, the patient should:

1. Wash hands with soap and warm water and dry thoroughly.
2. Correctly assemble the nebulizer.
3. If required, follow manufacturer's instructions in performing a functionality test prior to the first use of a new nebulizer, as well as after each disinfection, to verify proper operation.
4. Pour the solution into the medication reservoir. Do not exceed the volume recommended by the manufacturer.
5. Sit in an upright position.
6. Turn on the power.
7. Hold the nebulizer in the position recommended by the manufacturer.
8. Breathe normally with occasional deep breaths if warranted.
9. If the treatment must be interrupted, turn off the unit to avoid waste.
10. At the completion of the treatment, disassemble and clean as recommended by the manufacturer.
11. When using a mesh nebulizer, do not touch the mesh during cleaning. This will damage the unit.
12. Once or twice a week, disinfect the nebulizer, following the manufacturer's instructions.

General Steps To Avoid Reduced or No Dosing for All Nebulizers: When using nebulizers, the following steps should be used in order to avoid reduced or no dosing during aerosol treatment.

The patient should:

1. Read and follow the instructions.
2. Make sure that the nebulizer is properly assembled.
3. Make sure that the nebulizer is cleaned and dried between uses.
4. Make sure that the nebulizer operated in its proper orientation.

Troubleshooting

Problem with Jet Nebulizers: Absent or Low Aerosol

Causes

Loose or unattached connections

Inappropriate flowmeter setting

Obstruction in the orifice of the jet nebulizer

Solutions

Check the connections and make sure that they are properly attached.

Check the flowmeter setting and adjust the flow if it is not appropriate.

Check the orifice of the jet nebulizer and clear obstructions when needed.

Problems with Mesh and Ultrasonic Nebulizers: The Unit Does Not Operate or Produce Aerosol

Causes

Incorrect battery installation (seen in both mesh and ultrasonic nebulizers)

External power source disconnection (seen in both mesh and ultrasonic nebulizers)

Solutions

Check the battery installation and reinstall if needed.

Check the connections with the AC adapter and the electrical output

Technique Box 1. (continued)

Overheated unit (seen in ultrasonic nebulizers)	Turn off the unit, wait until it cools down and then restart it.
Incorrect connection of the control module cable (seen in mesh nebulizers)	Check the connections with the control module cable and attach them properly, if needed.
Malfunctioning electronics (seen in both mesh nebulizers and ultrasonic nebulizers)	Replace the unit.
Power aerosol output or long treatment time due to clogged mesh	Clean according to manufacturers instructions.

When Is the Treatment Finished?

Often, individuals tap the sides of the nebulizer in order to increase the drug output. Others continue aerosol therapy past the part of sputtering. Typically the treatment is considered over with the onset of nebulizer sputtering. Some nebulizers will sputter for extended periods of time after the majority of the inhaled dose has been administered. Evidence suggests that after the onset of sputter, very little additional drug is inhaled.^{22,39} Because the time it takes to administer the drug is a critical factor for patient adherence to therapy, some clinicians have adopted recommendations to stop nebulizer therapy at, or one minute after, the onset of sputter. Newer electronic nebulizers may use microprocessors that monitor how much dose has been administered and automatically turn off the nebulizer at the end of each dose.

3. INHALERS

The pressurized metered-dose inhaler and dry-powder inhaler are medical aerosol delivery devices that combine a device with a specific formulation and dose of drug. Each actuation of the inhaler is associated with a single inspiration by the patient. These are typically single, patient-use devices dispensed from the pharmacy with a specific quantity of medication and disposed of when the medication has been depleted.

Inhalers are approved by the FDA Center for Drug Evaluation and Research (CDER) as drug and device combinations. Inhaler-based drugs must have reproducible doses (+/- 20) from first to last dose and have a shelf life with drug of at least 12–24 months.

There are a large variety of inhaler designs, and many drugs are available only in a single inhaler form (Figure 9). Patients are frequently prescribed several types of inhalers with different instructions for operation. Confusion between device operations can result in suboptimal therapy. For example, pMDIs typically require slow inspiratory flow (<30 L/min), while a DPI may require high peak inspiratory flow rates (30–60 L/min) to disperse a full dose. Patients may confuse which inspiratory flow pattern to use with which device and may get much less drug from both devices. When prescribing, clinicians may want to employ a minimum number of devices to enhance patient technique and adherence. Education and repetitive return demonstration is also a key to proper inhaler use.

Anticholinergics

**Spiriva®
Handihaler®**
(tiotropium bromide)
Inhalation Powder
Boehringer Ingelheim
Pharmaceuticals, Inc.



Atrovent® HFA
(ipratropium bromide HFA)
Inhalation
Aerosol
Boehringer Ingelheim
Pharmaceuticals, Inc.



**Tudorza™
Pressair™**
(aclidinium bromide)
Inhalation Powder
Forest Pharmaceuticals, Inc.



Anticholinergics/ β₂-Agonist Combination

**Combivent®
Respimat**
(ipratropium bromide
and albuterol sulfate)
Inhalation Aerosol
Boehringer Ingelheim
Pharmaceuticals, Inc.



β₂-Agonists

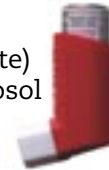
Foradil® Aerolizer®
(Formoterol fumarate)
Inhalation Powder
Novartis Pharmaceuticals



Maxair™ Autohaler™
(pirbuterol acetate)
Inhalation Aerosol
Graceway Pharmaceuticals



ProAir® HFA
(albuterol sulfate)
Inhalation Aerosol
Teva Specialty
Pharmaceuticals



Proventil® HFA
(albuterol sulfate)
Inhalation Aerosol
3M Pharmaceuticals Inc.



Arcapta™ Neohaler™
(indacaterol)
Inhalation Powder
Novartis Pharmaceuticals



Xopenex® HFA
(levalbuterol tartare)
Inhalation Aerosol
Sepracor Inc.



Ventolin® HFA
(albuterol sulfate HFA)
Inhalation Aerosol
GlaxoSmithKline



Corticosteroids

Alvesco®
(ciclesonide)
Inhalation
Aerosol
Nycomed



**Asmanex
Twisthaler®**
(mometasone)
Inhalation
Powder
Schering Corporation



Flovent® Diskus®
(fluticasone propionate)
Inhalation
Powder
GlaxoSmithKline



Flovent® HFA
(fluticasone propionate)
Inhalation Aerosol
GlaxoSmithKline



**Pulmicort®
Flexhaler®**
(budesonide)
Inhalation Powder
AstraZeneca LP



QVAR®
(beclomethasone dipropionate)
Inhalation
Aerosol
Teva Specialty Pharmaceuticals



β₂-Agonist/Corticosteroid Combination

Advair Diskus®
(fluticasone propionate and salmeterol)
Inhalation Powder
GlaxoSmithKline



Advair® HFA
(fluticasone propionate and salmeterol xinafoate)
Inhalation Aerosol
GlaxoSmithKline



Relenza®
(zanamivir)
Inhalation Powder
GlaxoSmithKline



Dulera®
(mometasone furoate/
formoterol fumarate dihydrate)
Inhalation Aerosol
Merck



Symbicort®
(budesonide and formoterol fumarate dihydrate)
Inhalation Aerosol
AstraZeneca



TOBI Podhaler
(tobramycin)
Inhalation
Powder
Novartis Pharmaceuticals



Figure 9. Various inhalers currently available in the United States

4. PRESSURIZED METERED-DOSE INHALERS

Since the development of the pMDI by Dr. George Maison in 1955, it has become the most common aerosol generator prescribed for patients with asthma and COPD. This is because it is compact, portable, easy to use, and provides multi-dose convenience.

Advantages and Disadvantages of pMDIs

The pMDI was designed and developed as a drug and device combination that delivers precise doses of specific drug formulations. Unlike nebulizers, drug preparation and handling are not required with pMDIs, and the internal components of pMDIs are difficult to contaminate. Table 5 gives the advantages and disadvantages associated with the use of pMDIs.

Table 5. Advantages and disadvantages of the pMDI

(Modified, with permission, from Reference 5)

Advantages	Disadvantages
Portable, light, and compact	Hand-breath coordination required
Multiple dose convenience	Patient activation, proper inhalation pattern, and breath-hold required
Short treatment time	Fixed drug concentrations and doses
Reproducible emitted doses	Reaction to propellants by some patients
No drug preparation required	Foreign body aspiration from debris-filled mouthpiece
Difficult to contaminate	High oropharyngeal deposition
	Difficult to determine the dose remaining in the canister without dose counter

Types of pMDIs

There are two major types of pMDIs: conventional pMDIs and breath-actuated pMDIs. Regardless of manufacturer or active ingredient, the basic components of the pMDI include the canister, propellants, drug formulary, metering valve, and actuator. The characteristics of each pMDI component are described in Table 6.

Table 6. Basic components of the pMDI

(From Reference 5 with permission)

Component	Particulars
Canister	Inert, able to withstand high internal pressures and utilize a coating to prevent drug adherence
Propellants	Liquefied compressed gases in which the drug is dissolved or suspended
Drug Formulary	Particulate suspensions or solutions in the presence of surfactants or alcohol that allocate the drug dose and the specific particle size
Metering Valve	Most critical component, crimped onto the container and is responsible for metering a reproducible volume or dose, includes elastomeric valves for sealing and preventing drug loss or leakage.
Actuator	Frequently referred to as the “boot,” the actuator is partially responsible for particle size based on the length and diameter of the nozzle for the various pMDIs. (Each boot is unique to a specific pMDI/drug.)
Dose Counter	This component provides a visual tracking of the number of doses remaining in the pMDI.

Conventional pMDI

As seen in Figure 10, the pMDI consists of a canister, the medication, the propellant, a metering valve, the mouthpiece, and the actuator.⁴⁰ The medication represents only 1–2% of the mixture emitted from the pMDI and is either suspended or dissolved in the mixture. The propellant of the pMDI makes up 80% of the mixture. The metering valve acts to prepare a pre-measured dose of medication along with the propellant.

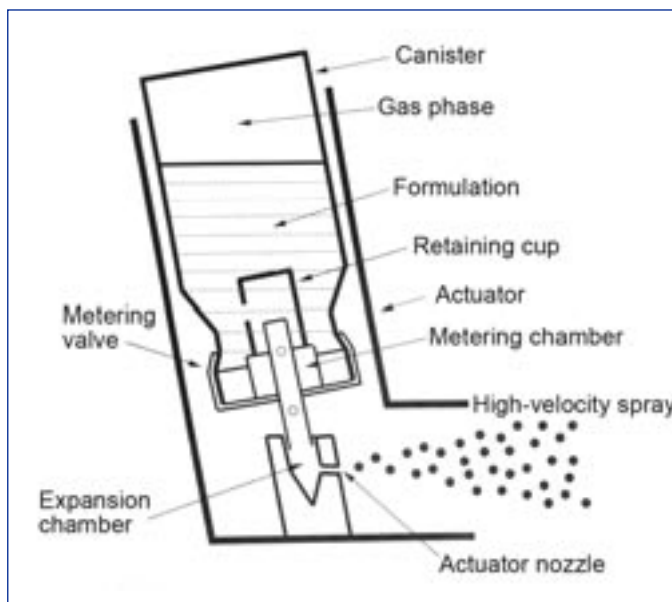


Figure 10. Standard components of pMDI

(Modified with permission from Reference 40)

The conventional pMDI has a press-and-breathe design. Depressing the canister into the actuator releases the drug-propellant mixture, which then expands and vaporizes to convert the liquid medication into an aerosol. The initial vaporization of the propellant cools the

aerosol suspension. The canister aligns the hole in the metering valve with the metering chamber when it is pressed down. Then, the high propellant vapor pressure forces a pre-measured dose of medication out of the hole and through the actuator nozzle. Last, releasing the metering valve refills the chambers with another dose of the drug-propellant mixture.

As discussed earlier, there are two types of propellants used in pMDIs: the older CFC and the newer HFA. (Note: As of this printing, Maxair is the only CFC pMDI left on the market with a required conversion date to HFA propellant by Dec. 31, 2013 . All others have converted to HFA propellant or are no longer available.) HFA pMDIs (Figure 11, left) have a softer spray than CFC pMDIs (Figure 11, right). Also, HFA pMDIs have a much warmer spray temperature than CFC pMDIs. Due to the cold mist from a pMDI, inhalation may be interrupted by patient sensitivity. Health care providers must understand the subtle yet important differences in characteristics between CFC and HFA pMDIs (see Table 7). Clinicians should therefore explain to their patients how the feel and taste of the HFA pMDI will be different from that of the CFC pMDI to which they may be accustomed.



Figure 11. Spray differences between HFA pMDI (left) and CFC pMDI (right).
(From *New York Times*, with permission)

Table 7. Differences in characteristics between CFC and HFA pMDIs
(From Reference 5, with permission)

Physical Component	CFC	HFA
Dose Delivery		
From a near-empty canister	Variable	Consistent
With variable ambient temperature	Variable	Consistent (to -20°C)
Spray		
Force	Higher Impaction	Lower (3 times)
Temperature	Colder	Warmer
Volume	Higher	Lower
Taste	Different from HFA	Different from CFC
Breath-hold	Less important	More important
Priming	Important following short period of nonuse	Longer time of nonuse allowed without priming
Nozzle Cleaning	Not necessary	Periodically necessary to prevent clogging

Breath-actuated pMDI

The Maxair Autohaler® was the first flow-triggered breath-actuated pMDI. It was designed to eliminate the need for hand-held coordination during drug administration. Its mechanism is triggered by inhalation through a breath-actuated nozzle, which provides an automatic response to the patient's inspiratory effort. In order to release the drug with the Autohaler, the lever on top of the device must be raised before use. Nozzle size, cleanliness, and lack of moisture are the 3 most important factors affecting the amount of drug delivered by breath-actuated pMDIs. If the patient has good coordination with the conventional pMDI, the use of a breath-actuated pMDI may not be necessary because it may not improve drug delivery.^{41,42} Nonetheless, studies have proven that breath-actuated pMDIs improve the delivery of inhaled medication in patients with poor coordination.⁴¹ It must be noted that the Autohaler uses CFCs. Figure 12 shows the standard components of the Autohaler.

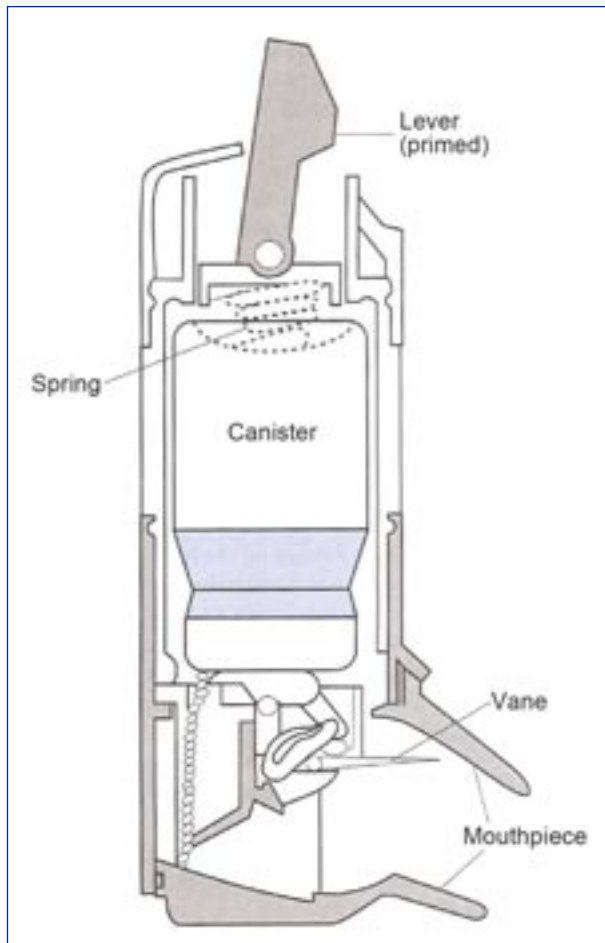


Figure 12. Standard components of the Autohaler

Currently Available pMDI Formulations

A number of aerosol formulations are available for use in pMDIs today (refer to Figure 9). Pressurized metered-dose inhalers are presently used to administer beta-2 agonists, anticholinergics, anticholinergic/beta-2 agonist combinations, and corticosteroids.

Factors Affecting pMDI Performance and Drug Delivery

Most pMDIs are designed to deliver a drug dose of 100 μm per actuation. Just like other aerosol generators, drug delivery with a pMDI is approximately 10–20% of the nominal dose per

actuation. The particle size of aerosols produced by the pMDI is less than 5 µm. Several factors influence pMDI performance and aerosol drug delivery. Understanding the effects of these factors will improve the efficacy of pMDIs when used for patients with pulmonary diseases. Therefore, both health care providers and patients must actively control the following effects.

- **Shaking the Canister:** Not shaking a pMDI canister that has been standing overnight can decrease total and respirable dose by as much as 25–35%. This occurs because the drugs in pMDI formulations are usually separated from the propellants when standing.⁴³ Therefore, pMDIs must be shaken several times before the first actuation in order to refill the metering valve with adequately mixed suspension from the canister.¹⁶
- **Storage Temperature:** Outdoor use or storage of pMDIs in very cold weather may significantly decrease aerosol drug delivery.⁴²
- **Nozzle Size and Cleanliness:** The amount of medication delivered to the patient is dependent upon nozzle size, cleanliness, and lack of moisture. Actuator nozzle is pMDI specific, and the coordination of the nozzle with the medication will influence both inhaled dose and particle size. White and crusty residue due to crystallization of medication may impede drug delivery. Therefore, the nozzle should be cleaned periodically based on the manufacturer's recommendations.
- **Timing of Actuation Intervals:** The rapid actuation of more than 1 puff with the pMDI may reduce drug delivery because of turbulence and the coalescence of particles.⁴³ A pause between puffs may improve bronchodilation, especially during asthma exacerbations with episodes of wheezing and poor symptom control.⁴⁴ In other cases, such as in the day-to-day management of preadolescents with a beta agonist (terbutaline) and a corticosteroid (budesonide), pauses between puffs have not been found to be beneficial.⁴⁵

Although early research was mixed regarding the importance of a pause between the 2 actuations, recent literature suggests there should be a pause of 30-60 seconds between actuations for effective aerosol therapy.^{5,10,17}

- **Priming:** “Priming” is releasing one or more sprays into the air or valved holding chamber. Initial and frequent priming of pMDIs is required to provide an adequate dose. The drug may be separated from the propellant and other ingredients in the canister and metering valve when the pMDI is new or has not been used for awhile. Because shaking the pMDI will mix the suspension in the canister but not the metering chamber, priming of the pMDI is required. Table 8 provides the recommended guidelines for priming the various pMDIs available on the market.

Table 8. Priming requirements for commercially available pMDIs
(Modified, with permission, from Reference 5)

Generic Name	Brand Name	Time to Prime	No. of Sprays
Short-acting Bronchodilators			
Albuterol Sulfate HFA	ProAir HFA®	New and when not used for 2 weeks	3
	Proventil® HFA	New and when not used for 2 weeks	4
	Ventolin® HFA	New and when not used for 14 days	4
Pirbuterol	Maxair Autohaler®	New and when not used for 2 days	2
Levalbuterol HCl	Xopenex HFA™	New and when not used for 3 days	4
Ipratropium Bromide HFA	Atrovent HFA®	New and when not used for 3 days	2
Ipratropium Bromide/ Albuterol Sulfate Combination	Combivent® HFA	New and when not used for 24 hours	3
Inhaled Corticosteroids			
Beclomethasone Propionate HFA	QVAR	New and when not used for 10 days	2
Ciclesonide	Alvesco®	New and when not used for 10 days	3
Fluticasone Propionate	Flovent HFA	New	4
		Not used more than 7 days or if dropped	1
Combination Drugs			
Budesonide combined with Formoterol	Symbicort HFA	New and not used more than 7 days or if dropped	2
Fluticasone combined with Salmeterol	Advair HFA	New	4
		Not used more than 4 weeks or if dropped	2

- **Characteristics of the Patient:** Characteristics of the patient using the pMDI will result in a variability of aerosol deposition. For example, aerosol deposition will be lower in infants and children due to differences in their anatomy and their physical and cognitive abilities.
- **Breathing Techniques:** There are 2 primary techniques for using a pMDI without a spacer: the open-mouth technique and the closed-mouth technique. The manufacturers of pMDIs universally recommend the closed-mouth technique for using a pMDI. In this method, the pMDI mouthpiece is placed between the patient's sealed lips during drug administration. On the other hand, some researchers and clinicians have advocated an open-mouth technique in an attempt to reduce oropharyngeal deposition and increase lung dose.^{46,47}

The open-mouth technique was recommended when all pMDIs used CFC propellants. When using the open-mouth technique, the inhaler is placed 2 finger widths away from the lips of an open mouth and aimed at the center of the opening of the mouth. Studies suggest that the open-mouth technique reduces unwanted oropharyngeal deposition by allowing the aerosol plume more distance to slow down before reaching the back of the mouth and up to 2-fold more drug deposition to the lung than when using the closed-mouth technique.^{46,48}

In contrast, other researchers suggest that the open-mouth technique does not offer any advantage over the closed-mouth technique^{49,50} but that it does create additional hazards such as the aerosol plume being misdirected from the mouth and into the eye or elsewhere.⁵¹ Therefore, the best technique should be determined based on the patient's physical abilities, coordination, and preference. If the patient is well coordinated and can master the open-mouth technique better, it can be used by following the directions below. Also, the clinician should continuously observe the patient's aerosol administration technique and correct it when appropriate.

Drug-delivery Technique

Because different types of pMDIs are available, the health care provider should carefully review operation instructions prior to giving aerosol therapy and certainly prior to instructing patients in at-home use. Proper technique is provided in Technique Box 2.

Technique Box 2. Steps for Correct Use of pMDIs

Techniques for pMDIs

Open-mouth Technique: The patient should be instructed to:

1. Remove the mouthpiece cover and shake the pMDI thoroughly.
2. Prime the pMDI into the air if it is new or has not been used for several days.
3. Sit up straight or stand up.
4. Breathe all the way out.
5. Place the pMDI two finger widths away from their lips.
6. With mouth open and tongue flat (tip of tongue touching inside of their lower front teeth), tilt outlet of the pMDI so that it is pointed toward the upper back of the mouth.
7. Actuate the pMDI as patient begins to breathe in slowly.
8. Breathe slowly and deeply through the mouth and hold their breath for 10 seconds. If patient cannot hold their breath for 10 seconds, then for as long as possible.
9. Wait one minute if another puff of medicine is needed.
10. Repeat Steps 1-9 until the dosage prescribed by the physician is reached.
11. If taking a corticosteroid, patient should rinse their mouth after the last puff of medicine, spit out the water, and not swallow it.
12. Replace the mouthpiece cover on the pMDI after each use.

Closed-mouth Technique: The patient should be instructed to:

1. Remove the mouthpiece cover and shake the inhaler thoroughly.
2. Prime the pMDI into the air if it is new or has not been used for several days.
3. Sit up straight or stand up.
4. Breathe all the way out.
5. Place the pMDI between the teeth; make sure the tongue is flat under the mouthpiece and does not block the pMDI.
6. Seal the lips.
7. Actuate the pMDI as the patient begins to breathe in slowly over a period of 3–5 seconds.
8. Hold the breath for 10 seconds. If the patient cannot hold breath for 10 seconds, then for as long as possible.
9. Wait one minute if another puff of medicine is needed.
10. Repeat Steps 1–9 until the dosage prescribed by the patient's physician is reached.
11. If taking a corticosteroid, patient should rinse mouth after the last puff of medicine and spit out the water so as not to swallow it.
12. Replace the mouthpiece cover on the pMDI after each use.

Breath-actuated pMDI (Autohaler) Technique: When using the Autohaler, the patient should be instructed to:

1. Warm the pMDI canister to hand or body temperature.
2. Remove the mouthpiece cover and check for foreign objects.

Technique Box 2 (continued)

3. Keep the Autohaler in a vertical position with the arrow pointing up, and do not block the air vents.
4. Prime the Autohaler into the air if it is new or has not been used recently.
5. Push the lever up.
6. Push the white test fire slide on the bottom of the mouthpiece for priming the Autohaler.
7. Push the lever down to release the second priming spray.
8. Return the lever to its down position and raise the lever so that it snaps into place.
9. Sit up straight or stand up.
10. Shake the Autohaler 3 or 4 times.
11. Breathe out normally, away from the Autohaler.
12. Place the pMDI between the teeth. Make sure the tongue is flat under the mouthpiece and does not block the pMDI.
13. Seal the lips around the mouthpiece.
14. Inhale deeply through the mouthpiece with steady moderate force.
15. Pay attention to the click sound and the feel of a soft puff when the Autohaler triggers the release of medicine.
16. Continue to inhale until the lungs are full.
17. Remove the mouthpiece from the mouth.
18. Hold breath for 10 seconds or as long as possible.
19. Repeat steps above until the dosage prescribed by the patient's physician is reached.
20. Replace the mouthpiece cover and make sure the lever is down.

General Steps To Avoid Reduced or No Dosing for pMDIs: When using pMDIs, the following steps should be used in order to avoid reduced or no dosing during aerosol treatment. The patient should:

1. Remove the cap of the pMDI from the boot.
2. Prime as directed (Table 8).
3. Clean and dry the boot of the pMDI based on the manufacturer's guidelines.
4. Track remaining doses.

Troubleshooting

Problem with the pMDI: Absent or Low Aerosol

Causes

Incorrect pMDI assembly

Incorrect pMDI and valved holding chamber assembly
Empty the pMDI

Solutions

Check the assembly and reassemble when needed.
Check the assembly of the pMDI/spacer and reassemble if needed.
Check the dose counter or daily log sheet to ensure there is enough medicine in the canister; if not, replace the pMDI.

How Do We Know the pMDI Is Empty?

Since the pMDI's introduction in the 1950s, it has not been packaged with dose counters that allow patients to determine when a pMDI should be discarded.⁵²⁻⁵⁴ After the pMDI delivers the number of puffs stated on the label, it may look, taste, and feel like it is still working, but the dose delivered may be very low. This "tailing-off effect" may last long after the pMDI is "empty of drug."^{17,55} Also, the pMDI without a dose counter could lead to wastage if the inhaler is discarded prematurely. Indirect methods (e.g., floating the canister in water) are misleading and can reduce the ability of the pMDI to work properly.^{54,56,57} Therefore, they should not be used to determine the amount of medication remaining in the canister.

The only reliable method to determine the number of doses remaining in a pMDI is to count the doses given either manually or with a dose counter. Manual methods include reading the

label to determine the total number of doses available in the pMDI and using a log to indicate every individual actuation given (including both priming and therapy doses). Once the dose limit has been reached, properly dispose of the pMDI. Unfortunately, manually counting doses may be impractical and undependable, especially in patients who use reliever medications on the go. Therefore, the FDA requires new pMDIs to have integrated dose counters and recommends that all pMDIs have dose-counting devices that indicate when the pMDI is approaching its last dose.⁵⁸ Ventolin HFA and Flovent HFA have built-in dose counters (Figure 13).

External dose counters are also available and can be attached to the top of the pMDI canister or to the boot of the device. When the pMDI is actuated, it counts down the number of actuations from the total remaining in the canister.



Figure 13. Integral dose counter on Ventolin HFA (left) and Flovent HFA pMDI (right)

As mentioned, there are now several mechanical or electronic dose counters available from third parties for use by attachment to a range of pMDIs (see Figure 14). Although research has confirmed acceptable performance and patient satisfaction with pMDIs with external dose counters,⁵⁹⁻⁶¹ care must be taken to assure that a third-party dose counter works with the specific pMDI being used.^{22,62}

Some of the built-in counters may prevent the pMDI from fitting into a spacer. Improper fitting of the canister may interfere with proper actuation and result in no or partial drug being emitted and in a miscount of remaining doses.⁶² Using a third-party dose-counting device increases the cost of aerosol therapy, which may limit their wide acceptance.



Figure 14. Currently available external pMDI dose counters on the market

With any third-party counter, the product label and accompanying package information for each pMDI should be read before use and the manufacturer's recommended doses should be followed. When attempting to keep track of the number of puffs remaining in the pMDI, the following steps should be taken:

Without dose counter, the user should:

1. Determine the number of puffs that the pMDI has when it is full.
2. Calculate how long the pMDI will last by dividing the total number of puffs in the pMDI by the total puffs used (for a total of 8 puffs per day). This canister will last 25 days ($200 \div 8 = 25$ days). Also, please remember that the medication will run out sooner if the pMDI is used more often than planned.
3. Identify the date that the medication will run out and mark it on the canister or on the calendar.
4. Keep track of how many puffs of medicine administered on a daily log sheet and subtract them to determine the amount of medication left in the pMDI.
5. Keep the daily log sheet in a convenient place such as bathroom mirror.
6. Replace the pMDI when all of the puffs have been administered.

With dose counter, the user should:

1. Determine how many puffs of medicine that the pMDI has when it is full.
2. Track the pMDI actuations used and determine the amount of medication left in the pMDI by checking the counter display.
3. Learn to read the counter display. Each dose counter has a specific way of displaying doses remaining in the canister. For example, turning red indicates that the number of actuations is less than 20 puffs and it is time to refill the pMDI. Reading the manufacturer's guidelines to interpret the counter display is recommended before its use.
4. When the last dose is dispensed, properly dispose of the pMDI.

Cleaning: Please refer to the Infection Control section for the cleaning instructions for inhalers.

5. METERED-DOSE INHALER ACCESSORY DEVICES

Metered-dose inhaler accessory devices were designed to overcome the difficulties experienced when using a pMDI and are available in different forms and sizes. The use of these devices improves the effectiveness of aerosol therapy and reduces oropharyngeal deposition by adding volume and space between the metering valve and the patient's mouth. They overcome problems with hand-breath coordination.

While the term spacer is used in clinical practice to generically refer to all types of pMDI accessory devices, these devices are categorized into spacers or valved holding chambers based on their design. A spacer is a simple tube or extension device that adds space and volume between the pMDI and mouth with no one-way valves to contain the aerosol plume after pMDI actuation.

A valved holding chamber is a spacer device with one-way valve(s) to contain the aerosol inside until inhaled and to direct exhalation away from the aerosol in the chamber, reducing aerosol losses from poor hand-breath coordination. In addition to the major design difference that defines spacers versus valved holding chambers, there are other design differences among brands of holding chambers and spacers. Volume may vary, although in the United States most holding chambers/spacers are less than 200 mL. While boots are designed specific to each pMDI, the canister nozzles vary and may not fit any one specific nozzle receptacle, reducing drug efficacy. Figure 15 shows examples of spacers and holding chambers. Azmacort and InspiroEase are no longer used.



Figure 15. Examples of valved holding chambers and spacers

Spacers

The use of a spacer with pMDIs should produce at least an equivalent inhaled dose and clinical effect to that of a correctly used pMDI alone. A spacer provides additional volume that slows the aerosol velocity from a pMDI, allowing a reduction in particle size. Aerosol retention and

discharged dose depends on the size and shape of the spacer, plus electrostatic charge on the inner walls of plastic spacers. Spacers decrease oral deposition, but they only provide limited protection against poor hand-breath coordination. When using a spacer, it is important for the patient to coordinate their inhalation to occur within 1 to 2 seconds after actuating the inhaler. Spacers may be an integral part of the pMDI mouthpiece, whereas others require removal of the inhaler canister from the manufacturer’s actuator and placing it into a special opening on the spacer, such as OptiHaler® (Philips Respironics, Murrysville, PA). It is important to understand that dose delivery can be affected in some spacer designs if the device does not fit the pMDI properly or if the design uses a special opening or actuator incorporated into the spacer itself.

Occasionally, health care providers or patients construct homemade holding chambers from plastic containers (e.g., soda bottle) or other devices (e.g., empty toilet paper roll). These may function as a spacer and provide protection against reduced dose with pMDI actuation before inhalation, but they do not protect against actuation during exhalation. Also, their performance is variable, and they should not be considered as a suitable replacement for a commercially available spacer.

Valved Holding Chambers

A valved holding chamber (VHC) has a low-resistance one-way valve that allows aerosol particles to be contained within the chamber for a short time until an inspiratory effort opens the valve. Although the presence of a one-way valve prevents aerosol particles from exiting the chamber until inhalation begins, optimal aerosol dosing still depends on inhaling as close to or simultaneously with pMDI actuation into the chamber.

Time delays can significantly reduce the available dose for inhalation from a VHC. The one-way valve should have a low resistance so that it opens easily with minimal inspiratory effort. Valves placed between the chamber and the patient also act as a barrier, further reducing oropharyngeal deposition. Ideally, there should be a signal to provide feedback if inspiratory flow is too high. Children with low tidal volumes may need to take multiple breaths from a VHC through a facemask for a single pMDI actuation. In this case, the VHC should incorporate one-way valves for both inhalation and exhalation to decrease rebreathing and avoid exhaling aerosol from the chamber. A VHC with mouthpiece costs as little as \$15–\$40, and a static-free device with mask can cost as much as \$50–\$60.

Drug-delivery Technique

While spacers and VHCs provide many benefits for optimal drug delivery when used in conjunction with pMDIs, there are also potential problems with their use (see Table 9).

Table 9. Advantages and disadvantages of holding chambers or spacers (“add-on” devices) used with pMDIs (Modified, with permission, from Reference 5)

Advantages	Disadvantages
Reduced mouth/throat drug impaction and loss	Large and cumbersome compared to the pMDI alone
Increased inhaled drug by 2–4 times than the pMDI alone	More expensive and bulky than a pMDI alone
Allows use of pMDI when the patient is short of breath	Some assembly may be needed
No drug preparation required	Patient errors in firing multiple puffs into chamber prior to inhaling or delay between actuation and inhalation
Simplifies coordination of pMDI actuation and inhalation	Possible contamination with inadequate cleaning

Improper technique may decrease drug delivery or, in some cases, cause the dose to be lost. Possible causes of decreased drug delivery include multiple actuations into the device, electrostatic charge, inhaling before actuating the pMDI, or delay between actuation and inhaling the dose. In children, lack of a proper mask fit, a spacer volume that is greater than tidal volume, and crying are problematic. Proper technique is provided in Technique Box 3.

Technique Box 3. Steps for Correct Use of pMDI with Spacer/VHC

Technique for pMDIs with Spacer/VHC: The patient should be instructed to:

1. Remove the mouthpiece cover and shake the inhaler thoroughly.
2. Prime the pMDI per manufacturer's recommendation.
3. Assemble the apparatus and check for foreign objects.
4. Keep the canister in a vertical position.
5. Sit up straight or stand up.
6. Breathe all the way out.
7. Follow the instructions below based on the type of device interface used:
 - With the mouthpiece:**
 - a. Place the mouthpiece of the spacer between their teeth. Make sure that their tongue is flat under the mouthpiece and does not block the pMDI and seal their lips.
 - b. Actuate the pMDI as patient begins to breathe in slowly. Also make sure to inhale slowly if the device produces a "whistle" indicating that inspiration is too rapid.
 - c. Move the mouthpiece away from the mouth and hold breath for 10 seconds. If patient cannot hold their breath for 10 seconds, then hold for as long as possible.
 - With the mask:**
 - d. Place the mask completely over the nose and mouth and make sure it fits firmly against the face.
 - e. Hold the mask in place and actuate the pMDI as patient begins to breathe in slowly. Also make sure to inhale slowly if the device produces a "whistle" indicating that inspiration is too rapid.
 - f. Hold the mask in place while the child takes six normal breaths (including inhalation and exhalation), and remove the mask from the child's face.
8. Wait 30–60 seconds if another puff of medicine is needed.
9. Repeat steps above until the dosage prescribed by the patient's physician is reached.
10. If taking a corticosteroid, patient should rinse mouth after the last puff of medicine, spit out the water, and not swallow it.
11. Replace the mouthpiece cover on the pMDI after each use.

General Steps To Avoid Reduced or No Dosing for pMDIs with Spacer/VHC: When using pMDIs with spacer or VHC, the following steps should be taken in order to avoid reduced or no dosing during aerosol treatment. The patient should:

1. Assure proper fit of the pMDI to the spacer or VHC.
2. Remove cap from the pMDI boot.
3. Clean and reassemble the pMDI spacers and VHCs based on the manufacturers' instructions.
4. Wash and rinse the inside of the VHC before using, with warm soapy water. This will reduce/eliminate static charge (unless it is a static-free VHC).

6. DRY-POWDER INHALERS

Dry-powder inhalers (DPIs) are portable, inspiratory flow-driven inhalers that are used to administer dry-powder formulations to the lungs. DPIs do not contain propellant and are breath-actuated. The patient's inspiratory effort, both their inspiratory flow rate and the volume inhaled, creates the energy to separate the small drug particles from larger carrier particles and disperse the particles as an aerosol. DPIs coordinate release of the drug with the act of inhalation and have been developed to overcome the difficulties of using metered-dose inhalers. They are often prescribed with the goal of providing the patient with an overall more user-friendly and more predictable therapy.

Advantages and Disadvantages of DPIs

Dry-powder inhalers have both advantages and disadvantages as seen in Table 10. Because they do not require hand-held coordination, the patient's inspiratory effort must be adequate enough to draw the drug from the device, and for delivery into the airways.

Table 10. Advantages and disadvantages of DPIs

(Modified, with permission, from Reference 5)

Advantages	Disadvantages
Small and portable	Dependence on patient's inspiratory flow
Built-in dose counter	Patient less aware of delivered dose
Propellant free	Relatively high oropharyngeal impaction
Breath-actuated	Vulnerable to ambient humidity or exhaled humidity into mouthpiece
Short preparation and administration time	Limited range of drugs
	Different DPIs with different drugs
	Easy for patient to confuse directions for use with other devices

It is important for the patient to understand how the DPI works and how it should be used. For example, the patient should know that they should not exhale into the device. This will prevent the introduction of ambient humidity into the mouthpiece and the resulting negative effect to the medication. Such precautions, and others explored in greater detail below, should be considered by health care providers when prescribing a DPI. It is also very important to periodically reassess the patient's technique.

Types of DPIs

Currently, DPIs can be classified into 3 categories based on the design of their delivery device: single-dose DPIs, multiple unit-dose DPIs, and multiple-dose DPIs (Figure 16). While the single-dose DPIs have individually wrapped capsules that contain a single dose of medication, multiple unit-dose DPIs disperse individual doses that are premeasured into blister packs of medication by the manufacturer. The third type, the multiple-dose DPI, either measures the dose from a powder reservoir or uses blister strips prepared by the manufacturers to deliver repeated doses contained within the device. Regardless of the type of DPI, they all have the same essential components incorporated with the inhaler. They all have a drug holder, an air inlet, an agglomeration compartment, and a mouthpiece. The design of these components allows DPIs to induce sufficient turbulence and particle-to-particle collision that detaches particles from their carrier surface and separates larger particles into smaller particles.

Single-dose DPIs

Single-dose DPIs operate by evacuating powder medication from a punctured capsule. The Aerolizer and the HandiHaler® are examples of the single-dose DPIs (Figure 16 below). While the Aerolizer is used for the delivery of formoterol, the HandiHaler is utilized for the administration of tiotropium bromide. Although the Aerolizer and HandiHaler have different configurations, their principle of operation is similar. When using a single-dose DPI, the user places each capsule into the drug holder. Then, the user must prime the device by piercing the single-dose capsule and allowing entrainment of air into the device for dispersion with inhalation. The primary disadvantage of single-dose DPIs is the time needed to load a dose for each use. Also, patients should be instructed never to swallow the capsules.



Figure 16. Currently available dry-powder inhalers

Multiple Unit-dose DPIs

The Diskhaler® (GlaxoSmithKline, London, United Kingdom) is an example of the multiple unit-dose DPI. It is used for the administration of zanamivir through a rotating wheel that contains a case with 4 or 8 blisters of medication. Each blister is mechanically punctured when the cover is lifted, allowing the medication to be inhaled through the mouth. When using the Diskhaler, the patient's peak inspiratory flow rate must be greater than 30-60 L/min to achieve an adequate drug deposition into the lungs.

Multiple-dose DPIs

Multiple-dose DPIs measure doses from a powder reservoir or disperse individual doses through pre-metered blister strips. The most common types of multi-dose DPIs include the Twisthaler, the Flexhaler® and the Diskus. The Twisthaler is a multi-dose DPI used to deliver mometasone furoate. The Flexhaler delivers budesonide, and the Diskus administers salmeterol and fluticasone, or a combination of salmeterol and fluticasone.

In the Twisthaler and the Flexhaler, the DPI nozzle is comprised of two parts: a lower swirl chamber and an upper chimney in the mouthpiece, which produce a stronger vortex with an increased number of particle collisions for deagglomeration. When using a new Flexhaler, it should be primed by holding it upright and then twisting and clicking the brown grip at the

bottom twice. The Twisthaler does not require priming before use.

The Diskus is a multi-dose DPI that contains 60 doses of dry-powder medication individually wrapped in blisters. The blister wrap protects the drug from humidity and other environmental factors. Sliding the dose-release lever punctures the wrapped blister on a foil strip and prepares the dose for inhalation. When the Diskus cover is closed, the dose-release lever is automatically returned to its starting position. As with the Twisthaler, no priming is necessary with the Diskus.

Currently Available DPI Formulations

As seen in Figure 16, the device design largely determines whether a DPI model is a single dose (loading a single dose prior to each use), a multiple unit-dose (loading 4 or 8 blisters of medication), or a multiple-dose (containing an entire month's prescription).

Factors Affecting the DPI Performance and Drug Delivery

Health care providers and patients must actively control the following effects:

Resistance and Inspiratory Flow: Each type of DPI has a different resistance to airflow that determines how much peak inspiratory flow needs to be created in the device to release the correct amount of drug. For example, the HandiHaler has a higher resistance than the Diskus and therefore requires a greater inspiratory effort. When the patient inhales through the DPI, they create airflow with a pressure drop between the intake and exit of the mouthpiece. Thus, the patient can lift the powder from the drug reservoir, blister, or capsule depending on the model being used. The patient's inspiratory effort is also important in its breaking down of the powder into finer particles. Whereas higher peak inspiratory flow rates improve drug separation, fine-particle production, and lung delivery, excessive inspiratory flow can increase impaction on the oral cavity and thus decrease total lung deposition.

DPIs depend on the patient's ability to create adequate peak inspiratory flow rate. Very young children and patients with acute airflow obstruction due to asthma or COPD may not be able to generate an adequate peak inspiratory flow rate when using the DPI. Because very low peak inspiratory flow rates result in reduced drug delivery, especially fine-particle delivery, potential DPI patients should be evaluated for the ability to generate an optimal peak inspiratory flow rate for a particular DPI. If a patient is unable to effectively use a DPI, another aerosol device must be considered.

Exposure to Humidity and Moisture: Because all DPIs are affected by humidity and moisture, which can cause powder clumping and reduce deaggregation and fine-particle development and dispersement during inhalation, they must be kept dry. Capsules and drug blisters generally offer more protection from ambient humidity than a reservoir chamber containing multiple doses for dispensing. Therefore, designs with a reservoir chamber (e.g., the Twisthaler) should be protected from humidity and moisture as much as possible. Whereas it is easy to keep the Twisthaler out of the bathroom, avoiding use in ambient humidity is difficult if it is carried to the beach, kept in a house with no air conditioning, or left in a car. An alternative DPI design or availability of the drug in a different aerosol system (e.g., a pMDI) might be considered for such situations. All DPIs are also affected by exhaled air introduced into the mouthpiece, especially after the device is cocked and loaded and when the powder is exposed. Therefore, patients must be instructed to exhale away from the DPI prior to inhalation.

Drug-delivery Technique

Because different types of DPIs are available on the market, health care providers should carefully review operation instructions prior to giving aerosol therapy and certainly prior to instructing patients in at-home use. Proper technique is provided in Technique Box 4.

Technique Box 4. Steps for Correct Use of Each Model of DPIs

Technique for Single-dose DPIs

Aerolizer®: The patient should be instructed to:

1. Remove the mouthpiece cover.
2. Hold the base of inhaler and twist the mouthpiece counter clockwise.
3. Remove capsule from foil blister immediately before use.
4. Place the capsule into the chamber in the base of the inhaler.
5. Hold the base of the inhaler and turn it clockwise to close.
6. Simultaneously press both buttons in order to pierce the capsule.
7. Keep the head in an upright position.
8. Do not exhale into the device.
9. Hold the device horizontal, with the buttons on the left and right.
10. Place the mouthpiece into the mouth and close lips tightly around the mouthpiece.
11. Breathe in rapidly and as deeply as possible.
12. Remove the mouthpiece from the mouth and hold your breath for 10 seconds (or as long as comfortable).
13. Do not exhale into the device.
14. Open the chamber and examine the capsule; if there is powder remaining, repeat the inhalation process.
15. After use, remove and discard the capsule. Do not store the capsule in the Aerolizer.
16. Close the mouthpiece and replace the cover.
17. Store the device in a cool, dry place.

HandiHaler®: The patient should be instructed to:

1. Peel back the aluminum foil and remove a capsule immediately before using the HandiHaler.
2. Open the dust cap by pulling it upward.
3. Open the mouthpiece.
4. Place the capsule in the center chamber; it does not matter which end is placed in the chamber.
5. Close the mouthpiece firmly until you hear a click; leave the dust cap open.
6. Hold the HandiHaler with the mouthpiece up.
7. Press the piercing button once and release; this makes holes in the capsule and allows the medication to be released when you inhale.
8. Exhale away from the HandiHaler.
9. Place the mouthpiece into the mouth and close lips tightly around the mouthpiece.
10. Keep head in an upright position.
11. Breathe in at a rate sufficient to hear the capsule vibrate, until the lungs are full.
12. Remove the mouthpiece from the mouth and hold breath for 10 seconds (or as long as comfortable).
13. Exhale away from the HandiHaler.
14. Repeat the inhalation from the HandiHaler.
15. Open the mouthpiece, remove the used capsule, and dispose of it. Do not store capsules in the HandiHaler.
16. Close the mouthpiece and dust cap for storage of the HandiHaler.
17. Store the device in a cool, **dry** place.

Technique for the Multiple Unit-dose DPI

Diskhaler®: The patient should be instructed to:

1. Remove the cover and check that the device and mouthpiece are clean.
2. Extend tray and push ridges to remove tray.
3. Load medication disk on the rotating wheel.
4. Pull the cartridge all the way out and then push it all the way in until the medication disk is seen in the dose indicator. This will be the first dose that will be given to the patient.
5. Keep the device flat and lift the back of the lid until it is lifted all the way up to pierce the medication blister.

Technique Box 4. (continued)

6. Click back into place.
7. Move the Diskhaler away from your mouth and breathe out as much as possible.
8. Place the mouthpiece between the teeth and lips and make sure the air hole on the mouthpiece is not covered.
9. Inhale as quickly and deeply as possible.
10. Move the Diskhaler away from the mouth and hold breath for 10 seconds (or as long as possible).
11. Breathe out slowly.
12. If another dose is needed, pull the cartridge out all the way and then push it back in all the way in order to move the next blister into place. Then repeat Steps 4 through 12.
13. Place the mouthpiece cover back on after the treatment. Make sure the blisters remain sealed until inspiration in order to protect them from humidity and loss.

Technique for Multiple-dose DPIs

Diskus®: The patient should be instructed to:

1. Open the device.
2. Slide the lever from left to right.
3. Breathe out normally; do not exhale into the device.
4. Place the mouthpiece into the mouth and close lips tightly around the mouthpiece.
5. Keep device horizontal while inhaling dose with a rapid and steady flow.
6. Remove the mouthpiece from the mouth and hold breath for 10 seconds (or as long as comfortable).
7. Be sure not to exhale into the device.
8. Store the device in a cool, **dry** place.
9. Observe the counter for the number of doses remaining and replace when appropriate.

Twisthaler®: The patient should be instructed to:

1. Hold the inhaler straight up with the pink portion (the base) on the bottom.
2. Remove the cap while it is in the upright position to ensure the right dose is dispensed.
3. Hold the pink base and twist the cap in a counter-clockwise direction to remove it.
4. As the cap is lifted off, the dose counter on the base will count down by one. This action loads the dose.
5. Make sure the indented arrow located on the white portion (directly above the pink base) is pointing to the dose counter.
6. Breathe out normally — do not exhale into the device.
7. Place the mouthpiece into the mouth, with the mouthpiece facing toward you, and close the lips tightly around it.
8. Inhale the dose with a rapid and steady flow while holding the Twisthaler horizontal.
9. Remove the mouthpiece from the mouth and hold breath for 5 to 10 seconds (or as long as possible).
10. Be sure not to exhale into the device.
11. Immediately replace the cap, turn in a clockwise direction, and gently press down until you hear a click.
12. Firmly close the Twisthaler to assure that the next dose is properly loaded.
13. Be sure that the arrow is in line with the dose-counter window.
14. Store device in cool, **dry** place.

Flexhaler®: The patient should be instructed to:

1. Twist the cover and lift it off.
2. Hold the Flexhaler in the upright position (mouthpiece up) while loading a dose.
3. Do not hold the mouthpiece when the inhaler is loaded.
4. Twist the brown grip fully in one direction as far as it goes. It does not matter which way you turn it first.
5. Twist it full back in the other direction as far as it goes.
6. Make sure to hear a click during each of the twisting movements.

Technique Box 4. (continued)

7. Be sure not to exhale into the device.
8. Place the mouthpiece into your mouth, seal the mouthpiece with your lips, and inhale deeply and forcefully through the inhaler.
9. Remove the inhaler from your mouth and exhale.
10. Make sure that you do not blow into the mouthpiece.
11. If more than one dose is required, repeat the steps above.
12. Put the cover back on the inhaler and twist it shut.
13. Rinse your mouth with water after each dose to reduce the risk of developing thrush. Do not swallow the rinsing water.

Turdoza Pressair: The patient should be instructed to:

1. Wash and dry your hands thoroughly.
2. Remove the protective cap by gently squeezing the marked arrows on each side of the cap and pulling outward.
3. Hold the inhaler with the mouthpiece facing toward you and the green button on top. DO NOT place in your mouth yet.
4. Press the green button all the way down and release it. DO NOT hold the button down.
5. Check the control window on the device (above the mouthpiece) to ensure the color has changed from red to green, indicating the dose and device are ready for use.
6. Exhale away from the device before placing the mouthpiece into your mouth.
7. Place the mouthpiece into your mouth and breathe in quickly and deeply.
8. You will hear a CLICK when the dose is delivered, but continue with your deep breath until your lungs are filled.
9. Remove the device from your mouth and breathe out.
10. Check the control window on the device (above the mouthpiece) to ensure the color has changed from green to red. IF NOT, repeat Step 7.
11. Replace the protective cap on the mouthpiece.

General Steps To Avoid Reduced or No Dosing for DPIs: When using DPIs, the following steps should be taken in order to avoid reduced or no dosing during aerosol treatment. The patient should:

1. Read and follow the instructions for proper assembly.
2. Make sure to keep the DPI clean and **dry**.
3. Keep the DPI in proper orientation during the treatment.
4. Be sure to puncture the capsule or blister pack.
5. Do not exhale into the DPI.
6. Make sure to generate adequate inspiratory flow.
7. Track the doses remaining in the DPI.

Troubleshooting

Problem with DPIs: Malfunctioning DPIs

Causes

Incorrect DPI assembly

Failure to discharge medicine

Empty DPI

Solutions

Check the assembly and reassemble, when needed.

Replace the unit.

Check the dose counter to ensure that it is not empty. Otherwise, replace the DPI.

How Do We Know That the DPI Is Empty?

Single-dose DPI: Single-dose DPIs such as the Aerolizer and the HandiHaler use a single capsule for each dose, and only full capsules should be used when each dose is given. The capsule should be inspected following the treatment to assure that the complete dose was inhaled by the patient. If there is powder remaining, the capsule should be returned to the inhaler and inhalation should be repeated.⁶³ The capsule should be disposed of after treatment. Prescription renewal should be based on the remaining capsules.

Multiple Unit-dose DPI: The Diskhaler is a multiple unit-dose DPI with a refill disk that contains 4- or 8-unit-dose blisters.⁶⁴ Because there is not a dose counter on the DPI, doses must be tracked manually. Therefore, visual inspection will confirm use of all packets. The disk is disposed of when all the doses have been used.

Multiple-dose DPIs: Multiple-dose DPIs historically come with integrated mechanical devices that indicate the number of doses remaining in the inhaler.⁶³ The devices give a particular display when the doses are coming to an end so that a new DPI can be ordered. The dose counter of each type of multiple-dose DPI is explained in Table 11 below.

Table 11. Dose counters for multiple-dose DPIs

	Flexhaler	Twisthaler	Diskus
Dose Container	Reservoir	Reservoir	Blister Strip
Number of Doses	60 or 120	30	60
Type of dose indicator	“0”	“01”	Red numbers
Meaning of dose indicator	Although the indicator counts down every time a dose is loaded, it will not move with each individual dose but in intervals of 5 or so doses. The indicator is marked in intervals of 10 doses alternating numbers and dashes. When it is down to “0”, it must be thrown away.	The dose display showing “01” indicates the last dose of medicine in the Twisthaler and the medicine must be refilled.	The numbers turning red in the dose display indicates that there are 5 doses left. When the dose window shows “0”, there is no medicine left and the diskus should be disposed.

7. CRITERIA FOR SELECTING AN AEROSOL DELIVERY DEVICE

The selection of the delivery device is very important for optimizing the results of aerosol drug therapy. Evidence indicates that under ideal conditions, all 3 types of aerosol generators can be equally effective if they are used correctly by the patient.¹¹ The criteria to select an aerosol generator can be divided into 4 categories: patient-related, drug-related, device-related, and environmental and clinical factors.

Patient-related Factors

Age, Physical, and Cognitive Ability of Patients: An aerosol delivery device should be selected by considering the patient's age and physical and cognitive ability. Aging changes anatomic and physiologic factors such as airway size, respiratory rate, and lung volume.^{17,65-71} The patient's cognitive ability to understand how and when to use a device and drug as well as physical ability and coordination in using an aerosol delivery device should guide the selection.^{11,17,65,70,72-74,122} Aerosol devices have different requirements for proper use. For guidance about the device selection in infants and pediatrics, see Section 8 (Neonatal and Pediatric Aerosol Drug Delivery).

As for adults and the elderly who cannot manage hand-held coordination or proper inhalation technique, pMDIs may not be a good option.^{72,75-77} Also, the inability to generate sufficient peak inspiratory flow (>30–60 L/min) precludes the use of aerosol delivery devices such as DPis.^{72,78}

Preference of Patients: Patient preference is a critical factor in the selection of an aerosol delivery device and the effectiveness of aerosol therapy. Patients tend to use devices they prefer more regularly than devices they dislike.⁷⁹⁻⁸¹ Therefore, the selection of an aerosol delivery device should be tailored according to the patient's needs and preferences.

Drug-related Factors

Availability of Drug: Some drug formulations are available with only one type of inhaler. If a drug can be administered with the 3 types of aerosol delivery devices, the health care provider should select an aerosol generator based on the patient's needs and preference.^{11,22,74} Otherwise, a drug formulation that can be used with only a single aerosol device dictates which aerosol device to choose.

Combination of Aerosol Treatments: Many patients are prescribed more than one inhaled drug. In that case, using the same type of aerosol delivery device may increase the patient's adherence to therapy while minimizing the confusion caused by the use of different aerosol devices.^{11,22,82}

Device-related Factors

Convenience of Aerosol Device: Selecting the most convenient aerosol device for the patient is very important for adherence. Ease of use, shorter treatment time, portability, ease of cleaning, and maintenance required for each device should guide the selection process. For example, a rescue medication needs to be small, light, and portable so the patient can easily have it available when needed.^{64,74} Also, nebulizers may be less preferable for delivering inhaled medications as they are more expensive, require a power source, and need regular maintenance.^{64,83,84} When all other factors are equal, the most convenient device should be chosen for each patient.

Durability of Aerosol Generator: A selected aerosol device should have good durability so that it can withstand rigorous treatment and cleaning procedures every day. Devices that require extensive cleaning are not a good choice for patients unwilling to routinely clean and maintain the device.

Cost and Reimbursement of Aerosol Devices: It is very important to select an aerosol device that has the least out-of-pocket expense for the patient. Patients do not use drugs and devices they cannot afford.⁸⁵⁻⁸⁷ The costs to patients depend on the presence and type of medical insurance they have.⁷⁴ If the “best” device/drug is not one the patient can afford, the least costly aerosol device and drug combination should be identified to meet the patient’s needs. Therefore, it is important to work with the patient to identify strategies to access affordable drug/device options to meet their clinical needs. If all the other factors are constant, the least costly aerosol delivery device and drug combination should be selected.

Environmental and Clinical Factors

When and where the aerosol therapy is required can impact device selection. For example, therapy that is given routinely, once or twice a day, before or after bedtime does not need to be as portable as rescue medications that may be required at any time. Also, noisy compressors may not be good in small homes where a late-night treatment might awaken other members of the family. In environments where patients are in close proximity to other people, second-hand exposure to aerosols may be a factor, and devices that limit or filter exhaled aerosol should be selected.

8. NEONATAL AND PEDIATRIC AEROSOL DRUG DELIVERY

Aerosol drug administration differs fundamentally in infants and children. Cognitive ability (i.e., understanding how and when to use a device and drug) and physical ability (i.e., coordination needed to use that device) as well as age-related anatomic and physiologic factors (i.e., airway size, respiratory rate, lung volumes) create substantial challenges for effective aerosol delivery at each stage of development.^{65-68,88} Understanding these challenges can optimize aerosol drug delivery and its therapeutic outcomes in younger patients. This section explores the challenges and solutions that may optimize aerosol drug delivery in infants and pediatric patients.

Age and Physical Ability

Selection of an aerosol device is critical to successful aerosol therapy in infants and children.^{65,73,88} Children under the age of 3 may not reliably use a mouthpiece, making delivery via mask necessary for both nebulizers and pMDIs.⁸⁸⁻⁹² Especially at low tidal volumes, VHCs are the preferred method for pMDI delivery in infants and small children.^{90,91} Breathing patterns, inspiratory flow rates, and tidal volumes change with age. Even healthy children below 4 years of age cannot reliably generate sustained inspiratory flow rates of 30–60 L/min required for optimal use of many DPIs. Thus, the use of breath-actuated nebulizers or DPIs may not be reliable in children younger than 4 years.^{68,93}

Age and Cognitive Ability

The choice of aerosol device should be tailored to the patient's age and to cognitive ability to use the device correctly. Table 12 presents the recommended ages for introducing different types of aerosol delivery devices and their interfaces to children.^{65-67,93-96} Small-volume nebulizers and pMDIs with VHCs are recommended for use with infants and children up to 5 years of age.^{66,67,93} Since children up to 3 years of age cannot use a mouthpiece, both nebulizers and pMDIs with valved holding chambers should be administered via masks.^{66,90,91} Independent of age, an appropriately fitted facemask should be used until the child can comfortably use a mouthpiece. A child below 5 years of age may not be able to master specific breathing techniques.^{66,67,93} With low tidal volumes and short inspiratory times, breath-actuated nebulizers may increase inhaled dose compared to continuous nebulization.⁹⁷ It may take additional time to administer that dose. Also, time constraints and portability of compressor nebulizers make them less desirable for preschool children.⁶⁶ Once children reach age 4, they may have a sufficient understanding of how to use a pMDI or DPI successfully.^{68,93} It is generally accepted that the cognitive ability to control breathing and hand/breath coordination develops by age 5 or 6.^{65,66,94}

Table 12. Age guidelines for the use of various aerosol delivery devices

Type of Aerosol Generator	Age
Small-volume nebulizer with mask	≤ 3 years
Small-volume nebulizer with mouthpiece	≥ 3 years
pMDI with holding chamber/spacer and mask	< 4 years
pMDI with holding chamber/spacer	≥ 4 years
Dry-powder inhaler (DPI)	≥ 4 years
Metered-dose inhaler (MDI)	≥ 5 years
Breath-actuated MDI (e.g., Autohaler)	≥ 5 years
Breath-actuated nebulizers	≥ 5 years

Aerosol Drug Delivery in Distressed or Crying Infants

Inhaled drugs should be given to infants when they are settled and breathing quietly. Crying children receive virtually no aerosol drug to the lungs,^{89,95,98,99} with most of the inhaled dose depositing in the upper airways or pharynx and then swallowed.^{66,67,99,100} Therefore, it is essential to develop approaches that minimize distress before administering aerosol drugs. These approaches include, but are not limited to, playing games, comforting babies, and providing other effective forms of distraction.

Patient-device Interface

Even infants and small children can make known their preferences for specific devices. This should be a consideration in device selection. Using a device that is preferred by the child and parent can increase adherence, inhaled dose, and desired clinical response.

Mouthpiece or Face Mask?

Mouthpieces and facemasks are commonly used for aerosol drug delivery in children above 3 years of age. Studies suggest that the mouthpiece provides greater lung dose than a standard pediatric aerosol mask^{97,103} and is effective in the clinical treatment of children.^{97,104,105} Consequently, the use of mouthpieces should be encouraged, but a mask that is consistently used is better than a mouthpiece that is not.

Importance of a Closely Fitting Face Mask

A good facemask seal is a critical factor in achieving optimal drug deposition and avoiding aerosol getting into the eyes. Even small leaks around the facemask may decrease the amount of drug inhaled by children and infants.¹⁰⁶⁻¹¹⁰ Initially, a small child may refuse to use a facemask when feeling sick or irritable. However, parental education, play activities, encouragement to hold the mask firmly against the child's face, and close supervision can reduce poor tolerance of face masks and improve aerosol drug delivery.

Face Mask or Blow-by?

Blow-by is the administration of aerosolized drug through the nebulization port of a nebulizer that is directed toward the patient's face. Although blow-by is a technique commonly used for crying babies or uncooperative children, it has been documented that it is less efficient compared with a facemask as aerosol drug deposition decreases significantly because the distance from the device to the child's face is increased. Therefore, evidence suggests blow-by to be ineffective and its use should be discouraged.^{90,106,111,112}

Parent and Patient Education

Children may demonstrate poor adherence to aerosol drug delivery because they lack the ability to use a device correctly or contrive to use it ineffectively.^{113,114} As children grow and their therapy needs change, they need to be taught the best techniques for the use and maintenance of aerosol devices. Therefore, the effects of medications prescribed, the importance of aerosol therapy, and the proper use of aerosol delivery devices should be explained to the patient and the parent. After initial training is provided, frequent follow-up demonstrations are essential to optimize aerosol drug delivery and adherence to prescribed therapy in infants and children.

9. INFECTION CONTROL

Certain aerosol devices can become contaminated with pathogens from the patient, the care provider, and the environment. For example, the contamination of small-volume nebulizers has been documented in patients with cystic fibrosis,²⁴⁻²⁶ asthma,^{27,28} and immunodeficiency.¹¹⁵ In the absence of infection control, an aerosol device will be contaminated and may cause bacterial colonization in the respiratory tract.^{24-26,29,116} Therefore, it is essential to establish a management system that will reduce nosocomial infections, length of stay in the hospital, and costs associated with hospitalization.^{28,116,117}

Patient Education and Awareness

Patient Education: It has been well documented that drug delivery devices (most notably SVN) used at home are frequently contaminated with bacteria.^{27,28,118,119} Therefore, health care providers must emphasize to patients and caregivers through repeated instruction the importance of appropriately cleaning and periodically disinfecting aerosol equipment. Written instructions should also be provided and reviewed frequently at subsequent encounters.

Patient Adherence: Approximately 85% of patients with cystic fibrosis fail to disinfect their nebulizers at home.¹²⁰ It has been determined that in addition to the constraints of cleaning and disinfecting instructions provided by the manufacturers, adherence can be influenced by personal, socio-cultural, and psychological factors.¹²¹ Changing jet nebulizers every 5 days, using disposable equipment with health insurance approval, and partnering with patients to increase adherence can increase patient compliance to infection control and minimize the risk of infection.⁸⁰

Cleaning and Maintenance of Aerosol Delivery Devices

Preventing Infection and Malfunction of Home Aerosol Devices: Cleaning instructions for the different types of aerosol devices vary and are given below.

- **Pressurized Metered-dose Inhalers:** The plastic container of pMDIs should be cleaned at least once a week^{122,123} as shown in Table 13.

Table 13. Cleaning pMDI plastic containers

Cleaning the pMDI

Frequency of cleaning: Once a week and as needed.
Observe the area where the drug sprays out from the inhaler.
Clean the inhaler if powder is present in or around the hole.
Remove the pMDI canister from the plastic container so it does not get wet.
Rinse the plastic container with warm water and shake out to remove excess water.
Place on a clean paper towel and dry overnight.
Replace the canister back inside the pMDI and recap the mouthpiece.

Cleaning the Autohaler

Frequency of cleaning: Once a week and as needed.
Remove the mouthpiece cover.
Turn the Autohaler upside down.
Wipe the mouthpiece with a clean, dry cloth.
Gently tap the back of the Autohaler so the flap comes down and the spray hole can be seen.
Clean the surface of the flap with a dry cotton swab.
Recap the mouthpiece and make sure that the lever is down.
May need to use a small needle to remove the debris from the inhaler orifice (frequently seen in ProAir HFA)

- **Metered-dose Inhaler Accessory Device:** When a valved holding chamber is used with a pMDI, it should be cleaned before first use and then periodically cleaned based on the manufacturers' suggestions. Table 14 provides the steps that are used for cleaning the pMDI accessory device.

Table 14. Cleaning instructions for pMDI accessory device

Cleaning the Chamber Device

Frequency of cleaning: Once a week or more often as needed.

Disassemble the device for cleaning.

Soak the spacer parts in warm water with liquid detergent and gently shake both pieces back and forth.

Shake out to remove excess water.

Air dry spacer parts in the vertical position over night.

Do not towel dry the spacer as this will reduce dose delivery because of static charge.

Replace the back piece on the spacer when it is completely dry.

- **Dry-powder Inhaler:** It is important to note that moisture of any type will decrease the drug delivery of DPIs. For this reason, DPIs should not be submerged in water and should be kept as dry as possible. Patients should be advised to periodically wipe the mouthpiece of the DPI with a clean, dry cloth and to follow the recommendations of the manufacturer for periodic cleaning.
- **Nebulizers:** In the home, nebulizers should be cleaned after every treatment. Proper cleansing of nebulizer equipment reduces infection risk. Parts of the aerosol drug delivery device should be rinsed and then washed with soap and hot water after each treatment, with care taken not to damage any parts of the compressor unit. Table 15 provides the cleaning instructions for the jet nebulizer. Ultrasonic nebulizers should be cleaned and disinfected based on the manufacturers' recommendations.

Table 15. Cleaning instructions for the jet nebulizer

Cleaning After Each Use

Wash hands before handling equipment.

Disassemble parts after every treatment.

Remove the tubing from the compressor and set it aside.

Note: Tubing should not be washed or rinsed.

Rinse the nebulizer cup and mouthpiece with warm running water or distilled water.

Shake off excess water.

Air dry on an absorbent towel.

Once completely dry, store the nebulizer cup and mouthpiece in a zip lock bag.

Disinfection: In order to minimize contamination, jet nebulizers should be periodically disinfected and replaced. Each manufacturer suggests a different method of disinfection for its product, and these steps should be followed per the manufacturers' guidance. Nebulizers used in the office setting should be discarded after each patient use. Nebulizers used in the home setting should be disinfected once or twice a week using one of the methods listed below.

- Soaking nebulizer parts in a solution of 1 part distilled white vinegar and 3 parts warm water for at least 30 minutes, or
- Soaking nebulizer parts in a commercial quaternary ammonium compound (e.g., Control III) for 10 minutes.

Note: Mixing the concentrate Control III with water can make a quaternary ammonium solution. Control III can be purchased from any home care company.

- Final Rinse: Plain tap water (not distilled or bottled) should be used for the final rinse.¹²³

Drying and Maintenance: Because bacteria grow in wet moist places, nebulizers should be thoroughly dried and stored in a clean, dry place between treatments. Allowing gas flow from the compressor to the nebulizer for a short time after it is rinsed can reduce drying time. It has been reported that nebulizer performance may change over time due to incorrect cleaning, maintenance, or disinfection procedures.¹²⁴ Nebulizers can be kept from being contaminated by following the manufacturers' instructions for care and cleaning. This is necessary for all aerosol devices used for inhaled medication. Finally, air compressor filters should be replaced or cleaned according to manufacturers' recommendations.

Preventing Infection and Malfunction of Aerosol Generators at Hospitals or Clinics:

- **Aerosol Generators:** If an aerosol generator is labeled "For Single Patient Use," it should be used on a single patient and then discarded.
- **Inhaled Drugs:** Multi-dose liquid drug containers have been associated with contaminated nebulizers and are a potential source of the spread of nosocomial infections.¹²⁵⁻¹²⁸ Therefore, unit-dose medications are recommended whenever possible.¹²⁹ Also, it is important to avoid contaminating drug solutions.
- **Infection Transmission:** The transmission of infection from health care provider to patient can be reduced with good hand-hygiene techniques such as washing with soap and water or with the use of alcohol-based hand sanitizers before and after providing treatment.^{130,131} The use of gloves should be considered an adjunct to hand hygiene. However, since gloves create a warm and moist environment that can support the growth of microbial contamination, providers must change gloves between patients and clean hands after gloves are removed.^{132,133} Placing a filter on the exhalation part of a nebulizer may provide protection from infection and reduce secondhand aerosol breathing in hospitals and outpatient clinics.

10. EDUCATING PATIENTS IN CORRECT USE OF AEROSOL DEVICES

A number of problems can occur with patient use of aerosol devices. Knowledge of these problems can help the health care provider better instruct patients and assist them in evaluating those patients with poor management of airways disease. Poor patient adherence to prescribed aerosol therapy or errors in the use of aerosol devices can dramatically reduce the effectiveness of inhaled drug therapy. Both of these problem areas should be evaluated and, if possible, ruled out in a patient who presents with poor control of their airway disease before other changes in their disease management are initiated.

Patient Adherence and Outcomes

A general concern with the use of inhaled medications is patient adherence with prescribed use. This problem is not unique to inhaled drugs; across all chronic illnesses, patients take only approximately 50% of medications prescribed for those conditions.¹³⁴ “Adherence” refers to a patient’s choice to follow a prescribed therapy, whereas “compliance” suggests passive following of the orders of a health care provider. Of course, patient adherence to treatment is preferable as it is founded on a therapeutic partnership between the patient and the health care provider.

With regard to inhaled therapy, a retrospective review of the literature demonstrates that 28-68% of patients do not use the MDIs or DPIs correctly.^{14,135} Continued regular contact with the health care team helps ensure proper device use, which has been shown to deteriorate over time.¹³⁵ Adherence rates have also been shown to drop with an increase in the degree of difficulty in using an inhaler device if the number of inhalers prescribed increases or if the required number of doses increases.¹³⁶

There are several important factors that can influence adherence and outcome. They include, but are not limited to, individual characteristics and circumstances, the degree of adherence to the treatment plan, and the quality of the patient/provider relationship. Individual patient characteristics include numerous factors with variable impact. These are psychosocial as well as situational. Patient characteristics can potentially influence a patient’s ability to properly use specific inhaling devices. For example, patients with COPD represent a medically diverse population, each with unique characteristics such as lung function, comorbidities, differing levels of cognitive function, hand strength, and lifestyle settings. All of these can impact adherence to therapy, therapeutic outcomes, and quality of life.¹⁴ It has been reported in the literature that a patient’s preference for a device closely correlates to correctness in device handling. Probability of errors is lower if the device is perceived as easy to use and therefore preferred by patients.¹³⁷

There is also emerging evidence to suggest an association between depression and medication non-adherence, which health care professionals need to consider when interacting with patients. Smith et al studied adherence to therapy after discharge in patients hospitalized with asthma and found that depression was associated with an 11.4-fold higher likelihood of non-adherence to therapy compared to those without depression.¹³⁸ Another study reported a 49% overall prevalence of psychiatric disorders in patients with COPD, resulting in a reduced confidence in their ability to control respiratory symptoms.¹³⁹ A high prevalence of psychological disorders among COPD patients has been associated with functional disability and reduced quality of life, leaving these patients more likely to be depressed, to feel unsupported by clinic staff, and to be non-adherent.¹⁴⁰

Non-adherence to medication regimens can be related to practical issues such as difficult access to a pharmacy, lack of or cost of transport, immobility, and problems related to side-effects. Adherence may also be adversely affected if the patients believe they cannot afford the costs associated with prescription medication or are not eligible for free prescriptions. Utilization of generic drugs may be beneficial in these instances where patients can fill prescriptions at local retailers that offer a 30-day supply on hundreds of generic prescriptions for \$4, or a 90-

day supply for \$10. National prescription assistance programs for low-income families are also available and include the Partnership for Prescription Assistance and the Together RX Access Program. These programs each have specific participation requirements, but all require that patients show evidence to support limited income.

In Medicare beneficiaries with COPD, out-of-pocket inhaler costs were found to be a significant barrier to adherence with inhaled medications, even after the implementation of Medicare Part D.¹⁴¹ One study found that patients with newly diagnosed COPD or asthma were 25% less likely to initiate inhaled corticosteroids if a co-payment or deductible was required.¹³⁶ These findings underscore the need for clinicians to ascertain if their patients who use inhalers have difficulty paying for them so that therapies can be adjusted and referrals can be made to prescription assistance programs.

An additional factor is the patient/health care provider relationship. The knowledge medical caregivers provide to patients about evidence-based guideline recommendations along with their willingness to systematically educate patients can both positively impact the patient-health care provider communication.¹³⁶

A study by Cabana et al identified that primary care pediatricians did not routinely provide asthma education in accordance with the National Asthma Education and Prevention Program's EPR-3 asthma guidelines and also triaged which families received additional asthma education rather than education for all.¹⁴²

Health care providers rely on their patients to inform them of symptoms, concerns, general well being, and response to treatment. Patients, in turn, rely on health care providers to monitor their disease, provide appropriate treatment, and explain their disease management strategy. Unfortunately, this balance is often difficult to achieve. Considerable communication gaps between physicians and patients were identified in The Asthma Control and Expectations survey conducted in the United Kingdom. This survey involved more than 1,000 patients with asthma. Findings revealed that 89% of patients did not discuss with their physician the impact their asthma symptoms had on their lifestyle.^{134,136}

Time and resource constraints challenge the ability of health care providers to provide quality disease management education in the primary care setting. However, regular contact between the patient and health care team presents an opportunity for health care providers and patients to reassess the status of the patient's condition (physical, psychological, and cognitive abilities), and to determine whether a change in the treatment or the inhaler device is warranted. Worsening symptoms or increasing frequency of exacerbations may not always indicate disease progression but may instead indicate a patient's inability to use an inhaler device optimally.^{14,143}

Simple interventions such as making an effort to ensure continuity of care by contacting patients who miss appointments, simplifying treatment regimens, providing individualized counseling and instruction — which includes the family or significant other — and close follow-up and supervised self monitoring may improve treatment outcomes for both short and long term.

For the chosen therapy to be optimal, it must be individualized for the patient's disease state, medical needs, lifestyle, and personal preferences.¹⁴ It must be patient-centered and should include (1) understanding the patient's desire to focus on personalized care according to their needs and values, and (2) anticipating services based on evidence-based guidelines.

One major problem associated with adherence is incorrect technique when using aerosol devices. Unfortunately, there is no perfect or error-proof drug delivery device on the market today. Critical device handling errors can be minimized when health care providers (1) instruct patients in the essential steps required for adequate drug delivery via inhalation devices and (2) observe patient return demonstrations. It is not enough to simply refer patients to device instructions. The pMDI is recognized as a difficult inhaler for patients to use without proper training. Even holding chambers and spacers introduced to address these issues present additional problems. DPIs were also introduced, in part, with the rationale that their use would be

simpler than a pMDI.¹⁴⁴⁻¹⁴⁵ Nebulizers are probably the simplest inhaler type for a patient to use if we assume that assembly, proper cleaning, and maintenance are not problems. However, there can be problems with all types of inhaler devices. Table 16 lists the common errors and mistakes that can occur with each type of device.^{121,144,145}

Table 16. Common problems, disadvantages, and errors with each type of aerosol generator
(Modified, with permission, from References 5 and 122)

Pressurized Metered-dose Inhalers
Errors in technique: <ul style="list-style-type: none">• Failure to coordinate pMDI depression (actuation) on inhalation• Too short a period of breathhold after inhalation• Too rapid an inspiratory flow rate• Inadequate priming/shaking/mixing before use• Abrupt discontinuation of inspiration as aerosol hits throat• Actuating pMDI at point that lung is expanded (total lung capacity)• Actuating pMDI prior to inhalation• Firing pMDI multiple times during single inhalation• Firing pMDI into mouth but inhaling through nose• Exhaling during actuation• Putting wrong end of inhaler in mouth• Holding canister in the wrong position• Failing to remove cap before use• Excessive use of pMDI beyond rated capacity (loss of dose count)• Failure to clean boot• Wasting of remaining doses Lack of adequate patient training in use of pMDI Impairment of thinking abilities of users Lack of adequate hand strength or flexibility to activate pMDI
Valved Holding Chambers/Spacers
Incorrect assembly of add-on device Failure to remove electrostatic charge in non-electrostatic holding chambers/spacers, which can decrease emitted dose in new holding chamber/spacer Lengthy delay between pMDI actuation and inhalation from holding chamber/spacer Inhaling too rapidly Firing multiple puffs into holding chamber/spacer before inhaling Lack of patient instruction in assembly or use
Dry-powder Inhalers
Errors in technique: <ul style="list-style-type: none">• Not inhaling through device correctly while loading dose• Failure to pierce or open drug package• Using the inhaler in wrong manner (orientation)• Failure to prime• Exhaling through the mouthpiece• Not exhaling completely (to residual volume) before inhaling• Not inhaling forcefully enough• Inadequate or no breathhold• Exhaling into mouthpiece after inhaling Use of multi-dose reservoir designs in high ambient humidity that can reduce fine particle dose Lack of patient instruction in assembly or use
Nebulizers
Failure to assemble equipment properly Spillage of dose by tilting some nebulizers Failure to keep mouthpiece in mouth during nebulization Failure to mouth breathe

Common Patient Errors with pMDIs

Although poor hand-breath coordination with a pMDI has long been recognized as a problem, there are a number of other potential mistakes a patient can make when using a pMDI (Table 16). Failure to shake a pMDI before each use can interfere with correct drug release. Failure to prime a pMDI can also affect correct drug release. A very practical problem and a real inconvenience for users is the lack of a built-in dose counter to indicate when a pMDI is empty. Dose counters are commercially available, but this may involve purchasing an additional item. In one survey, 72% of patients said they continued to use their pMDI until there was no sound when it was actuated.⁸⁷ A pMDI can continue to produce a spray with propellant but little or no drug if it is actuated after its rated capacity, whether that is 120 or 200 puffs. Health care providers should instruct patients on the importance of tracking the number of doses remaining in the pMDI.

Common Patient Errors with Holding Chambers/Spacers

Common errors that can occur with valved holding chambers/spacers are also listed in Table 16. Incorrect assembly of the holding chamber/spacer is a potential problem. Many patients mistakenly believe that pausing before inhaling from a valved holding chamber/spacer after the MDI is actuated has no effect on the delivered dose. This technique can cause reduced drug availability. The ideal technique is to place the mouthpiece between the lips and take a slow, deep inhalation beginning when the pMDI is actuated. Available dose can also be reduced if multiple puffs are fired into a valved holding chamber/spacer followed by a single inhalation.

An electrostatic charge may be present on the inside walls of new plastic valved holding chambers/spacers. This results in the aerosol particles from the newer HFA pMDI clinging to the inside walls and is known as an electrostatic drug loss since the drug clinging to the walls is not inhaled. Electrostatic charge can be minimized by soaking the spacer/valved holding chamber in a mixture of 3-4 drops of common liquid dish detergent in 2-3 cups of lukewarm water. After soaking for 5-10 minutes, only rinse the detergent from the mouthpiece and the outside of the spacer/valved holding chamber. Next, allow the spacer/valved holding chamber to air dry so the dried detergent coats the inside and creates a barrier to the clinging particles. Another way to reduce electrostatic loss is to actuate the pMDI 10-20 times into the spacer/valved holding chamber before taking a treatment.^{37,146} However, this strategy is wasteful and expensive. An alternate strategy is to purchase a spacer/valved holding chamber that has been specially manufactured to resist electrostatic charges. This feature should be listed on the device itself or on the product literature.

Common Patient Errors with DPIs

Problems have also been identified with patient use of DPIs (Table 16). Error rates, defined as failure to correctly perform an essential step, have been shown to be similar for pMDIs and DPIs.³⁸ One of the unfortunate aspects of DPIs is that the models currently available in the United States all have a somewhat different design. They look different, and there are differences in the details of cocking and loading the DPIs.¹⁴¹ One of the highest error rates is failing to hold the device correctly, which is an aspect of loading and cocking the device for use. Should a patient drop or tilt a device like the Diskus after cocking and loading, a second cock and reload will be required to ensure the correct dose.

Common Patient Errors with SVNs

The usual problems cited with SVNs are not problems of patient use but rather general disadvantages with this type of aerosol device (Table 16). Disadvantages include bulk and size of equipment, need for external power source (compressed gas or electricity), and lengthy treatment times. Of all the inhaler devices, however, nebulizers are the simplest for patients to use. Patients use normal tidal breathing and approximately 60-90 inhalations (with most devices) to inhale the aerosol. In addition, newer nebulizer technology is directed at reducing the overall

size of devices, eliminating the need for an external power source, providing shorter treatment times, and eliminating drug loss during exhalation.

Instructing and Evaluating Patients in the Use of Inhaler Devices

There is an increasing variety of aerosol devices and operation, even within the same category of device type (e.g., DPIs). Confusion and errors of use can result. The following general steps are recommended for clinicians to ensure correct patient use:

1. Review device instructions carefully and practice with a placebo device prior to teaching others.
2. Demonstrate assembly and correct use of device to patients using a checklist.
3. Provide the patient with written instructions on how to use the device and include a written plan for use of the medication (frequency based on symptoms).
4. Have the patient practice using the device while being observed by the clinician, and repeat this returned demonstration at every patient visit.
5. Review patient use of the device at each return visit.
6. Review the patient's understanding of the inhaled medications at each return visit (when to use, purpose of drug, prescribed frequency).
7. Have a high index of suspicion for incorrect use or non-adherence if poor management of airway disease occurs.

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LIST OF ACRONYMS AND TERMINOLOGY

Acronyms

AAD	adaptive aerosol delivery
CDER	Center for Drug Evaluation and Research
CFC	chlorofluorocarbon
DPI	dry-powder inhaler
FDA	U.S. Food and Drug Administration
HFA	hydrofluoroalkane
ICS	inhaled corticosteroids
LABA	long-acting beta agonist
MDI	metered-dose inhaler
pMDI	pressurized metered-dose inhaler
SABA	short-acting beta agonist
SVN	small-volume nebulizer
VHC	valved holding chamber

Terminology

Definitions of key terms used in aerosol drug delivery are listed below in alphabetical order.

aerosol: a suspension of liquid and solid particles produced by an aerosol generator such as the small-volume nebulizer (SVN), the pressurized metered-dose inhaler (pMDI), or the dry-powder inhaler (DPI)

aerosol deposition: process of aerosol particles depositing on absorbing surfaces

aerosol generator: a device used for producing aerosol particles

aerosol output: mass of medication exiting an aerosol generator

aerosol therapy: delivery of solid or liquid aerosol particles to the respiratory tract for therapeutic purposes

chlorofluorocarbon (CFC): a liquefied gas propellant, e.g., Freon, originally used in pMDIs (Its use was banned due to concerns over depletion of the ozone layer.)

dry-powder inhaler (DPI): an aerosol device that delivers the drug in a fine, micronized powder form, typically with a breath-actuated dosing system

fine-particle fraction (FPF): percentage of the aerosol between 1–5 microns (μm) that deposits in the lung

hydrofluoroalkane (HFA): A nontoxic liquefied gas propellant developed to be more environmentally friendly than CFCs and used to propel the drug from a pMDI

inhaled dose: the proportion of nominal or emitted dose that is inhaled

inhaler: device used to generate an aerosolized drug for a single inhalation

nebulizer: an aerosol generator producing aerosol particles from liquid-based formulations (There are two classes of nebulizers – jet nebulizers and electronic nebulizers.)

nominal dose: the total drug dose placed in the nebulizer

plume: a bolus of aerosol leaving the pMDI or other aerosol devices

pressurized metered-dose inhaler (pMDI): a drug device combination that dispenses multiple doses by means of a metered valve

spacer: a valveless extension device that adds distance between the pMDI outlet and the patient's mouth

valved holding chamber (VHC): a spacer with a one-way valve used to contain aerosol particles until inspiration occurs

LIST OF FIGURES, TABLES, AND TECHNIQUE BOXES

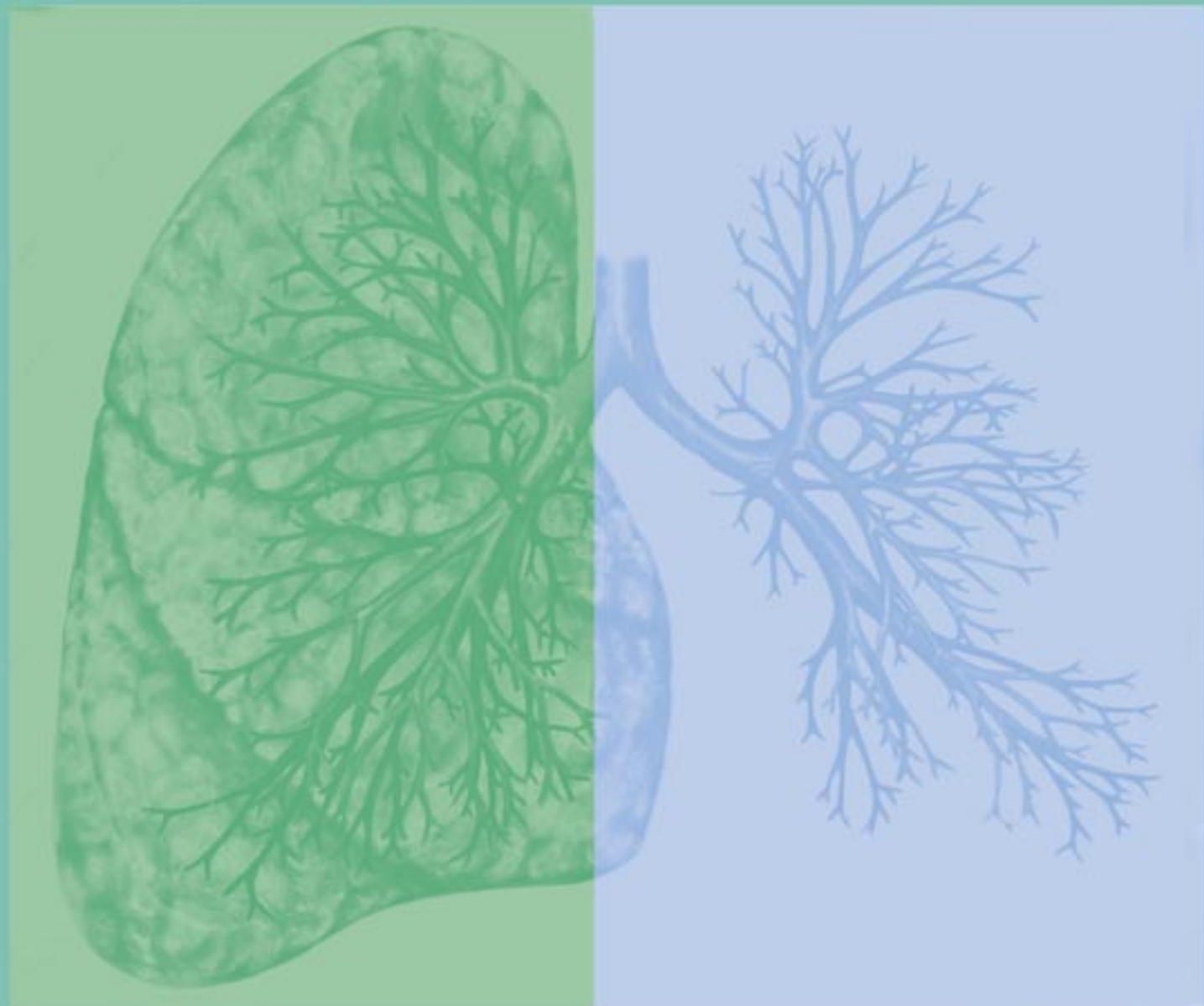
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Produced in collaboration with the
American Association for Respiratory Care



Supported by an educational grant from Philips Respironics

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