Pulmonary Disease Aerosol Delivery Devices

A Guide for Physicians, Nurses, Pharmacists, and Other Health Care Professionals

3rd Edition

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With a Foreword by
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Executive Director/Chief Executive Officer
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Foreward

The American Association for Respiratory Care (AARC) is happy to release the third edition of "Pulmonary Disease Aerosol Delivery Devices, A Guide 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 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, pressurized 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
Executive Director/Chief Executive Officer
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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.)

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.

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: A FACE MASK IS NEEDED WITH PHYSICAL OR COGNITIVE LIMITATIONS; CHILDREN REQUIRE ADULT ASSISTANCE FOR ACTUATION.	Canister nozzle can become obstructed if not periodically rinsed	Canister nozzle can become obstructed if not periodically rinsed

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
NOTE: ALL PATIENTS MUST BE CAPABLE OF GENERATING A MINIMUM PEAK INSPIRATORY FLOW RATE OF 30 L/MIN.	Difficult to contaminate	Difficult to use by very young and old

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
NOTE: A FACE MASK IS NEEDED WITH PHYSICAL OR COGNITIVE LIMITATIONS; CHILDREN REQUIRE ADULT SUPERVISION.	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

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 anticholinergic 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 onset 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 (ICS) 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 dyspho-

nia. 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 2017. Available at http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/ Accessed December 12, 2017

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Rau JL. The inhalation of drugs: advantages and problems. Respir Care 2005; 50(3):367-382.

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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 chronic obstructive pulmonary disease in 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 bronchodilation medication allowing for rapid reversal of acute bronchoconstriction
- Reduced incidence of systemic side effects related to lower bioavailability of systemic drugs.[1]

The National Heart, Lung, and Blood Institute (NHLBI), National Asthma Education and Prevention Program (NAEPP); World Health Organization (WHO); and 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 (NAEPP 2007, WHO 2016, GOLD 2017). As new macromolecular medications are developed, patients with nonrespiratory 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, the clinical situation, and the patient. To maximize the advantages of inhaled medications, the device selected should:

- Produce an accurate and consistent dose
- Appropriately transport aerosolized drug to the lungs
- Minimize oropharyngeal deposition and systemic side effects
- Be easy to administer
- Be cost effective.[1]

Inhaled drug therapies are the cornerstones of obstructive lung disease management.[2,3] Aerosol delivery devices have characteristics that can influence adherence, patient satisfaction, and clinical outcomes. Prescribing the appropriate aerosol device requires evaluation of patient variables, including selection to best meet patient clinical requirements, barriers to optimal administration, and ability for appropriate understanding and skill. The aim of inhaled therapy is to deliver agents directly to the lungs, rapid onset of action, and a lower required dose than systemic administration minimizing the potential for treatment-related adverse effects.[4]

Factors Affecting Aerosol Drug Deposition

Particle Size and Medication Properties

Drug deposition within the lung is influenced by multiple factors. Inhaled drug particles will deposit in different regions of the lung depending on the particle size. Particles <1 µm generally reach the peripheral airways and alveoli or are exhaled. Particles 1–5 µm will deposit in the large and conducting airways, while particles >5 µm will predominately deposit in the oropharynx. Particles that are 1–2 µm are optimal for deposition in the alveolar area.[5] The greater percentage of drug that is within the 1–5 µm range, the greater the potential for effective aerosol therapy. See Figure 1.

In order for inhaled drugs to reach the targeted receptors, they must penetrate the mucous layer and airway

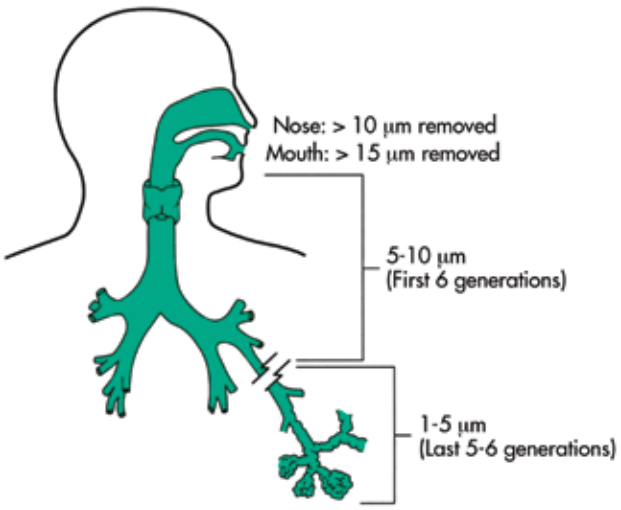


Figure 1. A simplified view of the effect of aerosol particle size on the site of preferential deposition in the airways
(From Reference 6, with permission)

mucosa. Ultimately, 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 anatomical structures of the lung 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.

Mucus plugging or atelectasis seen in cystic fibrosis or other mucus-producing diseases may also compromise effective distribution of particle depositions. 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.

Lung function plays a vital role in drug delivery. Anatomical changes occur with aging causing differences in airway geometry influencing drug deposition in the lungs. Additional factors of drug deposition include properties of medication to be delivered, type of aerosol generator used, patient technique, preference, and acceptance of the aerosol delivery device.[1]

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 below.

- **Small-Volume Nebulizer (SVN):** 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 (pMDI):** 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. The metering valve is designed to deliver a precise aerosol amount (20–100 µL) each time the device is actuated.[7]

  Pressurized metered-dose inhalers 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 should be used to improve medication delivery. These devices attach to the pMDI and temporarily hold the dispensed dose of medication, promoting better drug deposition. The chamber length increases the distance that drug particles travel from the pMDI mouthpiece to the patient's mouth.

  There are several valved holding chambers and spacers available with and without masks and are available by prescription. Patients need to be aware that while the pMDI itself is often covered by insurance, valved holding chambers and spacers may not be on the insurance formulary. Prescriptions must be written as a valved holding chamber and not a spacer, to assure the patient receives the best device for appropriate drug deposition.

- **Dry-Powder Inhaler (DPI):** The DPI is an aerosol device that delivers drugs 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.[6,8–11] For example, using proper technique, approximately 20-40 µg will reach the lung when administering a 200 µg dose of medication. 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.[8] 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.

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.

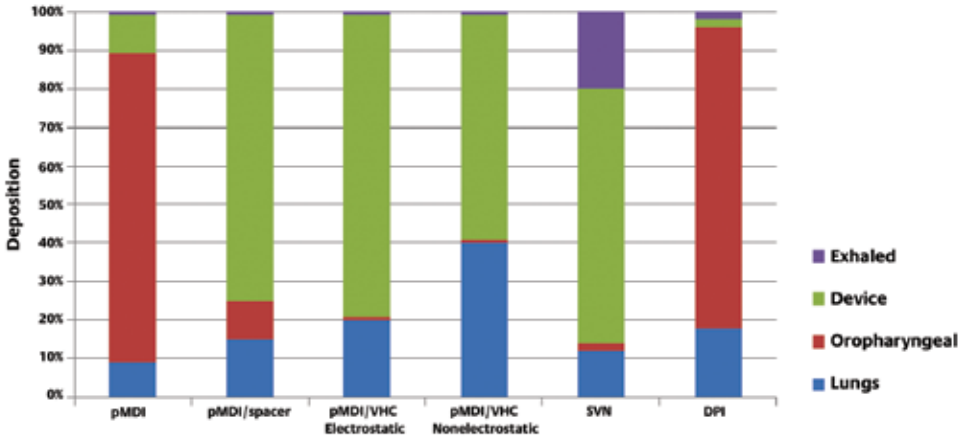


Figure 2. Drug deposition with common aerosol inhaler devices. Shown by color are the varying percentages of drug lung deposition and drug loss in the oropharynx, device, and exhaled breath.

pMDI = pressurized metered-dose inhaler; VHC = valved holding chamber; SVN = small-volume nebulizer; DPI = dry-powder inhaler
(Modified, with permission, from References 9 and 12)

Table 1. Differences in nominal (total) dose between a pMDI and an SVN for different drug formulations (Modified, with permission, from Reference 13)

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.[14] For bronchodilators, the same clinical response is often achieved with the labeled dose from the pMDI, despite the higher nominal dose for the nebulizer. Each device, if administered correctly, can be effective for achieving good clinical outcomes.

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.[15] A new device, the Respimat® inhaler, has shown lung depositions as high as 40%.[16] 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 physical and cognitive) 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 prescribed, 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.[17]

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.[18] 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.

Aerosolized drugs and delivery devices are not without shortcomings. Advantages and disadvantages associated with their use are summarized in Table 2 (on page 12).

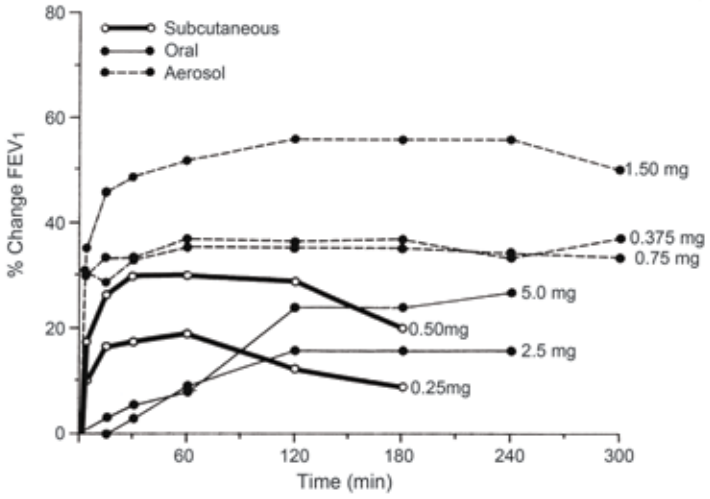


Figure 3. Changes in FEV_1 for 3 different routes of administration with terbutaline. Greater clinical effect was seen with drugs delivered as inhaled aerosol from a pMDI, compared to similar or larger doses delivered orally or by subcutaneous injection.
(From Reference 19, with permission)

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: Inhaled medications should be administered with caution. Most hazards associated with aerosol therapy are attributed to adverse reactions to the drug being used. Adverse reactions include headache, insomnia, and tachycardia and/or nervousness with adrenergic agents, local topical effects with anticholinergics, and systemic/local effects of corticosteroids.[20-21] 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.[21-23] If bronchospasm occurs during aerosol therapy, then therapy should immediately be discontinued. 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.[24-26] An increase in drug concentration may be due to evaporation,

Table 2. Advantages and disadvantages of the inhaled aerosolized drugs

(Modified, with permission, from Reference 1)

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.

heating, or the inability to nebulize suspensions efficiently.[21,23,26-27] 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.[28-33] The risk of transmission of an infection is dependent upon the duration of exposure to 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. 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.[34-36]

Currently Available Aerosol Drug Formulations

Some aerosol drugs are available in more than one formulation. New aerosol drugs are 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.

Table 3. Currently available aerosol drug formulations with corresponding inhaler devices and costs for use in the United States.

HFA = hydrofluoroalkane; pMDI = pressurized metered-dose inhaler; SVN = small-volume nebulizer; DPI = dry-powder inhaler
Cost information from www. goodrx.com. Prices used were from WalMart in 2017.

Short-Acting Bronchodilator

Drug	Brand	Device	Strength	Doses	Cost	Cost/Dose
Albuterol Sulfate	AccuNeb®	SVN	0.63	25	$50.20	$2.01
			1.25	25	$50.20	$2.01
	Albuterol Sulfate	SVN	2.5	25	$15.30	$0.61
	ProAir® HFA	pMDI		200	$58.99	$0.30
	ProAir RespiClick®	DPI		200	$55.73	$0.28
	Proventil® HFA	pMDI		200	$73.74	$0.37
	Ventolin® HFA	pMDI		200	$56.42	$0.28
Levalbuterol	Xopenex® Inhalation Solution	SVN	0.31/3ml	24	$39.16	$1.63
			0.63/3ml	24	$39.16	$1.63
			1.25/3ml	24	$39.16	$1.63
			1.25/0.5ml	24	$23.08	$0.96
	Xopenex HFA™	pMDI		200	$61.61	$0.31

Table 3. (continued)

Short-Acting Bronchodilator (continued)

Drug	Brand	Device	Strength	Doses	Cost	Cost/Dose
Ipratropium Bromide	Ipratropium Bromide	SVN	vial	25	$4.57	$0.18
	Atrovent HFA®	pMDI		200	$331.32	$1.66
Ipratropium Bromide and Albuterol Sulfate	Ipratropium Bromide and Albuterol Sulfate	SVN		120	$59.57	$0.25
	DuoNeb®	SVN		120	$284.54	$2.37
	Combivent® Respimat®	pMDI		120	$336.97	$2.81

Long-Acting Bronchodilator

Drug	Brand	Device	Strength	Doses	Cost	Cost/Dose
Aclidinium Bromide	Tudorza Pressair®	DPI	400 mcg	60	$318.10	$5.30
Arformoterol	Brovana®	SVN	15 mcg/2ml	30 60	$457.06 $907.12	$15.24 $15.12
Formoterol	Perforomist®	SVN	20 mcg/2ml	60	$873.92	$9.57
Indacaterol	Arcapta®	DPI	75 mcg	30	$227.70	$7.59
Salmeterol	Serevent®	DPI	50 mcg	60	$340.31	$5.67
Tiotropium	Spiriva® Spiriva Respimat® Spiriva Respimat®	DPI pMDI pMDI	18 mcg 1.5 mcg 2.5 mcg	30 30 30	$359.25 $359.25 $359.25	$11.98 $11.98 $11.98
Olodaterol	Striverdi Respimat®	pMDI	2.5 mcg	60	$180.74	$3.01
Umeclidinium	Incruse® Ellipta®	DPI	62.5 mcg	30	$314.17	$10.47
Glycopyrrolate	Seebri Neohaler	DPI	15.6 mcg	60	$313.67	$5.23
Glycopyrrolate	LONHALA MAGNAIR	VMN	25mcg	60	$1189.85	$19.80

Mucoactive Drugs

Drug	Brand	Device	Strength	Doses	Cost	Cost/Dose
Dornase Alpha	Pulmozyme®	SVN	2.5mg/2.5ml	30	$3173.13	$105.77
N-Acetylcysteine		SVN	4ml/10%	1	$2.46	$2.46
			10ml/10%	1	$4.16	$1.64
			30ml/10%	1	$9.81	$1.31
			4ml/20%	1	$3.21	$3.21
			10ml/20%	1	$6.02	$2.41
			30ml/20%	1	$12.00	$1.60
Hyperosmolar Saline	HyperSal®	SVN	3.5%	60	$52.99	$0.88
			7%	60	$91.94	$1.03
	PulmoSal™ (ph 7.4)	SVN	7%	60	$51.94	$0.87

Table 3. (continued)

Corticosteroids

Drug	Brand	Device	Strength	Doses	Cost	Cost/Dose
Beclomethasone	QVAR™ 40	pMDI	40 mcg	120	$162.14	$1.35
	QVAR™ 80	pMDI	80 mcg	120	$211.57	$1.76
Budesonide	Pulmicort Respules	SVN	0.25 mg	30	$277.14	$9.24
			0.5 mg	30	$324.93	$10.83
			1.0 mg	30	$642.92	$21.43
	Generic	SVN	0.25 mg	30	$63.48	$2.12
			0.5 mg	30	$73.47	$2.45
			1.0 mg	30	$145.49	$4.85
	Pulmicort® Flexhaler®	DPI	90 mcg	120	$164.14	$1.37
			180 mcg	120	$214.12	$1.79
Ciclesonide	Alvesco®	pMDI	80 mcg	60	$243.51	$4.06
			160 mcg	60	$243.51	$4.06
Flunisolide	Aerospan®	pMDI	80 mcg	120	$214.56	$1.79
Fluticasone propionate	Flovent Diskus®	DPI	50 mcg	60	$165.03	$2.75
			100 mcg	60	$173.96	$2.90
			250 mcg	60	$226.57	$3.78
	Flovent HFA®	pMDI	44 mcg	120	$173.96	$1.45
			110 mcg	120	$226.57	$1.89
			220 mcg	120	$348.05	$2.90
	ArmonAir® RespiClick®	DPI	55 mcg	60	Newly approved	
			113 mcg	60	No pricing available	
			232 mcg	60		
Fluticasone furoate	Arnuity® Ellipta®	DPI	100 mcg	30	$164.41	$4.48
			200 mcg	30	$214.43	$7.15
Mometasone furoate	Asmanex® HFA	pMDI	100 mcg	120	$191.68	$1.60
			200 mcg	120	$224.06	$1.87
	Asmanex®	DPI	110 mcg	30	$190.00	$6.33
			220 mcg	30	$205.00	$6.83

Table 3. (continued)

Combination Drugs

Drug	Brand	Device	Strength	Doses	Cost	Cost/Dose
Fluticasone and Salmeterol	Advair HFA®	pMDI	45/21 mcg 115/21 mcg 230/21 mcg	120 120 120	$285.26 $352.74 $461.72	$2.38 $2.94 $3.85
	Advair Diskus®	DPI	100/50 mcg 250/50 mcg 500/50 mcg	60 60 60	$285.26 $352.74 $461.72	$4.75 $5.88 $7.70
	AirDuo RespiClick®	DPI	55/14 mcg 113/14 mcg 232/14 mcg	60 60 60	Newly approved No pricing available	
Budesonide and Formoterol	Symbicort®	pMDI	80/4.5 mcg 160/4.5 mcg	120 120	$270.22 $307.87	$2.25 $2.57
Mometasone/ Formoterol	Dulera®	pMDI	100/4 mcg 200	120 120	$290.54 $290.54	$2.42 $2.42
Fluticasone furate/ Vilanterol	Breo® Ellipta®	DPI	100/25 mcg 200/25 mcg	60 60	$314.80 $314.80	$5.25 $5.25
Tiotropium/ Olodaterol	Stiolto® Respimat®	pMDI	2.5/2.5 mcg	60	$333.16	$5.55
Umeclidinium/ Vilanterol	Anoro® Ellipta®	DPI	62.5/25 mcg	60	$333.16	$5.55
Indacaterol/ Glycopyrrolate	Utibron Neohaler®	DPI	27.5/15.6 mcg	60	$313.67	$5.23
Formoterol/ Gylcopyrrolate	Bevespi Aerosphere®	pMDI	9/4.8 mcg	120	$333.16	$2.78

Other Drugs

Drug	Brand	Device	Strength	Doses	Cost	Cost/Dose
Zanamivir	Relenza®	DPI	5 mg	20	$65.49	$3.28
Tobramycin generic Bethkis Tobi Podhaler	TOBI®	SVN SVN DPI	300mg/5ml 300mg/5ml 300mg/4ml 28 mg	56 56 56 224	$7,578.95 $1590.21 $5862.93 $9152.54	$135.33 $28.40 $209.40 $40.85
Aztreonam	Cayston®	SVN	75 mg	84	$8254.28	$98.27
Cromolyn Sodium		SVN	20mg/2ml	60	$211.63	$3.53
Ribavirin	Virazole®	SPAG	6g	1	$25766.30	$25766.30
Mannitol	Aridol®	DP	Bronchial Challenge Test Kit, No pricing available			

2. Aerosol Drug Delivery: Small-Volume Nebulizers

Small volume nebulizers (SVNs) are aerosol generators that convert liquid drug solutions or suspensions into aerosols and delivered to the lower respiratory tract. Nebulizers have been the cornerstone of medical aerosol therapy in the acute and critical care setting. SVNs 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.[37]

Types of Small-Volume Nebulizers

There are two main types of SVNs: 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. Jet nebulizers are effective in delivering medications that cannot be delivered with a pMDI or DPI. The compressor or electronics are generally durable

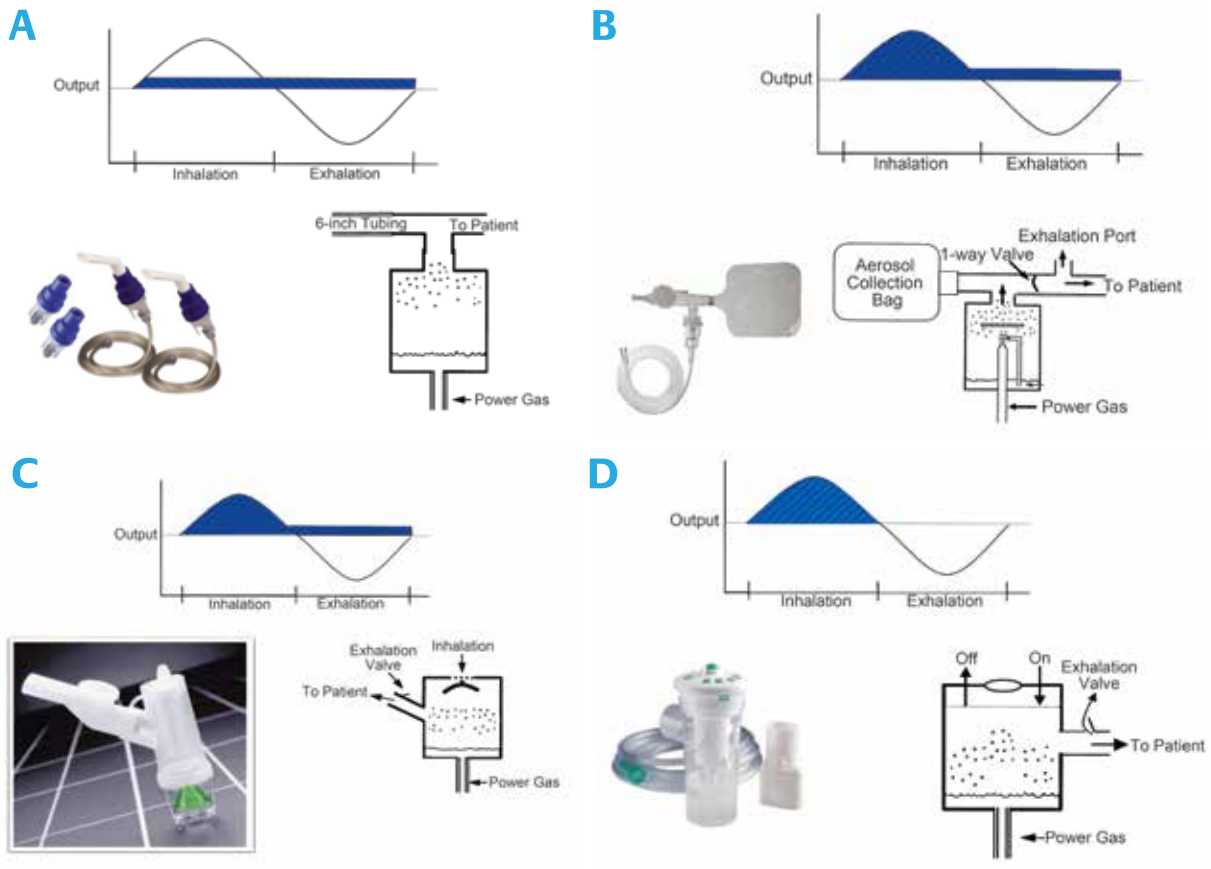


Figure 4. A. Standard T-piece jet nebulizer with reservoir tubing; **B.** Jet nebulizer with collection bag; **C.** Breath-enhanced jet nebulizer; **D.** Breath-actuated jet nebulizer (From Reference 9, with permission)

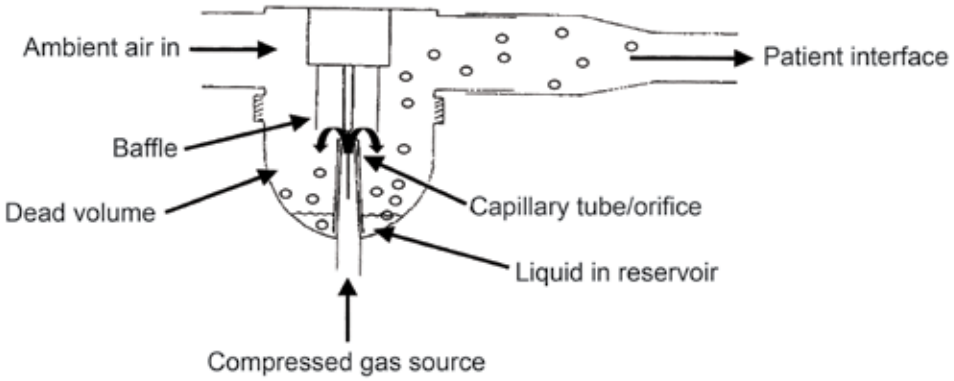


Figure 5. Labeled schematic illustration of the operation of a standard jet nebulizer

and long lasting, whereas nebulizer cups and accessories require frequent replacement.

Jet nebulizers require 2 to 10 liters per minute of pressurized gas generated as a jet through a small opening, generating a region of sub-ambient 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 (see page 17) 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, page 17).[38-39] 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, Andover, MA) and the Micro Mist® (Teleflex Medical, Research Triangle Park, NC).

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.

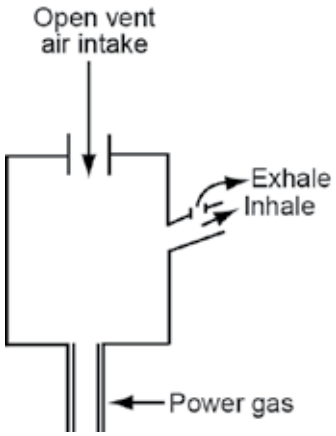


Figure 6. Schematic diagram of a breath-enhanced nebulizer

B. Jet Nebulizer with Collection Bag: These types of nebulizers generate aerosol by continuously filling a reservoir bag (Figure 4-B, page 17). 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.[40]

C. Breath-Enhanced Jet Nebulizer: Breath-enhanced nebulizers use 2 one-way valves to prevent the loss of aerosol to environment (Figure 4-C, page 17). 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 7. An ultrasonic nebulizer (left) and a vibrating mesh nebulizer (right)

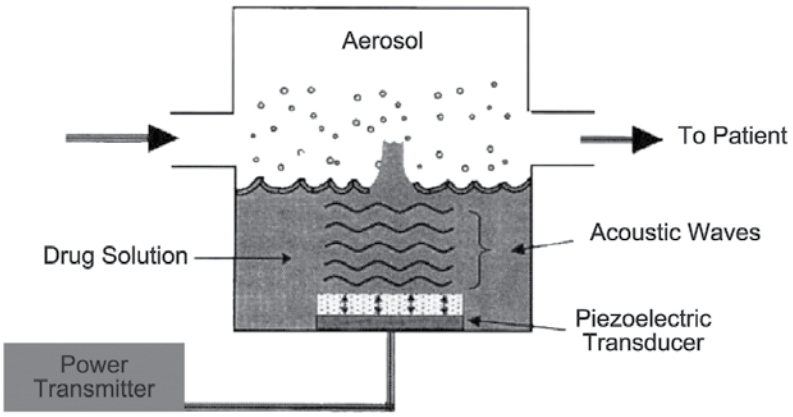


Figure 8. Components and operation principle of an ultrasonic nebulizer (From Reference 9, with permission)

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 (page 17).[39] Moreover, since the newer, fully integrated breath-actuated nebulizers produce an aerosol with more than 70% of aerosol particles in the desirable 3 µm 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 SVNs 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.

The primary difference is electronic nebulizers do not use a compressor. 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 incorporate a piezoelectric crystal vibrating at high frequencies (1-3 MHz) to produce aerosol. A transducer converts 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. Ultrasonic nebulizers have large residual volumes and are unable to aerosolize viscous solutions and can degrade heat-sensitive materials. Therefore, ultrasonic nebulizers should not be used to nebulize suspensions, such as budesonide, or proteins.[41]

A potential concern with the use of ultrasonic nebulizers is drug inactivation by ultrasonic waves. Fatty acid contamination, caused by oils or lotions on the hands, can alter the surface tension of the liquid and may impede nebulization. Small-volume ultrasonic nebulizers are commercially available for delivery of inhaled bronchodilators. Large volume ultrasonic nebulizers are used for sputum induction. Figure 8 shows the operating principle of an ultrasonic nebulizer.

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. In some instances, because of the higher efficiency of these nebulizers, it may be necessary to adjust medication dosage to prevent a possible adverse effect because of overdose.

The aerosol is generated as a fine mist, and no internal baffling system is required. These nebulizers are portable, battery-operated, and highly efficient.[37] 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.

Table 4. Advantages and disadvantages of SVNs (Modified, with permission, from Reference 9)

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 is 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
Variability in performance characteristics among different types, brands, and models	Assembly and cleaning are required.
Normal breathing pattern can be used, and an inspiratory pause (breath-hold) is not required for efficacy.	Contamination is possible with improper handling of drug and inadequate cleaning.

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.

There are various types of SVNs available. One group is powered by compressed gas (pneumatic) and the other by electrical current (electronic). Table 4 illustrates the advantages and disadvances of small-volume nebulizers.

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.[9,42-43]

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.[9,43] 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 perform tidal 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.

The MAGNAIR (Figure 9) is a closed-system nebulizer utilizing eFlow® technology developed by PARI. Traditionally, nebulizers use an open-system that allows medication from the vial to be placed directly into the medication cup of the nebulizer. MAGNAIR uses a sealed unit dose vial that is inserted into the cap of the MAGNAIR handset and pierced open once the cap is closed. This eliminates manual filling, reducing the chance for medication to be wasted or spilled.

The MAGNAIR is a vibrating mesh nebulizer producing a MMAD (mass median aerodynamic diameter) of 3.7 µm with a total administration time less than 3 minutes. Patients are initially prescribed a LONHALA MAGNAIR starter kit that contains a 30-day supply of LONHALA unit dose vials and the MAGNAIR nebulizer system.

Future prescriptions are supplied as a refill kit containing a 30-day supply of medication and a new nebulizer. The old nebulizer should be discarded at the end of each 30-day cycle. The nebulizer should only be used to nebulize LONHALA; no other medication should be used with the MAGNAIR nebulizer system. The MAGNAIR nebulizer is portable and powered by 4AA batteries or an AC adapter.

LONHALA (glycopyrrolate) is a long-acting muscarinic antagonist (LAMA) used to treat COPD twice daily. A one milliliter LONHALA unit dose vial contains 25 mcg and must be used with the MAGNAIR nebulizer system.

Figure 9. The Magnair is a vibrating mesh nebulizer (With permission from Sunovion)

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. Assemble tubing, nebulizer cup, and mouthpiece (or mask).
2. Place medicine into the nebulizer cup.
3. Sit in an upright position.
4. Connect the nebulizer to a power source.
5. Breathe normally with occasional deep breaths until sputter occurs or until the end of nebulization.
6. Keep the nebulizer vertical during treatment.
7. 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. Correctly assemble the nebulizer per manufacturer's specifications.
2. If applicable, 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.
3. Pour the solution into the medication reservoir. Do not exceed the volume recommended by the manufacturer.
4. Sit in an upright position.
5. Turn on the power.
6. Hold the nebulizer in the position recommended by the manufacturer.
7. Follow the instructions for breathing technique that is recommended by the manufacturer for these uniquely designed mesh and ultrasonic nebulizers.
8. If the treatment must be interrupted, turn off the unit to avoid waste.
9. At the completion of the treatment, disassemble and clean as recommended by the manufacturer.
10. When using a mesh nebulizer, do not touch the mesh during cleaning. This will damage the unit.
11. 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 and all connections are secured tightly.
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	Solutions
Loose or unattached connections	Check the connections and make sure that they are properly attached.
Inappropriate flowmeter setting	Check the flowmeter setting and adjust the flow if it is not appropriate.
Obstruction in the orifice of the jet nebulizer	Check the orifice of the jet nebulizer and clear obstructions when needed.

Technique Box 1. Steps for Correct Use of Nebulizers (continued)

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

Causes	Solutions
Incorrect battery installation (seen in both mesh and ultrasonic nebulizers)	Check the battery installation and reinstall if needed.
External power source connection (seen in both mesh and ultrasonic nebulizers)	Check the connections with the AC adapter and the electrical output.
Overheated unit (seen in ultrasonic nebulizers)	Turn off the unit, wait until it cools down, and restart the unit.
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.

When Is the Treatment Finished?

Individuals often 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.[26,44] 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 (pMDI) and dry-powder inhaler (DPI) are medical aerosol delivery devices containing dissolved or suspended drug with hardware needed to contain the formulation. The internal hardware allows efficient and consistent dose delivery.[45] 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.

As part of the United States Food and Drug Administration (FDA), the Center for Drug Evaluation and Research (CDER) regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs. Inhalers are approved by the 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 11). 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. Patient education that includes return demonstration at every patient encounter is imperative to assure proper inhaler technique.

The In-Check DIAL (Figure 10) is a handheld low-range inspiratory flow measurement device with a dial top used to measure inspiratory flow rate. The In-Check DIAL can be adjusted to accurately simulate the resistance of various inhaler devices, which allows the clinician to assess patient technique.

Figure 10. In-Check DIAL G16 (Clement Clarke International Ltd)

Figure 11. Common Inhalers Available in the United States

Anticholinergics/β_2-Agonist Combination

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

Stiolto® Respimat®
(tiotropium bromide and olodaterol)
Inhalation Spray
Boehringer Ingelheim Pharmaceuticals, Inc.

Utibron™ Neohaler®
(indacaterol and glycopyrrolate)
Inhalation Powder
Sunovion Pharmaceuticals Inc.

Anoro® Ellipta®
(umeclidinium and vilanterol)
Inhalation Powder
GlaxoSmithKline

Bevespi Aerosphere™
(glycopyrrolate and formoterol fumarate)
Inhalation Aerosol
AstraZeneca Pharmaceuticals

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.

Incruse® Ellipta®
(umeclidinium)
Inhalation Powder
GlaxoSmithKline

Seebri™ Neohaler®
(glycopyrrolate)
Inhalation Powder
Sunovion Pharmaceuticals Inc.

β_2-Agonists

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

ProAir® RespiClick®
(albuterol sulfate)
Inhalation Powder
Teva Specialty Pharmaceuticals

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

Arcapta™ Neohaler™
(indacaterol)
Inhalation Powder
Novartis Pharmaceuticals

Striverdi® Respimat®
(olodaterol)
Inhalation Spray
Boehringer Ingelheim Pharmacueticals, Inc.

Xopenex® HFA
(levalbuterol tartare)
Inhalation Aerosol
Sunovion Pharmaceuticals Inc.

Ventolin® HFA
(albuterol sulfate HFA)
Inhalation Aerosol
GlaxoSmithKline

Serevent® Diskus®
(salmeterol xinafoate)
Inhalation Powder
GlaxoSmithKline

Serevent® HFA
(salmeterol xinafoate)
Inhalation Aerosol
GlaxoSmithKline

Corticosteroids

Alvesco®
(ciclesonide)
Inhalation Aerosol
Nycomed

Asmanex Twisthaler®
(mometasone)
Inhalation Powder
Schering Corporation

Flovent® Diskus®
(fluticasone propionate)
Inhalation Powder
GlaxoSmithKline

ArmonAir™ RespiClick®
(fluticasone propionate)
Inhalation Powder
Teva Specialty Pharmaceuticals

Arnuity® Ellipta®
(fluticasone furoate)
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

Aerospan®
(flunisolide)
Inhalation Aerosol
Mylan Pharmaceuticals

β_2-Agonist/Corticosteroid Combination

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

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

Breo® Ellipta®
(fluticasone furoate and vilanterol)
Inhalation Powder
GlaxoSmithKline

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

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

AirDuo RespiClick®
(fluticasone propionate and salmeterol)
Inhalation Powder
Teva Specialty Pharmaceuticals

Other

Relenza®
(zanamivir)
Inhalation Powder
GlaxoSmithKline

TOBI® Podhaler®
(tobramycin)
Inhalation Powder
Novartis Pharmaceuticals

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.

Types of pMDIs

There are two types of pMDIs: conventional pMDIs and liquid metered-dose inhalers (LMI) (soft-mist inhalers). 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.

Conventional pMDI

As seen in Figure 12 (on page 27), the pMDI consists of a canister, the medication, the propellant, a metering valve, the mouthpiece, and the actuator.[46] 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.

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

Table 5. Advantages and disadvantages of the pMDI (Modified, with permission, from Reference 9)

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 in 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

Table 6. Basic components of the pMDI (From Reference 9 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 that is crimped onto the container and is responsible for metering a reproducible volume or dose Elastomeric valves for sealing and preventing drug loss or leakage
Actuator	Frequently referred to as the "boot," 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

nozzle. Last, releasing the metering valve refills the chambers with another dose of the drug-propellant mixture.

Hydrofluoroalkane (HFA) is the propellant used in pMDIs today.

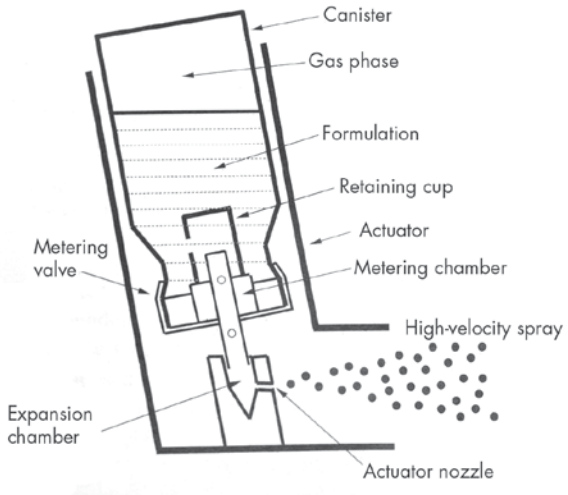


Figure 12. Standard components of a pMDI (Modified with permission from Reference 40)

Table 7. Characteristics of a HFA pMDI

Physical Component	HFA
Dose Delivery	
From a near-empty canister	Consistent
With variable ambient temperature	Consistent (to -20°C)
Spray	
Force	Low (plume)
Temperature	Warm
Volume	Low
Taste	Has a taste
Breath-Hold	Very important
Priming	Priming is needed
Nozzle Cleaning	Periodically necessary to prevent clogging

Figure 13. Respimat® soft-mist inhaler

Soft-Mist pMDI

The Respimat® (Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) is a propellant-free soft-mist inhaler. The Respimat® utilizes mechanical energy in the form of a tensioned spring to generate the soft aerosol plume. The energy from turning the transparent base to the right one-half turn draws a predetermined metered volume of solution from the medication cartridge through a capillary tube into a micro-pump. When the dose release button is depressed, the energy from the spring forces the solution to the mouthpiece, creating a soft aerosol plume that lasts approximately 1.5 seconds. Similar to pMDIs, the Respimat® will need to be primed before use and at times when the device has had no use. If not used for more than 3 days, actuate the inhaler once. After more than 21 days of no use, it is recommended to actuate the device until aerosol is seen, then actuate 3 more times. Since the device is propellant free, there is no need to shake it. The Respimat® has a dose indicator and will lock once all medication is used. Figure 13 shows the standard components of the Respimat®.

Currently Available pMDI Formulations

A number of aerosol formulations are available for use in pMDIs today (refer to Figure 11). 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.[47] 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.[48]

- **Storage Temperature:** Outdoor use or storage of pMDIs in very cold weather may significantly decrease aerosol drug delivery.[49]

- **Nozzle Size and Cleanliness:** The amount of medication delivered to the patient is dependent upon nozzle size, cleanliness, and lack of moisture. The 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

(Continued on page 30)

Table 8. Priming requirements for commercially available pMDIs (Modified, with permission, from Reference 9)

Short-Acting Bronchodilators

Generic Name	Brand Name	Time to Prime	No. of Sprays
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
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

Generic Name	Brand Name	Time to Prime	No. of Sprays
Beclomethasone Dipropionate	QVAR® HFA	New and when not used for 10 days	2
Ciclesonide	Alvesco® HFA	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
Mometasone	Asmanex® HFA	New and not used for 5 days	4
Flunisolide	Aerospan® HFA	New and not used for 2 weeks	2

Combination Drugs

Generic Name	Brand Name	Time to Prime	No. of Sprays
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 and when not used for 4 weeks	4
		or if dropped	2
Mometasone furoate and Formoterol fumarate Dihydrate	Dulera® HFA	New and not used for 5 days	4

Anticholinergics

Generic Name	Brand Name	Time to Prime	No. of Sprays
Ipratropium bromide	Atrovent® HFA	New and not used for 3 days	2

(Continued from page 28)

of particles.[47] A pause between puffs may improve bronchodilation, especially during asthma exacerbations with episodes of wheezing and poor symptom control.[50] 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.[51]

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.[9,12,21]

- **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.

- **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:** The technique for using a pMDI without a spacer: is 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.[52-54]

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 (on page 31).

How Do We Know the pMDI is Empty?

The only reliable method to determine the number of doses remaining in a pMDI is to track the doses given either manually or with a dose counter. The dose counter is located on top of the canister or in the boot of the device. When the pMDI Is actuated, it counts down the number of actuations for the total remaining in the canister. Most pMDIs today have dose counters built-in to the device.

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 Figures 14–16, page 33). Although research has confirmed acceptable performance and patient satisfaction with pMDIs with external dose counters,[55-57] care must be taken to assure that a third-party dose counter works with the specific pMDI being used.[26,58]

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.

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.[58]Using a third-party dose-counting device increases the cost of aerosol therapy, which may limit their wide acceptance.

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:

(Continued on page 33)

Technique Box 2. Steps for Correct Use of pMDIs

Technique for pMDIs

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 their teeth; make sure that their tongue is flat under the mouthpiece and does not block the pMDI.
6. Seal their lips.
7. Actuate the pMDI as they begin to breathe in slowly.
8. Hold their breath for 10 seconds. If they 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 2–10 until the dosage prescribed by the patient's physician is reached.
11. If taking a corticosteroid, she/he should rinse the 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.

Liquid Metered-Dose Inhaler (LMI) Soft Mist (Respimat®) Techniques: When using the Respimat®, the patient should be instructed to:

Preparation

1. With the orange cap closed, press the safety catch while pulling off the clear base. Be careful not to touch the piercing element located Inside the bottom of the clear base.
2. Push the narrow end of the cartridge Into the Inhaler. The base of the cartridge will not sit flush with the Inhaler. About 1/8 of an inch will remain visible when the cartridge is correctly inserted.
3. The cartridge can be pushed against a firm surface to ensure it is correctly inserted.
4. Do not remove the cartridge once It has been inserted Into the inhaler.
5. Write the discard by date on the label of the inhaler. The discard date is 3 months form the date the cartridge is inserted.
6. Put the clear base back Into place. Do not remove the clear base again. The inhaler should not be taken apart after they have inserted the cartridge and put the clear base back.

Priming

7. Hold the inhaler upright with the orange cap closed to avoid accidental release of dose
8. Turn the clear base In the direction of the white arrows on the label until It clicks (half a turn).
9. Flip the orange cap until it snaps fully open.
10. Point the inhaler toward the ground. Press the dose-release button. Close the orange cap.
11. Repeat steps 7-11 until the spray is visible.

Patient-Use Instructions:

1. Hold the inhaler upright with the orange cap closed to avoid accidental release of dose.
2. Turn the clear base in the direction of the white arrows on the label until it clicks (half turn).
3. Flip the orange cap until it snaps fully open.
4. Breathe out slowly and fully, and then close lips around the end of the mouthpiece without covering the air vents.
5. Point inhaler toward the back of mouth.
6. While taking in a slow deep breath through the mouth press the dose-release button and continue to breathe in slowly for as long as possible.
7. Hold breath for 10 seconds or for as long as comfortable.
8. Close the orange cap until next prescribed dose.

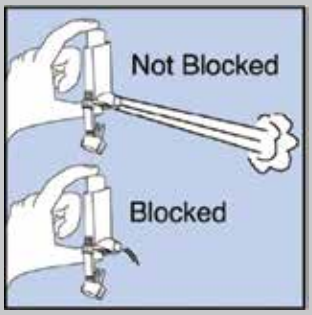
Technique Box 2. Steps for Correct Use of pMDIs (continued)

Technique for pMDIs

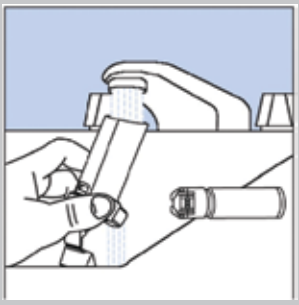
General Steps To Avoid Reduced or No Dosing for pMDIs:

When using pMDIs, the following steps should be used in order to avoid reduced or no dosing during aerosol treatment. The patient should:

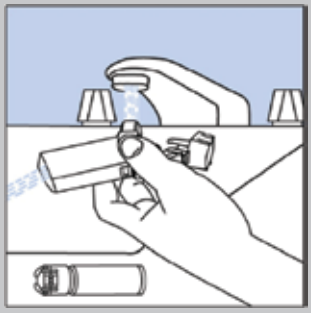
1. Remove the cap of the pMDI from the boot.
2. Prime as directed (Table 8, page 29).
3. Clean and dry the boot of the pMDI based on the manufacturer's guidelines. They tend to get blocked if not cleaned and primed properly.



Example of blocked spray



Example of how to clean the inhaler to keep it clean so medicine build-up will not block the spray. Take the canister out of the actuator, and take the cap off the mouthpiece.



Turn the actuator upside down and run warm water through the mouthpiece for about 30 seconds. Shake off as much water from the actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat washing.

Let the actuator air-dry overnight. When dry, put the protective cap on the mouthpiece and then put the canister Into the actuator.

4. pMDIs with dose counters will track remaining doses. For those without counters, the patient must track doses manually using a daily log sheet or a dose counter that can be purchased separately from the pMDI and attached to the device.

Troubleshooting

Problem with the pMDI: Absent or Low Aerosol

Causes	Solutions
Incorrect pMDI assembly	Check the assembly and reassemble when needed.
Incorrect pMDI and valved holding chamber assembly	Check the assembly of the pMDI/spacer and reassemble if needed.
Empty pMDI	Check the dose counter or daily log sheet to ensure there is enough medicine in the canister, if not, replace the pMDI.

(Continued from page 30)

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 ÷ 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 (on page 50) for the cleaning instructions for inhalers.

Figure 14. Integral dose counter on Ventolin HFA (top) and Symbicort pMDI (bottom)

Figure 15. Integral dose counter on Combivent Respimat

Figure 16. Currently available external pMDI dose counters on the market

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 which 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 until inhaled and 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 17 shows examples of spacers and holding chambers. Azmacort and InspiroEase are no longer used.

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, and electrostatic charge on the inner walls of plastic spacers. Spacers decrease oral deposition, but they only provide

Figure 17. Examples of valved holding chambers and spacers

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. 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.

pMDIs may come with a spacer already attached to the pMDI, such as Aerospan®, and do not require an additional spacer or chamber for use.

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 and an inspiratory flow indicator to note that. Children with low tidal volumes may need to take several breaths from a VHC through a face mask 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 with pMDIs, there are also potential problems with their use (see Table 9).

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

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

Advantages	Disadvantages
Reduced oropharyngeal drug impaction and loss	Large and cumbersome compared to the pMDI alone
Increased inhaled drug by two to four times than the pMDI alone	More expensive and bulky than a pMDI alone
Allows use of the pMDI during acute airflow obstruction with dyspnea	Some assembly may be needed
No drug preparation required	Patient errors in firing multiple puffs into chamber prior to inhaling or there is a delay between actuation and inhalation
Simplifies coordination of pMDI actuation and inhalation	Possible contamination with inadequate cleaning
Helps reduce local and systemic side effects[1]	

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.

Cleaning: Please refer to the Infection Control section on page 50 for cleaning instructions for the pMDI chamber and collapsible bag device.

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 into the air if it is new or has not been used for several days.
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 and seal their lips. Make sure that their tongue is flat under the mouthpiece and does not block the pMDI.
   b. Actuate the pMDI as they begin 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 their breath for 10 seconds. If they cannot hold their breath for 10 seconds, then hold for as long as possible.
   With the mask:
   a. Place the mask completely over the nose and mouth and make sure it fits firmly against the face.
   b. Hold the mask in place and actuate the pMDI as they begin to breathe in slowly. Also make sure to inhale slowly if the device produces a “whistle” indicating that inspiration is too rapid.
   c. Hold the mask in place while the child takes six normal breaths (including inhalation and exhalation), then remove the mask from the child’s face.
8. Wait 15–30 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, rinse the mouth after the last puff of medicine, spit out the water, and do 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: 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.

6. Dry-Powder Inhalers

Dry-powder inhalers (DPIs) are portable, inspiratory flow-driven inhalers that are used to administer medication in the form of dry powder to the lungs. DPIs became widely available when the manufacturing of metered-dose inhalers with CFC propellants was outlawed. Because each manufacturer obtains a patent for the DPI design, multiple DPIs exist, unlike one common pressurized metered-dose inhaler.[59]

An ideal DPI would include:

- ease of use, portability, and affordability
- consistent delivery of medication independent of airflow resistance
- drug deaggregation engineering to deliver high percentages of medication to the lung
- secure storage of the medication
- a visual indicator for when the inhaler is ready to be used
- audible feedback for correct inhalation technique
- a mechanism to prevent more than one dose being delivered at one time
- an indicator to show how many doses are remaining
- a locking mechanism when the device is empty
- the ability to deliver more than one medication at a time
- the availability of multiple medications with the same DPI design.[60]

Types of DPIs

Currently, DPIs can be classified based on the design of their dose device: single-dose DPIs and multiple-dose DPIs (Figure 18).[61] Regardless of the type of DPI, they all have the same essential components incorporated within the inhaler. They all have a drug holder, an air inlet, a powder dispersion 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 for adequate lung deposition.

Single-Dose DPIs

Single-dose DPIs operate by evacuating powder medication from a punctured capsule. The HandiHaler®,

Figure 18. Currently available dry-powder inhalers

Neohaler®, and Podhaler™ are single-dose DPIs. One advantage of single dose-DPIs is the visibility of seeing the empty capsule after the dosage has been delivered. The primary disadvantages of single-dose DPIs are the dexterity needed to load a dose for each use and the confusion of the dosage delivery system with using capsules for inhalation instead of orally. Table 10 lists the products available as single-dose DPIs.

Multiple Unit-Dose DPIs

Multiple-dose DPIs reassure doses of medication from a reservoir of powder within the inhaler or from an individual pre-measured blister strip. Multiple dose DPIs offer ease of use both with preparing the inhaler for use and delivering the medication to the lungs. One disadvantage with the multiple-dose DPI is sometimes the lack of knowing if a dose was received. Examples of multiple-dose DPIs are listed in Table 10.

Table 10. Types of DPIs

Single-Dose DPI		
Handihaler	Spiriva (Tiotropium)	Long-acting muscarinic antagonist (LAMA)
NeoHaler	Arcapata (Indacaterol) Seebri (Glycopyrrolate) Utibron (Glycopyrrolate/Indacaterol)	Long-acting Beta$_2$-agonist (LABA) LAMA Combination LAMA/LABA
Podhaler	TOBI (Tobramycin)	antibacterial aminoglycoside
Multiple-Dose DPI		
Blister Strip Package		
Diskus	Advair (Fluticasone/Salmeterol) Flovent (Fluticasone) Serevent (Salmeterol)	ICS/LABA ICS LABA
Ellipta	Anoro (Umeclidinium/Vilanterol) Arnuity (Fluticasone Furoate) Breo (Fluticasone Furoate/Vilanterol) Incruse (Umeclidinium)	LAMA/LABA ICS ICS/LABA LAMA
Cartridge		
PressAir	Tudorza (Acidinium)	LAMA
Reservoir		
Flexhaler	Asmanex (Mometasone)	ICS
RespiClick	ProAir (Albuterol) AirDuo (Fluticasone Propionate/Salmeterol) ArmonAir (Fluticasone/Propionate)	SABA ICS/LABA ICS
Twisthaler	Pulmicort (Budesonide)	ICS
Rotadisk		
Diskhaler	Relenza (Zanamavir)	Influenze neuraminidase inhibitor (NAI)

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

HandiHaler®: The patient should be instructed to:

1. Open the dust cap by pulling it upward.
2. Open the mouthpiece by pulling it upward.
3. Peel back the aluminum foil and remove a capsule immediately before using the HandiHaler.
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 and dispose of the used capsule by inverting the inhaler over the wastebasket. Do not store capsules in the HandiHaler.
16. Close the mouthpiece and dust cap for storage of the HandiHaler.

Neohaler®: The patient should be instructed to:

1. Remove the mouthpiece cover.
2. Hold the base of the inhaler and tilt the mouthpiece to open the Neohaler.
3. Remove capsule from the foil blister immediately before use.
4. Place the capsule into the chamber in the base of the Neohaler.
5. Close the inhaler and listen for a CLICK.
6. Hold the inhaler upright with the mouthpiece pointing up.
7. Press both piercing buttons on the sides together firmly at the same time. Listen for a CLICK.
8. Release the piercing buttons.
9. Breathe out away from the inhaler.
10. Place the mouthpiece into the mouth and close lips tightly around the mouthpiece. Make sure that the piercing buttons are to the left and right of the inhaler (not up and down).
11. Breathe in rapidly, steadily and deeply. Press the piercing buttons while breathing in. A WHIRRING noise will be heard if the medication is inhaled properly.
12. Remove the mouthpiece from the mouth and hold your breath for 5 to 10 seconds (or as long as comfortable).
13. Breathe out away from the inhaler. 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 Neohaler.
16. Close the mouthpiece and replace the cover.

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

Technique for Single-Dose DPIs (continued)

Podhaler®: The patient should be instructed to:

1. Hold base of the storage case and unscrew lid in a counter-clockwise direction. Set the lid aside.
2. Hold the Podhaler device and unscrew the mouthpiece in a counter-clockwise direction. Set the mouthpiece aside on a clean, dry surface.
3. Take out one capsule from the blister card. Only expose one capsule at a time.
5. Place the capsule in the chamber at the top of the Podhaler device right away.
6. Remove the Podhaler device from the base of the case. Hold the Podhaler device with the mouthpiece pointed down. Put your thumb on the blue button. Press the blue button all the way down one time and release.
7. Breathe out all the way without blowing or exhaling into the mouthpiece.
8. Place your mouth over the mouthpiece and close your lips tightly around the mouthpiece.
9. Inhale deeply with a single breath.
10. Remove the Podhaler device from your mouth, and hold your breath for about 5 seconds.
11. Repeat the inhalation from the Podhaler.
12. Unscrew the mouthpiece and remove the capsule from the chamber by tilting the Podhaler device so the capsule falls into the palm of your hand.
13. Hold the capsule up to the light and check to make sure the capsule is empty of powder. Throw away the empty capsule.
14. Repeat steps 3 -13 three more times for a total of 4 capsules equivalent to one dose of medication. Remove twice daily.
15. Place the Podhaler device back into the storage case base and replace the lid back onto the storage case base by screwing the lid in a clock-wise direction.

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.
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 3 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.

Diskus®: The patient should be instructed to:

1. Hold the Diskus in the left hand and place the thumb of the right hand in the thumb grip. Push the thumb grip away. A CLICK will be heard.
2. Hold the Diskus in a level, flat position, like a sandwich.
3. Slide the lever from left to right. A CLICK will be heard. The indicator will count down by one.
4. Breathe out away from the inhaler. Do not exhale into the device.
5. Place the mouthpiece into the mouth and close lips tightly around the mouthpiece.
6. Keep device horizontal while inhaling the dose quickly and deeply. Do not breathe in through the nose.
7. Remove the mouthpiece from the mouth and hold breath for 10 seconds (or as long as comfortable).
8. Close the Diskus by placing your thumb in the thumb grip and slide it back towards you as far as it will go. A CLICK will be heard.
9. Rinse mouth with water and spit after using Advair or Flovent Diskus. Do not swallow.

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

Technique for the Multiple Unit-Dose DPI (continued)

Ellipta®: The patient should be instructed to:

1. Slide the cover open and listen for a CLICK. The counter should count down by one.
2. Breathe out away from the Ellipta.
3. Securely place lips of mouth on the curved part of the mouthpiece. Do not block vents with fingers.
4. Inhale one long, steady, deep breath in through the mouth and not the nose.
5. Remove the inhaler from the mouth and hold breath for 3-4 seconds.
6. Breathe out away from the inhaler slowly and gently. Do not take another dose even if there is no taste or feeling.
7. Slide the cover up.
8. Rinse your mouth with water and spit after use if using the Arnuity or Breo Ellipta.

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).
3. Twist the brown grip fully in one direction as far as it goes. It does not matter which way it is turned initially.
4. Twist the brown grip fully back in the other direction as far as it goes.
5. Make sure to hear a CLICK during each of the twisting movements.
6. Do not exhale into the device.
7. Place the mouthpiece into the mouth, seal the mouthpiece with the lips, and inhale deeply and forcefully through the inhaler.
8. Remove the inhaler from the mouth and exhale away from the inhaler.
9. If more than one dose is required, repeat the steps above.
10. Put the cover back on the inhaler and twist it shut.
11. Rinse your mouth with water and spit after using the Flexhaler.

Pressair®: The patient should be instructed to:

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

RespiClick®: The patient should be instructed to:

1. Open the cap all the back until a CLICK is heard. Opening the inhaler activates a dose of medication.
2. Breathe out away from the inhaler then place mouth on the mouthpiece.
3. Do not block the vents with fingers or lips.
4. Inhale deeply through the mouth.
5. Hold breath for 10 seconds or as long as comfortable.
6. Breathe out away from the inhaler.
7. Check the dose counter on the back. The counter should count down by one if a dose was delivered.
8. Close the cap after each inhalation.

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

Technique for the Multiple Unit-Dose DPI (continued)

Twisthaler®: The patient should be instructed to:

1. Hold the inhaler straight up with the pink portion (the base) on the bottom.
2. Hold the pink base and twist the cap in a counter-clockwise direction to remove it.
3. As the cap is lifted off, the dose counter on the base will count down by one. This action loads the dose.
4. Make sure the indented arrow located on the white portion (directly above the pink base) is pointing to the dose counter.
5. Breathe out away from the inhaler.
6. Place the mouthpiece into the mouth and close the lips tightly around it. Do not block the vents on the side of the inhaler.
7. Inhale the dose with a rapid and steady flow while holding the Twisthaler horizontally.
8. Remove the mouthpiece from the mouth and hold breath for 5 to 10 seconds (or as long as comfortable).
9. Exhale away from the Twisthaler.
10. Immediately replace the cap by lining the arrow on the cap with the dose-counter window.
11. Turn the cap in a clockwise direction until a CLICK is heard. The next dose is now properly loaded.

General Steps for DPIs to Avoid Reduced or No Dosing:

1. Do not swallow the capsules.
2. Puncture the capsule or blister pack; puncture capsules only once.
3. Do not use capsules with inhalers from other medications.
4. Avoid shaking the DPIs.
5. Keep the DPI in the proper orientation during inhalation.
6. Make sure to generate adequate inspiratory flow.
7. Do not exhale into the DPI.
8. Use a new inhaler with each refill of medication.
9. Do not use a spacer device with DPIs.
10. Store all DPIs in a dry place at room temperature with deviations of temperature permitted from 59°F to 86°F (15°C to 30°C).

Advantages and Disadvantages of DPIs

Dry-powder inhalers have both advantages and disadvantages as seen in Table 11. DPIs are often prescribed with the goal of providing the patient with an overall more user-friendly inhaler than the metered-dose inhalers. Removing coordination with inspiration and activation of the inhaler is a big advantage. The patient's inspiratory effort, however, must be adequate enough to draw the drug from the device, and to deliver the drug into the airways. This required inspiratory effort is a limitation of the DPI devices and DPIs are not approved for all ages.

See Table 12 for approved ages for DPIs. DPI medications are also more susceptible to the environment and have a limited shelf-life. Table 13 provides the storage information and describes the dose indicator for each DPI. Most DPIs contain small amounts of lactose. The lactose additive is a large particle that acts a carrier for the medication and adds a sweet taste so the patient is aware that a dose was received. The amount of lactose is so small, that the lactose does not affect lactose-intolerant patients. However, if a patient has severe milk-protein allergies, DPIs should be avoided.

Table 11. Advantages and disadvantages of DPIs (Modified, with permission, from Reference 9)

Advantages	Disadvantages
Small and portable	Age limitations
Built-in dose counter	Limited shelf-life and product stability
Propellant free	Upper respiratory side effects, cough
Breath-actuated	Various DPI designs
Short preparation and administration time	Lactose, milk protein allergy

Table 12. Approved Ages for DPIs

Diskhaler	≥ 5 years old
Diskus	≥ 4 years old
Ellipta, Arnuity	≥ 12 years old
Ellipta, Anoro, Breo and Incruse	≥ 18 years old
Flexhaler	≥ 6 years old
HandiHaler	≥ 18 years old
Neohaler	≥ 18 years old
Podhaler	≥ 6 years old
Pressair	≥ 18 years old
RespiClick, ProAir	≥ 4 years old
RespiClick, AirDuo and Armonair	≥ 12 years old
Twisthaler	≥ 12 years old

Table 13. DPI Indicator and Storage

Inhaler type	Indicator	Storage and Cleaning
Diskhaler	Five Rotadisks with each Rotadisk containing 4 blisters of drug	Expires with the date on the inhaler Replace mouthpiece cover after use Discard after 5 days of treatment
Diskus	Counter, 28 or 60 doses Small numbers Numbers 5 to 0 will show in red	Discard 6 weeks after opening foil package or two months for (100 and 250 mcg Flovent) Write the date of removal from the foil packaging on the Diskus Keep dry at all times, do not wash
Ellipta	Counter, 7 (Anoro, Incruse institutional), 14 (Arnuity and Breo institutional) or 30 doses Numbers 9 to 0 will show in red	Wipe the mouthpiece with a dry tissue, if needed Discard 6 weeks after opening if not empty
Flexhaler	Counter, 60 or 120 doses Indicator is marked in intervals of 10 Counts down with each turn of the grip See the indicator move after 5 doses Empty when "0" is in the middle of the indicator with a red background	Keep dry at all times Wipe the mouthpiece once a week with a dry tissue
HandiHaler	Capsules: 5 (institutional), 30, 90	Store capsules in foil blister Remove capsule immediately before use Do not store capsules in the inhaler Tap the inhaler upside down to remove powder build up or capsule pieces Rinse the inhaler, mouthpiece, center chamber and piercing button with warm water Allow to air dry for 24 hours
Neohaler	Capsules: 6 (Utibron institutional) 30 (Arcapta only), 60	Keep the inhaler dry Wipe the mouthpiece with a lint-free, dry cloth, if needed Do not store capsules in the inhaler Keep capsules in the foil package until ready for use
Podhaler	Capsules: 4 weekly pack (224 capsules and 5 Podhalers) or 7 day pack (56 capsules) or one 1 one day pack (8 capsules)	Wipe mouthpiece with dry cloth, if needed Use a new Podhaler every 7 days Keep capsule in foil packaging and only expose 1 capsule at a time
Pressair	Counter, 60 doses Dose counter decreases by intervals of 10 "0" red background in the middle of the counter Locks when empty	Discard after 45 days if not empty Keep dry at all times Wipe mouthpiece with a dry tissue, if needed
RespiClick, Proair	Counter, 200 doses Numbers turn red 20 to 0	Discard after 13 months, if not empty Wipe mouthpiece with a dry tissue, if needed If any part of the inhaler gets wet, get a new inhaler
RespiClick, AirDuo and Armonair	Counter, 60 doses Dose counter displays the number of doses left in the inhaler in units of 2	Discard after 30 days, if not empty Keep dry at all times Wipe mouthpiece with a dry tissue, if needed
Twisthaler	Counter: 7 and 14 (institutional), 30 and 60 doses Locks when empty "00"	Discard after 45 days, if not empty Wipe mouthpiece with a dry cloth, if needed Keep dry at all times

Factors Affecting 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.

How Do We Know That the DPI is Empty?

Single-Dose DPIs: 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 DPIs: 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.

7. Criteria For Selecting an Aerosol Delivery Device

The selection of the aerosol delivery device is important for patient satisfaction. The criteria to select an inhaled medication can be divided into four categories: patient-related, drug-related, device-related, and environmental and clinical factors.

Patient-Related Factors

Diagnosis, Age, Physical, and Cognitive Ability of Patients: The selection of a medication for inhalation will initially depend upon the patient's diagnosis. Medications are available in specific devices, limiting the choice of the medication made by the physician and the patient. An aerosol delivery device should be selected by considering the patient's age, physical and cognitive ability. Aging changes anatomic and physiologic factors such as airway size, respiratory rate, and lung volume.[21,61-65] 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.[14,21,61,66,68-71]

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.[68,72-74] Also, the inability to generate sufficient peak inspiratory flow (>30–60 L/min) precludes the use of aerosol delivery devices such as DPIs.[68,75]

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.[76-78] The costs depends upon the presence and type of medical insurance of the patient.[70] Insurance formularies should be reviewed before selecting and prescribing a medication.[79] 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.

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.[80-82] Tailoring the aerosol regimen according to the patient's needs and preferences should help with adherence.

Drug-Related Factors

Availability of Drug: Some medications are available with only one type of aerosol device and this can prohibit incorporating the patient's needs and preference. If the medication is available in multiple aerosol delivery devices, the health care provider should make the selection based upon the patient's insurance coverage and preference.[14,26,70] Many inhalers include more than one medication or once daily formulations to improve adherence and quality of life. Limiting the number of aerosol delivery devices can ease the burden on the patient. [14,26,83]

Device-Related Factors

Convenience of Aerosol Device: Selecting the most convenient aerosol device for the patient is important for adherence. Ease of use, shorter treatment time, portability 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.[60,70] Also, nebulizers may be less preferable for delivering inhaled medications as they are more expensive, require a power source, and need regular maintenance.[60,84-85] When all other factors are equal, the most convenient device should be chosen for each patient.

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, secondhand 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.[61-64,86] 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.[61,69,86] Children under the age of 3 may not reliably use a mouthpiece, making delivery via mask necessary for both nebulizers and pMDIs.[87-90] Especially at low tidal volumes, VHCs are the preferred method for pMDI delivery in infants and small children.[88-89] 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.[64,91]

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 14 presents the recommended ages for introducing different types of aerosol delivery devices and their interfaces to children.[61-63,91-94] Small-volume nebulizers and pMDIs with VHCs are recommended for use with infants and children up to 5 years of age.[62-63,91] 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.[62,88-89] 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.[62-63,91] With low tidal volumes and short inspiratory times, breath-actuated nebulizers may increase inhaled dose compared to continuous nebulization.[95] It may take additional time to administer that dose. Also, time constraints and portability of compressor nebulizers make them less desirable for preschool children.[62] Once children reach age 4, they may have a sufficient understanding of how to use a pMDI or DPI successfully.[64,91] It is generally accepted that the cognitive ability to control breathing and hand/breath coordination develops by age 5 or 6.[61-62,92]

Table 14. 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 nebulizer	≥ 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,[87,93,96-97] with most of the inhaled dose depositing in the upper airways or pharynx and then swallowed.[62-63,97-98] 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[95,99] and is effective in the clinical treatment of children.[95,100-101] 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.[102-106] 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.[88,102,107-108]

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.[109-110] 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

Health care professionals are the frontline defense for implementing infection control practices to prevent infections and transmission of organisms. Infection control is a critical component in preventing microbial contamination of respiratory equipment, which can result in significant adverse clinical outcomes. Aerosol devices can become contaminated with pathogens from the patient, the care provider, and the environment. Contamination of small-volume nebulizers has been documented in patients with cystic fibrosis,[28-30] asthma,[31-32] and immunodeficiency.[111] Literature has shown when nebulizers are not cleaned and appropriately maintained, colonization of Pseudomonas species, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus cereus, and B. cepacia may be present. [28-30,33,112] Colonization is more often seen in respiratory equipment used at home and is directly linked to sanitation and hygiene practices by the patients. Establishment of a management system that will reduce nosocomial infections, length of stay in the hospital, costs associated with hospitalization, and incorporate patient education is essential.[32,112,114]

Patient Education and Awareness

Patient Education: Patient education strategies are the foundation of achieving successful clinical outcomes. Every patient encounter must address assessment of disease status, adherence to the medical treatment regimen, and infection control. Health care providers must emphasize to patients and caregivers the importance of appropriately cleaning and periodically disinfecting aerosol equipment. Return demonstration of administering the prescribed medical treatment regimen, including device cleaning must be implemented using verbal, visual, tactile, and written education learning styles.[115]

Patient Adherence: Approximately 85% of patients with cystic fibrosis fail to disinfect their nebulizers at home.[116] 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.[117] 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.[81] Establishing adherence strategies tailored to the patient's needs may prevent or reduce infectivity and susceptibility rates.

Clinical pearl: Unit-dose medications are suggested to reduce the risk of infection.

Cleaning and Maintenance of Aerosol Delivery Devices

Preventing Infection and Malfunction of Home Aerosol Devices: Cleaning instructions for various aerosol devices vary and are illustrated below.

- **Pressurized Metered-Dose Inhalers:** The plastic container of pMDIs should be cleaned at least once a week[71,118] as shown in Table 15.
- **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 16 provides the steps that are used for cleaning the pMDI accessory device.
- **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 wipe the mouthpiece of the DPI with a clean, dry cloth after each use.

Table 15. Cleaning the pMDI canister

Frequency of cleaning: at least 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 to avoid getting it 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 to allow the flap to come down and the spray hole to 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)

Table 16. Cleaning instructions for valved holding chamber or spacer

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

Disassemble the device for cleaning.

Soak the valved holding chamber or spacer 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 overnight.

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.

Table 17. Cleaning instructions for the jet nebuilzer[119]

The 2012 AARC Clinical Practice Guideline states, "Jet nebulizers should be cleaned, rinsed with sterile water, and air-dried between treatments on the same patient."

Clean 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 in Table 18.

1. Clean the nebulizer parts with dish detergent and water. Tap water is acceptable for this step only.
2. Disinfect with one of the following options (choice based on permission by the manufacturer and patient preference):

Table 18. Cold and Heat Disinfection Methods

Cold method:

Soak in 70% isopropyl alcohol for 5 minutes. → Do not mix isopropyl alcohol and hydrogen peroxide.

Soak in 3% hydrogen peroxide for 30 minutes.

Rinse with sterile water only. Do not use tap water for rinsing.

Heat method:

Boil for 5 minutes OR microwave for 5 minutes.

Wash in a dishwasher if the dishwasher achieves a temperature of 158°F or 70°C for 30 min. Use an electric steam sterilizer.

Rinse (if using a cold disinfectant) with sterile water.

Air-dry thoroughly prior to storage.

Note: Manufactures instructions for use are not always compatible with all of the disinfecting options in evidence-based practice guidelines and vice versa.[115]

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.[120] 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.[121-124] Therefore, unit-dose medications are recommended whenever possible.[125] Also, it is important to avoid contaminating drug solutions.
- **Infection Transmission:** The transmission of infectious agents 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.[126-127] 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.[128-129] 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.

Table 19. Resources for Infection Prevention and Guidelines

American Association for Respiratory Care	rc.rcjournal.com/content/57/4/613.full.pdf
Association for Professionals in Infection Control and Epidemiology (APIC)	http://www.apic.org/
Centers for Disease Control and Prevention	www.cdc.gov/mmwr/preview/mmwrhtml/rr5303a1.htm
Centers for Disease Control and Prevention (CDC)/ Healthcare Infection Control Practices Advisory Committee (HICPAC)	https://www.cdc.gov/hicpac/
Cystic Fibrosis Foundation	https://www.cff.org/For-Caregivers/Clinical-Care-Guidelines/Infection-Prevention-and-Control-Care-Guidelines/
Healthcare Infection Control Practices Advisory Committee (HICPAC)	https://www.cdc.gov/hicpac/ https://www.cdc.gov/hicpac/pdf/guidelines/Disinfection_Nov_2008.pdf
Infectious Diseases Society of America	https://www.idsociety.org/Index.aspx
Occupational Safety and Health Administration (OSHA)	https://www.osha.gov/Publications/OSHA3512.pdf
Society for Healthcare Epidemiology of America (SHEA)	http://www.shea-online.org/
World Health Organization	http://www.wpro.who.int/publications/docs/practical_guidelines_infection_control.pdf

10. Educating Patients in the 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.[130] "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 their MDIs or DPIs correctly.[17,131] Continued regular contact with the health care team helps ensure proper device use, which has been shown to deteriorate over time.[132] 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.[131]

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, and differing levels of cognitive function, hand strength, and lifestyle settings. All of these can impact adherence to therapy, therapeutic outcomes, and quality of life.[17] 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.[133]

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.[134] 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.[135] 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.[136]

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 medications, when available, is recommended to help lower the cost. National prescription assistance programs for low-income families are also available and include the Partnership for Prescription Assistance, the Together RX Access Program and NeedyMeds. 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.[137] 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.[133] 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.[133] 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.[138] Although a physician's intervention is very effective at decreasing health care usage, lack of time for clinical visits makes education a challenging component for a physician. A systematic review by Clark et al found that a multi-disciplinary team of health care providers working together to educate the patient and the caregiver help reduce asthma-related symptoms and improve quality of life.[139]

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.[131,133]

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.[17,140]

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.[17] The medication 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.[141-143] 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 20 lists the common errors and mistakes that can occur with each type of device.[117,142-143]

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 20). Failure to shake most pMDIs or to prime the inhaler can decrease the amount of medication

Table 20. Common problems, disadvantages, and errors with each type of aerosol generator
(Modified, with permission, from References 9 and 71)

Pressurized Metered-Dose Inhalers

Errors in technique

- Inadequate priming/shaking/mixing before use
- Excessive priming of the inhaler prior to every dose
- Failing to sit up tall or stand
- Failing to tilt head upright
- Failing to remove cap before use
- Positioning the inhaler incorrectly for inhalation
- Failing to coordinate pMDI depression (actuation) on inhalation
- Actuating pMDI at point that lung is expanded (total lung capacity)
- Actuating pMDI prior to inhalation
- Actuating pMDI multiple times during single inhalation
- Actuating pMDI into mouth but inhaling through nose
- Swallowing the medication after actuation of the inhaler instead of inhaling
- Exhaling during actuation
- Inhaling too rapidly during actuation
- Abrupt discontinuation of inspiration as aerosol hits the throat
- Lack of breath holding after inhalation
- Using the inhaler when the mouthpiece is not clean
- Using the inhaler when the indicator is at "0" or the inhaler is empty
- Lack of adequate hand strength or flexibility to actuate pMDI
- Mixing up the pMDI rescue inhaler and controller medication, especially if the inhalers are the same color (i.e., ProAir and Symbicort)

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

- Swallowing the capsule for inhalation instead of using the capsule in the inhaler
- Failure to pierce the capsule or load the dose
- Positioning the inhaler or the body incorrectly for inhalation
- Shaking the inhaler
- Covering the air vents
- Exhaling into the inhaler
- Continuing to pierce the capsule while inhaling the medication
- Inhaling too slowly and too shallow of a breath
- Using the inhaler when it is empty
- Storing capsules within the inhaler
- Washing the inhaler or getting the inhaler wet

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

delivered. Using the pMDI when it is empty continues to be a problem, even with dose indicators. In one survey, 72% of patients said they continued to use their pMDI until there was no sound when it was actuated.[78] A pMDI can continue to produce a spray with propellant but little or no drug if it is actuated after its rated capacity.

Common Patient Errors with Holding Chambers/Spacers

Common errors that can occur with valved holding chambers/spacers are also listed in Table 20. 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. The 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. 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.[41,143] 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 20). DPI designs and uses vary depending upon the medication regimen prescribed. All of this variance among the DPIs can be challenging and confusing for the patient and the health care provider. The overall technique of inhaling the medication using a DPI is the same for all of the devices. Newer designs are decreasing the number of steps needed to deliver the medication to the lungs and making dose indicators more visible. Combining medications into one inhaler is decreasing the number of inhalers needed. Cost and frequent formulary changes remain a problem for both patients and prescribers. Confusion with duplications of therapy is common when an insurance formulary change occurs.

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 20). 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 return demonstration at every patient visit.
5. Review patient use of the device at each return visit.
6. Review the understanding of the patient on the proper use of the devices at each return visit (when to use, purpose of drug, prescribed frequency).

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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

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