

Practical Problems With Aerosol Therapy in COPD

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Introduction

Problems With Use of MDIs

Synchronizing Inhalation With MDI Actuation

Lack of a Dose Counter

Medical Personnel Knowledge of MDI Use

Patient Factors Associated With Poor MDI Use

Possible Solutions to MDI Misuse

Problems With Use of Holding Chambers/Spacers

Effect of Time Delay and Electrostatic Charge

Effect of Multiple MDI Actuations

Lack of Provider Knowledge

Problems With DPIs

Differences in DPI Models and Use

Lack of Provider Knowledge of DPI Use

Effect of Humidity on DPI Dose

Effect of Inspiratory Flow on Emitted DPI Dose

Problems With Use of SVN

Use of a Breath-Actuated pMDI

A Solution to Inhaler Misuse: Design Convergence?

Inhaled aerosol drugs commonly used by patients with chronic obstructive pulmonary disease include short-acting and long-acting bronchodilators, as well as corticosteroids. These agents are available in a variety of inhaler devices, which include metered-dose inhalers (MDI), breath-actuated MDIs, nebulizers, and, currently, 5 different models of dry powder inhaler (DPI). There is evidence to suggest that multiple inhaler types cause confusion among patients and increase errors in patient use. Problems with MDIs include failure to coordinate inhalation with actuation of the MDI, inadequate breath-hold, and inappropriately fast inspiratory flow. Lack of a dose counter makes determining the number of remaining doses in an MDI problematic. Patient misuse of MDIs is compounded by lack of knowledge of correct use among health-care professionals. Several factors often seen with elderly patients have been identified as predictive of incorrect use of MDIs. These include mental-state scores, hand strength, and ideomotor dyspraxia. Holding chambers and spacers are partially intended to reduce the need for inhalation-actuation coordination with MDI use. However, such add-on devices can be subject to incorrect assembly. Possible delays between MDI actuation and inhalation, rapid inspiration, chamber electrostatic charge, and firing multiple puffs into the chamber can all reduce the availability of inhaled drug. Because they are breath-actuated, DPIs remove the need for inhalation-actuation synchrony, but there is evidence that patient errors in use of DPIs may be similar to those with MDIs. One of the biggest problems is loading and priming the DPI for use, and this may be due to the fact that every DPI model in current use is different. Medical personnel's knowledge of correct DPI use has also been shown to be lacking. The optimum inhalation profiles are different for the various DPIs, but, generally, chronic obstructive pulmonary disease patients have been shown to achieve a minimum

therapeutic dose, although the inhaled amount may be suboptimal. A limitation of DPIs that have multidose powder reservoirs (eg, the Turbuhaler) is ambient humidity, which can reduce the released dose. Small-volume nebulizers are limited by bulk, treatment time, and variable performance, but are easy for patients to use. Important features identified by patients for an ideal inhaler are ease of use during an attack, dose counter, and general ease of use and learning. A breath-actuated-pMDI, such as the Autohaler, ranked at the top of inhaler preference in a study of 100 patients with airflow obstruction, compared to DPIs and MDIs. Short of a universal simple inhaler, patient and caregiver education remains the best solution to correct patient errors in use. *Key words: inhaler, chronic obstructive pulmonary disease, metered-dose inhaler, nebulizer, dry powder inhaler, holding chamber, spacer, breath-actuated pressurized inhalers.* [Respir Care 2006;51(2):158–172. © 2006 Daedalus Enterprises]

Introduction

Treatment of pulmonary disease with inhaled aerosol drugs offers advantages over systemic therapy, including a more rapid onset and reduced adverse effects, with both bronchodilators and corticosteroids, because of direct targeting of the lungs.^{1–2} There are currently a number of different aerosol-delivery devices for drugs to treat airways disease. The 3 major categories of aerosol generators are metered-dose inhaler (MDI), dry powder inhaler (DPI), and small-volume nebulizer (SVN). Holding chambers and spacers are a fourth category of aerosol device, used in conjunction with MDIs. Although MDIs are uniform in appearance and operation, at the present time there are 2 propellant systems in clinical use during the transition from chlorofluorocarbon (CFC) to non-CFC propellants in MDIs. Hydrofluoroalkanes (HFAs) have emerged as MDI propellants to replace the ozone-unfriendly CFCs. HFA 134a is the propellant in the recently approved HFA MDIs in the United States.³ The 2 types of propellant have different plume characteristics, with the newer HFAs giving a warmer and softer plume perceived by patients.⁴ A variation on the traditional MDI is the breath-actuated pMDI (pMDI), such as the Maxair Autohaler (3M Pharmaceuticals), which is intended to facilitate the coordination of inhalation with actuation. In the DPI category there are currently 5 devices, all of which operate differently, with a 6th device (the Twisthaler, to deliver mometasone) recently made available. Table 1 lists aerosol drugs commonly used in chronic obstructive pulmonary disease (COPD), along with the corresponding aerosol device types used for their delivery.

Figure 1 shows pictures of each aerosol device category and model currently used in the United States. The

Table 1. Aerosol Drug Formulations and Corresponding Inhaler Devices Available in the United States in 2005

Drug	Aerosol Inhaler Device
Short-Acting Bronchodilators	
Albuterol	CFC-MDI, HFA-MDI, SVN
Terbutaline	CFC-MDI
Pirbuterol	Breath-actuated pressurized MDI (Autohaler)
Levalbuterol	HFA-MDI,* SVN
Ipratropium	HFA-MDI, SVN
Long-Acting Bronchodilators	
Salmeterol	DPI (Diskus)
Formoterol	DPI (Aerolizer)
Tiotropium	DPI (HandiHaler)
Corticosteroids	
Beclomethasone	HFA-MDI
Triamcinolone	CFC-MDI
Flunisolide	CFC-MDI
Fluticasone	CFC-MDI, DPI (Rotadisk)
Budesonide	SVN, DPI (Turbuhaler)
Mometasone	DPI (Twisthaler)
Ciclesonide*	HFA-MDI

CFC = chlorofluorocarbon

MDI = metered-dose inhaler

HFA = hydrofluoroalkane

SVN = small-volume nebulizer

DPI = dry powder inhaler

* Food and Drug Administration approval received

existing variety of aerosol devices means that a COPD patient is likely to have a CFC or HFA MDI, probably with a holding chamber or spacer, or an SVN for short-acting bronchodilator delivery, along with one or more models of DPI for long-acting bronchodilator therapy and/or inhaled corticosteroid therapy, based on current COPD treatment guidelines.⁵ Several recent meta-analyses showed that any of the inhaler device types can be equally effective in treating patients.^{6–8} The primary qualifications are that the patient is able to use the

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Fig. 1. Variety of inhaler devices potentially used by patients with chronic obstructive pulmonary disease for delivery of aerosolized drugs. In addition to small-volume nebulizers and pressurized metered-dose inhalers (pMDIs) with holding chamber or spacer, there are currently 5 different models of dry powder inhaler, with a 6th model, the Twisthaler, recently made available.

device correctly and that the drug is available in the device.

There is evidence that use of multiple inhaler types leads to confusion for patients, resulting in errors of use. A study by van der Palen et al with asthma patients found that a higher percentage of subjects showed no inhalation errors when only one inhaler was used, compared to 2 or more inhalers.⁹ The percentage of patients performing all the essential steps of inhaler use was greater when a combination of DPIs was used, compared to a combination of an MDI and DPI.⁹

The following case study, adapted from Seeto and Lim,¹⁰ illustrates some practical problems with certain inhalers and with multiple inhaler types, as well as solutions tailored to the patient's needs and situation. A 55-year-old female accountant in Australia was diagnosed with non-atopic asthma approximately 5 years ago. She had a 15-

year history of smoking, but had stopped 3 years ago. Her hobbies included swimming and sailing, year-round, and she lived in a coastal area. In the previous year she was prescribed a budesonide Turbuhaler (Pulmicort) 400 μ g twice a day, along with a combination of ipratropium and albuterol in an MDI, for as-needed use. She had no holding chamber for the MDI. At the end of winter she complained of a "cold," with increased shortness of breath, and she used her short-acting bronchodilator every 6 hours. She saw her general practitioner a few days later and was put on oral prednisone. Her doctor also recommended doubling her budesonide dose. She failed to improve after several days and was admitted. She was given intravenous hydrocortisone and every-4-h nebulized short-acting bronchodilators. Her symptoms improved, and her medications were weaned progressively. During admission, a review of her inhaler technique found that both her MDI and DPI

technique were poor. Instruction was not entirely successful, because of poor inspiration-actuation coordination with the MDI. She was prescribed a single inhaler type, an Autohaler formulation of albuterol and ipratropium, and beclomethasone.* This simplified her inhaler use, obviated the holding chamber, allowed use of just one breathing pattern, and eliminated the moisture-sensitive Turbuhaler, which might have been impaired by the humid environment of her hobbies. She was subsequently maintained successfully on this regimen.

Misuse of inhaler devices can lead to inadequate drug dosing and suboptimal disease control, as illustrated anecdotally in the latter case study. Giraud and Roche found that misuse of MDIs, which was mainly due to poor coordination, was frequent and associated with poorer asthma control in patients treated with inhaled corticosteroid.¹¹ Although nebulizers are considered the easiest of the inhaler types for patients to use, Corden et al found that patient compliance with home nebulizer therapy in COPD was on average 57%.¹² Poor compliance, a form of misuse of therapy, was negatively correlated with the total score on the St George's Respiratory Questionnaire, in which a higher score indicates greater quality-of-life impairment.

Problems with inhaler use were recently reviewed by Fink and Rubin.¹³ They note estimates that 28–68% of patients do not use their MDIs or DPIs well enough to benefit from the prescribed drug. They also point out that improper inhaler use results in \$7–15.7 billion wasted, with no benefit to the patient. They also note that, corresponding to poor patient use of inhalers, only 2 of 40 textbooks used in physician training included a list of simple steps for proper MDI use.

Problems With Use of MDIs

The original pMDI was developed by 3M Laboratories and introduced in 1956 as an alternative to the somewhat cumbersome, breakable glass-bulb nebulizers used for asthma treatment.^{14,15} The pMDI offers a compact, portable, stand-alone metering system for the inhalation of drugs, with good dose consistency. Dosing usually consists of 2 actuations/inhalations, requiring only a minute or so. Yet difficulty in patient use of the seemingly simple “press and breathe” MDI was recognized as early as 1965, in a report by Saunders, which found that 14 of 25 patients incorrectly used the MDI.¹⁶ Three different reports in 1976 documented patient errors in MDI use, with estimates that 32–96% of patients committed errors.^{17–19} Other studies continued to confirm this in the 1980s and 1990s.^{20–21}

* Autohaler formulations of the combination of albuterol and ipratropium, and of beclomethasone, are available in Australia, but not the United States.

Table 2. Problems Patients May Have When Using Metered-Dose Inhalers

Problem	Percent of Patients
Error in technique	
Failure to coordinate MDI actuation with inhalation	27
Too short a period of breath-hold after inhalation	26
Too rapid an inspiratory flow	19
Inadequate shaking/mixing before use	13
Abrupt discontinuation of inspiration as aerosol hits throat (“cold Freon” effect)	6
Actuating MDI at total lung capacity	4
Firing MDI multiple times during single inhalation	3
Firing MDI into mouth but inhaling through nose	2
Exhaling during activation	1
Putting wrong end of inhaler in mouth	< 1
Holding canister in the wrong position	< 1
Lack of a dose counter	
Excessive use of MDI beyond rated capacity	ND
Waste of remaining doses	ND
Lack of health-care provider knowledge of correct MDI use	ND
Lack of adequate patient training in use of MDI	ND
Cognitive impairment of user	ND
Lack of adequate hand strength or flexibility to activate MDI	ND
Ideomotor dyspraxia	ND

MDI = metered-dose inhaler

ND = no data available

(List of errors in technique and percentage occurrence are based on McFadden.²² Other problems are discussed and referenced in the text.)

Table 2 lists problems that patients may encounter in the use of MDIs. Several key problems with MDI use seen in the literature are reviewed.

Synchronizing Inhalation With MDI Actuation

McFadden cataloged the frequency of patient errors with MDIs, based on 12 studies, involving 955 subjects who committed 1,536 errors (see Table 2).²² The most frequent MDI error was failure to coordinate actuation with inha-

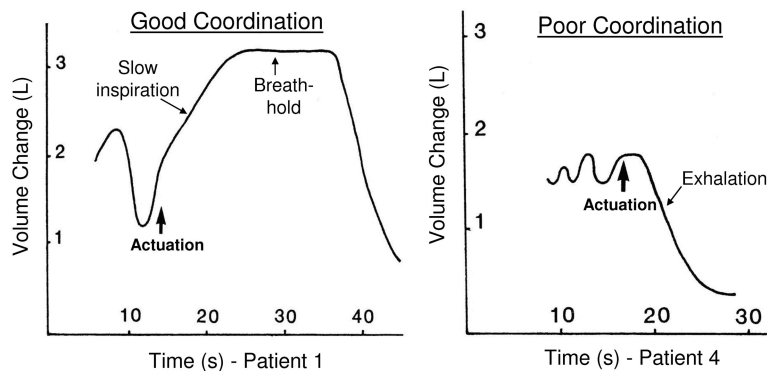


Fig. 2. Tracings of respiratory maneuvers, showing inhaled volume plotted against time for 2 patients using a metered-dose inhaler (MDI). Left: Patient 1 actuates the MDI at exhalation and uses a slow inhalation (11.6 L/min) and a 12-second breath-hold. Right: Patient 4 actuates the MDI after a shallow inhalation, followed by a deep exhalation. (From Reference 23, with permission.)

lation, also known as “hand-breathing coordination,” followed closely by too short a breath-hold. Other errors included high inspiratory flow, not shaking the MDI prior to use, and stopping inspiration when the MDI spray hits the throat. Figure 2 illustrates correct use of an MDI and failure to perform a correct breathing maneuver when actuating the MDI, based on data from Newman et al.²³

Lack of a Dose Counter

Another practical problem for patients who use MDIs is the difficulty in determining the number of doses remaining in the device. Ideally, a patient knows the dose rating (eg, 200 puffs) for a given MDI/drug formulation, and keeps track of how many actuations he or she has used. This is most easily done if the MDI is used on a regular basis, so the total number of puffs can be divided by the number of puffs per day to give the days until a refill is needed. Yet Ogren et al found that 54% of patients surveyed were unaware of the maximum number of actuations listed by the manufacturer for their MDI; only 8% reported counting the actuations used.²⁴ However, with irregular or as-needed use, the only way to count doses used/remaining is with a log or tally sheet, which requires additional patient effort.

Rubin and Durotoye asked clinic patients how they determined that the MDI was empty, and 72% reported the MDI was empty if there was no sound when the canister was actuated.²⁵ Their study showed that CFC canisters (Ventolin, Serevent, and Flovent) had a mean of $86 \pm 14\%$ more audible puffs than the maximum number of doses stated by the manufacturer. Since propellant can release an aerosol plume with little or no drug beyond the maximum number of puffs (“tail-off”),²⁶ patients can under-dose using this method. Twenty percent of subjects said they replaced the canister when it was “old,” with no precise time given. Another 14% reported “after a month

or so,” or “after awhile.” In the same study, the authors found that 78% of patients knew they should shake a canister before actuation, to mix the propellant and drug, but only half of the patients actually did so when asked to demonstrate MDI use. Use of canister flotation to determine fullness is not reliable, and water can obstruct the MDI valve.²⁵

Medical Personnel Knowledge of MDI Use

A number of studies have shown a disturbing lack of knowledge of correct MDI use on the part of health-care professionals. Interiano and Guntupalli studied the performance of both patients and health-care providers in using an MDI and classified performance as good (5–6 steps performed correctly), fair (3–4 steps), or poor (< 2 steps).²⁷ They found that only 13% of 40 general-medicine patients, versus 62% of 60 pulmonary medicine patients, had good performance. House staff and nurses were less proficient than respiratory therapists (RTs) in use of the MDI, with 43%, 4%, and 85% rated good, respectively.

Similar findings were seen in a study by Guidry et al, in which 92% of RTs demonstrated at least 4 of 7 MDI steps correctly, compared to 65% of internal medicine residents, 57% of nurses, and 57% of nonpulmonary faculty.²⁸ Similar results were seen in a study of emergency physicians, house staff, and nurses.²⁹ Kesten et al found that 62% of pharmacists performed all 11 steps correctly from a checklist on MDI use.³⁰ Inadequate knowledge of MDI use by health-care professionals compounds the problem of poor MDI use by patients.

Patient Factors Associated With Poor MDI Use

Studies have examined demographic as well as other variables that might be associated with or predictive of poor MDI technique. Mental/cognitive status in older sub-

jects has emerged in several studies as predictive of the ability to use an MDI correctly.^{31–33} Gray et al found no association between age, sex, or years of education and prediction of incorrect MDI use among subjects with a mean age of 69.7 years.³¹ They did find that a Mini Mental State Examination, and hand strength (measured as pinch gauge and with a dynamometer) were significantly associated with correct MDI use. Correct MDI users had higher Mini Mental State Examination scores; of those with a score ≥ 24 , 70% were correct users versus 30% incorrect users. Of those with a score < 24 , 32% were correct and 68% incorrect users.

Allen and Ragab found that a sample of patients age 76–94 years could have a normal Abbreviated Mental Test, while the Mini Mental Test and ideomotor dyspraxia test both correlated significantly with inhaler technique.³² Their study supported the view that patients with undetected cognitive impairment and subclinical dyspraxia (disturbance in the control and execution of volitional movements) may have difficulty mastering an adequate MDI technique, even despite training.

Allen and Prior likewise found that MDI competence was significantly related to Mental Status Questionnaire scores, but not to age or diagnosis.³³ They also found that patients who had an MDI prescribed in hospital were significantly more likely to be competent than those who received the prescription from a general practitioner. This finding is consistent with that of Interiano and Guntupalli, that a higher percentage of pulmonary patients than general-medicine patients were classified as good MDI performers.²⁷

De Blaquiére et al used discriminant analysis to identify patient characteristics predictive of incorrect MDI use.³⁴ Their study found that bronchodilator responsiveness, a history of additional teaching on proper technique, verbal knowledge of correct inhaler maneuvers, and patient perception of the importance of inhaler use all predicted correct MDI use. Although sex was not predictive of correct inhaler technique in other studies,^{31–33} Goodman et al found that a significantly higher proportion of male than female subjects age 20–81 years (mean 38 y) performed an acceptable MDI maneuver (43% vs 4%).³⁵ This difference may be related to the sample age range.

Possible Solutions to MDI Misuse

In his analysis and review of improper MDI techniques, McFadden suggested several options: holding chamber or spacer, breath-actuated pMDI, and breath-actuated DPI.²² Each of these device types are intended to simplify MDI use, especially the problem of actuation-inhalation coordination. With the possible exception of breath-actuated pMDIs which are discussed below, these inhaler options/devices have also exhibited problems with patient use.

Table 3. Common Problems and Errors in the Use of Holding Chambers and Spacers

Incorrect assembly of add-on device
Added equipment bulk to portable MDI
Presence of electrostatic charge in many holding-chambers/spacers, which can decrease emitted dose in a new holding-chamber/spacer
Lengthy delay between MDI actuation and inhalation from the holding-chamber/spacer
Inhaling too rapidly
Firing multiple puffs into the holding-chamber/spacer before inhaling
Lack of provider knowledge of assembly or use
MDI = metered-dose inhaler

Further, not all aerosol drugs are available in each device type, which limits the options in choice of device.

Problems With Use of Holding Chamber or Spacer

A holding chamber (or spacer) can achieve 2 primary purposes: simplified MDI inhalation, and reduced oropharyngeal drug deposition.^{36–37} A major disadvantage of these add-on devices is additional cost to the medical system and the potential for new patient errors. The added size of a holding chamber or spacer defeats one of the primary advantages of the MDI, which is its compact size and portability, and, to some extent, its immediate readiness for inhalation. Table 3 lists common errors and problems with holding chambers and spacers.

Effect of Time Delay and Electrostatic Charge

Aerosol drug particles discharged into a holding chamber or spacer can be lost to the chamber walls by inertial impaction (large, fast-moving particles), gravitational sedimentation (smaller particles), and electrostatic attraction between the drug particles and the wall of the chamber. Time delay between actuation and inhalation increases particle-loss from sedimentation and electrostatic charge, and can reduce the fine-particle mass available for inhalation. Wildhaber et al found that CFC albuterol aerosol particles $< 6.8 \mu\text{m}$ delivered via a small plastic spacer decreased from 33% of the actuated dose with no delay, down to 12.3% and 8.6% with 5-s and 20-s delays, respectively.³⁸ Reducing electrostatic charge on the spacer with ionic detergent increased small-particle delivery by 47–71%. The effect of delay was also minimized by removal of the electrostatic charge. Similar findings have been seen in other investigations with albuterol or cromolyn sodium.^{39–42} Electrostatic charge in a holding chamber or spacer can be reduced by washing with ionic detergent.^{38,40} Priming, or actuating the MDI 12 or 20 times into a holding chamber also reduces electrostatic charge

but less effectively than washing,^{42a} and is wasteful of MDI doses. Recently, 2 holding chambers constructed of charge-dissipative materials (Pari Vortex, Monaghan Aero-Chamber Max) to eliminate electrostatic charge have been marketed.^{42b}

Effect of Multiple MDI Actuations

Multiple actuations of an MDI into a holding chamber prior to inhalation can also reduce the dose availability, compared to a single actuation per inhalation. This is probably due to the time delay introduced by multiple firings before inhalation. Research in our laboratory showed that the dose of CFC albuterol delivered per actuation for 3 holding chambers (AeroChamber, ACE, and InspirEase) declined 8%, 17%, and 20%, respectively, with 2 multiple actuations.⁴³ Although total dose availability increases with 2 actuations, compared to only one, it will be less than that with 2 separate actuations/inhalations. Similar results were seen in other studies.^{38–40}

Lack of Provider Knowledge

There are data to indicate that lack of provider knowledge of correct inhaler use is not limited to MDIs alone. Hanania et al assessed knowledge and ability to use an MDI, an MDI with holding chamber (AeroChamber), and a DPI (Turbuhaler) among RTs, registered nurses, and medical house physicians.⁴⁴ Mean knowledge scores for all devices was highest among the RTs ($67 \pm 5\%$), followed by physicians ($48 \pm 7\%$) and nurses ($39 \pm 7\%$). In particular, demonstration scores for MDI and holding chamber use among RTs, nurses, and physicians were $98 \pm 2\%$, $78 \pm 20\%$, and $57 \pm 31\%$, respectively. The study acknowledged that more RTs (77%) received formal instruction on use of aerosol devices than either nurses (30%) or physicians (43%). A study by Kesten et al showed poor MDI use scores among pharmacists and found that only 47% of pharmacists performed all 11 steps from a checklist for use of MDI with AeroChamber.³⁰ The Kesten et al³⁰ study was published in 1993, and the Hanania et al⁴⁴ was published in 1994, so the holding chamber used in those tests (AeroChamber) was not newly introduced.

Problems With DPIs

Difficulty in synchronizing inhalation and MDI actuation was noted by Bell and colleagues as a rationale for the introduction, in 1971, of the DPI SpinHaler, for delivery of cromolyn sodium.⁴⁵ DPIs, which require breath-actuation for dose release, offer the compact efficiency of MDIs while removing the troublesome hand-breath coordination required with MDIs. A systematic review of inhaler devices by Brocklebank and associates combined results from

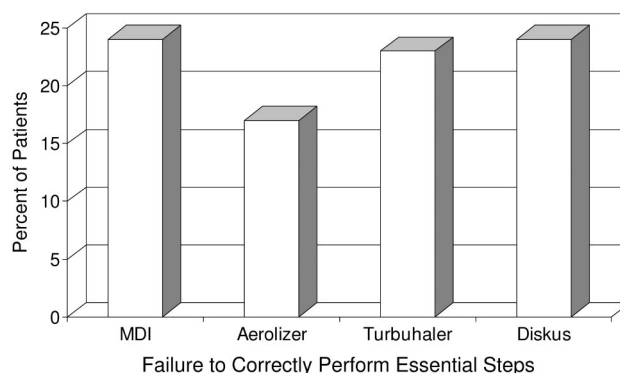


Fig. 3. Percentages of patients who failed to correctly perform essential steps in inhaler use that are considered critical for reliable drug delivery to the lungs, with a metered-dose inhaler (MDI) and 3 models of dry powder inhaler. (Based on data from Reference 46.)

studies of more than one inhaler type, and found that maximum or “ideal” inhaler scores were achieved by 59% of subjects with DPIs, 43% with MDI alone, and 55% with MDI plus holding chamber.⁷ These aggregate data support the intuitive view that DPIs are used correctly more often than are MDIs alone. However, patient instruction in correct inhaler use eliminated that difference, increasing the percentage of subjects who showed correct technique to 63% for MDI alone and to 65% for DPIs.⁸ Such data provide evidence of the positive effect of teaching to achieve correct inhaler use.

There is other evidence that similar numbers of experienced asthma and COPD patients exhibit errors in using DPIs as in use of MDIs. Melani and associates found, in a large multicenter survey, that similar percentages of patients failed to perform essential steps needed for reliable lung delivery of inhaled aerosol in both MDI and DPI use.⁴⁶ Figure 3 illustrates such percentages for use of MDIs and 3 DPIs (Aerolizer, Turbuhaler, and Diskus). In the United States, these 3 DPIs are delivery vehicles for formoterol (Foradil), budesonide (Pulmicort), and salmeterol (Serevent), as well as the combination of salmeterol and fluticasone (Advair), respectively. Except for the Aerolizer, 23–24% of patients failed to perform essential steps in inhaler use, and 17% of patients did so when using the Aerolizer. Using data from the study by Melani et al, Table 4 lists errors and limitations in the use of DPIs.

van Beerendonk et al assessed inhalation technique among asthma and COPD patients and reported that 52% of the patients exhibited “skill” mistakes with the Diskhaler DPI, compared to 55% with an MDI.⁴⁷ The percentage of mistakes was higher for the Rotahaler and Ingelheim DPIs (73% and 80%). Non-skill mistakes (those requiring only teaching or verbal instruction, not actual training and practice) were also more frequent with the 3 DPIs evaluated (Diskhaler, Rotahaler, Ingelheim) than with an MDI (on average 86%, compared to 57%). Such data cast doubt

Table 4. Errors, Problems, and Limitations in the Use of Dry Powder Inhalers

Problem	Percent of Patients
Error in Technique	
Not holding device correctly (upright)	35
Exhaling through the mouthpiece	19
Not exhaling to residual volume before inhaling	24
Not inhaling forcefully	17
Inadequate or no breath-hold	23
Exhaling into mouthpiece after inhaling	20
Dependence on user's inspiratory flow rate and profile	ND
Reduced fine-particle dose in high ambient humidity, with multi-dose reservoir designs (eg, Turbuhaler)	ND
Lack of provider knowledge of assembly or use	ND

ND = no data available
(Percentage values are averages from error values for 3 different DPIs: Aerolizer, Turbuhaler, and Diskus.⁴⁶)

on the view that patients will have fewer errors with DPIs than with MDIs, despite the fact that with DPIs breath-actuation should automatically coordinate breathing with aerosol-release. There seem to be several factors associated with patient error or suboptimal use of DPIs.

Differences in DPI Models and Use

One potential challenge with DPI use is the fact that each DPI operates differently in loading and priming for use. Although Melani et al found that 92–98% of patients loaded the 3 studied DPIs successfully, only 58% and 72% held the Aerolizer and Turbuhaler inhalers upright during loading.⁴⁶ Patients may also become confused by the different inhalation patterns required for optimal MDI and DPI use. Melani et al found that 12–22% of patients did not inhale forcefully when using the 3 DPIs.

Data in the literature differ on which DPI model has the fewest patient use errors. In 2 studies by van der Palen et al, the Diskhaler (also known as Rotadisk) had the highest patient-performance scores.^{9,48} In contrast, a study by Oliver and Rees found that patient errors that caused zero drug delivery were most common with the Diskhaler.⁴⁹ The Diskhaler is a multiple-unit-dose device, meaning that a cassette of drug blisters must be loaded every 4 or 8 doses.

Diggory et al compared performance scores in elderly inhaler-naïve subjects for the delivery of zanamivir, an influenza drug, from a Diskhaler and a Turbuhaler (Euro-

pean name for Turbuhaler).⁵⁰ They found poorer performance with the Diskhaler than with the Turbuhaler. Scores for loading and priming were poor with 19 of the 38 patients (50%) using the Diskhaler after initial teaching, compared to 2 of 35 (6%) using the Turbuhaler. Such differences in patient performance might be partly explained by the different study populations. In both of the studies by van der Palen et al,^{9,48} the patients tended to be younger, with a mean age of 55 years (range 18–65 y) in one study.⁴⁸ Mean patient age in the study by Oliver and Rees was 67 years (range 53–81 y).⁴⁹ Mean patient age in the study by Diggory et al was 83 years (range 71–99 y), and they did not routinely use inhalers.⁵⁰

Lack of Provider Knowledge of DPI Use

As with MDIs and MDI/holding-chamber combinations, there is evidence of poor provider knowledge on correct use of DPIs. The previously cited study by Hanania et al, on MDI plus holding chamber use, also found demonstration scores for RTs, nurses, and physicians in use of the Turbuhaler of $60 \pm 30\%$, $12 \pm 23\%$, and $21 \pm 30\%$, respectively.⁴⁴ It should be pointed out that the Turbuhaler was relatively new even in Canada, where the study was conducted. The authors noted that practical skills with the aerosol devices (MDI, MDI with holding chamber, and DPI) studied were roughly proportional to the length of time the device had been in use. Similar results were seen for pharmacists' use of the DPI, Turbuhaler, with only 29% performing all 11 checklist items correctly.³⁰

Effect of Humidity on DPI Dose

Humidity is a concern with DPIs because of the potential for powder clumping and reduced dispersal of fine-particle mass.⁵¹ The humidity can be from the ambient air or, more directly, from patient exhalation into the mouthpiece. With the 3 DPIs evaluated by Melani et al, 17–23% of the patients exhaled through the mouthpiece.⁴⁶ The design of the DPI influences the effect of humidity, with multidose reservoirs (eg, the Turbuhaler) more vulnerable than powdered drug protected in individual blister packs or capsules, such as in the Diskus.

Meakin et al found that 70% ambient humidity reduced the amount of drug released within 2 hours, from about 55% of the nominal dose claim to 20% with the Turbuhaler—a reduction that lasted up to 4 days.⁵² Figure 4 illustrates the decrease in fine-particle mass that can occur with high ambient humidity (30°C and 75% relative humidity) with a salmeterol Diskus and a terbutaline Turbuhaler.⁵³ Because drug powder is contained within a blister strip, the Diskus provides more protection from humidity than does the Turbuhaler. Presumably, once the drug powder is metered for inhalation, by either opening the blister,

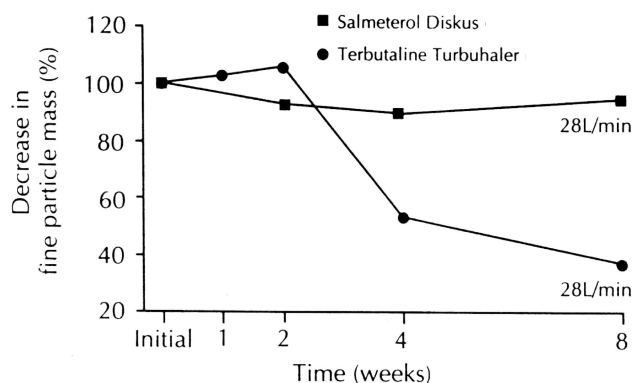


Fig. 4. Change in fine-particle mass as a percentage of initial value, for delivery of salmeterol with a Diskus and terbutaline with a Turbuhaler, with a relative humidity of 75% at 30°C. Humidity conditions were designed to simulate use in a bathroom. (From Reference 53, with permission.)

piercing a capsule, or releasing drug from a reservoir, high humidity from direct exhalation could reduce the dose with any DPI design.

Another factor that must be considered with humidity is the type of drug in the DPI. Though some drug particles show greater adhesion and reduced fine-particle mass as humidity increases, other particles dominated by electrostatic forces could show *decreased* adhesion with higher humidity levels. Tobyn et al reported opposite effects of humidity on the separation-energy required with drug powders for albuterol and a corticosteroid. These data indicated that higher relative humidity of up to 75% would favor powder deaggregation with a corticosteroid due to reduction of electrostatic attraction among the particles.⁵⁴ Thus, humidity can cause variance in delivery from DPIs with different drugs.

Effect of Inspiratory Flow on Emitted DPI Dose

All currently used DPIs in the United States rely on patient inspiratory effort to lift drug powder from the metering chamber (Turbuhaler), blister (Diskus, Rotadisk), or capsule (Aerolizer, HandiHaler) and to deaggregate the powder into particles small enough to reach the lungs.⁵⁵ More forceful inhalation generally results in better deaggregation, more fine particles, and a higher lung deposition. Potentially severe airflow limitation in COPD, especially during a severe exacerbation, raises the concern about whether such patients can perform adequate inhalation through a DPI. Several inhaled drugs recently approved for use with COPD patients include tiotropium (Spiriva), in the HandiHaler DPI, and salmeterol/fluticasone combination (Advair) in the Diskus DPI. Formoterol (Foradil) has also been released in the Aerolizer DPI.

The DPIs in current use have inherent but different resistances, so the inspiratory flow needed to create the pres-

sure-drop necessary for optimal drug delivery differs among DPI models. For example, Turbuhaler has a higher resistance than Diskus. A mean peak inspiratory flow (PIF) of 82 L/min through a Diskus inhaler gave a mean pressure drop of 35.7 cm H₂O, whereas a mean PIF of 54 L/min through the Turbuhaler gave a mean pressure drop of 40.8 cm H₂O.⁵⁶ Pedersen et al found that terbutaline delivered with a Turbuhaler was effective at flows as low as 30 L/min in asthmatic children, although improvement in forced expiratory volume in the first second (FEV₁) was less at flows of 13 or 22 L/min.⁵⁷ Nielsen et al found that salmeterol delivered via Diskus gave protection from exercise-induced asthma in children at either 30 or 90 L/min.⁵⁸ These studies indicated that both DPIs can be effective for bronchodilator delivery at 30 L/min, which is lower than the recommended 60 L/min.

Dewar et al studied the ability of 100 patients (mean age 69.1 y) with peak expiratory flow \leq 200 L/min or FEV₁ \leq 1 L to inhale through a Turbuhaler.⁵⁹ All patients were able to generate a minimum flow of 28 L/min, with a mean flow of 53 L/min. The distribution of flow rates is shown in Figure 5. Burnell et al used an inhalation simulator with inhalation profiles recorded from COPD patients whose FEV₁ was \leq 30% of predicted (severe obstruction) to determine dosing performance of the Diskus with fluticasone and Turbuhaler with budesonide.⁵⁶ Fine-particle mass as a percentage of labeled dose claim was higher with the Diskus (17.5% on average) than with the Turbuhaler (13.5% on average). Drug delivery of fine-particle mass was more dependent on PIF with the Turbuhaler than with the Diskus. In vitro measurement of drug delivery, even with actual patient inhalation profiles, does not equate to clinical effect, however, which was not measured.

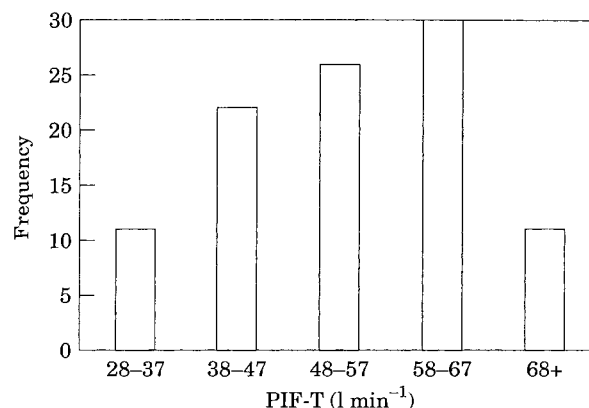


Fig. 5. Distribution of peak inspiratory flow through a Turbuhaler (PIF-T) in patients of mean age 69 years with severe airway obstruction. No patient demonstrated a PIF-T of $<$ 28 L/min, which is near the lower limit of 30 L/min considered effective for a therapeutic response with a bronchodilator from the Turbuhaler. (From Reference 59, with permission.)

Broeders et al studied the inhalation profiles of 15 patients hospitalized with exacerbations of obstructive lung disease through 4 placebo inhaler devices: an MDI, an MDI with Volumatic, a Diskus, and a Turbuhaler.⁶⁰ Figure 6 shows the percentage of optimum inhaler use based on defined inhalation characteristics. Optimum Diskus use was defined as a PIF > 30 L/min, whereas optimum Turbuhaler use was > 60 L/min. It can be seen in Figure 6 that the inhalation profiles achieved by COPD patients during exacerbation gave optimum use of the Diskus 100% of the time, which was better than that with the MDI/Volumatic or Turbuhaler. Optimum use of the MDI was lowest. The authors concluded that the Diskus and MDI/Volumatic could be used effectively in an acute phase of COPD, but the Turbuhaler only after the 5th day of hospitalization in the patients studied. In their study, all patients were able to achieve a PIF of ≥ 30 L/min through the Turbuhaler, which was below optimum, but Pedersen et al found that flow clinically effective for delivery of terbutaline.⁵⁷

The HandiHaler is another high-resistance DPI; with the capsule in place, the flow resistance is 40.8 cm H₂O at 39 L/min.⁶¹ Chodosh et al stratified COPD patients into 3 levels of severity, based on the percent of predicted FEV₁ ($\leq 27\%$, 28–45%, and 46–65%) and the inspiratory flow through the HandiHaler.⁶¹ They also measured fine-particle mass (ie, particles < 5 μ m) and fine-particle fraction from the HandiHaler at flows between 20 and 60 L/min, using a cascade impactor modified for different flows. At approximately 20 L/min the pierced capsule in the HandiHaler vibrates, giving a distinct rattle.⁶¹ Figure 7 shows the

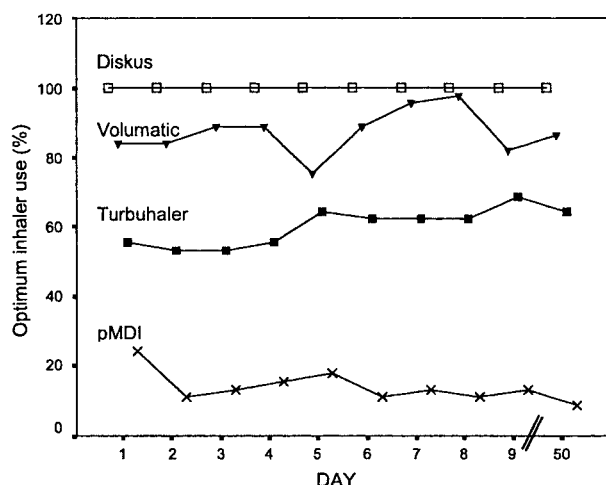


Fig. 6. Percentages of hospitalized patients who demonstrated optimum inhalation characteristics for use of different inhalers during the first 9 days of an exacerbation of chronic obstructive pulmonary disease (5 asthmatics, 10 COPD) and on day 50. The mean percentages of optimum profiles over the entire study period, for Diskus MDI with Volumatic, Turbuhaler, and pMDI, were 100%, 87%, 60%, and 14%, respectively. (From Reference 60, with permission.)

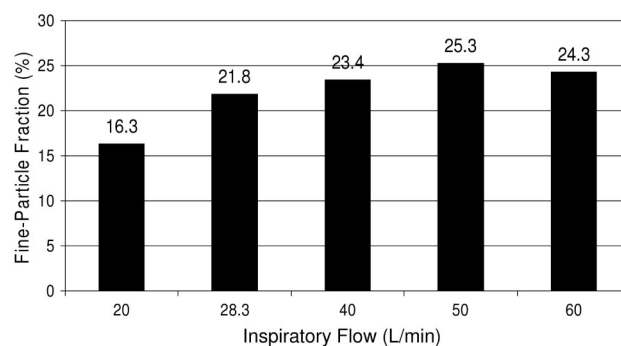


Fig. 7. In vitro measures of fine-particle fraction, calculated as the fine-particle mass of drug divided by the nominal dose, for delivery of tiotropium at various inspiratory flows from the HandiHaler dry powder inhaler. (Based on data from Reference 61.)

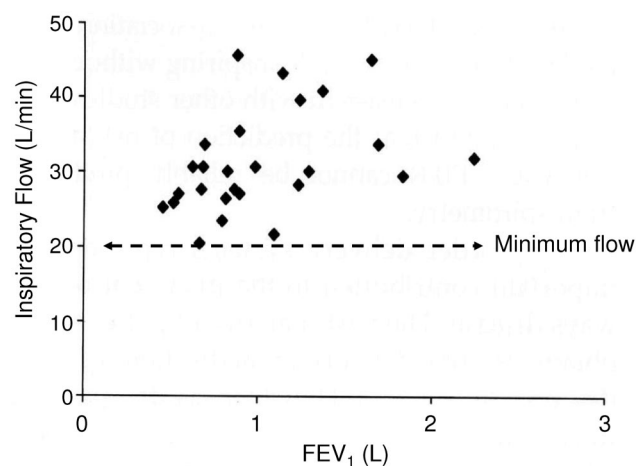


Fig. 8. Relationship between the peak inspiratory flow through the HandiHaler and forced expiratory volume in the first second (FEV₁) for 26 subjects with chronic obstructive pulmonary disease. Based on in vitro data shown from the same study as in Figure 7, a minimum inspiratory flow of 20 L/min resulted in delivery of medication. (From Reference 61, with permission.)

in vitro measure of fine-particle fraction at the flows tested. There was delivery of drug in the fine-particle fraction at flows as low as 20 L/min, although this was lower than at flows of ≥ 28.3 L/min.

Figure 8 illustrates the relationship of PIF to FEV₁ and shows that all patients could achieve the minimum flow of 20 L/min to obtain drug in the fine-particle-fraction range. Dahl et al assessed HandiHaler versus MDI in COPD patients in Denmark, and found that the proportion of patients who correctly used the HandiHaler (versus the MDI) on the first of 3 attempts was 59.7% and 54.7%, respectively.⁶² A higher proportion of patients had fewer errors with the HandiHaler (35.3%) than with the MDI (15.1%) after 4 weeks of instruction.

Based on the data available in studies cited with COPD patients,^{56,59–61} including those with COPD exacerbations,

such patients are able to use DPIs with at least minimum inspiratory flow, although perhaps not with optimal flow. The clinical use of DPIs may become more complex if a DPI model is introduced that does not rely on patient effort to deaggregate the powder but instead provides active drug-dispersion to the user. In such an inhaler, a high inspiratory flow could decrease the lung delivery, analogous to an MDI, in which the aerosol cloud is generated by the canister, not by the patient's inspiratory effort.⁵⁵ An example of a DPI with an active dispersion assist is the Spiros (also known as the Dryhaler) from Dura Pharmaceuticals in California.⁶³ Having DPIs that require different inhalation patterns is another potential source of confusion for patients and caregivers.

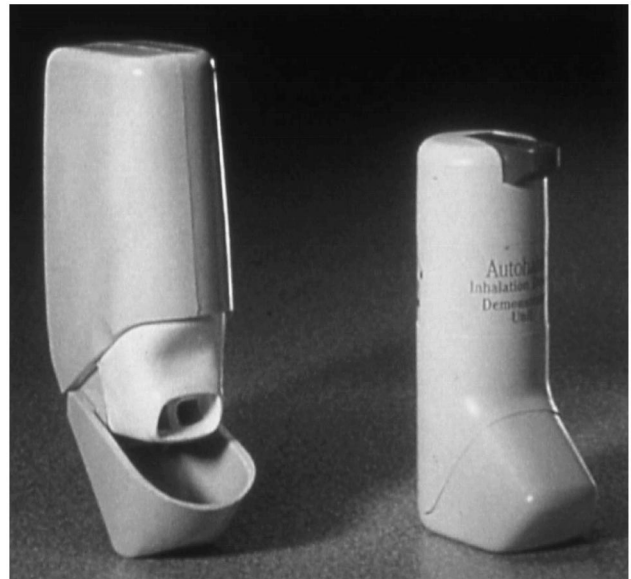
Problems With Use of SVNs

There is a gap in the literature with respect to patient problems with nebulizers. This is probably because, of all the inhaler types, nebulizers offer the simplest use to patients: proper nebulizer use requires only normal tidal breathing, with no breath-hold, and 60–90 inhalations in which to acquire the aerosol. The usual problems cited with SVNs are not ones of patient use, but, rather, other disadvantages of SVNs, including bulk and size of equipment, possible need for compressor or gas source, need for external power source, and lengthy treatment time.¹⁰ In addition, there is variability in hand-held nebulizer performance,⁶⁴ and in compressor ability to nebulize different solutions.⁶⁵ These are not problems patients have *using* nebulizers. In fact, Thorsson and Geller, in a recent review of factors that guide the choice of a delivery device for inhaled corticosteroids, recommended nebulizers for patients of any age who cannot coordinate or activate an MDI or DPI because of dyspnea.⁶⁶

A study by Corden et al found poor compliance (mean 57%) with home nebulizer therapy among COPD patients, although the patients exhibited good inhalation data on testing.¹² In another study of home aerosol therapy with COPD patients, 75% preferred a jet nebulizer for effectiveness (better benefit) and 70% judged MDI therapy as more acceptable to them.⁶⁷

Use of a Breath-Actuated pMDI

Interestingly, in 1976, Coady et al published an evaluation of a “breath-actuated pressurized aerosol” (breath-actuated pMDI) developed to overcome the problem of synchronizing MDI actuation with patient inspiration.⁶⁸ This was the Duo-Haler (3M Pharmaceuticals), which was somewhat large, generated a loud click when the valve was triggered, and required what was described as a “generous” inspiratory flow for activation.⁶⁹ Subsequently, in 1988, 3M Pharmaceuticals released the Autohaler with a



1970: Duo-Haler. Large, loud click, high inspiratory flow
1988: Autohaler. Small, quiet, lower inspiratory flow (26–30 L/min)

Fig. 9. Two breath-actuated pressurized metered-dose inhalers: the Duo-Haler and the Autohaler. (Photograph courtesy of 3M Pharmaceuticals.)

formulation of the short-acting β_2 agonist pirbuterol (Maxair), with a CFC propellant. Both devices are shown in Figure 9.

The newer breath-actuated pMDI Autohaler required about 27 L/min of inspiratory flow for actuation, and a redesigned metering valve gave the Maxair Autohaler a rounder, gentler aerosol plume than that of the CFC MDI of albuterol (Ventolin) (information courtesy of 3M Pharmaceuticals). The Autohaler preserves the compact portability and short treatment time of the MDI and automates MDI actuation with inspiration.

Fergusson et al showed that 97% of patients with severe airflow limitation ($FEV_1 < 1.0$ L, or peak expiratory flow < 200 L/min) were able to actuate the Autohaler on their first (94%) or second (additional 3%) attempt.⁶⁹ Of the 5 patients (of 156) who failed, all were able to generate sufficient inspiratory flow to trigger the Autohaler, but these 5 subjects apparently performed incorrect inspiratory maneuvers through the breath-actuated pMDI.

Chapman et al found that the breath-actuated pMDI was used successfully 64% of the time (compared to 36% with an MDI) by a group of elderly subjects who had a mean age of 71 years.⁷⁰ That study reported that patients preferred the breath-actuated pMDI to the MDI by 71% to 19%.

Newman et al measured a mean lung deposition of only 7.2% versus 20.8% for albuterol inhaled from an MDI versus the Autohaler among subjects with poor MDI co-

ordination.⁷¹ Lenney et al assessed use and patient preference with 7 inhalers, in a group of 100 patients, age 22–88 years, diagnosed with airflow obstruction, of whom 33% had an $FEV_1 \leq 1.0$ L.⁷² The highest performance assessment grades were found with 2 breath-actuated MDIs: the Easi-Breathe and the Autohaler; these were followed by the Accuhaler (Diskus) and the Clickhaler, both DPIs. The worst performance was with the MDI alone; the MDI with a Volumatic holding chamber, and the Turbohaler were second worst in performance scores. Patients ranked the Easi-Breathe and the Autohaler as their first and second preferences among the 7 inhaler systems.

Outside of the United States there are newer drug formulations for breath-actuated MDIs. In vitro testing by Kamin et al demonstrated a higher fine-particle mass and significantly smaller mass median aerodynamic diameter with a solution of the corticosteroid budesonide from the Autohaler with HFA propellant (3M Pharmaceuticals, Borken, Germany), compared to budesonide from a Turbohaler or fluticasone propionate from a Diskus (both DPIs), as shown in Figure 10.⁷³ The current primary limitation of breath-actuated pMDIs is the lack of drug formulations in the United States for this delivery device. Only pirbuterol (Maxair) is currently available in the United States.

A Solution to Inhaler Misuse: Design Convergence?

Fink has stated that, “Management of chronic airways disease is 10% medication and 90% education.”⁷⁴ A recent study by Song et al showed that the error rate with MDI use among hospitalized patients with a mean age of 68 years was reduced from 6.72 (out of 15) errors per patient to 2.43, with only 5–10 min of RT instruction, which included encouragement to use a spacer.⁷⁵

The fact that there are 3 categories of inhaler (MDI, DPI, SVN) with add-on holding chamber or spacer for MDI use, differences among individual models within each category, and different breathing patterns for each category makes education and instruction a necessity for correct inhaler use, but also complicates such instruction. Confusion and lack of knowledge of correct use of MDIs and DPIs has been evidenced in both patients and caregivers, indicating the need for training. At the same time, a trend toward simplification and a reduction in the increasing variability among inhaler types should reduce the need for lengthy instruction in inhaler use. In a study by Serra-Batiles et al, which compared the Diskus and Turbohaler, patients ranked the features of an ideal inhaler (Table 5).⁷⁶ Related to the preceding comments, it is of note that the top 3 features are: ease of use during an attack (ie, quick use during stress and anxiety), knowing how many doses are left, and overall ease of use. These 3 features are identical to the top 3 features identified in a study of

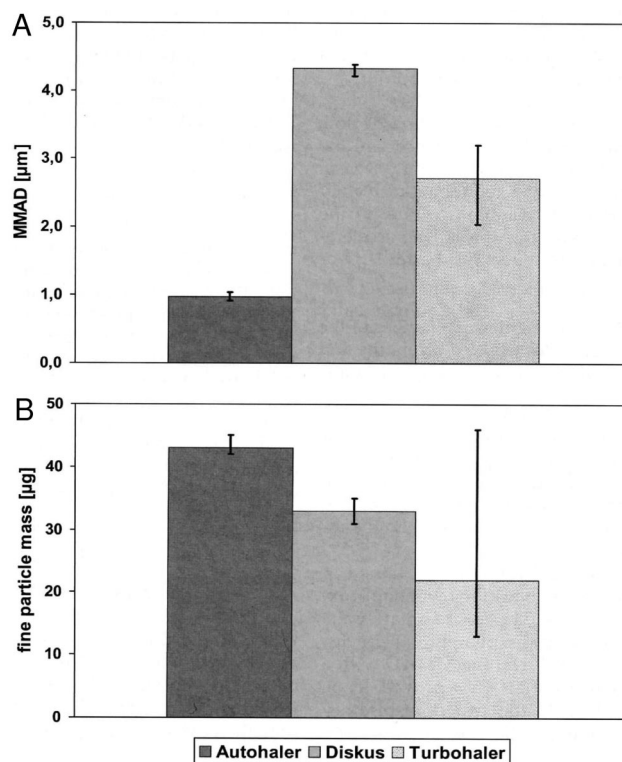


Fig. 10. In vitro measurements of aerosol output characteristics of a corticosteroid with 3 different breath-actuated inhalers: budesonide from a Turbohaler, fluticasone propionate from a Diskus (Accuhaler), and hydrofluoroalkane-propelled beclomethasone from an Autohaler. A: Mass median aerodynamic diameter (MMAD). B: Fine-particle mass (particles ≤ 4.7 μ m). Autohaler and Turbohaler were tested at 36 L/min. Diskus was tested at 30 L/min. The error bars indicate the range of values measured. (From Reference 73, with permission.)

patient preference for the Diskus and the HandiHaler, by Moore and Stone.⁷⁷ With each of the inhaler types and devices, there are classic problems that complicate patient use:

MDIs: discoordination of actuation and inhalation; no dose counter

Holding chamber or spacer: additional bulk; additional cost (ie, in addition to the cost of primary aerosol device)

DPIs: differences in loading and priming among different models; need for patient inspiratory effort

SVNs: need for power source; often large and bulky; lengthy treatment time

An inhaler that is easy to learn and use may alleviate recurring problems of patient and provider lack of knowledge in correct use. Simplified inhaler design and easy use may also improve use among patients who have cognitive impairment or physical limitations of poor hand strength, arthritis, or lack of hand flexibility.

While it is certainly a quixotic suggestion, one solution to the current “inhaler maze” would be a *universal inhaler*:

Table 5. Features of an Ideal Inhaler Device Judged Most Important by Patients*

Feature	Percent Who Chose the Feature
Ease of use during an attack	82.8
Knowing how many doses are left	62.1
Ease of use (overall)	60.9
Ease of learning to use	59.2
Hygiene	58
Comfortable mouthpiece	53.3
Ease of carrying around	40.8
Can feel that the dose was taken	38.5
Pleasant taste of drug	35.5
Possibility of recycling	34.3
Moisture-proof	33.3
Lightweight	25.4
Discreetness	24.3
Small size	23.7
Attached cover	22.5
Refillable unit	20.7
Design	11.2

* By 169 patients in a study by Serra-Batlles et al.⁷⁶

one general type of inhaler for all aerosol drugs, which operates basically the same with any formulation *from the patient/caregiver point of view*, with one breathing pattern. Even if the internal mechanism (eg, nozzle block, metering valve) differed, perhaps solutions, suspensions, and powders could be aerosolized with greater external uniformity. Such a trend is conceptualized in Figure 11, and would help to reduce the patient and provider confusion seen with multiple, and multiplying, inhaler types.

I think an example of this trend can be found among existing inhaler devices such as the Respimat (Boehringer Ingelheim) and a breath-actuated pMDI such as the Autohaler (3M Pharmaceuticals) or the Easi-breathe (Ivax Corp.). Other examples could undoubtedly be found. The former device is a nebulizer and the latter two are pMDIs. The Autohaler was shown in Figure 9, and the Respimat is seen in Figure 12. The Respimat is not available in the United States, and as previously stated, there is only one breath-actuated-pMDI device and one drug (Autohaler-pirbuterol) available in the United States currently. Both the Respimat and breath-actuated-pMDIs are small, portable, easy to use under emergency conditions, require no external power source, have short dose delivery times and the Respimat can record the number of doses.⁷⁸ All of these were features ranked highly by patients in the study by Serra-Batlles et al.⁷⁶ Further, it is interesting that the Respimat and Autohaler represent 2 different categories of inhaler (an SVN and an MDI) but they represent *convergence* rather than *divergence* in inhaler design develop-

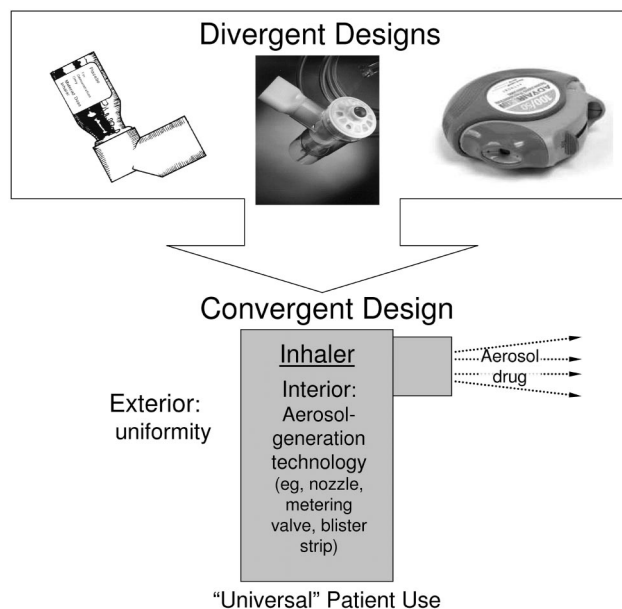


Fig. 11. Conceptual illustration of a change from increasingly diverse inhaler design toward design convergence, in which there is increased exterior uniformity and uniformity of use, from the patient/user point of view, although the interior aerosol-generation technology might still vary. In effect, the inhaler becomes a “black box” in which different internal mechanisms generate the same output for the patient.

ment. Myrna Dolovich termed the Respimat a “metered-dose liquid inhaler”—in effect a marriage of MDI portability with SVN ease of use.⁷⁹ I believe such convergence, rather than the increasing diversity we are seeing in inhaler design today, is a principle that can offer assistance in overcoming inhaler misuse. Of course, the ultimate solution to inhaler misuse, at least to unintentional patient/

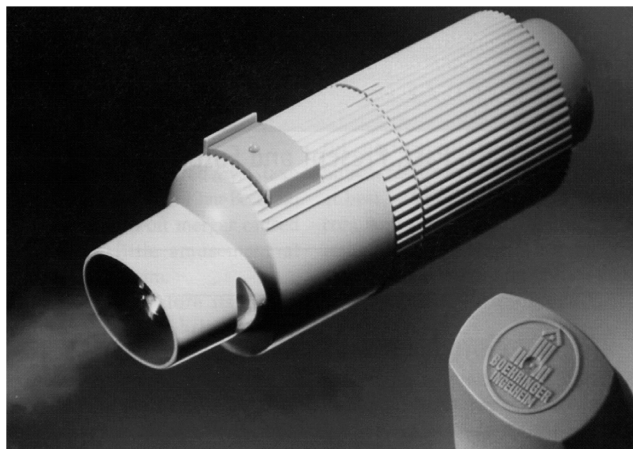


Fig. 12. The Respimat from Boehringer Ingelheim, is an MDI-sized, hand-held, multidose device using mechanical power from a spring to release metered doses of about 15 μ l of volume in a slow gentle release > 1 second (“soft mist”). The inhaler can record the number of doses used. (Courtesy Boehringer Ingelheim)

caregiver error, will be education: in correct inhaler operation; in the importance of inhaled drugs for disease management; and on the worthwhile risk/benefit ratio of inhaled drugs for those concerned with adverse effects.

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