



Inhaler treatment options in COPD

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ABSTRACT: A variety of inhaler devices are available for delivering treatments to patients with chronic obstructive pulmonary disease, and new inhalers are currently being developed. Each type of device has advantages and disadvantages, and the methods of preparation and use vary between them. The differences in instructions for use can easily confuse patients and health providers alike, resulting in incorrect use of many inhalers. “Crucial” errors in inhaler technique, whereby no drug is deposited in the lungs, must be avoided. Any type of inhaler can be misused so that little or no drug is deposited in the lungs.

It is now increasingly widely recognised that a successful treatment outcome in chronic obstructive pulmonary disease depends as much on the inhaler device as it does on the drug. Inhaler choice in chronic obstructive pulmonary disease should take into account whether the patient is likely to use it correctly, as well as patient preference and the likelihood of adherence to treatment.

KEYWORDS: Chronic obstructive pulmonary disease, dry powder inhaler, pressurised metered-dose inhaler, soft mist inhaler, spacer device

The inhaled route is preferred for the delivery of bronchodilators and corticosteroids used in the maintenance therapy of asthma and chronic obstructive pulmonary disease (COPD). Small doses of drugs are delivered direct to their site of action, leading to a rapid onset of action and a low incidence of side-effects. While guidance about appropriate selection of drugs for inhalation therapy is easily obtained [1–3], it is more difficult to source advice about the choice of inhaler device, despite the availability of several different types. The American College of Chest Physicians (ACCP) recently published evidence-based guidelines that listed eight points for consideration when selecting an inhaler, including taking account of any specific device preference the patient or clinician might have and whether a given patient can use the device properly [4]. Hence, an understanding of inhaler technology and issues of correct *versus* incorrect use are key factors affecting inhaler choice.

In this article, the main types of inhaler available for COPD therapy will be reviewed briefly, together with current understanding about correct and incorrect techniques for each device (table 1), and the advantages and disadvantages of the different types (table 2). Although nebulisers are frequently used to deliver COPD treatment, particularly to less mobile patients, most current designs are bulky and inconvenient, and treatment times are long. Therefore, they are better categorised as fall-back devices for most

COPD patients. As they are not true competitors to pressurised metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) for outpatient use, they have not been considered in this article.

It is assumed that inhaled drugs must be deposited within the lungs if they are to exert a beneficial effect [5]. Therefore, it is important to distinguish between “crucial” (or “essential”) errors, which are likely to result in no drug reaching the lungs, and “non-crucial” errors, which are likely to result in a reduced amount of drug reaching the lungs compared with that attained using the correct technique [6]. Not all crucial errors are equally common in practice; table 3 shows the crucial errors made when using the device types covered in this article. Although a patient may know how to use a device correctly, this does not necessarily predict good compliance, as patients may contrive to use their inhalers incorrectly [7]. It may therefore be useful to distinguish between three types of compliance: “device competency”, those who are able to use the device correctly but do not always do so in practice; “technique compliance”, those who actually do use it correctly; and “regimen compliance”, those who take the treatment as agreed with the prescriber.

PRESSURISED METERED-DOSE INHALERS

The pMDI was first introduced in 1956 to provide a delivery system for inhaled bronchodilators with a multi-dose capability and reproducible

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TABLE 1 Correct techniques for different types of inhaler and the errors patients are known to make

Device	Correct technique	Errors in technique
“Press and breathe” pMDI	Remove mouthpiece cap	Failure to remove mouthpiece cap*
	Shake inhaler (suspensions only)	Inhaler not shaken
	Hold inhaler upright	Inhaler upside down*
	Breathe out	No exhalation
	Place mouthpiece between lips	
	Fire while breathing in deeply and slowly	Firing device before start of inhalation
		Firing device at or after end of inhalation*
		Inhaling through nose*
	Continue to inhale after firing	Stopping inhalation as device is fired*
	Hold breath (10 s)	Fast inhalation No/short breath-hold
Breath-actuated pMDI	Remove mouthpiece cap	Failure to remove mouthpiece cap*
	Shake inhaler (suspensions only)	Inhaler not shaken
	Hold inhaler upright	Inhaler upside down*
	Prepare device (e.g. lift lever)	Failure to prepare device correctly*
	Breathe out	No exhalation
	Place mouthpiece between lips	Poor seal around mouthpiece
		Using “open mouth” inhalation technique*
	Breathe in deeply and slowly	Weak inhalation, failure to trigger device*
	Continue to inhale after firing	Inhaling through nose*
	Hold breath (10 s)	Stopping inhalation as device is fired* Fast inhalation No/short breath-hold
“Press and breathe” pMDI plus spacer	Remove mouthpiece cap	Inappropriate handling (static charge)
	Shake inhaler (suspensions only)	Failure to remove mouthpiece cap*
	Hold inhaler upright	Inhaler not shaken
	Insert pMDI into spacer	Inhaler upside down*
	Breathe out	No exhalation
	Fire while breathing in deeply and slowly	Long delay before inhalation
		Multiple actuation
		Weak inhalation, failure to open valve*
	Continue to inhale after firing	Inhaling through nose*
	Hold breath (10 s)	Stopping inhalation as device is fired* Fast inhalation No/short breath-hold
DPIs	Remove cover (device specific)	Failure to remove cover*
	Load dose (device specific)	Incorrect dose loading*
	Pierce capsule (single-dose devices)	Failure to pierce capsule*
	Breathe out	Breathing out into device*
	Place mouthpiece between lips	Inhalation vents blocked [†]
		Poor seal round mouthpiece
		Using “open-mouth” inhalation technique*
	Inhale deeply and quickly	Not inhaling quickly enough*
		Insufficient “acceleration”
	Hold breath (10 s)	Inhaling through nose* No/short breath-hold
Store in cool dry place	Inappropriate storage	
RespiMat[®] Soft Mist[™] Inhaler[#]	Hold upright and turn base	Failure to prime device/load dose*
	Open mouthpiece cap	Failure to open mouthpiece cap*
	Breathe out	No exhalation
	Put mouthpiece between lips	Mouthpiece vents blocked [†]
	Press dose release button while breathing in deeply and slowly	Firing device before start of inhalation
		Firing device at or after end of inhalation*
	Continue to inhale after firing	Inhaling through nose*
		Stopping inhalation as device is fired*
		Fast inhalation
	Hold breath (10 s)	No/short breath-hold

pMDI: pressurised metered-dose inhaler; DPI: dry powder inhaler. *: crucial error, likely to result in zero lung deposition of drug; #: manufactured by Boehringer Ingelheim GmbH & Co. KG, Ingelheim, Germany; †: error that may be crucial.

TABLE 2 Advantages and disadvantages of different inhaler devices

Device	Advantages	Disadvantages
“Press and breathe” pMDI	<ul style="list-style-type: none"> Compact Portable 100+ doses Convenient Quick to use Relatively cheap Cannot contaminate contents 	<ul style="list-style-type: none"> Contains propellants Not breath-actuated Many patients cannot use it correctly (e.g. coordination difficulties, “cold Freon” effect) Usually low lung deposition/high oropharyngeal deposition
Breath-actuated pMDI	<ul style="list-style-type: none"> Compact Portable 100+ doses Convenient Quick to use Breath-actuated (no coordination needed) Cannot contaminate contents 	<ul style="list-style-type: none"> Contains propellants “Cold Freon” effect Usually low lung deposition/high oropharyngeal deposition
“Press and breathe” pMDI plus spacer	<ul style="list-style-type: none"> 100+ doses Quick to use Easier to coordinate Tidal breathing often OK Less oropharyngeal deposition Usually higher lung deposition than a pMDI 	<ul style="list-style-type: none"> Contains propellants Not very portable or convenient Not breath-actuated Plastic spacers may acquire static charge
DPI	<ul style="list-style-type: none"> Compact Portable Convenient (multi-dose devices) Quick to use Breath-actuated (no coordination needed) Usually higher lung deposition than a pMDI Do not contain propellants 	<ul style="list-style-type: none"> Work poorly if inhalation is not forceful enough Many patients cannot use them correctly (e.g. capsule handling problems for elderly) Most types are moisture sensitive
Respimat® Soft Mist™ Inhaler*	<ul style="list-style-type: none"> Compact Portable Multi-dose device (1 month’s supply) Convenient Probably easier to use correctly than pMDI High lung deposition Does not contain propellants 	<ul style="list-style-type: none"> Not breath-actuated Not currently available in most countries

pMDI: pressurised metered-dose inhaler; DPI: dry powder inhaler. *: manufactured by Boehringer Ingelheim GmbH & Co. KG, Ingelheim, Germany.

dosing characteristics [8]. pMDIs contain propellants, which are currently being changed from chlorofluorocarbons (CFCs) to hydrofluoroalkanes (HFAs) because the former damage the ozone layer in the stratosphere [9]. The pMDI produces a rapid-moving plume of aerosol, the duration of which is typically 0.1–0.4 s [10]. The velocity of the aerosol plume may be 8 m·s⁻¹ at a distance of 10 cm from the actuator, and is even higher at distances closer to the nozzle [10]. The plume often feels cold on the back of the throat as the propellants evaporate. Most pMDIs only deposit 10–20% of the dose in the lungs, even with good inhaler technique, and most of the dose is deposited in the oropharynx. Higher lung deposition and lower oropharyngeal deposition may be achieved with some recent formulations, where the drug is formulated as a solution in HFA propellant, rather than as a suspension of micronised particles [11].

Correct pMDI technique involves firing the pMDI, while breathing in deeply and slowly, and then following inhalation with a breath-holding pause to allow particles to sediment on the airway surfaces [12, 13]. Most instructions recommend placing the mouthpiece between closed lips, but it’s also possible to hold the inhaler between open lips or even a few centimetres from the open mouth [14]. Misuse of pMDIs is common among patients [15, 16] and poor understanding of how to use a pMDI also appears to be widespread amongst health professionals [17, 18]. Most importantly, the pMDI must not be fired after the patient has completed inhalation, as there will then be no airstream to carry the aerosol into the lungs. Some aerosol will probably still reach the lungs if the pMDI is fired shortly before inhalation begins. Failure to correctly time firing with inhalation is sometimes termed “poor coordination” [19]. The second major problem with pMDI

TABLE 3 Crucial errors in inhaler use

Error	Devices affected				
	pMDI	BA pMDI	pMDI + spacer	DPI	Respimat® Soft Mist™ Inhaler [§]
Failure to remove mouthpiece cap or device cover	✓	✓	✓	✓	✓
Incorrect preparation/priming of device or loading of dose*		✓		✓	✓
Failure to pierce capsule				✓ [#]	
Inhaler upside down	✓	✓	✓		
Breathing out into device*				✓	
Firing device at or after end of inhalation*	✓				✓
Open-mouth inhalation technique		✓		✓	
Weak or very slow inhalation*		✓ [†]	✓ ⁺	✓ [‡]	
Inhaling through nose	✓	✓	✓	✓	✓
Stopping inhalation as device is fired*	✓	✓	✓		✓

pMDI: pressurised metered-dose inhaler; BA pMDI: breath-actuated pMDI; DPI: dry powder inhaler. *: common errors; #: single-dose devices; †: failure to trigger device; +: failure to open spacer valve; ‡: too slow to aerosolise the dose; §: manufactured by Boehringer Ingelheim GmbH & Co. KG, Ingelheim, Germany.

use is the so-called “cold Freon” effect, where the cold blast of propellants causes patients either to stop inhaling or to inhale *via* the nose [20]; this is probably less marked with HFA formulations. Patients who make errors in inhalation technique derive less clinical benefit than those with good technique [21], and this is particularly marked in those with poor coordination [22].

Despite the difficulties of using them correctly, pMDIs remain popular for delivering inhaled therapies in asthma and COPD because of their practical advantages: pMDIs contain at least 100 doses and are compact, portable, convenient and relatively inexpensive.

BREATH-ACTUATED PRESSURISED METERED-DOSE INHALERS

Since poor coordination between firing and inhaling is usually considered to be the most significant problem patients have with pMDIs [19], the development of breath-actuated (BA) pMDIs is logical. Two such devices (Autohaler™ (3M Pharmaceuticals, St Paul, MN, USA) and Easibreathe™ (Ivax, Miami, FL, USA)) are currently being marketed and several others are in development [11]. With BA pMDIs, the patient's inhalation through the device triggers a mechanism that fires the pMDI, so that firing and inhaling are automatically coordinated. These devices can achieve good lung deposition and clinical efficacy in patients unable to use a standard “press and breathe” pMDI correctly because of coordination difficulties [23].

BA pMDIs do not solve cold Freon problems and would be unsuitable for a patient who has this kind of difficulty using pMDIs. However, errors when using BA pMDIs are less frequent than when using a standard pMDI [24, 25]. It is essential that the BA pMDI is correctly prepared (*e.g.* by raising the priming lever, removing the mouthpiece cover *etc.*); the inhalation must also be strong enough to trigger the firing mechanism (the triggering flow is 20–30 L·min⁻¹ for currently available devices).

PRESSURISED METERED-DOSE INHALERS PLUS SPACER DEVICES

Spacer devices are attachments to the inhaler mouthpiece with a volume ranging from 20–750 mL. Their design and performance has been discussed in detail elsewhere [26, 27]. Many have a one-way valve in the mouthpiece, which prevents the patient blowing the dose away after firing. However, inhalation must be strong enough to trigger the one-way valve, otherwise no dose will be delivered. Spacers overcome coordination problems because inhalation can take place either as the device is fired into the spacer or after a short pause, with the latter method being recommended for some models. Cold Freon problems are unlikely with spacer devices because the point of aerosol generation is more remote from the mouth compared with a pMDI.

Tidal breathing from the spacer after firing a dose may be acceptable for some models [28] but multiple actuations, long delays between firing and inhaling, and the accumulation of static charge on some plastic spacer devices are likely to reduce the dose available for inhalation [29, 30]. Ideally, each pMDI dose should be inhaled separately from the spacer. Specific handling and washing techniques for different spacers are generally recommended to minimise static charge build-up.

While spacers are good drug-delivery devices, they suffer from the obvious disadvantages of making the entire delivery system less portable, compact and convenient than a standard pMDI.

DRY POWDER INHALERS

DPIs were first introduced in 1970, and the earliest models were single-dose devices containing the powder formulation in a gelatine capsule, which the patient loaded into the device prior to use. Since the late 1980s, multi-dose devices have been available, giving the same degree of convenience as a pMDI. The first of these was the Turbuhaler™ (AstraZeneca, Lund, Sweden). By early 2005, at least 17 DPIs were marketed in different countries, consisting of both single-dose and

multi-dose models [31]. Most multi-dose DPIs hold the powder in a reservoir, from which individual doses are metered, but the Diskus® (GlaxoSmithKline, North Carolina, NC, USA) holds the doses in individually sealed foil blisters. DPIs may be more expensive than pMDIs but this will vary according to pricing policies in different countries.

All currently marketed DPIs are breath-actuated and no propellants are needed to generate the aerosol [32]. The patient's inhalation through the device is used to disperse the powder formulation and to deliver it into the lungs. However, patients can make crucial errors with a DPI; for instance, by failing to load a dose correctly or by exhaling into the DPI so that the dose is blown away [33]. Unless clearly instructed, some patients might not know that they must firmly seal their lips around the mouthpiece, causing them to attempt an "open mouth" inhalation technique that will not deliver any dose. The Turbuhaler™ DPI, and possibly other DPIs in which doses are metered from a bulk powder reservoir, must be kept upright (held vertically) when loading a dose before inhalation, so that the dosing chamber will fill under gravity [34]. Compared with a standard pMDI, fewer patients demonstrate errors in inhaler technique with a DPI [24, 25]. Many DPIs must be stored in a dry environment to prevent the drug formulation being degraded by moisture.

DPIs tend to work better with rapid and forceful inhalation, since this disperses the powder formulation into small "respirable" particles as efficiently as possible [31]. Delivery to the lungs may be reduced with slow inhalation and for each DPI it is necessary for patients to attain a minimum inhaled flow rate in order to ensure that some drug is delivered to the lungs [6]. It is also desirable that the rate of increase of inhaled flow at the start of inhalation should be as high as possible [35]. This is sometimes called high flow "acceleration" or high "early flow".

In theory, the need to inhale forcefully could be a problem for some patients, especially those with more severe obstructive airways disease. However, a recent review [36] concluded that most patients can generate sufficient flows through DPIs to benefit from them, including 98% of asthmatic patients undergoing severe exacerbations needing hospitalisation. Most studies in which patients' inhaled flow rates through DPIs were assessed, have involved asthmatic patients. However, in one study [37], COPD patients with a mean forced expiratory volume in one second (FEV₁) of 0.7 L could generate peak inhaled flow rates of 28–78 L·min⁻¹ via the Turbuhaler™ DPI.

SOFT MIST INHALERS

The development of soft mist inhalers (SMIs) has opened up new opportunities for inhaled drug delivery. SMIs use liquid formulations similar to those in nebulisers, but are generally multi-dose devices that have the potential to compete with pMDIs and DPIs in the portable inhaler market.

While a number of SMIs are known to be in development [38, 39], the only device currently marketed is Respimat® Soft Mist™ Inhaler (Boehringer Ingelheim GmbH & Co. KG, Ingelheim, Germany). This device contains sufficient doses of a bronchodilator formulation for 1 month's dosing, stored in a fluid reservoir [40]. Respimat® Soft Mist™ Inhaler is powered

by the energy of a compressed spring inside the inhaler; no propellants are required. Individual doses are delivered *via* a precisely engineered nozzle system as a slow-moving aerosol cloud (hence the term "soft mist"). The velocity of the spray from Respimat® Soft Mist™ Inhaler is only about one-tenth of that from a CFC-based pMDI [10]. However, scintigraphical studies have shown that lung deposition is several times higher than that from a CFC-based pMDI [41], and clinical trials have confirmed that drugs delivered by the Respimat® Soft Mist™ Inhaler are effective in correspondingly smaller doses in COPD patients [42].

Respimat® Soft Mist™ Inhaler is a "press and breathe" device, and the correct inhalation technique closely resembles that used with a pMDI. While coordination between firing and inhaling is required, the low spray velocity and long duration of the aerosol cloud (typically 1–1.5 s) should enable patients to coordinate firing and inhaling more easily than with a pMDI [43]. Respimat® Soft Mist™ Inhaler has been used relatively little in clinical practice to date, and could prove to have advantages or disadvantages additional to those listed in table 2.

CONCLUSION

A variety of inhaler devices are now available to deliver inhaled drugs to patients with COPD. The inhaled drug delivery field is a dynamic one, with many inhalers available already and new ones being introduced on a regular basis. The plethora of inhaler devices available, requiring different inhalation techniques for optimal drug delivery, may confuse patients and healthcare providers alike, a situation described as "device dementia" [44]. That said, a number of actions or steps are common to all types of devices reviewed in this article (table 4). For healthcare professionals and patients, these are arguably the most important elements of inhaler technique for the purposes of teaching and learning how to use each device, as most patients are likely to try more than one type of inhaler device during their lifetime and mastering a new device will thus be made easier. The final step in the sequence for all devices is the breath-hold. Studies of pMDI use show that lung deposition is greater after holding the breath for 10 s than for 4 s [45], because the extra time allowed for sedimentation in the small airways of the lung increases the amount of inhaled drug that is deposited. Given that the particle size distribution of aerosols delivered by the other

TABLE 4 Common requirements for all devices reviewed

- Remove mouthpiece cap if present
- Orientate inhaler correctly (e.g. upright for pMDI)
- Breathe out
- Place mouthpiece between lips
- Breathe in deeply and slowly*.*#
- Hold breath for 10 s

pMDI: pressurised metered-dose inhaler. *: breathe in deeply and quickly for dry powder inhalers; #: for "press and breathe" pMDI, actuate inhaler while breathing in.

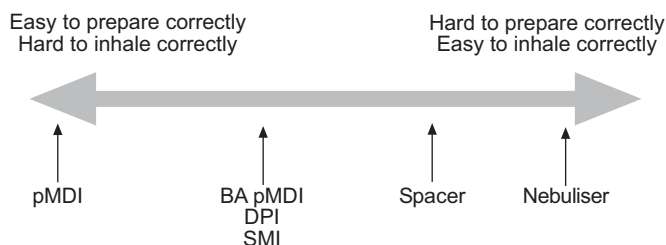


FIGURE 1. Diagrammatic scale contrasting ease of use with ease of preparation. pMDI: pressurized metered-dose inhaler; BA pMDI: breath-actuated pMDI; DPI: dry powder inhaler; SMI: soft mist inhaler.

devices in this article is quite similar to that from pMDIs, breath-holding is likely to have equal value in patients who use them.

There is no perfect inhaler, and each has advantages and disadvantages, but there is increasing recognition that a successful clinical outcome is determined as much by choice of an appropriate inhaler device as by the drugs that go in them [46]. Drug delivery from all inhaler devices depends on how the patient prepares the device and then inhales from it. The relative difficulties in completing these two steps correctly can be shown on a scale (fig. 1), with pMDI being the easiest to prepare (and hardest to inhale from correctly) and nebulisers at the opposite end. The best device for COPD patients is arguably one for which both these steps can be performed successfully without major challenges.

There is evidence that a patient is most likely to use correctly an inhaler that he or she prefers [25], and each patient's choice of device will be determined by individual perceptions of how its advantages and disadvantages balance out. This decision could be quite different to the judgement of a prescriber or a formulator, who may give more weight to technical points. Choice of an inhaler device should therefore take into account the likelihood that patients will be able to use a particular device correctly, cost-effectiveness, preference and likely compliance.

SUMMARY

- A variety of portable inhaler devices are now available for treating patients with chronic obstructive pulmonary disease and more new designs are in development; each type of device has advantages and disadvantages.
- The plethora of inhalers with differing instructions may confuse patients and healthcare providers alike.
- Any inhaler can be misused so that little or no drug is deposited in the lungs.
- "Crucial" errors in inhaler technique, resulting in no drug deposition in the lungs, must be avoided.
- There is increasing recognition that a successful treatment outcome in chronic obstructive pulmonary disease depends as much on the inhaler device as on the drug.
- Inhaler choice in chronic obstructive pulmonary disease should take into account: the likelihood of the patient using the inhaler correctly; patient preference; and likely compliance.

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