

special report

Device Selection and Outcomes of Aerosol Therapy: Evidence-Based Guidelines*

American College of Chest Physicians/American College of Asthma, Allergy, and Immunology

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Background: The proliferation of inhaler devices has resulted in a confusing number of choices for clinicians who are selecting a delivery device for aerosol therapy. There are advantages and disadvantages associated with each device category. Evidence-based guidelines for the selection of the appropriate aerosol delivery device in specific clinical settings are needed.

Aim: (1) To compare the efficacy and adverse effects of treatment using nebulizers vs pressurized metered-dose inhalers (MDIs) with or without a spacer/holding chamber vs dry powder inhalers (DPIs) as delivery systems for β -agonists, anticholinergic agents, and corticosteroids for several commonly encountered clinical settings and patient populations, and (2) to provide recommendations to clinicians to aid them in selecting a particular aerosol delivery device for their patients.

Methods: A systematic review of pertinent randomized, controlled clinical trials (RCTs) was undertaken using MEDLINE, EmBase, and the Cochrane Library databases. A broad search strategy was chosen, combining terms related to aerosol devices or drugs with the diseases of interest in various patient groups and clinical settings. Only RCTs in which the same drug was administered with different devices were included. RCTs (394 trials) assessing inhaled corticosteroid, β_2 -agonist, and anticholinergic agents delivered by an MDI, an MDI with a spacer/holding chamber, a nebulizer, or a DPI were identified for the years 1982 to 2001. A total of 254 outcomes were tabulated. Of the 131 studies that met the eligibility criteria, only 59 (primarily those that tested β_2 -agonists) proved to have useable data.

Results: None of the pooled metaanalyses showed a significant difference between devices in any efficacy outcome in any patient group for each of the clinical settings that was investigated. The adverse effects that were reported were minimal and were related to the increased drug dose that was delivered. Each of the delivery devices provided similar outcomes in patients using the correct technique for inhalation.

Conclusions: Devices used for the delivery of bronchodilators and steroids can be equally efficacious. When selecting an aerosol delivery device for patients with asthma and COPD, the following should be considered: device/drug availability; clinical setting; patient age and the ability to use the selected device correctly; device use with multiple medications; cost and reimbursement; drug administration time; convenience in both outpatient and inpatient settings; and physician and patient preference. (CHEST 2005; 127:335–371)

Key words: aerosols; bronchodilators; corticosteroids; drug delivery systems; dry powder inhalers; metaanalysis; metered-dose inhalers; nebulizers

Abbreviations: CFC = chlorofluorocarbon; DPI = dry powder inhaler; ED = emergency department; MDI = metered-dose inhaler; NPPV = noninvasive positive pressure ventilation; PEFR = peak expiratory flow rate; RCT = randomized controlled trial; sGaw = specific airway conductance

The use of inhaled aerosol medications for the treatment of pulmonary diseases, which became well-established in the last half of the 20th century, has advantages over oral and parenteral routes of delivery. The use of inhaled aerosols allows selective treatment of the lungs directly by achieving high drug concentrations in the airway while reducing systemic adverse effects by minimizing systemic drug levels.¹ Inhaled β_2 -agonist bronchodilators produce a more rapid onset of action than oral delivery. Some drugs are only active with aerosol delivery (eg, for asthma patients, cromolyn and ciclesonide; for cystic fibrosis patients, dornase alfa). Aerosol drug delivery is painless and often convenient. For these reasons, the National Asthma Education and Prevention Pro-

gram guidelines² favor aerosol inhalation over the oral route or parenteral (ie, subcutaneous, IM, or IV) route. Similarly, the National Heart, Lung, and Blood Institute/World Health Organization Global Initiative for Chronic Obstructive Lung Disease recommended that bronchodilator medications are central to symptom management in COPD patients and that inhaled therapy is preferred.³

There are also disadvantages to aerosol drug therapy. One of the most important disadvantages is that specific inhalation techniques are necessary for the proper use of each of the available types of inhaler device. A less than optimal technique can result in decreased drug delivery and potentially reduced efficacy.^{4,5} Improper inhaler technique is common among patients.^{6–8} The proliferation of inhalation devices that are available for patients has resulted in a confusing number of choices for the health-care provider and in confusion for both clinicians and patients trying to use these devices correctly. Several studies have demonstrated lack of physician, nurse, and respiratory therapist knowledge of device use.^{9–13} Inhaler devices are less convenient than oral drug administration insofar as the time required for drug administration may be longer and some patients may find the device less portable. This is particularly true for conventional compressed-air nebulizers, the oldest of the currently used types of aerosol delivery devices.

Device manufacturers have long been aware of the importance of portability and ease of use with aerosol delivery devices. As a result, these devices have evolved over time. From the 19th century until 1956, compressed-air nebulizers (also called *jet nebulizers*) were the only devices that were in common clinical use for the administration of inhaled aerosol drugs. In 1955, the pressurized metered-dose inhaler (MDI) was developed at Riker Laboratories (now 3M Pharmaceuticals; St. Paul, MN).¹⁴ Ultrasonic nebulizers, which utilize high-frequency acoustical energy for the aerosolization of a liquid, were introduced in the 1960s.^{15,16} In 1971, Bell and colleagues¹⁷ introduced the first dry powder inhaler (DPI), known as the *Spinhaler*, for the inhalation of cromolyn sodium. This and subsequent DPIs have been “breath-actuated,” providing drug only when demanded by patient inhalation, thus avoiding a common error with MDI use, the improper timing of inhaler actuation. Breath-actuated MDI devices (eg, the Autohaler; 3M Pharmaceuticals) are also triggered by patient inhalation to release the drug on demand.

Investigators developed open-tube spacer devices, intended for use with MDIs, in the late 1970s.^{18–20} The addition of a one-way valve (holding chamber)¹⁸ or blind reservoir (ie, reverse-flow spacer)^{21,22} al-

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Professor Dolovich has served as a speaker for Forest Laboratories, 3M Pharma, and Aventis, and as a consultant for GlaxoSmithKline and Delex Therapeutics, and has received research funding from 3M Pharma, Trudell Medical International, and Altana Pharma. Dr. Ahrens, in the past 12 months, has received research funding from or has had a consulting relationship with the following organizations with a potential financial interest in the subject of the manuscript: AstraZeneca; Aventis; Boehringer Ingelheim; GlaxoSmithKline; Innovata Biomed Limited; Medic-Aid Limited; Monaghan Medical Corporation; and 3M Corporation. Dr. Hess has served as a consultant for Pari and has received research funding from Cardinal Health. Dr. Anderson has participated in clinical trials for GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, and Novartis. Dr. Dhand has served as a speaker for GlaxoSmithKline and Boehringer Ingelheim, has sponsored meetings for GlaxoSmithKline, Boehringer Ingelheim, and Sepracor, and has performed research funded by Sepracor Inc and Omron. Dr. Rau has no financial interest or involvement in any organization with a direct financial interest in the subject of this article, but he has served as a consultant for Respironics, as a speaker for Sepracor Pharmaceutical, and as a consultant and speaker for and performed research funded by Trudell Medical International and Monaghan Medical Corporation. Dr. Smaldone has served as a consultant to several device and pharmaceutical companies that are connected to aerosol therapy, primarily the nebulization of drugs. Those companies with a direct financial interest in nebulization include Monaghan/Trudell Medical International, Aerogen, Pari, and Profile Therapeutics.

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lowed the aerosol delivered by the MDI to be contained in the spacer for a finite period of time, thereby circumventing the need for the coordinated actuation of the MDI with inhalation. Other spacer/holding chamber designs followed, and today there are several devices that vary in design, shape, size, and assembly. The design of MDIs changed little between 1956 and the 1980s. However, the 1987 Montreal protocol mandated the phaseout of the use of chlorofluorocarbons (CFCs) as propellants in all MDIs. This resulted in a redesign of MDIs in the 1990s, utilizing hydrofluoroalkane propellants.²² Some of these formulations produce aerosols with different characteristics that behave differently in patients than their predecessors.²³

Each type of aerosol device has its own advantages and disadvantages (Table 1). Nebulizer/compressor systems require minimal patient cooperation and coordination, but are cumbersome and time-consuming to use. Matching nebulizers with associated air compressors is necessary to assure optimal efficiency of drug delivery. MDIs are quicker to use and highly portable, but require the most patient training to ensure coordination for proper use. Up to 70% of patients fail to use them properly. The improper timing of MDI actuation with breath initiation is a common problem.⁷ DPIs are easier to use than MDIs because they are breath-actuated, but require a relatively rapid rate of inhalation in order to provide the energy necessary for drug aerosolization.

Table 1—Advantages and Disadvantages of Each Type of Aerosol-Generating Device or System Clinically Available*

Type	Advantages	Disadvantages
Small-volume jet nebulizer	Patient coordination not required Effective with tidal breathing High dose possible Dose modification possible No CFC release Can be used with supplemental oxygen Can deliver combination therapies if compatible	Lack of portability Pressurized gas source required Lengthy treatment time Device cleaning required Contamination possible Not all medication available in solution form Does not aerosolize suspensions well Device preparation required Performance variability Expensive when compressor added in
Ultrasonic nebulizer	Patient coordination not required High dose possible Dose modification possible No CFC release Small dead volume Quiet Newer designs small and portable Faster delivery than jet nebulizer No drug loss during exhalation (breath-actuated devices)	Expensive Need for electrical power source (wall outlet or batteries) Contamination possible Not all medication available in solution form Device preparation required before treatment Does not nebulize suspensions well Possible drug degradation Potential for airway irritation with some drugs
Pressurized MDI	Portable and compact Treatment time is short No drug preparation required No contamination of contents Dose-dose reproducibility high Some can be used with breath-actuated mouthpiece	Coordination of breathing and actuation needed Device actuation required High pharyngeal deposition Upper limit to unit dose content Remaining doses difficult to determine Potential for abuse Not all medications available Many use CFC propellants in United States
Holding chamber, reverse-flow spacer, or spacer	Reduces need for patient coordination Reduces pharyngeal deposition	Inhalation can be more complex for some patients Can reduce dose available if not used properly More expensive than MDI alone Less portable than MDI alone Integral actuator devices may alter aerosol properties compared to native actuator
DPI	Breath-actuated Less patient coordination required Propellant not required Small and portable Short treatment time Dose counters in most newer designs	Requires moderate to high inspiratory flow Some units are single dose Can result in high pharyngeal deposition Not all medications available

*Modified from Dolovich et al.¹⁴²

Younger patients and patients in acute distress may not be able to generate the necessary flow rates.^{2,24} Breath-actuated MDIs are also easier to use, but are currently available in the United States for only a single drug (*ie*, the β_2 -agonist pirbuterol). Holding chambers used with MDIs remove the necessity of careful timing between inhalation and MDI actuation. However, they are more bulky to carry than the MDI by itself or a DPI. The improper use of holding chambers (*eg*, placing multiple puffs in the chamber before inhalation or waiting too long between MDI actuation and inhalation) can actually reduce drug delivery to the lungs.

Several factors can guide clinicians on the choice of a device for a specific patient. One factor is the age of the subject (Table 2).² Another factor is the availability of the drug formulation, as not all drugs are available in each type of aerosol delivery device. The clinical setting (*eg*, outpatient, emergency department (ED), hospitalized inpatient, or intensive care setting) and the disease being treated (*eg*, COPD vs asthma) also influence the choice of aerosol device.

Several systematic reviews and metaanalyses related to the selection of an aerosol delivery device have been published. In a metaanalysis, Turner et al²⁵ concluded that bronchodilator delivery by means of nebulizer or MDI is equivalent in the treatment of adults with acute airflow obstruction. A systematic review by Amirav and Newhouse²⁶ compared MDIs with accessory devices to nebulizers in children with acute asthma. While their results showed no differences between the types of delivery systems, it was concluded that the MDI with an accessory device (*ie*, a spacer or holding chamber) should be considered the preferred mode of aerosol delivery. A systematic review²⁷ of the management of acute exacerbations of COPD concluded that there is insufficient evidence that either an MDI or a nebulizer is superior. Cates et al²⁸ and Cates,²⁹ in systematic reviews of spacers and holding chambers vs nebulizers for β_2 -agonist treatment of acute asthma, concluded that an MDI with a holding chamber produces

outcomes that are at least equivalent to those achieved with the use of a nebulizer. Several systematic reviews^{30–32} have compared MDIs to DPIs and have concluded that there is no evidence that either device is superior to the other for bronchodilator therapy.

While systematic reviews provide key evidence summaries, they do not present specific recommendations for practice. The reasons for this include a focus on restricted populations and outcomes, and the lack of a process to ensure recommendations reflect patients' values and preferences.³³ However, clinicians require information and guidance concerning the best estimates of benefits and risks of alternatives, and concerning the explicit tradeoffs between these benefits and risks, or, in other words, evidence-based guidelines. Therefore, despite the availability of the above systematic reviews, we believe that evidence-based guidelines are still needed. Consequently, the intent of this project was to assess the available scientific evidence addressing the question of whether device selection affects efficacy and the adverse effects of treatment. Therefore, we set out to systematically review relevant evidence from randomized, placebo-controlled clinical trials and to provide general recommendations based on the tradeoffs that this evidence provides. Our recommendations relate to issues that clinicians should consider in selecting a particular therapeutic aerosol delivery device for their patients in each of several commonly encountered clinical settings.

METHODOLOGY

We undertook a systematic overview of the pertinent literature. The databases that were searched were MEDLINE, Embase, and the Cochrane Library (Table 3, available on-line only). A broad search strategy was chosen to combine terms relating to aerosol devices or drugs with those relating to the diseases of interest in various patient groups and in a number of clinical settings (Fig 1). Only randomized controlled trials (RCTs) in human subjects published in English were selected. The search identified an initial set of approximately 2,100 publications spanning the years 1972 to 2000. Two reviewers independently assessed each abstract of these publications to determine whether they met the eligibility criteria (*ie*, RCT addressing the relevant population, intervention, and outcome). This review identified 394 RCTs assessing inhaled corticosteroid, β_2 -agonist, and anticholinergic agents that were delivered by MDI, MDI with spacer/holding chamber, nebulizer, or DPI. These 394 studies were coded (for setting, population, disease, and device) to provide a second

Table 2—General Age Requirements for Correct Use of Aerosol Delivery Device Types*

Aerosol Delivery Method	Minimum Age
Small-volume nebulizer	≤ 2 yr
MDI	> 5 yr
MDI with chamber	> 4 yr
MDI with chamber and mask	≤ 4 yr
MDI with endotracheal tube	Neonate
Breath-actuated MDI	> 5 yr
DPI	≥ 5 yr

*Based on National Asthma Education and Prevention Program.²

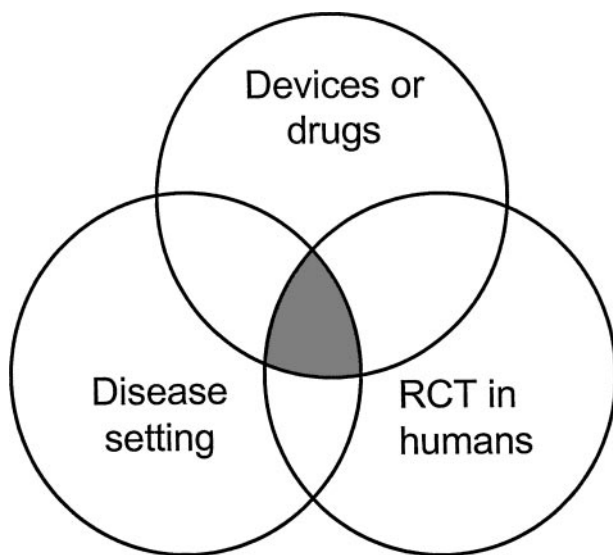


FIGURE 1. Studies selected included those overlapping (illustrated by shaded area) devices or drugs, disease setting, and RCTs.

screening to identify studies in which the same drug was administered with different devices. Studies were excluded if they only compared devices of the same type (eg, DPI with DPI) or only compared oral or parenteral therapy with the aerosol therapy. Data were then extracted from the remaining 131 studies. A total of 254 outcomes were tabulated (Table 4, available on-line only). Because this proved unwieldy, we created a taxonomy of 10 categories (Table 5) and, as many of the outcomes were similar expressions of the same measurement, specified a hierarchy of outcomes within this taxonomy. Of the 131 studies, only 59 proved to have useable data

(Table 6). These studies primarily tested β_2 -agonists. Few studies of corticosteroids met our eligibility criteria.

Separate metaanalyses were carried out for each specific clinical setting being considered. The weighted standardized difference between treatment groups in the outcome of interest was calculated using the mean scores and their SDs. We combined results across end points of FEV₁, peak flow, and specific airway conductance (sGaw), and calculated the effect size in SD units. For studies that made measurements at multiple time points, the last time point was used for analysis. For studies with multiple doses, analyses using the first dose and the last dose were performed. All outcomes reported are in SD units. In studies that provided data for more than one of these outcomes, we used the outcome that was highest in the hierarchy. To assess whether the magnitude of the heterogeneity of differences in the apparent treatment effect across studies was greater than one might expect by chance, we conducted a test based on the χ^2 distribution with $N - 1$ degree of freedom, where N is the number of studies. No important effects were seen in any of the group analyses, and there was very little heterogeneity in any of the data. In general, our statistical methods relied on the approaches described by Fleiss³⁴ and by Hedges and Olkin.³⁵

We found that the studies were heterogeneous in purpose, design, and patient selection, and determined that these descriptors would influence the interpretation and relevance of the studies for clinical use by patients. Therefore, we grouped the studies that were reviewed into three general types

Table 5—Ranked Taxonomy of Outcomes*

Outcome	Ranking
FEV ₁	FEV ₁ ; FEV ₁ % predicted; FEV ₁ L/% predicted; FEV ₁ /FVC ratio; FEV ₁ mL; FEV ₁ % change from initial; FEV ₁ % predicted % change from initial
PF	PF L/min; PEF – AM pre, PEF – PM pre, PEF – AM post, PEF – PM post; we decided there was little to choose between the additional measures, though in general pre should be chosen over post and AM should be chosen over PM
Mechanics	sGAW; sGAW s/kPa; the rest were arbitrary
Symptoms/physical findings	Asthma score, dyspnea score, wheeze, sleep disturbances, and dyspnea on exertion; the rest were arbitrary within the following categories: shortness of breath, unspecified symptoms, cough, physiologic measures
FVC	FVC; FVC mL; FVC % predicted; FVC L/% predicted; the following were arbitrary: IVC should be the last choice
FEF _{25–75%}	FEF _{25–75} (112) + FEF _{25–75} ; FEF _{25–75} % predicted; the rest were arbitrary
Blood gas	SaO ₂ ; PO ₂ ; PCO ₂ ; pH
Adrenergic use	β_2 -adrenergic use, total No. of doses, BD puffs
Technique/preference	Preference for technique, device rating; the following were arbitrary: design should be second to last choice, taste should be the last choice
Heart rate, BP, ECG	Heart rate; pulse rate; heart rate increase

*PF = peak flow; PEF = peak expiratory flow; IVC = inspiratory vital capacity; FEF_{25–75%} = forced expiratory flow, midexpiratory phase, BD = bronchodilator.

Table 6—Reasons Trials Were Not Included in Analysis

Comparison	Studies, No.	Reasons for Exclusion						Total for Analysis, No.
		Not RCT	Not Comparison of Interest	Not Independent Subgroups	Only Usable Baseline Data	No Useable Data	No Comparable Trials or Outcomes	
Overall	131	3	20	2	7	30	11	59
MDI vs DPI	45	1	0	0	2	12	2	28
Nebulizer vs MDI + spacer	32	0	0	1	2	6	4	19
MDI vs MDI + spacer	17	0	1	0	3	7	2	5
DPI vs MDI + spacer	14	2	0	0	0	4	4	4
DPI vs nebulizer	3	0	0	0	0	0	3	0
MDI vs nebulizer	5	0	0	0	0	1	4	0
Intermittent vs continuous nebulizer	7	0	0	1	0	2	0	4

(types 1, 2a, and 2b) based on the intended purpose and specific study design used.

Type 1 Trials: Device Performance Under Conditions of Actual Clinical Use

These trials were intended to compare the effectiveness of the devices and drug being studied in a setting of “real-world” clinical use with the measured outcomes relevant to the accepted indication for the drug in this setting. Studies that compared the effect of a β_2 -agonist agent delivered by nebulizer, DPI, and/or MDI in patients presenting to the ED with acute asthma are an example of this type of study. These studies typically evaluate outcomes such as improvement in lung function and oxygenation or hospital admission rate. Studies that compare the effect of inhaled corticosteroids delivered by different devices over a period of weeks, and assess daily asthma symptoms, β_2 -agonist use, and daily peak flow measurement are other examples of such studies.

Type 2 Trials: Device Performance in the Clinical Laboratory Setting

These studies compare drug delivery to the lungs and the clinical response to drugs administered by different devices under carefully controlled clinical laboratory conditions. These studies were typically performed to satisfy regulatory requirements during the process of drug development and registration. Participating patients are usually carefully trained in and monitored for the proper use of the devices. These studies do not directly evaluate the performance of the devices in settings and conditions in which patients actually use them as part of the management of their asthma or COPD (eg, a patient who awakens in the night with acute bronchospasm). The most common examples of this type of study are

outpatient evaluations of devices containing short-acting β_2 -agonists. Most of these studies measure increases in lung function in response to the β_2 -agonist in patients who have developed a mild-to-moderate degree of bronchospasm after having their usual asthma medication withheld. A few measure the inhibition of bronchial provocation with exercise compounds (eg, methacholine or histamine). Type 2 studies can be divided into two subtypes based on the kind of analysis performed in the study.

Type 2a Trials: Analyzing Differences in Response Variables: These studies typically compare mean increases in lung function values (eg, FEV₁) produced by the different devices. These studies are termed *response axis comparisons* by the US Food and Drug Administration and are now widely recognized to be relatively insensitive to true differences in drug delivery by different devices.³⁶ Typically, the doses used are near the top of the β_2 -agonist dose-response curve that patients exhibit in this setting. As a result, the studies are commonly unable to distinguish differences in response to either a different dose via the same device or to delivery by different devices.

Type 2b Trials: Estimating Differences in Clinical Potency: These studies establish dose-response curves for each of the devices being compared and then use differences in the position of these curves to estimate differences in the clinical potency of the devices (known as the relative potency or potency ratio). The results of this analysis yield statements such as “1 actuation (or microgram of drug) delivered from ‘device A’ is equivalent to ‘X’ number of actuations (or micrograms) delivered from ‘device B.’” The analysis also calculates a confidence interval for the estimate of the relative potency as an indicator of how reliable the estimate is. These studies are

termed “dose-scale comparisons”³⁶ and are recognized as being the most reliable way of identifying true difference in drug delivery to the site of action in the lung.

Members of the Writing Committee assumed responsibility for drafting individual sections of the final document, including the recommendations. To grade the strength of the recommendations, we used a system adopted by the Health and Science Policy Committee of the American College of Chest Physicians (Table 7). The draft document was reviewed by all members of the Writing Committee for content and accuracy.

RESULTS AND RECOMMENDATIONS

Device Selection in the Hospital Acute Care Setting

Aerosol Delivery of Short-Acting β_2 -Agonists in the Hospital ED: Nineteen RCTs that compared aerosol delivery devices in the ED met the criteria for inclusion in the analysis. All used a parallel design and assessed the response to one of three β_2 -agonist

bronchodilators (*ie*, albuterol, metaproterenol, or terbutaline). No studies were available that compared nebulizers to MDIs alone in patients with acute asthma presenting to the ED. The majority of these studies compared delivery by nebulizer to that by an MDI with a spacer/holding chamber. All were type 1 studies that enrolled patients presenting to the ED with acute asthma symptoms. Only 3 of the 19 studies included in the analysis studied delivery by DPI in the ED setting. None of the studies specifically stated that they had screened patients for their ability to use the device correctly. The studies also omitted a detailed discussion of the device technique that was used to inhale the medications. Most of these studies measured acute physiologic responses to treatment, and a smaller number measured effects on asthma sign/symptom scores. Few studies offer other clinically important outcome measures such as hospital admission rate, time in the ED, and readmissions to the ED. The cost of care and the fraction of patients who cannot use the device correctly were not reported in any of the studies. Eight stud-

Table 7—Scheme Used to Grade Recommendations

Grading of the strength of the recommendations is based on both the quality of the evidence and the net benefit of the diagnostic or therapeutic procedure:						
A	Strong recommendation					
B	Moderate recommendation					
C	Weak recommendation					
D	Negative recommendation					
I	No recommendation possible (inconclusive)					
E/A	Strong recommendation based on expert opinion only					
E/B	Moderate recommendation based on expert opinion only					
E/C	Weak recommendation based on expert opinion only					
E/D	Negative recommendation based on expert opinion only					
Quality of the evidence						
Good	Evidence is based on good RCTs or metaanalyses					
Fair	Evidence is based on other controlled trials or RCTs with minor flaws					
Low	Evidence is based on nonrandomized, case-control, or other observational studies					
Expert opinion	Evidence is based the consensus of the carefully selected panel of experts in the topic field.					
	There are no studies that meet the criteria for inclusion in the literature review.					
Net benefit						
These levels of net benefit to the patient (adjusted for risk) are based on clinical assessment of the test or procedure:						
Substantial						
Intermediate						
Small/weak						
None						
Conflicting						
Negative						
Relationship of strength of the recommendations scale to quality of evidence and net benefits						
	Net Benefit					
Quality of Evidence	Substantial	Intermediate	Small/Weak	None	Conflicting	Negative
Good	A	A	B	D	I	D
Fair	A	B	C	D	I	D
Low	B	C	C	I	I	D
Expert opinion	E/A	E/B	E/C	I	I	E/D

Table 8—Short-term Nebulizer vs MDI + Spacer/Holding Chamber Studies Using β_2 -Agonists for Pediatric Patients in the Acute Care Setting*

Study/Year/Study Type	Total Patients/ Patients per Group, No.	Lost to Follow-up, No. (Time)	Age Range	Drug/Device† (Dose)
Pediatric ER				
Ploin et al ⁴⁰ /2000/type 1	64/(32/31)	4	MDI: 12–51 mo (24.8 mo)‡ NEB: 11–56 mo (25.5 mo)‡	Albuterol/MDI + Babyhaler spacer (0.05 mg/kg) Nebulizer (0.15 mg/kg)
Rubilar et al ⁴² /2000/type 1	132	9	MDI: 7.2 ± 4.7 mo§ NEB: 8.5 ± 5.4 mo§	Albuterol/MDI + Aerocell spacer (0.2 mg q10 min) Hudson Updraft II nebulizer (0.25 mg/kg q13 min)
Schuh et al ⁴³ /1999/type 1	90/(30/30/30)	16 (5–17 yr)	5–17 yr (9.1)‡	Albuterol/MDI + AeroChamber spacer: GpI (< 25 kg 0.6 mg; 25–34 kg 0.8 mg; > 34 kg 1 mg; GpII 0.2 mg) WhisperJet Nebulizer GpIII (0.15 mg/kg to max of 5 g)
Robertson et al ⁴¹ /1998/ type 1	58/(155)	(4–12 yr)	4–12 yr MDI: 6.9 ± 2.4 yr§ NEB: 7.0 ± 2.5 yr§	Albuterol/< 25 kg: MDI + Volumatic spacer (0.6 mg) NEB (2.5 mg) > 25 kg: MDI + Volumatic spacer (1.2 mg) NEB (5.0 mg)
Williams et al ⁴⁴ /1996/type 1	60	0 (6 yr)	> 6 yr AeroChamber: 9.2 ± 2.8 yr§ ACE: 10.5 ± 31 yr§ NEB: 11.5 ± 3.3 yr§	Albuterol/MDI + AeroChamber and ACE spacer (0.36 mg q20 min) NEB (2.5 mg q 30 min)
Lin and Hsieh ³⁹ /1995/type 1	117	6	MDI: 5–16 yr (8.1 yr) NEB: 5–15 yr (8.4 yr)‡	Terbutaline/MDI + AeroChamber spacer (0.75 mg) NEB (2.5 mg)
Chou et al ³⁸ /1995/type 1	152	0 (2 yr)	> 2 yr	Albuterol/MDI + AeroChamber (0.3 mg) NEB (0.15 mg/kg up to 5.0 mg)
Pediatric ER and ICU				
Batra et al ³⁷ /1997/type 1	60 1–12 yr	0	1–12 yr MDI: 44.1 ± 25.8 mo§ NEB: 51.2 ± 27.1 mo§	Albuterol/MDI + M/S CiPLA spacer (0.2 mg) NEB (0.15 mg/kg)

*NS = not significant; NEB = nebulizer; % pred = % predicted. See Table 5 for abbreviations not used in the text.

†WhisperJet nebulizer, Intec Medical, Ingelwood, CO; Hudson UpDraft nebulizer II, model 1730, Hudson Oxygen Sales, Temecula, CA; Babyhaler spacer, GlaxoSmithKline France, Marly le Roi, France; ACE MDI spacer, DHD Healthcare, Wampsville, NY; M/S CiPLA spacer, M/S. CIPLA Ltd., Salem, Tamilnadu, India.

‡Median value in parentheses.

§Mean ± SD values.

||Weight > 25 g.

ies^{37–44} randomized pediatric patients to receive a β_2 -agonist agent by nebulizer or MDI with spacer/holding chamber (*ie*, Aerocell Lactantes [Grünwald-Danes; Chile], AeroChamber [Trudell Medical; London, ON, Canada], and Volumatic [Glaxo Wellcome; London, UK]) [Table 8]. Collectively, these studies enrolled patients with ages ranging from < 1 to 17 years. Most investigators reported no significant difference between these two techniques for pulmonary

function measures (*ie*, peak flow and FEV₁) or symptom scores. Metaanalyses of symptom scores and pulmonary function results showed no differences between the nebulizer and the MDI with a spacer/holding chamber (Fig 2, 3). One study⁴⁰ reported greater patient preference for the MDI with a spacer/holding chamber, and another study³⁸ reported shorter treatment times with the use of an MDI and a spacer/holding chamber. None of the studies included in the

Pulmonary Function	Vital Signs and Symptoms	Side Effects	Concomitant Care	Other Measures
Pulmonary index score ($p = 0.27$)			Preference for MDI + spacer > NEB ($p = 0.05$)	
	Respiratory rate nebulizer with MDI + spacer ($p = 0.01$) clinical score (NS)			
FEV ₁ % pred (NS)	Dyspnea score (NS)	Heart rate NEB with MDI + spacer ($p = 0.005$)	Accessory muscle score (NS)	
PF NEB > MDI + spacer ($p < 0.005$) (all patients)	Asthma score better after NEB than MDI + spacer ($p = 0.001$) (all patients)			
PF % pred (NS)	Respiratory rate (NS)			
FEV ₁ % pred MDI + spacer > NEB ($p = 0.039$); PF % pred MDI + spacer > Nebulizer ($p = 0.002$) FEF _{25-75%} % pred (NS) PF % pred (NS)	Clinical severity score (NS) Dyspnea score (NS) Severity score improvement (NS) Respiratory rate (NS) Dyspnea (NS)	Pulse rate (NS) Vomiting in ED MDI + spacer \leq NEB ($p < 0.05$) heart rate increase MDI + spacer \leq NEB ($p < 0.001$) Heart rate (NS)	Minutes to mean treatment time MDI + spacer \leq NEB ($p < 0.001$) No. of treatments NS Admission rate NS	SaO ₂ MDI + spacer with NEB ($p = 0.003$) SaO ₂ (NS) PO ₂ (NS) PCO ₂ (NS)

analysis evaluated DPI use in pediatric patients presenting to the ED.

In adult patients reporting to the ED with asthma symptoms (Table 9), six studies⁴⁵⁻⁵⁰ compared β_2 -agonist delivery by nebulizer to that by an MDI with a spacer/holding chamber. No study reported a significant difference in pulmonary function response to the two methods of delivery (Fig 3). Two studies^{47,48} addressed other important outcomes and reported no significant differences between devices for time in the ED, hospital admission rate, and frequency of ED discharge at 6 h. Similar findings were reported in studies⁵¹⁻⁵³ including both pediatric (*ie*, adolescent) and adult patients in ED settings. The three studies^{47,54,55} evaluating the use of a DPI

(*eg*, Rotahaler [GlaxoSmithKline; Ware, UK] and Turbuhaler [AstraZeneca; Lund, Sweden]) with adult patients in this setting reported no significant differences between DPI and the other two delivery methods for pulmonary function response and for other outcomes such as hours to hospital discharge (Table 10). Similar findings were noted for pediatric patients presenting to the ED in a study that was not included in this analysis.⁵⁶

One study⁵⁷ evaluated aerosol delivery devices in an ambulance setting. No significant differences were reported in pulmonary function response to a nebulizer, an MDI used alone, or an MDI with a spacer/holding chamber, but the effects on respiratory rate and duration of treatment were significantly

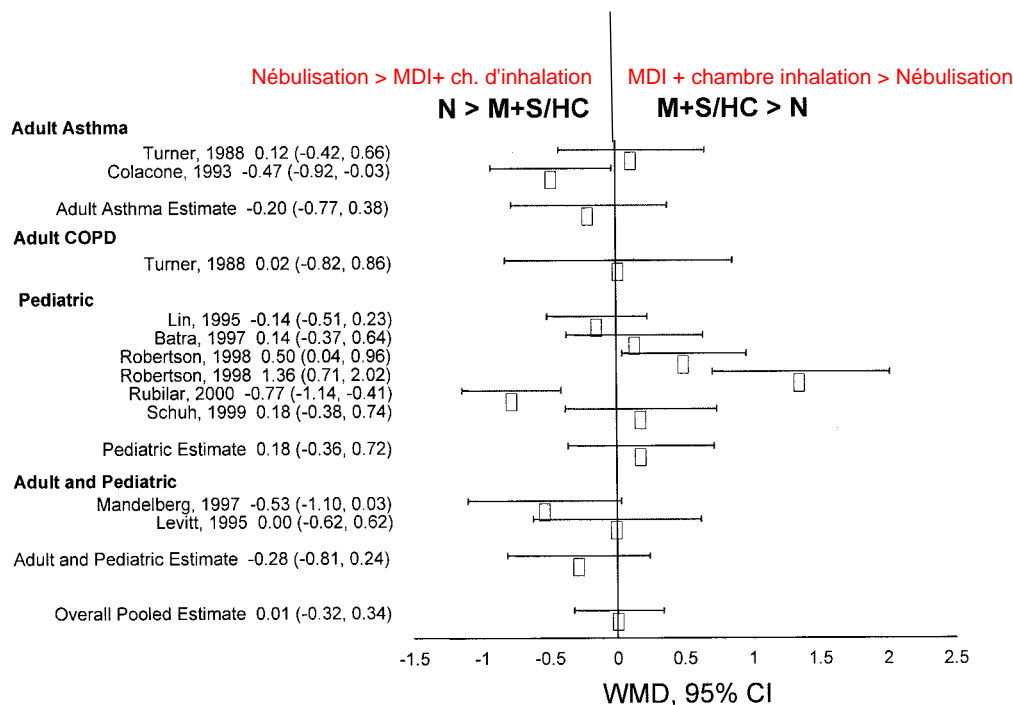


FIGURE 2. Weighted standardized mean difference (WMD) for symptom scores in ED/ICU trials using β_2 -agonists comparing nebulizer (N) vs MDI + spacer/holding chamber (M + S/HC).

better for the use of the MDI with holding chamber than for the other two methods.

Adverse effects appeared to be more common with nebulizer use. Heart rate change tended to be greater in patients using a nebulizer, but the effect across studies was significant only when pediatric and adult studies were analyzed together (Fig 4). These differences in heart rate between devices tended to be small in magnitude. One study³⁸ found vomiting to be more common with nebulizer use than with use of an MDI with a spacer/holding chamber, which likely was due to the larger dose given by nebulizer in these subjects.

Summary of RCT Results

- The delivery of β_2 -agonists in the ED setting by nebulizers or MDIs with holding chambers (eg, AeroChamber, Volumatic, or InspirEase [Key Pharmaceuticals; Kenilworth, NJ]) is equally effective for improving pulmonary function and reducing symptoms of acute asthma in both adult and pediatric patients (quality of evidence: good).
- The delivery of β_2 -agonists in the ED setting by DPI (eg, Rotahaler or Turbuhaler) has been inadequately studied, but trials in adults have suggested DPIs may be as effective as nebulizers or MDIs with spacer/holding chambers (quality of evidence: low).
- Nebulizer use in the ED setting is associated with greater increases in heart rate than with the use of an MDI with spacer/holding chamber, suggesting that a larger systemically absorbed dose is administered by nebulizers (quality of evidence: good).

Recommendations

1. Both the nebulizer and MDI with spacer/holding chamber are appropriate for the delivery of short-acting β_2 -agonists in the ED. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.
2. Because data for DPIs are limited, and high quality data for standard MDIs (without spacer/holding chamber) and breath-actuated MDIs are unavailable, we are unable to recommend the use of these devices in the ED until more information is available. Quality of evidence: low; net benefit: none; strength of recommendation: I.
3. Many factors would lead the clinician to appropriately select a particular type of aerosol delivery device in this setting. These factors include the patient's ability to use the device correctly, the preferences of the patient for the device, the unavailability of an appropriate drug/device combination, the compatibility between the drug and delivery device, the lack of time or skills to properly instruct the patient in the use of the device or to monitor the appropriate use, and the cost of therapy. Quality of evidence: low; net benefit: substantial; strength of recommendation: B.

Aerosol Delivery of Short-Acting β_2 -Agonists in the Inpatient Hospital Setting

Considering the common use of aerosolized drugs in hospitalized patients, there are surprisingly few

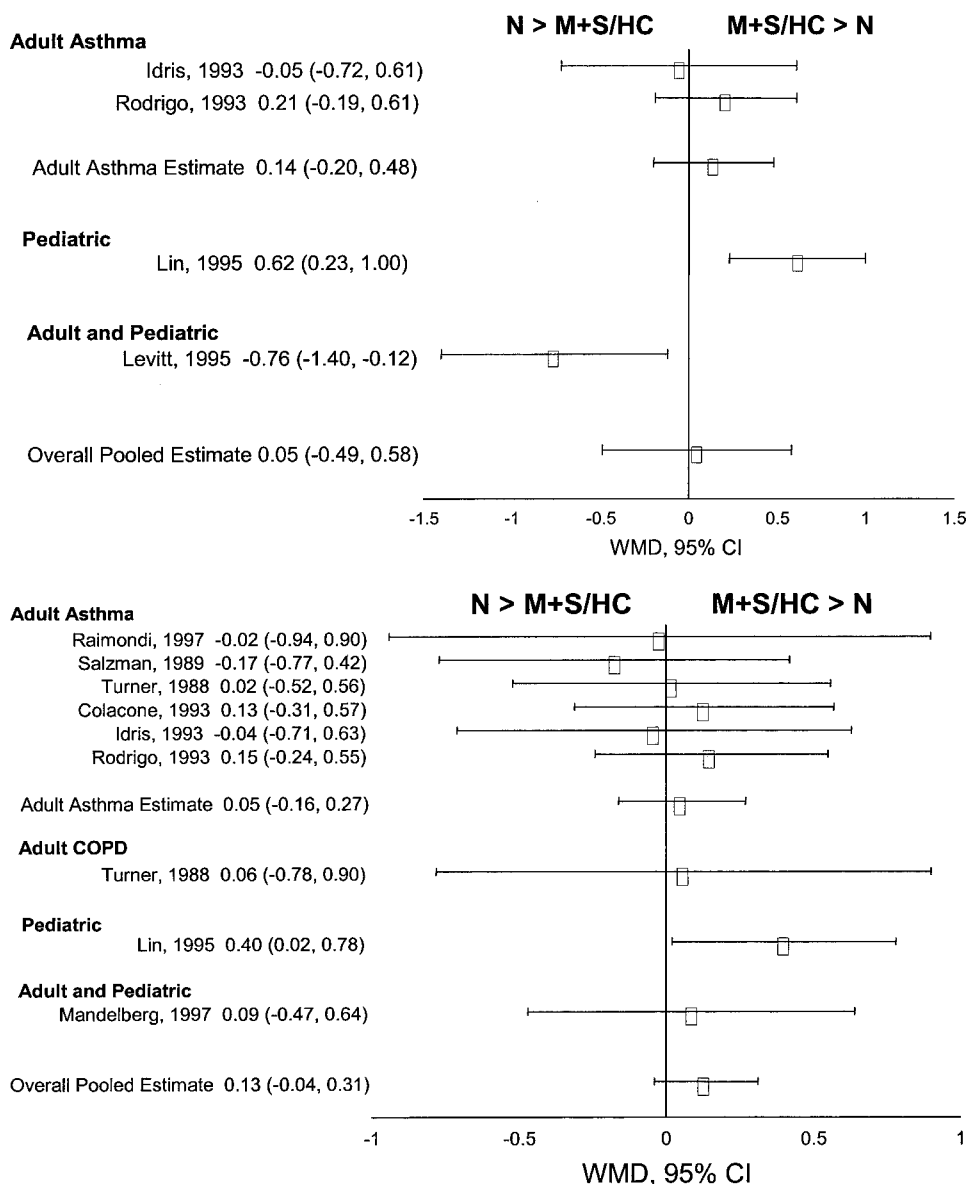


FIGURE 3. **Top:** weighted standardized mean difference for peak flow in ED/ICU trials using β_2 -agonists comparing nebulizer vs MDI + spacer/holding chamber. **Bottom:** weighted standardized mean difference for FEV₁ in ED/ICU trials using β_2 -agonists comparing nebulizer vs MDI + spacer/holding chamber. See the legend of Figure 2 for abbreviations not used in the text.

studies that have compared aerosol delivery devices in this setting (Table 11).^{53,58–63} Six type 1 studies^{53,58–61,63} included in the analysis compared nebulizers with MDIs having spacer/holding chambers in adult and pediatric patients. These studies reported no significant differences in pulmonary function between nebulizers and MDIs with spacer/holding chambers (Fig 5). One study⁶² compared MDI used alone with DPI use and also found no significant difference in peak expiratory flow rate (PEFR). However, as the deposition efficiency of the DPI tested was approximately half that of the MDI

tested, the authors elected to compare DPI doses that were twice that for the MDI, with the intent of producing equal responses. Other outcome variables such as length of hospital stay were similar for the nebulizer and MDI with a spacer/holding chamber. Reports of the cost of care are conflicting, without clear evidence of one device resulting in a greater cost than another. There is a paucity of data regarding the ability of patients to use these devices correctly in this setting. For β_2 -agonists, the impact of the differences in the time required to administer the therapy on patient responses was not analyzed.

Table 9—Short-term Nebulizer vs MDI + Spacer/Holding Chamber Studies Using β_2 -Agonists for Adult Patients in the Acute Care Setting*

Study/Year/Study Type	Total Patients, No.	Lost to Follow-Up, No.	Age Range	Drug/Device (Dose)
Adult ED studies				
Colacone et al ⁴⁵ /1993/type 1	85	5	MDI: 18–81 yr (41 yr) [†] NEB: 18–83 yr (43 yr) [†]	Albuterol/MDI + AeroChamber spacer (0.4 mg q30 min) NEB (2.5 mg q30 min, max 4 doses)
Idris et al ⁴⁶ /1993/type 1	35	0	MDI: 16–45 yr (25 yr) [†] NEB: 10–45 yr (23 yr) [†]	Albuterol/MDI + InspirEase spacer (0.36 mg q30 min) NEB (2.5 mg q30 min, max 6 doses)
Rodrigo and Rodrigo ⁴⁸ /1993/type 1	97	0	MDI: 18–50 yr (32.4 \pm 12.1 yr) [‡] NEB: 31.9 \pm 12.0 yr) [‡]	Albuterol/MDI + AeroChamber (0.4 mg q10 min, max 5.61 mg) NEB (1.5 mg q15 min, max 11.8 mg)
Salzman et al ⁴⁹ /1989/type 1	50	6	MDI: 32.5 \pm 12.5 yr [‡] NEB: 28.9 \pm 10.3 yr [‡]	Metaproterenol/MDI + AeroChamber (1 \times 500 μ g q5 min, max 1.95 mg) NEB (15 mg)
Raimondi et al ⁴⁷ /1997/type 1	18	0		Albuterol/MDI + AeroChamber spacer (0.4 mg) NEB (5.0 mg)
Adult ED/ICU				
Turner et al ⁵⁰ /1988/type 1	COPD group, 22; asthma group, 53	0	44 yr COPD group MDI: 55 \pm 4 yr [‡] NEB: 57 \pm 3 yr [‡] Asthma group: MDI: 38 \pm 3 yr [‡] NEB: 39 \pm 3 yr [‡]	Metaproterenol/MDI + InspirEase spacer (1.95 mg) NEB (15 mg)
Mandelberg et al ⁵² /1997/type 1	50	9	MDI: 65.8 \pm 13.64 yr [‡] NEB: 63.3 \pm 13 yr [‡]	Albuterol/MDI + Volumatic (0.2 mg albuterol sulfate) NEB (2.5 mg)
Levitt et al ⁵¹ /1995/type 1	40	0	MDI: > 18 yr (60.7 \pm 19 yr) [‡] NEB: 41.7 \pm 21 yr [‡]	Albuterol/MDI + AeroChamber (0.4 mg to max 2.4 mg q60 min for 180 min; mean total dose, 23.75 \pm 3.2 mg) NEB (15 mg/h for up to 3 hr; mean total dose, 28.1 \pm 7.3 mg)
Summer et al ⁵³ /1989/type 1	36	4	MDI: 63.19 yr [†] NEB: 62.69 yr [†]	Terbutaline/MDI + Brethancer spacer [§] (0.5 mg metaproterenol) NEB (15 mg)

*See Tables 5 and 8 for abbreviations not used in the text.

[†]Median values in parentheses.

[‡]Mean \pm SD values.

[§]Manufactured by the Asthma and Respiration Foundation of New Zealand, Wellington, NZ.

The inpatient setting presents a unique opportunity for health-care providers to instruct the patient on the proper use of each device, but the benefit of such an approach has not been assessed in randomized trials.

Summary of RCT Results

- In the inpatient setting, the available evidence suggests that there is **no difference in the pulmonary function response between using a nebulizer**

and using an MDI with a spacer/holding chamber for administering short-acting β_2 -agonist therapy (quality of evidence: good).

Recommendations

1. Both nebulizers and MDIs with spacer/holding chambers are appropriate for use in the inpatient setting. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.

Pulmonary Function	Vital Signs and Symptoms	Side Effects	Concomitant Care
FEV ₁ (NS)	Dyspnea score (NS)	Heart rate > 20 beats/min (NS)	
FEV ₁ % pred (NS) PF % pred (NS) FVC % pred (NS)	Respiratory rate (NS)	Heart rate (NS)	
FEV ₁ (NS) PF (NS) FVC (NS)		Tremor (NS)	β ₂ -adrenergic use (NS) Time in ED (NS) Hospital admission rate (NS)
FEV ₁ (NS) FVC (NS)	Respiratory rate (NS)	Pulse rate (NS)	
FEV ₁ (NS)			Hospital discharge at 6 h (NS)
FEV ₁ (NS)	Respiratory rate (NS) Borg scale (NS)	Heart rate MDI + spacer without NEB (p < 0.05)	
FEV ₁ (NS)	Respiratory improvement score-physician (NS) Respiratory improvement score-patient (NS)		
PF MDI + holding chamber < Nebulizer (p < 0.005)	Dyspnea score (NS)	Tremor (NS); heart rate (NS)	Hospital admission rate (NS)
FEV ₁ (NS) PF (NS) FVC (NS)			RCP time (NS) Length of stay (NS) Patient charge (NS)

2. Because the data for DPIs, standard MDIs without spacer/holding chambers, and breath-actuated MDIs have been inadequately studied in this setting, we are unable to recommend the use of these devices in patients requiring hospitalization for asthma or COPD until more information is available. Quality of evidence: low; net benefit: none; strength of recommendation: I.
3. Many factors would lead the clinician to appropriately select a particular type of aerosol delivery device in this setting. These include the patient's inability to use the device correctly, the preferences of the patient for the device, the unavail-

ability of the drug/device combination, the compatibility between the drug and the delivery device, the lack of time or skills to properly instruct the patient in the use of the device or in monitoring the appropriate use, and the cost of therapy. Quality of evidence: low; net benefit: substantial; strength of recommendation: B.

Intermittent vs Continuous Nebulizer Delivery of β₂-Agonists

Continuous aerosol bronchodilator therapy is used occasionally in patients with severe broncho-

Table 10—Short-term DPI Studies Using β_2 -Agonists in the Acute Care Setting*

Study/Year/ Study Type	Total Patients, No.	Lost to Follow-up	Age Range, yr	Drug/Device (Dose)	Pulmonary Function	Vital Signs and Symptoms	Side Effects	Concomitant Care
Nana et al ⁵⁴ /1998/type 1	86	0	MDI: 16–47 (37†) DPI: 16–49 (40†)	Albuterol/MDI + Volumatic (1 mg) DPI-Turbuhaler (2 mg)	FEV ₁ (NS) PIF (NS)	Symptom score (NS)		
Raimondi et al ⁴⁷ /1997/type 1	18	0	MDI: 33.7 ± 5.6† DPI: 42.8 ± 15†	Albuterol/MDI + AeroChamber (0.4 mg) DPI-Rotobaler (0.4 mg)	FEV ₁ (NS)			Hours to hospital discharge (NS)
Tonnesen et al ⁵⁵ /1994/type 1	68	6	50†	Terbutaline/MDI + Nebuhaler (2.5 mg) DPI-Turbuhaler (2.5 mg)	FEV ₁ (NS) PF (NS)	Respiratory rate (NS)	Heart rate (NS) Systolic BP (NS)	
Raimondi et al ⁴⁷ /1997/type 1	18	0	DPI: 42.8 ± 16† NEB: 39.1 ± 6.5†	Albuterol/DPI-Rotobaler (0.4 mg) NEB (5 mg)	FEV ₁ (NS)			Hours to hospital discharge (NS)

*PIF = peak inspiratory flow. See Tables 5 and 8 for abbreviations used in the text.

†Median value.

‡Mean ± SD values.

spasm in the ED or ICU. Its use is limited to the most severe exacerbations of asthma. One systematic review⁶⁴ supports the equivalence of continuous and intermittent albuterol nebulization in the treatment of acute adult asthma. Continuous vs intermittent administration of β_2 -agonists was compared in six randomized type 1 studies enrolling either adult patients or pediatric patients in the ED and ICUs (Table 12).^{65–70} These six studies reported no differences in pulmonary function changes comparing these administration approaches (Fig 6). Changes in asthma score and dyspnea are also similar for both modalities.^{65,70} Two studies have reported greater staff (*eg*, respiratory therapy) time requirements for intermittent nebulization compared to continuous nebulization.^{65,70} One study⁶⁹ reported a lower hospital admission rate with the use of continuous nebulization in an ED setting, but another study⁶⁵ reported no difference in admission rates. Decreased hospital length of stay was associated with the use of continuous nebulization in one study enrolling pediatric patients.⁷⁰ Two studies^{67,69} reported similar heart rate responses with continuous and intermittent nebulization.

Summary of RCT Results

- Pulmonary function and asthma symptom scores show similar benefits for continuous and intermittent nebulization of short-acting β_2 -agonists (quality of evidence: good).
- The time requirements for staff administration and maintenance of the therapy are less for continuous nebulization than for intermittent nebulization (quality of evidence: good).
- Adverse effects of β_2 -agonists are similar for continuous and intermittent nebulization of β_2 -agonists (quality of evidence: good).
- The effects of continuous vs intermittent nebulization of β_2 -agonists on hospital admission rate from the ED, hospital length of stay, and cost of care have not been adequately studied (quality of evidence: low).

Recommendation

1. Frequent intermittent nebulization and continuous nebulization are both appropriate alternatives in severely dyspneic patients in the ED or ICU. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.

Aerosolized β_2 -Agonists in Patients Receiving Mechanical Ventilation

Patients in the ICU, particularly those receiving mechanical ventilation, present unique challenges

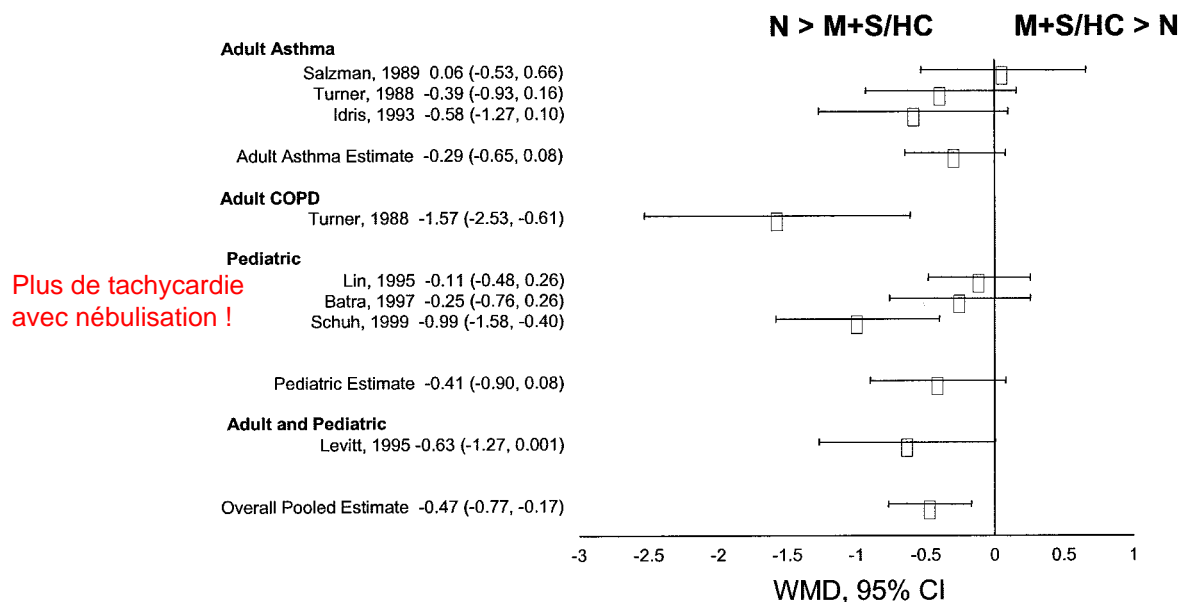


FIGURE 4. Weighted standardized mean difference for heart rate in ED/ICU trials using β_2 -agonists comparing nebulizer vs MDI + spacer/holding chamber. See the legend of Figure 2 for abbreviations not used in the text.

for aerosol delivery. Both MDIs and nebulizers can be adapted for use in ventilator circuits, the former requiring a spacer or connector with an integral actuator. Because of compatibility issues, it is currently not possible to use DPIs and breath-actuated MDIs to deliver inhalant medications via a ventilator circuit. Only three RCTs (Table 13) comparing these devices in mechanically ventilated patients were available for analysis. All were type I studies. These compared the effects of short-acting β_2 -agonists on pulmonary mechanics in infants with bronchiolitis, and in adults with asthma and COPD.^{71–73} None of these trials compared other outcomes such as the duration of mechanical ventilation, the length of stay in the ICU, the length of hospital stay, the cost of treatment, clinician preference, the relief of dyspnea, or the occurrence of pulmonary complications.

Albuterol was the drug employed in each of the three RCTs included in the analysis. The outcomes evaluated included changes in respiratory system compliance, airway resistance, and expiratory flows. In two of the studies,^{71,72} there were no differences in the response to albuterol between MDIs and nebulizers. In the other study,⁷³ the administration of up to 10 mg albuterol by MDI had no effect, whereas, the administration of 2.5 to 7.5 mg albuterol with a nebulizer produced significant reductions in airway resistance. In this study, however, the adapter employed to connect the MDI to the ventilator circuit had a very low drug

delivery efficiency.⁷³ This underscores the need to give careful attention to the specific details of the system used to deliver aerosolized drugs to intubated, mechanically ventilated patients.⁷⁴

Observational trials⁷⁵ have reported that the administration of albuterol with an MDI and chamber spacer produced responses that were comparable to those obtained with albuterol administered by nebulizer. In one randomized cross-over study (published following the literature search for these evidence-based guidelines), Duarte et al⁷⁶ reported that the airway response to albuterol via MDI with spacer and nebulizer were similar in duration and magnitude for mechanically ventilated patients with COPD. Although it is commonly accepted that an endotracheal tube may affect aerosol deposition patterns by providing a finer aerosol at the tube exit, the presence of airway disease may overwhelm this advantage.⁷⁷ There are no deposition/dose-response comparative studies in patients receiving mechanical ventilation, and, thus, no clear recommendations for the dosing of β -agonists in this setting can be made.

The adverse effects of β_2 -agonist administration during mechanical ventilation were determined in two studies. In one,⁷² no adverse effects were found after the administration of 270 μ g albuterol from an MDI or 2.5 mg administered with a nebulizer. In the study by Manthous et al,⁷³ premature beats and sinus tachycardia or tremors were noted after the administration of 7.5 mg

Table 11—Aerosol Delivery in Hospitalized Patients*

Study/Year/Study Type	Setting	Total Patients, No.	Lost to Follow-up, No.	Age Range	Drug/Device (Dose)
Short-term nebulizer vs MDI + spacer/holding chamber					
Pediatric					
Fuglsang and Pedersen ^{60/1986/type 1}	Pediatric, inpatient	21		7–14 yr	Terbutaline/NEB: Pari Inhaler Boy† (0.10 mg/kg) MDI + Nebuhaler (0.10 mg/kg)
Parkin et al ^{58/1995/type 1}	Pediatric, inpatient	60	9	1–5 yr (35 mo‡)	Albuterol + ipratropium/MDI + AeroChamber (0.5 mg albuterol + 0.04 mg ipratropium) NEB (0.15 mg/kg albuterol + 0.125 mg ipratropium)
Adult					
Berry et al ^{61/1989/type 1}	Adult COPD, inpatient	20	0	60–91 yr (67.9 ± 7.1 yr§)	Albuterol/MDI + InspirEase (0.36 mg) NEB (2.5 mg)
Pediatric/adult					
Summer et al ^{53/1989/type 1}	Adult/Pediatric, inpatient	36	4	MDI: 62.69 yr‡ NEB: 63.13 yr‡	Terbutaline/MDI + Brethancer spacer 0.5 mg metaproterenol Nebulizer: 15 mg
Jasper et al ^{59/1987/type 1}	Adult/Pediatric, inpatient	38	4	MDI: 52.7 ± 21.4 yr‡ NEB: 49.33 ± 9.1 yr‡	Metaproterenol/MDI + InspirEase (1.3 mg) NEB (15 mg)
Long-term nebulizer vs MDI + spacer/holding chamber					
Dewar et al ^{63/1999/type 1}	Pediatric, inpatient	78	16	> 3 yr NEB: 8.04 yr‡ MDI: 6.9 yr‡	Salbutamol/MDI + Volumatic (0.1 mg) NEB (5 mg)
Long-term MDI vs DPI					
Ruggins et al ^{62/1993/type 1}	Pediatric, inpatient	51	2	4–13 yr (9 yr‡)	Albuterol/MDI (Autohaler) (0.2 mg) DPI-Rotohaler (0.4 mg)

*SaO₂ = arterial oxygen saturation. See Table 8 for abbreviations not used in the text.

†Manufactured by Pari GmbH, Starnberg, Germany.

‡Median values.

§Mean ± SD values.

albuterol with a nebulizer. All of the patients who received a cumulative dose of 15 mg albuterol with a nebulizer developed tachycardia and premature heart beats. No changes in BP or other side effects have been described from albuterol administration in this group of patients.

Although evaluated only in non-RCT studies, several factors are known to have clinically important effects on aerosol delivery during mechanical ventilation. These include the position at which the nebulizer is placed in the circuit,^{78,79} the nebulizer brand and its fill volume,⁸⁰ the humidification of the inspired gas,⁸⁰ the treatment time,⁸⁰ the inspiratory time (duty cycle),^{79,80} intermittent vs continuous nebulization,⁷⁹ the ventilator brand,⁸¹ and the density of the carrier gas.⁸² It has been reported that the response to albuterol administered by MDI to mechanically ventilated patients with COPD was not affected by inspiratory flow pattern, pressure-

controlled ventilation vs volume-controlled ventilation,⁸³ the level of inspiratory flow,⁸⁴ the delivered tidal volume,⁸⁵ or the addition of an end-inspiratory pause.⁸⁶ When an MDI is used during mechanical ventilation, the use of a spacer device has been shown to increase deposition compared to other in-line actuators.⁸⁷

Noninvasive positive-pressure ventilation (NPPV) is increasingly used in the care of patients with acute exacerbations of COPD. No RCT has compared the delivery of aerosol medications by nebulizer or MDI in this setting. There have, however, been reports of the use of nebulizers⁸⁸ or MDIs⁸⁹ in conjunction with the use of NPPV.

Summary of RCT Results

- In children and adults receiving mechanical ventilation, the outcomes of β_2 -agonist administration

Pulmonary Function	Vital Signs/ Symptoms	Side Effects	Concomitant Care	Other Measures
FEV ₁ MDI + HC > NEB (p < 0.05)		Heart rate NS		
	Asthma score (NS) Symptoms at 7 d (NS) Symptoms at 14 d (NS)		Hours to Q4h (NS) Total number of doses (NS) Hours to discharge (NS)	
FEV ₁ (NS) FVC MDI + spacer < NEB (p < 0.01)	Borg scale (NS)			
FEV ₁ (NS) PF (NS) FVC (NS) FEV ₁ (NS) FVC (NS)			RCP time (NS) Length of stay (NS) Patient charge (NS) Annual hospital costs (NS)	
			Hospital length of stay (NS) cost NEB > MDI + spacer (p < 0.001) Nighttime asthma morbidity NEB > MDI + spacer (p < 0.05)	
PEFR (NS)		Heart rate increase MDI < DPI (p < 0.001)		SaO ₂ MDI > DPI (p < 0.05)

using an MDI with or without a spacer/holding chamber are no different than those observed following β_2 -agonist administration with a nebulizer (quality of evidence: fair).

- High doses of β_2 -agonists administered with a nebulizer are associated with a higher incidence of tachycardia and premature heart beats in mechanically ventilated patients, but there is no difference in adverse effects observed after the administration of albuterol with an MDI compared to those observed after the administration of the drug with a nebulizer (quality of evidence: fair).
- There is insufficient evidence to guide the choice of MDI or nebulizer for patients receiving NPPV (quality of evidence: low).

Recommendations

1. Both nebulizers and MDIs can be used to deliver β_2 -agonists to mechanically ventilated patients. Quality of evidence: fair; net benefit: substantial; strength of recommendation: A.

2. Careful attention to details of the technique employed for administering drugs by MDI or nebulizer to mechanically ventilated patients is critical, since multiple technical factors may have clinically important effects on the efficiency of aerosol delivery. Quality of evidence: low; net benefit: substantial; strength of recommendation: B.

DEVICE SELECTION IN THE OUTPATIENT SETTING

Short-Acting β_2 -Agonists for Asthma in the Outpatient Setting

Twenty-eight RCTs compared devices for the delivery of β_2 -agonists to outpatients. Most trials used a crossover design, and all were of type 2a or 2b. In other words, study outcomes assessed the comparability of the effect in the clinical laboratory setting in patients who had been carefully trained in and screened for proper use of the device. Consequently, they did not

Table 12—Intermittent vs Continuous Nebulizers Studies Using β_2 -Agonists*

Study/Year/Study Type	Setting	Total Patients, No.	Lost to Follow-up, No.	Age Range
Khine et al ⁶⁵ /1996/type 1	Pediatric, ER/ICU	73	3	2–18 yr Continuous: 86 ± 46 mo† Intermittent: 97 ± 50 mo†
Shrestha et al ⁶⁶ /1996/type 1	Adult Asthma, ER/ICU	165	0	High dose: 34.6 ± 10.6 yr St. Dose: 35.3 ± 10.7 yr Low dose: 32.4 ± 10.80 yr St. dose: 35.1 ± 10.4 yr
Reisner et al ⁶⁷ /1995/type 1	Adult Asthma, ER/ICU	22	2	Continuous: 30 ± 3.9 yr Intermittent: 39 ± 6.0 yr
Lin et al ⁶⁸ /1993/type 1	Adult Asthma, ER/ICU	38	0	Continuous: 39.8 ± 13.2 yr Intermittent: 40.6 ± 14.1 yr
Rudnitsky et al ⁶⁹ /1993/type 1	Adult Asthma, ER/ICU	99	0	Continuous: 35 ± 14 yr Intermittent: 36 ± 15 yr
Papo et al ⁷⁰ /1993/type 1	Pediatric, ER/ICU	17	0	Continuous: 1.8–16 yr (6 yr‡) Intermittent: 2.5–15 yr (4 yr‡)

*RVU = relative value unit; St = standard; RT = respiratory therapist. See Table 8 for abbreviations not used in the text.

†Mean \pm SD values.

‡Median values.

directly assess effectiveness as “quick relief” treatment for outpatient asthma symptoms (the primary role that these agents play in the treatment of asthma).^{2,3} Some

were single-dose studies in which each treatment was administered only once, with measurements being made before and after this treatment. In other studies,

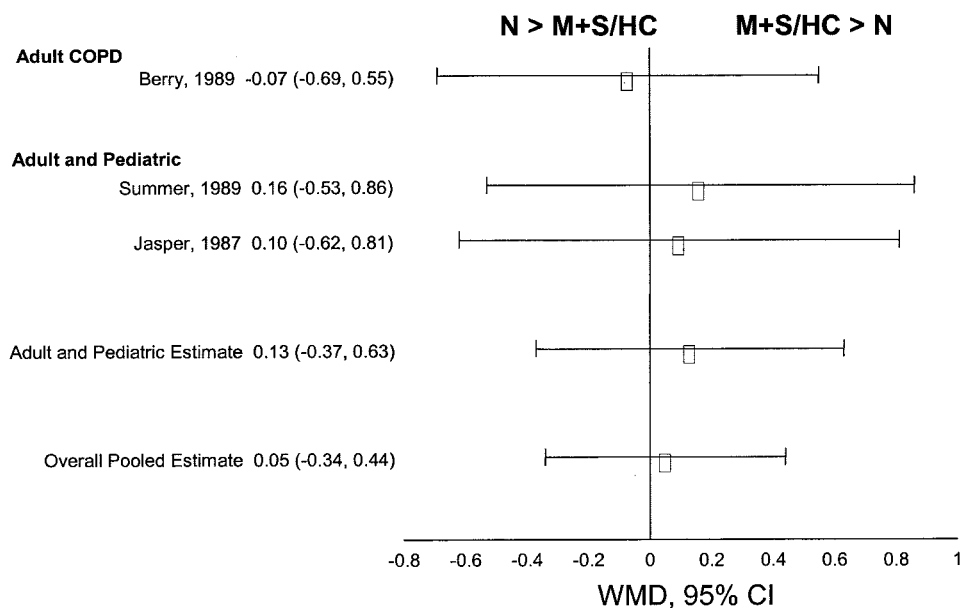


FIGURE 5. Weighted standardized mean difference for **FEV₁** in inpatient trials using β_2 -agonists comparing nebulizer vs MDI + spacer/holding chamber. See the legend of Figure 2 for abbreviations not used in the text.

Drug/Device (dose)	Pulmonary Function	Vital Signs/ Symptoms	Side Effects	Concomitant Care
Albuterol/NEB (0.3 mg/kg/h)		Asthma score (NS)		Hospital admission rate (NS) RT time (p < 0.001 intermittent > continuous)
Albuterol/NEB: Continuous (2.5, 7.5 mg/h)	FEV ₁ (p = 0.05 comparing all groups)			
Intermittent (2.5, 7.5 mg)				
Albuterol/NEB Continuous (7.5 mg/h)	FEV ₁ % pred (NS) PF % pred (NS)	Respiratory rate (NS)	Heart rate (NS)	
Intermittent (2.5 mg)				
Albuterol/NEB: Continuous (15.0 mg/h)	FEV ₁ (NS)			
Intermittent (5.0 mg)				
Albuterol/NEB: Continuous (5.0 mg/h)	PF (NS)		Heart rate (NS)	Admission rate (p < 0.03 intermittent > continuous)
Intermittent (2.5 mg)				RVU respiratory care time (p < 0.001 intermittent > continuous)
Albuterol (0.3 mg/kg/h)		Dyspnea score (NS) Time to dyspnea score < 5 (p = 0.03 intermittent > continuous)		Length of stay (p = 0.04 intermittent > continuous)

treatments were administered on a scheduled daily basis over varying periods of time from as short as 1 day up to a few months. With both of these approaches, however, the primary outcome assessed changes in lung function in the clinical laboratory. Daily asthma symptom scores and adverse effects, mainly changes in heart rate, were assessed in only a few trials.

Twenty-three studies^{90–99,101–103,106–115} (both type 2a and 2b) compared the responses to short-acting β_2 -agonists using a DPI vs those using an MDI (without a spacer/holding chamber) in adults with asthma (Tables 14, 15). Outcomes included some type of pulmonary function measurement in all but one trial. In that one study, cough score was the only useable outcome. Metaanalyses comparing FEV₁, PEFR, and sGaw responses from these studies showed no significant differences between devices, either by separate analysis or when pooled (Fig 7).

Six of the trials comparing MDI with DPI were analyzed separately because they employed similar (“comparable”) doses of the same drug in the two devices (Table 15).^{95,102,103,108,110,114} This allowed for a more direct assessment of device efficiency and effectiveness than in the studies that used different doses and/or drugs in the devices being compared. An analysis of these comparable dose studies also found no differences in FEV₁, PEFR, FVC, or symptoms (see Fig 8 on-line). For trials in which multiple sequential doses were administered by each device, the metaanalysis was per-

formed for both the lowest dose and for the highest dose administered (in 16 trials). Again, no differences were found for FEV₁, PEFR, sGaw, or FVC. Two studies compared cough or other symptoms,^{90,101} and three studies compared changes in heart rate changes.^{92,98,115} No differences were found between the MDI and the DPI in pooled analyses of these studies. However, one study¹¹⁶ reported greater improvements in FEV₁ for DPI use compared with MDI use, and another study⁹⁰ reported greater improvement in cough score for DPI use compared with MDI use.

Four studies compared the MDIs and DPIs in pediatric patients. Two studies^{117,118} investigated terbutaline delivered by MDI and by DPI (Turbuhaler). Another study¹¹⁹ evaluated fenoterol delivery by MDI and DPI. The fourth study¹²⁰ enrolled both pediatric and adult patients. None of these studies, either individually or when combined, showed a difference between use of the MDI and use of the DPI.

Fewer data are available comparing the effects of β_2 -agonists inhaled via an MDI without a spacer device vs those inhaled via an MDI with a spacer device in adults or children with asthma in the outpatient setting,^{100,121} and only one study¹²¹ met criteria for inclusion in the analysis. This study showed no difference between the two routes for the outcomes FEV₁, PEFR, or FVC (Table 16).

Eight type 2b studies that compared short-acting

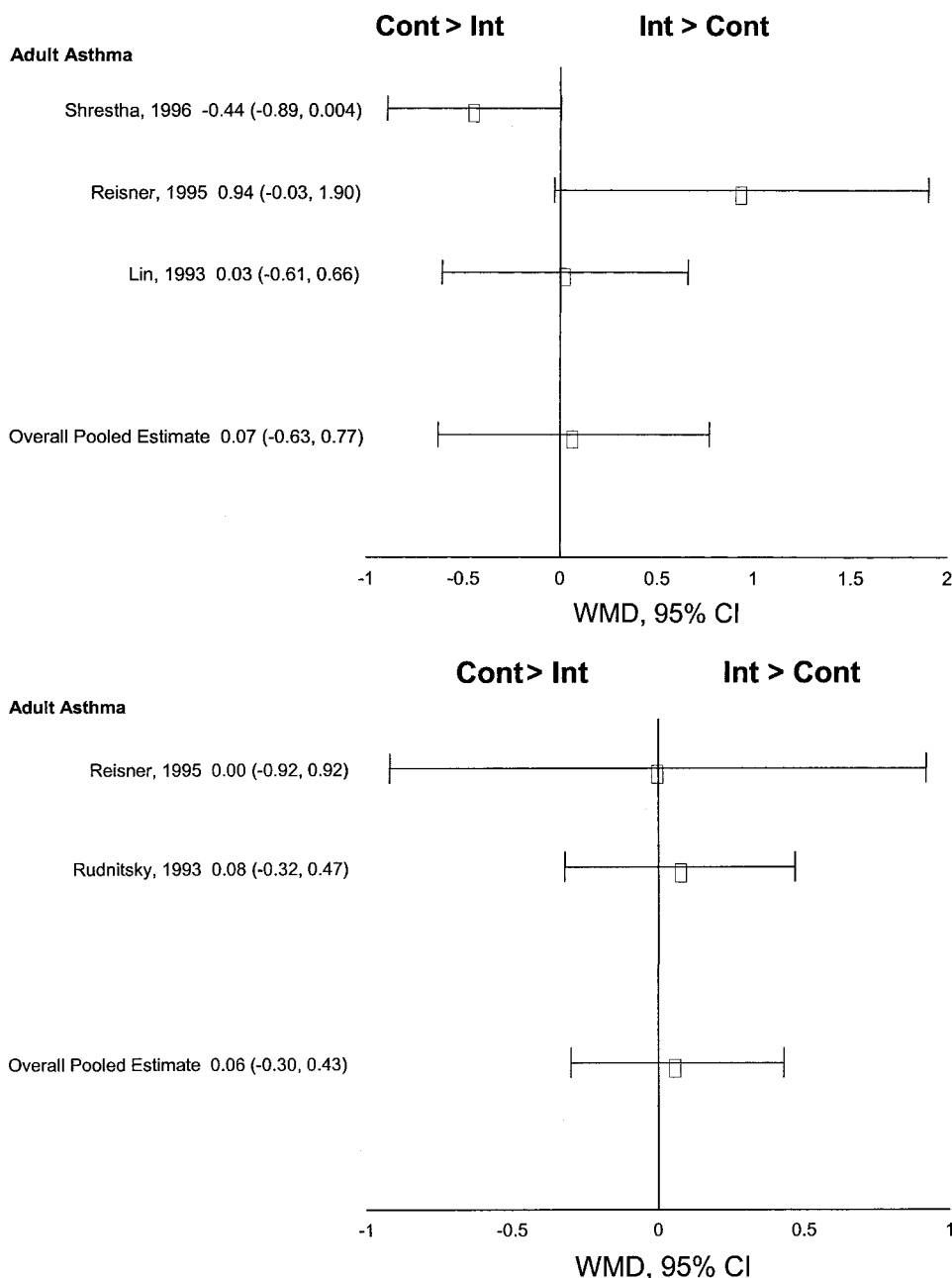


FIGURE 6. *Top*: weighted standardized mean difference for **FEV₁** in ED/ICU trials of β_2 -agonists comparing intermittent (Int) vs continuous (Cont) nebulization. *Bottom*: weighted standardized mean difference for **peak flow** in ED/ICU trials of β_2 -agonists comparing intermittent vs continuous nebulizers. See the legend of Figure 2 for abbreviations not used in the text.

β -agonist delivery by different devices were evaluated separately (Table 17). Three studies that compared the dose delivered by nebulizer and MDI with holding chamber each concluded that more than two MDI actuations are required to equal one nebulizer treatment. Pedersen and Bundgaard¹²² and Madsen et al¹²³ estimated that approximately four terbutaline MDI actuations are required to equal a single nebulized treatment with 2.5 to 4.0 mg of terbutaline. Blake et

al¹²⁴ estimated that approximately 10 MDI actuations of albuterol are required to equal one nebulizer treatment with 2.5 mg albuterol. It is for this reason the more than two MDI actuations are typically used in ED studies comparing MDIs with spacers/holding chambers and nebulizers (Table 8). Type 2B studies by Wong et al,¹²⁵ Lofdahl et al,¹²⁶ and Bondesson et al¹²⁷ compared albuterol delivery via DPI (Turbuhaler) and CFC MDI (Ventolin). All three studies estimated that

Table 13—Aerosol Delivery in Patients Receiving Mechanical Ventilation*

Study/Year/ Study Type	Setting	Patients, No.	Lost to Follow-up, No.	Age	Drug/Device (Dose)	Side Effects	Concomitant Care	Other Measures
Torres et al ⁷¹ / 1997/type 1	Pediatric, ICU	16	5	5.3 ± 7.6 mo† (0.44 yr†)	Albuterol/MDI + AirLife Medispace [§] (0.36 mg) NEB (1.5 mg)			Raw (NS) compliance (NS)
Manthous et al ⁷³ / 1993/type 1	Adult/pediatric, ICU	10	0	66.3 ± 9.75 yr‡	Albuterol/MDI + 1996 Intersurgical swivel Elbow spacer (1.0, 2.0, 3.0, 4.0 mg q30 min; cumulative dose 9 mg or 100 puffs) NEB (2.5, 7.5, 15.0 mg q30 min, cumulative dose 15 mg)	Toxic effects (NS)		Resistance pressure (NS)
Gay et al ⁷² /1991/type 1	Pediatric/adult, ICU	20	2	69 yr	Albuterol/MDI (0.27 mg) NEB (2.5 mg)		Time for administration (NS) Cost of unit dose (NS)	Expiratory flow at iso recoil prs 6 and 10 cm H ₂ O (NS)

*Raw = airways resistance; prs = pressure. See Table 8 for abbreviations not used in the text.

†Mean age.

‡Mean ± SD values.

§Manufactured by Baxter Healthcare, Deerfield, IL.

the dose delivered by the DPI was greater (1.38-fold, 1.98-fold, and 2.0-fold greater, respectively). Confidence intervals for these three estimates overlapped in the region, indicating a twofold to threefold greater potency for the Turbuhaler. In contrast, two type 2B studies^{112,128} comparing a Spiros DPI (Elan Pharmaceuticals; Dublin, Ireland) with a CFC MDI (Ventolin) estimated that these devices were approximately equipotent. This draws attention to the fact that differences in the relative amount of drug delivered to the lung depends not only on the general type of device used (DPI vs MDI) but also on the specific brand of device being compared (*eg*, Spiros DPI or Turbuhaler DPI).

Summary of RCT Results

- In the adult and pediatric **outpatient** population with asthma, available evidence comparing short-acting β_2 -agonist delivery by MDI and DPI show no differences in pulmonary function responses, symptom scores, or heart rate. This remains true when analysis is restricted to type 2b studies that estimate the doses required to produce equal levels of response (called *dose-axis comparisons*) [quality of evidence: good].
- In a limited number of type 2 studies comparing short-acting β_2 -agonists administered with an MDI to that with an MDI using a spacer or holding chamber, pulmonary function responses were found to be comparable (quality of evidence: low).
- **The use of nebulizers for the delivery of short-acting β_2 -agonists in the outpatient setting has not been adequately studied in RCTs** (quality of evidence: low).

Recommendations

1. For treatment of asthma in the outpatient setting, both the MDI, used with or without spacer/holding chamber, and the DPI are appropriate for the delivery of short-acting β_2 -agonists. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.
2. The appropriate selection of a particular type of aerosol delivery device in this setting includes the patient's ability to use the device correctly, the preferences of the patient for the device, the availability of the drug/device combination, the compatibility between the drug and delivery device, the lack of time or skills to properly instruct the patient in the use of the device or to monitor the appropriate use, the cost of the therapy, and the potential for reimbursement. Quality of evidence: low; net benefit: substantial; strength of recommendation: B.

Table 14—MDI vs DPI Using β_2 -Agonists in Adult Outpatients With Asthma*

Study/Year/Study Type	Total Patients, No.	Lost to Follow-up, No.	Age Range	Drug/Device (Dose)
Haahntela et al ¹⁰⁹ /1994/type 2A	20	0	23–66 yr (50 yr†)	Salbutamol/DPI-Easyhaler (0.09, 0.18, 0.36, 0.72 mg)
Bauer et al ¹¹⁵ /1993/type 2A	16	0	37–61 yr (47–25 \pm 1.6 yr‡)	Fenoterol/MDI + DPI (0.4 mg) DPI (Spinhaler): (10.0 mg colforsin)
Zainudin et al ¹¹¹ /1990/type 2A	9	0	20–68 yr	Salbutamol/DPI-Rotahaler (0.4 mg)
Johnsen and Weeke ⁹² /1988/type 2A	9	0	20–46 yr (30 yr†)	Terbutaline/DPI-Turbuhaler (0.25, 0.5, 1.0, 2.0, 4.0 mg)
Persson et al ⁹³ /1988/type 2A	13	1	20–59 yr (39 yr†)	Terbutaline/DPI-Turbuhaler (0.25, 0.5, 1.0, 2.0, 4.0 mg)
Lahdensuo et al ⁹⁴ /1986/type 2A	20	0	45–76 yr (62 yr†)	Fenoterol/DPI-FiO ₂ (0.2 mg)
Bundgaard et al ⁹⁷ /1983/type 2A	18	0	20–49 yr (37 yr†)	Fenoterol/DPI-FiO ₂ (0.6, 1.0 mg)
Dirksen and Groth ⁹⁸ /1983/type 2A	9	0	27–65 yr (47 \pm 4 yr‡)	Fenoterol/DPI-FiO ₂ (0.05, 0.1, 0.2, 0.4 mg)
Bundgaard and Schmidt ⁹⁹ /1982/type 2A	18	3	21–55 yr (39 yr†)	Fenoterol/DPI-FiO ₂ (0.2, 0.4 mg)
Geoffroy et al ¹¹² /1999/type 2B	60	16	18–65 yr (29.7 \pm 10.5 yr‡)	Albuterol/DPI-Spiros (0.09 mg)
Tammivaara et al ¹⁰¹ /1997/type 1	115	2	DPI: 49 \pm 13 yr‡ MDI: 45 \pm 14 yr‡	Albuterol/DPI (0.2 mg)
Vidgren et al ¹⁰⁶ /1995/type 2A	40	0	18–78 yr (39 yr†)	Salbutamol/DPI-Easyhaler (0.1 mg)
Jackson et al ¹⁰⁷ /1994/type 2A	10	0	19–66 yr (42 yr†)	Terbutaline/Turbuhaler (0.25 mg)
Nieminen et al ¹¹³ /1994/type 2A	21	4	20–73 yr (51 yr†)	Salbutamol/DPI-Easyhaler (0.18 mg)
Boe et al ⁹⁰ /1992/type 1	179	56	18–78 yr (51 yr†)	Terbutaline/Turbuhaler (0.5 mg)
Osterman et al ⁹¹ /1989/type 1	23	4	20–66 yr (46 yr†)	Terbutaline Turbuhaler (0.5 mg)
Kiveranta ⁹⁶ /1985/type 2A	20		18–57 yr (35 yr†)	Fenoterol/DPI-FiO ₂ (0.3 mg)

*pre = pretreatment; post = posttreatment; FiO₂ = fraction of inspired oxygen; Tmax = time to maximum response. See Table 8 for abbreviations not used in the text.

†Median values.

‡Mean \pm SD values.

Inhaled Corticosteroids for Asthma

Four trials^{90,104,105,106,129} comparing the use of a DPI with that of an MDI plus spacer for the inhalation of inhaled corticosteroids in adult^{90,104,105,129} asthmatic patients in the outpatient setting met the criteria for study inclusion (Table 18). No studies enrolling chil-

dren were eligible for inclusion. To be able to accurately compare device performance and efficacy, we required that the same drug be delivered via MDI/spacer and DPI, and this greatly limited the number of useable trials. In these four trials, the same dose of the same corticosteroid was used for the two delivery routes. The durations of these type 1 trials were

Pulmonary Function	Vital Signs/ Symptoms	Side Effects	Concomitant Care	Design/Duration
FEV ₁ (NS) PF (NS) FVC (NS) FEV ₁ (NS)	Heart rate (NS)	Adverse events (NS) Tremor amplitude MDI > DPI (p < 0.05) Serum K (NS)		Crossover cumulative dose/1 d Crossover/120 min
FEV ₁ (NS) PF (NS) FVC (NS) FEV ₁ (NS) FVC (NS) FEV ₁ (NS) FVC (NS) FEV ₁ MDI < DPI (p < 0.01) PF (NS) PF (NS)	Heart rate (NS)	Tremor amplitude MDI < DPI (p < 0.05) Tremor amplitude (NS)	Taste (NS)	Crossover/60 min Crossover cumulative dose/1 d Crossover cumulative dose/1 d Crossover/5, 15, 60 min
FEV ₁ (NS) PF (NS) PF (NS)	Heart rate (NS)	Tremor (NS)		Crossover dose
FEV ₁ (NS) PF (NS) FEV ₁ (NS)	Symptom score (day) (NS) Symptom score (night) (NS)		Tmax (NS) Duration of effect (NS) Onset time (NS) β ₂ -adrenergic use (NS)	Crossover, cumulative dose Crossover, dose Crossover/5 d
FEV ₁ (NS) PF (NS) FEV ₁ (NS) PF (NS) FVC (NS)			Tmax (NS) Preference for technique (NS)	Parallel/21, 84 d Crossover/2 d
FEV ₁ (NS) PF (NS) FVC (NS)		Adverse events (NS)	Ease of use (NS)	Crossover/3 d Crossover/2 d
	Cough MDI < DPI (p < 0.05)	Throat irritation MDI < DPI (p < 0.05) Mouth irritation MDI < DPI (p < 0.05) Tremor (NS)	Taste MDI < DPI Device rating MDI < DPI (p < 0.001) Difficulty learning to use MDI < DPI (p < 0.001) β ₂ -adrenergic use (NS) Preference for technique (NS)	Crossover/14 d
PEF AM pre (NS) PEF PM pre (NS) PEF AM post-MDI < DPI (p < 0.05) PEFR-AM (NS) PEFR-PM (NS)			Preference for technique (NS)	Crossover/14 d Crossover/35 d

relatively short. One trial was of 2 weeks duration, and the other three were of 4 weeks duration. Metaanalysis reported no difference for FEV₁, PEF, or symptom scores (see Fig 9 on-line). Two of the trials addressed subject preference, and there was a significant preference for the DPI over the MDI/spacer combination (p < 0.01) [see Fig 10 on-line]. We deem the incidence of oral candidiasis to be a crucial outcome, and no trial addressed this issue. There were no randomized control trials that were eligible for study inclusion that addressed other

device comparisons using inhaled corticosteroids (MDI vs MDI with spacer/holding chamber, and MDI used alone vs DPI).

Summary of RCT Results

- For adult patients with asthma in the outpatient setting, there are no differences in pulmonary function response or symptom scores when the same dose of the same corticosteroid is used in a DPI or MDI with spacer/holding chamber (quality of evidence: good).

Table 15—Trials Comparing MDI vs DPI Studies “Comparable Dose and Drug” β_2 -Agonists and Cromolyn Adult Outpatients With Asthma*

Study/Year/Study Type	Total Patients, No.	Lost to Follow-up, No.	Age Range	Drug/Device (Dose)
Nelson et al ¹¹⁴ /1999/type 2A	283	43	DPI 34.2 \pm 13.4 yr† MDI 34.6 \pm 15.4 yr† Placebo 32.4 \pm 14.1 yr†	Albuterol/MDI (0.09 mg) DPI-Spiros (0.108 mg)
Svedmyr et al ⁹⁵ /1982/type 2A	7	0	31–66 yr (51.28)‡	Salbutamol/MDI (0.1, 0.3, 0.8, 2.0, 4.4 mg) DPI-Rotahaler (0.2, 0.6, 1.8, 4.2, 9.0 mg)
Vilsvik et al ¹⁰³ /1991/type 2A	21	5	16–55 yr (30.6)‡	Albuterol/MDI (0.2 mg) Terbutaline/DPI-Turbuhaler (0.5 mg)
Mathieu et al ¹⁰² /1992/type 2A	12	1	31.6 yr‡	Salbutamol/MDI (0.2 mg) DPI-Diskhaler (0.4 mg)
Lantos et al ¹¹⁰ /1993/type 2A	15	0	18–54 yr (34)‡	Cromolyn/MDI (2.0 mg) DPI-Spinaler (20.0 mg)
Lindsay et al ¹⁰⁸ /1994/type 1	47	1	Adults 51 \pm 11 yr† Children 11 \pm 2 yr†	Salbutamol/MDI (0.2 mg) Terbutaline/DPI-Turbuhaler (0.5 mg)

*AUC = area under the curve. See Table 8 for abbreviations not used in the text.

†Mean \pm SD values.

‡Median values.

- Two studies indicated a significant patient preference for use of the DPI over that of the MDI with spacer/holding chamber (quality of evidence: good).
- No RCT adequately addressed the incidence of oral candidiasis (quality of evidence: low).

Recommendations

1. For the treatment of asthma in the outpatient setting, both the MDI with a spacer/holding chamber and the DPI are appropriate devices for the delivery of inhaled corticosteroids. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.
2. For outpatient asthma therapy, the selection of an appropriate aerosol delivery device for inhaled corticosteroids includes the patient's ability to use the device correctly, the preferences of the patient for the device, the availability of the drug/device combination, the compatibility between the drug and delivery device, the lack of time or skills to properly instruct the patient in the use of the device or monitor the appropriate use, the cost of therapy, and the potential for reimbursement. Quality of evidence: low; net benefit: substantial; strength of recommendation: B.

β_2 -Agonists and Anticholinergic Agents for COPD

Proving device efficacy can be difficult in COPD patients because the airway obstruction in such

patients shows limited reversibility with drug therapy. Seven studies^{130–136} comparing different delivery devices met the criteria for entry into this analysis (Table 19). Pooled analysis of these studies showed no evidence for superiority of any aerosol delivery device (nebulizer, MDI, or MDI with spacer in patients) for outpatients with COPD. While the data are quite limited for COPD patients, the experience in asthma patients supports the conclusions for COPD.

Turner et al,⁵⁰ in an acute setting adult trial, reported a significantly greater increase in heart rate for nebulizers compared to MDI without important differences in efficacy. Similar findings were reported by Berry et al⁶¹ for inpatients with COPD, but data are lacking for COPD patients treated in the outpatient setting. In an outpatient study of patients with COPD, Pauwels et al¹³¹ compared the use of an MDI and that of an MDI with a valved holding chamber following the inhalation of terbutaline, and reported that the MDI with holding chamber may be more effective than MDI alone. In an outpatient study of patients with asthma or COPD, Dorow and Hidingier et al¹³² reported no differences between the use of an MDI and that of MDI with a valved holding chamber.

Device differences have not been adequately studied for combination bronchodilator therapy (eg, Combivent; Boehringer-Ingelheim; Ridgefield, CT) or for steroid preparations in outpatients with COPD. Delivery systems for long-acting bronchodi-

Pulmonary Function	Vital Signs/Symptoms	Side Effects	Concomitant Care	Design/Duration
AUC serial FEV ₁ (p = 0.44)				Parallel/12 wk
FEV ₁ (NS)	Heart rate (NS)			Crossover/2 d
FVC (NS)				
PF (NS)				Crossover/15 min
FEV ₁ % pred (NS)				Crossover/unspecified
VC % pred (NS)				
PF % pred (NS)	Dyspnea episode duration (NS)		β ₂ -adrenergic use (NS)	Crossover/4 wk
FEV ₁ % pred (NS)	Wheeze (NS)	Adverse events (NS)	Preference for technique (NS)	Crossover/4 wk
PF % pred (NS)	Sleep disturbance (NS)			
FVC % pred (NS)	Total symptom score (NS)			

lators (*eg*, salmeterol and formoterol) also have not been adequately studied in this patient population.

The selection of an aerosol delivery device for the treatment of outpatients with COPD is determined by the formulation, the needs of the patient, clinician biases, and reimbursement. Although use of an MDI (with spacer and mask if necessary) may produce similar results, nebulizers are often used in sicker and less cooperative patients.

Summary of RCT Results

- In the outpatient management of COPD patients with β₂-agonist and anticholinergic agents, the available evidence shows no differences in pulmonary function responses between delivery devices (quality of evidence: good).
- Increases in heart rate were greater after the administration of albuterol by nebulizer than after administration by MDI (quality of evidence: good).

Recommendations

1. For the treatment of COPD in the outpatient setting, the MDI, with or without spacer/holding chamber, the nebulizer, and the DPI are all appropriate for the delivery of inhaled β₂-agonist and anticholinergic agents. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.
2. For outpatient COPD therapy, the selection of an appropriate aerosol delivery device for inhaled β₂-agonist and anticholinergic agents includes the patient's ability to use the device

correctly, the preferences of the patient for the device, the availability of the drug/device combination, the compatibility between the drug and the delivery device, the lack of time or skills to properly instruct the patient in the use of the device or monitor its appropriate use, the cost of therapy, and the potential for reimbursement. Quality of evidence: low; net benefit: substantial; strength of recommendation: B.

DISCUSSION

The results of this systematic review of RCTs were essentially the same in each of the clinical settings evaluated above. None of the pooled metaanalyses (Tables 20 and 21, available on-line only) showed a significant difference between devices in any efficacy outcome in any patient group. Thus, the relative effectiveness of delivery methods does not provide a clear basis for selecting one device over another. This does not mean that the device choice for a specific patient does not seem to matter. In essence, this says that each of the devices studied can work equally well in that setting in patients who can use them appropriately. This is an important statement because most studies, especially in the outpatient setting, select for patients who are capable of using each of the devices with the appropriate technique or train patients to use the appropriate technique. The RCTs included in this systematic review do not provide much information about who is likely to

use one device or another properly, nor do they address many other considerations that are important for choosing a delivery device for a specific patient in a specific clinical situation. These include the ability to use the device, patient preference, the availability of equipment, and cost. While the clinician is still left to select the method of delivery based on these other considerations, we have made general recommendations based on the results of the metaanalysis to guide the clinician in his/her selection of a delivery system. In addition, there are some obvious situations in which device selection clearly does matter. For example, in each of the clinical situations studied, there are some devices that were studied little or not at all. This appears to indicate a consensus that RCTs are not needed to determine that some devices are inappropriate for that clinical situation. For example, it is clear that infants and toddlers have virtually no chance of using an MDI (without spacer or holding chamber) or a DPI properly. Similarly, there are virtually no RCTs studying the MDI (without spacer or holding chamber) in the ED since most clinicians believe that the severe dyspnea experienced by many asthma patients in that setting would prevent them from using this device properly.

Consideration of the circumstances under which studies were performed is an important factor for interpreting the results of our systematic review. All of the RCTs performed in the acute care

settings (*ie*, ED, inpatient unit, or ICU) are type 1 trials (*ie*, they were performed under conditions of actual clinical use in the ED, inpatient unit, or ICU). These studies are reassuring in that both a nebulizer and an MDI with a valved holding chamber can work well in that setting. Similarly, MDIs with a reverse-flow spacer can be successfully used in these settings but not in intubated patients, unless they incorporate an interface to the ventilator circuit. Similarly, studies of inhaled corticosteroid use in outpatients, while limited in number, are type 1 studies that are performed under conditions of actual clinical use. The results are reassuring in that each device can work well in patients who know how to use them correctly.

Studies of β_2 -agonist use for outpatient asthma and COPD are less reassuring since virtually all of these were type 2 studies that were performed under laboratory conditions rather than conditions of actual clinical use. The studies indicate that under ideal conditions and in patients who are successfully taught to use the devices correctly, the devices being compared can each deliver sufficient quantities of drug to the airway to elicit the same response. However, the relationship between these laboratory studies and the use of the device in patient's daily lives is not clear. Many of these studies were performed for regulatory purposes as part of the evaluation of new formulations. These kinds of studies are typically designed to demonstrate equivalence with an existing

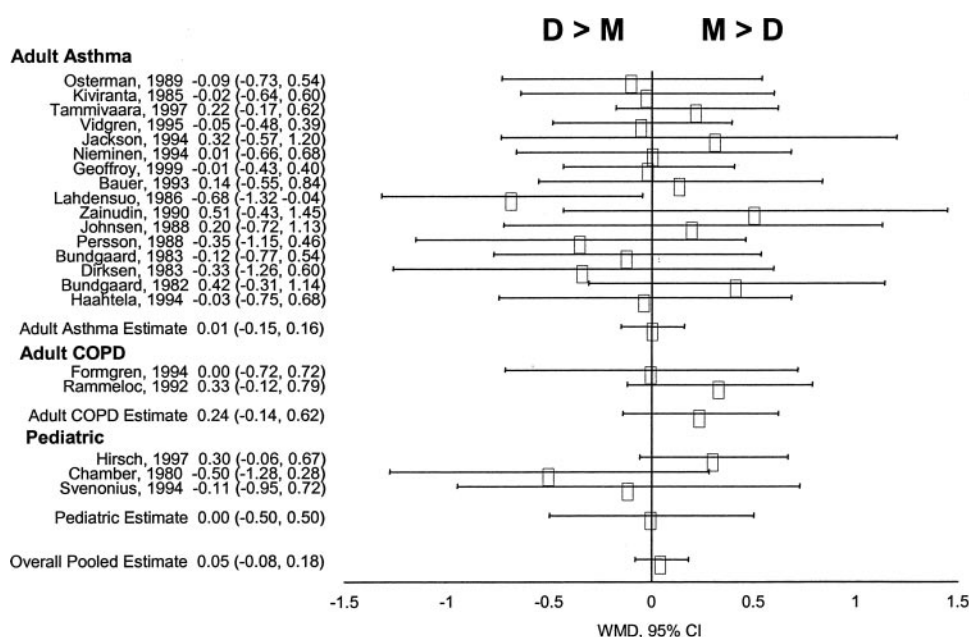


FIGURE 7. Weighted standardized mean difference for combined end point (FEV₁, PEFR, or sGaw) in outpatient β_2 -agonist trials comparing MDI (M) vs DPI (D). See the legend of Figure 2 for abbreviations not used in the text.

Table 16—MDI vs MDI + Spacer Studies Using β_2 -Agonists in Adult Outpatients With Asthma*

Study/Year/ Study Type	Setting	Total Patients, No.	Lost to Follow-up, No.	Age Range	Drug/Device† (Dose)	Pulmonary Function	Vital Signs/ Symptoms	Side Effects	Concomitant Care	Design/ Duration
Bloomfield et al ¹²¹ / 1979/type 2A	Adult Asthma, outpatient	10	0	62–77 yr	Terbutaline/ Tube Spacer (0.5 mg)	FEV ₁ (NS) PF (NS) FVC (NS)				Crossover/ 4 d

*See Table 8 for abbreviations not used in the text.

†Tube Spacer, AstraZeneca, Lund, Sweden.

device. The doses used were typically selected to ensure this, particularly in the nebulizer vs MDI RCTs.^{53,59,61,62} Thus, it is not surprising when these type 2 studies fail to show differences. It is also likely that the doses used in many of these laboratory-based studies produced responses that were near the plateau of the dose-response curve. Therefore, differences in drug delivery would not be reflected as a difference in response. However, these studies do not indicate that the device would perform equally well in more adverse, real-world situations, such as when a patient awakens at night with more bronchospasm and lower lung function than is typically studied in the clinical laboratory.^{137,138} Furthermore, these studies routinely exclude patients who cannot correctly use the devices being compared. The results clearly apply just to the subpopulation of patients who can use the device effectively.

Differences in systemic adverse effects were present only between the nebulizer and the MDI with holding chamber for albuterol delivery in the ED, and between the nebulizer and the MDI (used alone) for albuterol delivery in COPD outpatients. Heart rate was higher with nebulizer delivery. Vomiting was greater after nebulized albuterol administration than after albuterol administered by MDI with a valved holding chamber in children in the ED. These findings are most likely due to the larger doses of albuterol administered by the nebulizer compared to those administered by the MDI, resulting in greater systemic absorption.

We did not assess the power of individual studies *a priori*. Although it is likely that many studies were underpowered, the metaanalysis of these studies consistently fails to show a significant difference between devices. Moreover, our findings are consistent with those reported in other systematic reviews.^{25–28,30,31,64,139} However, our interpretation of these results differs from those offered by authors of some of the reviews. Notably, Turner et al²⁵ concluded that because no clear differences between devices could be found in the systematic review of RCTs, cost alone should drive the choice between devices. This interpretation of

the results of the systematic review was subsequently criticized in a number of letters to the editor,^{140,141} although the review itself was not. In their review, Amirav and Newhouse²⁶ also found no differences in pulmonary function response to nebulized albuterol and albuterol administered by an MDI with holding chamber in children treated in the ED setting. They also interpreted their results as demonstrating that cost alone should be the determining factor for the choice of device. The interpretation of our systematic review as well as those of other authors in existence is open to debate. While we make general recommendations, they are based on the metaanalysis of the data from the RCTs considered. We have avoided making specific recommendations that are not directly supported by the RCT results.

How then, in practice, does one select an aerosol delivery device for the patient? In other words, what practical advice can be given for device selection when the best evidence shows no difference in outcomes between devices? In the following list, we review the important issues for clinicians to consider when selecting an aerosol delivery device.

When selecting an aerosol delivery device, the following questions should be considered:

1. In what devices is the desired drug available?
2. What device is the patient likely to be able to use properly, given the patient's age and the clinical setting?
3. For which device and drug combination is reimbursement available?
4. Which devices are the least costly?
5. Can all types of inhaled asthma/COPD drugs that are prescribed for the patient (*eg*, short-acting β -agonist, corticosteroid, anticholinergic, and long-acting β -agonist) be delivered with the same type of device (*eg*, nebulizer, manually actuated MDI, MDI with spacer/holding chamber, or breath-actuated device [*ie*, automatically activated MDI or DPI])? Using the same type of device for all inhaled drugs may facilitate patient teaching and

Table 17—Type 2B Studies Comparing Short-Acting β -Agonist Delivery*

Study/Year	Subjects in Crossover Study, No.	Drug/Device (Dose)	Primary Outcome	Relative Potency Estimate
Pedersen and Bundgaard ¹²² /1983	13	Terbutaline/NEB (1, 4 mg) MDI with Nebuhaler (1 mg)	FEV ₁	1 mg by MDI = 4 mg by nebulizer (<i>ie</i> , 4 actuations = 1 nebulizer treatment)
Madsen et al ¹²³ /1982	13	Terbutaline (cumulative dosing)/ PARI-boy nebulizer (1.25, 2.5, 5.0 mg) MDI with Nebuhaler (0.125, 0.25, 0.50 mg)	FEV ₁	1 mg by MDI = 2.5 mg by nebulizer (<i>ie</i> , 4 actuations = 1 nebulizer treatment)
Blake et al ¹²⁴ /1992	12	Albuterol (noncumulative dosing)/ Hudson Updraft III nebulizer (0.625, 1.75, 2.5, 5.0 mg) MDI with InspirEase (1, 2, 4, 6 actuations; 90 mcg/actuation)	Histamine PC ₂₀ FEV ₁	0.9 mg by MDI = 2.5 mg by nebulizer (<i>ie</i> , 10 actuations = 1 nebulizer treatment)
Wong et al ¹²⁵ /1998	23	Albuterol (noncumulative dosing)/ Turbuhaler DPI (50, 100 μ g) MDI (100, 200, 400, 800 μ g)	Methacholine PC ₂₀ FEV ₁	1 μ g Turbuhaler = 1.38 μ g MDI (95% CI, 0.67–2.87)
Lofdahl et al ¹²⁶ /1997	50	Albuterol (noncumulative dosing)/ Turbuhaler DPI (50, 200 μ g) MDI (100, 400 μ g)	FEV ₁	1 μ g by Turbuhaler = 1.98 μ g by MDI (95% CI 1.2–3.2)
Bondesson et al ¹²⁷ /1998	12	Albuterol (cumulative dosing)/ Turbuhaler DPI and MDI (100, 200, 400, 800 μ g)	FEV ₁	1 μ g by Turbuhaler = 3.0 μ g by MDI (95% CI, 1.8–5.8)
Ahrens et al ¹²⁸ /1999	24	Albuterol (noncumulative dosing)/ Spiros DPI and MDI (90, 270 mg)	Methacholine PC ₂₀ FEV ₁	1 μ g by Spiros = 1.12 μ g by MDI (90% CI, 0.68–1.94)
Geoffroy et al ¹¹² /1999	44	Albuterol (noncumulative dosing)/ Spiros DPI and MDI (90, 180 μ g)	FEV ₁	1 μ g by Spiros = 1.13 μ g by MDI (90% CI, 0.65–2.25)

*PC₂₀ = provocative concentration of a substance causing a 20% fall in FEV₁; CI = confidence interval.

decrease the chance for confusion among devices that require different inhalation techniques.

- Which devices are the most convenient for the patient, family (outpatient use), or medical staff (acute care setting) to use, given the time required for drug administration and **device cleaning**, and the **portability** of the device?
- How durable is the device?
- Does the patient or clinician have any specific device preferences?

Finally, whichever device is chosen, it is clear that proper patient education on its use is critical and that the assessment of inhalation technique should be part of subsequent visits to the physician.¹⁴² Therefore, physicians, respiratory therapists, and nurses caring for patients with respiratory diseases should be familiar with issues related to performance and with the correct use of aerosol delivery devices. Patients must be adequately instructed in the correct use of aerosol delivery devices. If the selected delivery device should fail to provide satisfactory treatment or result in un-

acceptable side effects for the patient, both clinician and patient should recognize that there are other effective options.

SUMMARIES AND RESULTS

Aerosol Delivery of Short-Acting β_2 -Agonists in the Hospital ED

Summary of RCT Results:

- The **delivery of β_2 -agonists** in the ED setting by **nebulizers or MDIs** with holding chambers (*eg*, AeroChamber, Volumatic, or InspirEase) is **equally effective for improving pulmonary function and reducing symptoms of acute asthma in both adult and pediatric patients** (quality of evidence: good).
- The delivery of β_2 -agonists in the ED setting by DPI (*eg*, Rotahaler or Turbuhaler) has been inadequately studied, but trials in adults have suggested DPIs may be as effective as nebulizers or MDIs with spacer/holding chambers (quality of evidence: low).

Table 18—MDI + Spacer vs DPI Studies Using Corticosteroids in Adult Outpatients With Asthma*

Study/Year/ Study Type	Total Patients, No.	Lost to Follow-up, No.	Age Range	Drug/Delivery System (Dose)	Pulmonary Function	Vital Signs/ Symptoms	Side Effects	Concomitant Care	Design/Duration
Boe et al ¹⁰⁰ /1992/type 1	179	56	18–78 yr (51 yr†)	Budesonide/MDI + Nebulhaler (0.2 mg) DPI; Turbuhaler (0.2 mg)		Cough (p < 0.001) DPI > MDI + spacer		Device rating (p < 0.001) DPI > MDI + spacer Difficulty in learning to use (p < 0.001) DPI > MDI + spacer Time to learn to use (p < 0.001) DPI > MDI + spacer	Crossover/14 d
Morice et al ¹²⁹ /2000/type 2A	34	7	19–55 yr (23.3 ± 6.5 yr‡)	Beclomethesone/MDI + Volumatic (2 mg/d) DPI (2 mg/d)	PEFR-AM (NS)	Daytime symptom score (NS)			Crossover/4 wk
Nieminen and Lahdensuo ¹⁰⁴ / 1995/type 2A	24	0	20–65 yr (43 yr†)	Budesonide/MDI + Nebulhaler (0.4 mg) DPI; Turbuhaler (0.4 mg)	FEV ₁ (NS) PEFR-AM (NS) FVC (NS) FEF _{25–75} (NS)	Asthma score (NS) Daytime breathlessness (NS) Daytime wheezing (NS)		Preference (NS) β ₂ -adrenergic use (NS)	Crossover/4 wk
Vidgren et al ¹⁰⁵ /1994/type 2A	20	0	16–57 yr (36 yr†)	Beclomethesone/MDI + Volumatic (0.8 mg) DPI; Easyhaler (0.8 mg)	FEV ₁ (NS) PF (NS)	Symptom score (NS)		Preference (p < 0.001) DPI > MDI + spacer ease of use (NS)	Crossover/4 wk

*See Tables 5 and 8 for abbreviations not used in the text.

†Median values.

‡Mean ± SD values.

Table 19—Outpatient COPD Studies*

Study/Year/Study Type	Setting	Total Patients, No.	Lost to Follow-up, No.
Short-term MDI vs DPI studies using β_2 -agonists Formgren et al ¹³⁵ /1994/type 2A	COPD	15	0
Short-term MDI vs DPI studies using anticholinergics Gimeno et al ¹³³ /1988/type 2A	COPD	15	0
Rammeloc et al ¹³⁴ /1992/type 2A	COPD	44	6
Short-term MDI vs MDI + spacer studies using β_2 -agonists Formgren et al ¹³⁵ /1994/type 2A	Adult COPD	15	0
Pauwels et al ¹³¹ /1984/type 2A	Adult COPD	11	0
Dorow and Hiding ¹³² /1982/type 2A	Asthma + COPD	15	
Short-term MDI + spacer vs DPI studies using β_2 -agonists Formgren et al ¹³⁵ /1994/type 2A	COPD	15	0
Nebulizer vs DPI studies using β_2 -agonists Hansen, ¹³⁰ /1989/type 2A	COPD	25	3
Nebulizer vs MDI studies using β_2 -agonists Balzano et al ¹³⁶ /2000/type 1	Asthma and COPD	20	0

*sW = specific work of breathing; RV = residual volume; MEF = maximal expiratory flow. See Table 8 for abbreviations not used in the text.

†Mean \pm SD values.

‡Median values.

- Nebulizer use in the ED setting is associated with greater increases in heart rate than with the use of an MDI with spacer/holding chamber, suggesting that a larger systemically absorbed dose is administered by nebulizers (quality of evidence: good).

Recommendations:

1. Both the nebulizer and MDI with spacer/holding chamber are appropriate for the delivery of short-acting β_2 -agonists in the ED. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.
2. Because data for DPIs are limited, and high quality data for standard MDIs (without spacer/holding chamber) and breath-actuated MDIs are unavailable, we are unable to recommend the use of these devices in the ED until more information is available. Quality of evidence: low; net benefit: none; strength of recommendation: I.
3. Many factors would lead the clinician to appropriately select a particular type of aerosol de-

livery device in this setting. These factors include the patient's ability to use the device correctly, the preferences of the patient for the device, the unavailability of an appropriate drug/device combination, the compatibility between the drug and delivery device, the lack of time or skills to properly instruct the patient in the use of the device or to monitor the appropriate use, and the cost of therapy. Quality of evidence: low; net benefit: substantial; strength of recommendation: B.

Aerosol Delivery of Short-Acting β_2 -Agonists in the Inpatient Hospital Setting

Summary of RCT Results:

- In the inpatient setting, the available evidence suggests that there is no difference in the pulmonary function response between using a nebulizer and using an MDI with a spacer/holding chamber for administering short-acting β_2 -agonist therapy (quality of evidence: good).

Age Range	Drug/Device (Dose)	Pulmonary Function	Other Measures
44–72 yr (61 ± 9 yr†)	Terbutaline/Turbuhaler (1.0 mg)	FEV ₁ % pred (NS) FVC % pred (NS)	sGaw (NS) RV (NS)
28–72 yr (50.7 ± 18.8 yr†)	Ipratropium bromide MDI (0.04 mg) DPI (0.04, 0.2 mg) Ipratropium bromide + fenoterol/DPI (0.04 mg ipratropium bromide + 0.1 mg fenoterol)	FEV ₁ (NS) FVC (NS) FEV ₁ (NS) FVC (NS)	sW (NS)
44–72 yr (61 ± 9 yr†)	Terbutaline/MDI: 1 mg MDI + spacer (2.5 mg) Nebuhaler	FEV ₁ % pred (NS) FVC % pred (NS)	sGaw (NS)
18–65 yr	Terbutaline/Tube Spacer (0.25, 0.5, 0.75 mg)	FEV ₁ (NS) MEF 75% (p < 0.01) 0.25 mg, (NS) 0.5, 0.75 mg	
46–80 yr (59.5 yr‡)	Terbutaline/Nebuhaler (0.5 mg)	FEV ₁ (NS) PF (NS) FEF _{25–75} (NS)	
44–72 yr (61 ± 9 yr†)	Terbutaline/MDI + Nebuhaler (2.5 mg) DPI Turbuhaler (2.5 mg)	FEV ₁ % pred (NS) FVC % pred (NS)	sGaw (NS) RV (NS)
69.5 yr‡	Terbutaline/DPI-Turbuhaler (2 mg) Nebulizer (5 mg)	FEV ₁ (NS) FVC (NS)	
67 ± 2 yr†	Salbutamol, ipratropium bromide/MDI (0.6 mg salbutamol + 0.12 mg ipratropium bromide) NEB (1.875 mg salbutamol + 0.375 mg ipratropium bromide)	FEV ₁ (NS)	

Recommendations:

- Both nebulizers and MDIs with spacer/holding chambers are appropriate for use in the inpatient setting. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.
- Because the data for DPIs, standard MDIs without spacer/holding chambers, and breath-actuated MDIs have been inadequately studied in this setting, we are unable to recommend the use of these devices in patients requiring hospitalization for asthma or COPD until more information is available. Quality of evidence: low; net benefit: none; strength of recommendation: I.
- Many factors would lead the clinician to appropriately select a particular type of aerosol delivery device in this setting. These include the patient's inability to use the device correctly, the preferences of the patient for the device, the unavailability of the drug/device combination, the compatibility between the drug and the delivery device, the lack of time or skills to properly instruct the patient in the use of the device or in moni-

toring the appropriate use, and the cost of therapy. Quality of evidence: low; net benefit: substantial; strength of recommendation: B.

Intermittent vs Continuous Nebulizer Delivery of β_2 -Agonists

Summary of RCT Results:

- Pulmonary function and asthma symptom scores show **similar benefits** for continuous and intermittent nebulization of short-acting β_2 -agonists (quality of evidence: good).
- The **time requirements for staff administration and maintenance of the therapy are less** for continuous nebulization than for intermittent nebulization (quality of evidence: good).
- Adverse effects of β_2 -agonists are similar** for continuous and intermittent nebulization of β_2 -agonists (quality of evidence: good).
- The effects of continuous vs intermittent nebulization of β_2 -agonists on hospital admission rate from the ED, hospital length of stay, and cost of care have not been adequately studied (quality of evidence: low).

Recommendation:

1. Frequent intermittent nebulization and continuous nebulization are both appropriate alternatives in severely dyspneic patients in the ED or ICU. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.

Aerosolized β_2 -Agonists in Patients Receiving Mechanical Ventilation

Summary of RCT Results:

- In children and adults receiving mechanical ventilation, the outcomes of β_2 -agonist administration using an MDI with or without a spacer/holding chamber are no different than those observed following β_2 -agonist administration with a nebulizer (quality of evidence: fair).
- High doses of β_2 -agonists administered with a nebulizer are associated with a higher incidence of tachycardia and premature heart beats in mechanically ventilated patients, but there is no difference in adverse effects observed after the administration of albuterol with an MDI compared to those observed after the administration of the drug with a nebulizer (quality of evidence: fair).
- There is insufficient evidence to guide the choice of MDI or nebulizer for patients receiving NPPV (quality of evidence: low).

Recommendations:

1. Both nebulizers and MDIs can be used to deliver β_2 -agonists to mechanically ventilated patients. Quality of evidence: fair; net benefit: substantial; strength of recommendation: A.
2. Careful attention to details of the technique employed for administering drugs by MDI or nebulizer to mechanically ventilated patients is critical, since multiple technical factors may have clinically important effects on the efficiency of aerosol delivery. Quality of evidence: low; net benefit: substantial; strength of recommendation: B.

Short-Acting β_2 -Agonists for Asthma in the Outpatient Setting

Summary of RCT Results:

- In the adult and pediatric outpatient population with asthma, available evidence comparing short-acting β_2 -agonist delivery by MDI and DPI show no differences in pulmonary function responses, symptom scores, or heart rate. This remains true when analysis is restricted to type 2b studies that estimate the doses required to

produce equal levels of response (called *dose-axis comparisons*) [quality of evidence: good].

- In a limited number of type 2 studies comparing short-acting β_2 -agonists administered with an MDI to that with an MDI using a spacer or holding chamber, pulmonary function responses were found to be comparable (quality of evidence: low).
- The use of nebulizers for the delivery of short-acting β_2 -agonists in the outpatient setting has not been adequately studied in RCTs (quality of evidence: low).

Recommendations:

1. For treatment of asthma in the outpatient setting, both the MDI, used with or without spacer/holding chamber, and the DPI are appropriate for the delivery of short-acting β_2 -agonists. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.
2. The appropriate selection of a particular type of aerosol delivery device in this setting includes the patient's ability to use the device correctly, the preferences of the patient for the device, the availability of the drug/device combination, the compatibility between the drug and delivery device, the lack of time or skills to properly instruct the patient in the use of the device or to monitor the appropriate use, the cost of the therapy, and the potential for reimbursement. Quality of evidence: low; net benefit: substantial; strength of recommendation: B.

Inhaled Corticosteroids for Asthma

Summary of RCT Results:

- For adult patients with asthma in the outpatient setting, there are no differences in pulmonary function response or symptom scores when the same dose of the same corticosteroid is used in a DPI or MDI with spacer/holding chamber (quality of evidence: good).
- Two studies indicated a significant patient preference for use of the DPI over that of the MDI with spacer/holding chamber (quality of evidence: good).
- No RCT adequately addressed the incidence of oral candidiasis (quality of evidence: low).

Recommendations:

1. For the treatment of asthma in the outpatient setting, both the MDI with a spacer/holding chamber and the DPI are appropriate devices for the delivery of inhaled corticosteroids.

Quality of evidence: good; net benefit: substantial; strength of recommendation: A.

2. For outpatient asthma therapy, the selection of an appropriate aerosol delivery device for inhaled corticosteroids includes the patient's ability to use the device correctly, the preferences of the patient for the device, the availability of the drug/device combination, the compatibility between the drug and delivery device, the lack of time or skills to properly instruct the patient in the use of the device or monitor the appropriate use, the cost of therapy, and the potential for reimbursement. Quality of evidence: low; net benefit: substantial; strength of recommendation: B.

β_2 -Agonists and Anticholinergic Agents for COPD

Summary of RCT Results:

- In the outpatient management of COPD patients with β_2 -agonist and anticholinergic agents, the available evidence shows no differences in pulmonary function responses between delivery devices (quality of evidence: good).
- Increases in heart rate were greater after the administration of albuterol by nebulizer than after administration by MDI (quality of evidence: good).

Recommendations:

1. For the treatment of COPD in the outpatient setting, the MDI, with or without spacer/holding chamber, the nebulizer, and the DPI are all appropriate for the delivery of inhaled β_2 -agonist and anticholinergic agents. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.
2. For outpatient COPD therapy, the selection of an appropriate aerosol delivery device for inhaled β_2 -agonist and anticholinergic agents includes the patient's ability to use the device correctly, the preferences of the patient for the device, the availability of the drug/device combination, the compatibility between the drug and the delivery device, the lack of time or skills to properly instruct the patient in the use of the device or monitor its appropriate use, the cost of therapy, and the potential for reimbursement. Quality of evidence: low; net benefit: substantial; strength of recommendation: B.

Device Selection

When selecting an aerosol delivery device, the following questions should be considered:

1. In what devices is the desired drug available?
2. What device is the patient likely to be able to use properly, given the patient's age and the clinical setting?
3. For which device and drug combination is reimbursement available?
4. Which devices are the least costly?
5. Can all types of inhaled asthma/COPD drugs that are prescribed for the patient (eg, short-acting β -agonist, corticosteroid, anticholinergic, and long-acting β -agonist) be delivered with the same type of device (eg, nebulizer, manually actuated MDI, MDI with spacer/holding chamber, or breath-actuated device [ie, automatically activated MDI or DPI])? Using the same type of device for all inhaled drugs may facilitate patient teaching and decrease the chance for confusion among devices that require different inhalation techniques.
6. Which devices are the most convenient for the patient, family (outpatient use), or medical staff (acute care setting) to use, given the time required for drug administration and device cleaning, and the portability of the device?
7. How durable is the device?
8. Does the patient or clinician have any specific device preferences?

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