

Considerations for Optimal Inhaler Device Selection in Chronic Obstructive Pulmonary Disease

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Introduction

Inhalation is the standard route of administration for drugs used to treat chronic obstructive pulmonary disease (COPD) and asthma.¹ Inhalation is a quick drug delivery method that offers both efficacy and safety.^{2,3} Inhaled administration allows targeted delivery of the active drug to the site of action, enabling lower doses and resulting in fewer systemic adverse events than oral therapy.³ There are 4 main types of devices used to deliver inhaled medication: pressurized metered-dose inhalers (pMDIs), dry powder

inhalers (DPIs), soft mist inhalers (SMIs), and nebulizers. Each type of inhaler device is associated with advantages and limitations that determine their suitability for any given patient with COPD^{4,5} (**TABLE 1**).^{3,6,7} Understanding those advantages and limitations helps clinicians in choosing the proper device for the individual patient's clinical needs and preferences. However, with the wide range of permutations of drug combinations now possible, inhaler selection remains challenging.⁴ For all inhaler devices, adequate training for patients on how to use their device is required to achieve optimal therapeutic benefits.¹

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Device considerations

Examples of the different inhaler devices available for COPD treatments are provided in **FIGURE 1**, and their key characteristics are summarized in **TABLE 2**.^{3,7} Traditional pMDIs require actuation of the device at the beginning of a slow, deep inhalation to optimize drug delivery. This technique requires hand-breath coordination, which can be difficult for some patients, particularly those who are elderly or severely short of breath; spacers can be used in combination with pMDIs to help to overcome some technique issues (**FIGURE 1**).^{3,8} Breath-actuated (BA) pMDIs may also be used in some countries (though are not currently licensed in the United States); these devices release the dose on inhalation, removing the need for hand-breath coordination.³

DPIs are also breath-actuated, with the patient providing the force necessary to deliver the drug on inhalation; drug delivery with DPIs is therefore dependent on patients achieving a high enough peak inspiratory flow (PIF) rate to disperse the drug, in contrast to BA pMDIs, which are activated at a lower PIF rate.^{3,8} Generating the inspiratory flow required for effective function of DPIs can be problematic for some patients with COPD.⁹ Suboptimal PIF rates have been associated with age (≥ 60 years), female gender, shorter height, and lower values for forced vital capacity and inspiratory capacity as percentage predicted in stable patients with severe COPD¹⁰; in addition, patients with COPD can have a temporarily reduced PIF rate after hospitalization for an

TABLE 1 Key characteristics of different device types^{3,6,7}

Characteristics	pMDIs	DPIs	SMIs	Nebulizers
Ease of use	Requires coordination between actuation and inhalation (which can be eased when used in conjunction with a spacer, or by using a breath-actuated pMDI)	Varies; they are generally breath-actuated and do not require coordination between actuation and inhalation	Requires assembly and coordination between actuation and inhalation	No specific breathing techniques have to be taught for using nebulizers
Suitable for maintenance or reliever medication	Reliever and maintenance	Reliever and maintenance	Reliever and maintenance	Reliever and maintenance
Treatment time	Short	Short	Short	Longer than pMDIs / DPIs (duration depends on nebulizer device type)
Portability	High	High	High	Depends on type
Multi-dose device	Yes	Some DPIs	Yes	No
Dose counter	Yes	Yes	Yes	No

Abbreviations: DPIs, dry powder inhalers; pMDIs, pressurized metered-dose inhalers; SMIs, soft mist inhalers.

acute exacerbation.^{11,12} There is a range of DPIs available in three main categories: single-dose, multi-dose, and power-assisted devices.⁷ It is important to protect DPI devices from the effects of humidity, which can increase particle adhesion and therefore reduce efficacy.¹³

The SMI delivers the aerosol as a fine mist with slow velocity lasting >1 second, which is considerably slower than spray delivery with pMDIs.¹⁴ The aim of this design is to make it easier for patients to coordinate actuation with inhalation, but it is important to note that some coordination is still required for SMI devices to function correctly.¹⁴ In addition, the SMI is not dependent on a patient's ability to generate sufficient PIF for effective drug delivery. A limitation of the SMI is the need to assemble the device, as patients with poor manual dexterity may encounter difficulty when attempting to load the drug cartridge.¹⁵

Nebulizers deliver aerosolized drug in a fine mist. Newer-generation portable vibrating mesh nebulizers can deliver a dose over a period of ~2 minutes, compared with 10 minutes for conventional pneumatic devices.¹⁶ Patients find them effective and easy to use, and the newer generation devices overcome problems with portability and length of treatment, which may be an issue during the daytime for ambulatory patients, along with the requirement for cleaning after each dose.^{4,8} However, drug delivery may be somewhat compromised with nebulizers compared with other inhala-

tion devices, as medication can be dispersed into the atmosphere and lost, rather than inhaled.⁷ An additional point to consider is medication availability; some medications, particularly fixed-dose combination maintenance therapies, are currently unavailable in a nebulized format.¹⁶

The most important device-related factors influencing the site of deposition within the lungs are aerosol velocity and particle size of the inhaled drug.^{3,7,17} To maximize clinical effectiveness, adequate distribution throughout the lung is required to reach target sites of action for β_2 -agonists, anticholinergics, and corticosteroids.¹⁷ Particle size differs between inhaler device types, but all available devices generate drug particles sufficient for deposition throughout the lower airways and lung periphery, ie, within the range of 1–5 microns.^{3,18–21} Extra fine particles of <1 micron (or “sub-micron particles”) can be deposited deeper in the pulmonary acinus, but a higher fraction of such particles may be exhaled compared with particles 1–5 microns in size.^{3,20,22} In contrast, particles >5 microns deposit in the oropharynx and may be swallowed, potentially leading to systemic adverse effects.^{3,20,22}

When more than one drug is required, it may be preferable to deliver them via a single device where possible to facilitate patient compliance with correct technique, and decrease confusion about how to use different inhalers.²³ The inhaler device ideally serves as a platform on which many treatments

are available; the greater the number of devices employed by the patient, the greater the likelihood of making an error with the usage of each device.²⁴

Importance of proper inhaler technique

Errors relating to device handling are common in patients with COPD. The results of a meta-analysis by Chrystyn et al reported that overall error rates were high across all devices in patients with COPD and asthma, ranging from 50%–100%²⁵; the reported frequencies of patients with at least one error were 86.8% and 60.9% for pMDIs and DPIs, respectively. However, the authors note that heterogeneity between the studies used in the analysis was high, and suggest that future investigations should look to use a more standardized approach in assessment of inhaler device errors.²⁵ Moreover, further studies to investigate the frequency of errors in SMI devices, and to establish the relationship between critical errors in device handling and device efficacy, are warranted.

Handling errors are directly linked to compromised drug delivery and reduced treatment efficacy.³ This may lead to more frequent or inappropriate medication use that, in turn, could result in unnecessary dose increases by the physician due to perceived lack of efficacy, and subsequently more adverse effects.^{3,26–28} However, these errors can be addressed through proper training and demonstration.^{29–32}

Common device-handling errors include^{4,26,27,32,33}:

- **pMDIs:** not shaking the inhaler (for suspensions), not exhaling fully before actuation, inhaling too forcefully, and not holding their breath for long enough after inhalation.
- **DPIs:** exhaling into the device mouthpiece, not exhaling fully before inhalation, not inhaling deeply or forcefully enough, and not holding their breath after inhalation.
- **SMIs:** not rotating the inhaler with mouth cap facing upwards, rotating the inhaler while looking into the spray nozzle with the cap open (before inhalation), and not maintaining inhalation with drug spray.

Critical inhaler use errors (where an error results in no or an insufficient amount of medicine being delivered to the lungs, thereby leading to suboptimal disease control²⁵) are less common; the frequencies of these errors for pMDIs and DPIs are summarized in **TABLE 3**.²⁶

Incorrect inhaler use is a common cause of secondary nonadherence (ie, relating to incorrect medication use) among patients with COPD.^{4,34} Compromised inhaler technique and medication nonadherence jeopardize health outcomes and add to the economic burden of COPD.^{8,12,26}

FIGURE 1 Examples of different inhaler device and spacer types



Abbreviations: COPD, chronic obstructive pulmonary disease; DPIs, dry powder inhalers; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic receptor antagonist; pMDIs, pressurized metered-dose inhalers; SAMA, short-acting muscarinic receptor antagonist; SMI, soft mist inhalers.

Please note that some COPD drugs are available in other devices not shown in this figure. (A) Atrovent, a pMDI SAMA (also available in a nebulized format), (B) Symbicort, a pMDI LABA/ICS, (C) Serevent, a DPI LABA, (D) Anoro, a DPI LAMA/LABA, (E) Spiriva, an SMI LAMA (also available in a DPI device), (F) Vortex, a small volume valve spacer with nonelectrostatic interior, (G) Volumatic, a large volume spacer.

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TABLE 2 Characteristics of inhaler devices^{3,7}

Device type	Mechanism of action
HFA pMDI	Pressurized suspension of micronized drug particles distributed in propellant; others are ethanolic solutions Precise amount (20–100 µL) dispensed with each press of canister Shaking not required as with CFC pMDIs Pressing canister releases drug
Breath-actuated pMDI	Pressurized canister with flow-triggered system driven by a spring Inhalation drives spring to trigger inhalation Requires higher PIF than HFA pMDIs, but lower than DPIs
DPI	Dry powder inside capsule (manual loading) or inside device Micronized drug particles (1–5 µm) blended with inactive excipient (40 µm) or used alone Inhalation deaggregates medication particles and disperses them within airways Minimum PIF rate required for deaggregation (varies by DPI device) Passive (breath-actuated)
SMI	Propellant-free Drug stored inside cartridge (loaded on first use) Spring releases dose into micropump; dose released when button is pressed “Uniblock” passes dose through minute channels releasing jet streams of drug solution
Breath-enhanced jet nebulizer	Air stream moves through jet causing drug solution to be aerosolized; powered by compressor Additional room air taken into nebulizer during inhalation drives aerosolization Nebulizer drug solution cools during nebulization Vents the expired air outside device Tabletop and portable models available
Breath-actuated jet nebulizer	Air stream moves through tube causing drug solution to be aerosolized; powered by compressor Patient inhalation drives aerosolization (does not occur unless patient inhales) Tabletop and portable models available
Ultrasonic nebulizer	Piezoelectric crystals vibrate causing aerosolization Nebulized drug solution gets heated during nebulization Portable
Vibrating mesh nebulizer	Piezoelectric crystals vibrate a mesh plate causing aerosolization Very fine droplets No significant change in temperature of the solution during nebulization Lower residual drug remaining in chamber compared with jet nebulizers Portable

Abbreviations: CFC, chlorofluorocarbon; DPI, dry powder inhaler; HFA, hydrofluoroalkane; PIF, peak inspiratory flow; pMDI, pressurized metered-dose inhaler; SMI, soft mist inhaler.

A 2005 study estimated that over 20% of the \$25 billion spent on inhalers annually in the United States is wasted as a direct consequence of incorrect device handling.³⁵

Failing to inhale correctly to achieve the optimal inspira-

tory flow for the specific device being used—deep and slow for pMDIs, or forceful, quick and deep for DPIs—is a critical handling error for inhaler devices.²⁶ Significant associations between critical errors and clinical outcomes (hospitalization,

TABLE 3 Critical errors and their reported frequencies for pressurized metered-dose inhalers and dry powder inhalers²⁶

pMDIs		DPIs			
Critical error	Frequency (% of users)	Critical error	Frequency (% of users)		
			HandiHaler /Aerolizer	Diskus	Turbuhaler
Failure to remove mouthpiece cap	0.15	Failure of priming			
Actuation against teeth, lips, or tongue	0.7	Failure to open the device	0	0.65	0
Activation after end of inhalation	5	Failure to insert the capsule	9	NA	NA
Stopped inhalation immediately after firing	10	Failure to pierce the capsule	3	NA	NA
Inhalation through nose during and after actuation	2	Failure of loading			
		Incorrect dose loading	NA	7.3	14
		Keep inhaler inclined $\leq 45^\circ$ from the vertical axis during loading	NA	NA	23
		Inhaling by nose	2	1	0
		Not sealing lips around mouthpiece during inhalation	5	5	4
		Slow and not forceful inhalation	24	28	22

Abbreviations: DPI, dry powder inhaler; NA, not applicable; pMDI, pressurized metered-dose inhaler.

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emergency department visits, antibiotic courses, and corticosteroid courses) have been reported in COPD patients.²⁶ In a retrospective analysis of COPD inpatients, suboptimal PIF rates with DPIs were associated with worse scores on the COPD Assessment Test, higher COPD and all-cause readmission rates, and shorter time to next COPD exacerbation.¹²

Patient considerations

While various inhaled medications for COPD are available in different device types (TABLE 4), it is important to consider a patient's perspective as part of treatment and device selection. For example, the effectiveness of an inhaled drug is dependent on the patient's ability to use their prescribed inhaler correctly, which may be affected by physical issues (eg, poor manual dexterity, tremors, inspiratory flow rate) and cognitive or psychiatric issues (eg, poor memory/learning, depression).³⁶ It is also important to consider that patient preferences for inhaler devices may differ from the perspective of a physician (FIGURE 2).^{4,23,37,38}

One of the key factors affecting optimal drug delivery via

an inhaler is whether the patient can generate a sufficient or appropriate PIF rate.^{3,9,12,39–42} Inhalation flow rates required for optimal drug deposition in the lungs differ between device types: for pMDIs, slow and deep inhalation at a flow rate of <90 L/min is generally recommended, whereas most DPIs require a minimum flow rate of 30 L/min, and a flow rate of >60 L/min to function optimally.^{3,39,43,44} DPIs with higher resistance allow for lower inhalation flow rates since the device-generated turbulence results in better drug disaggregation and microdispersion. However, patients with weaker or less efficient respiratory muscles may still struggle to attain an adequate PIF rate.^{39,40} For this reason, it may be preferential for patients with a PIF rate of <30 L/min to use a pMDI or SMI device, rather than a DPI.

Poor inhaler technique is frequently reported in patients with COPD or asthma, irrespective of the device used and with considerable variability in handling error rates for each individual device.^{25,26,35,45} Although clinical evidence is limited,²⁵ research to date indicates that some DPIs may require less training than pMDIs.^{23,29,45,46} Therefore, DPI devices may

TABLE 4 Inhaled drugs by device type (with current FDA approval for patients with COPD)

		Drugs available						
		SAMA	SABA	SAMA/ SABA	LAMA	LABA	LAMA/ LABA	ICS/LABA ICS/ LAMA/ LABA
HFA MDIs		IPR (Atrovent) ^a	ALB (ProAir HFA, ^b Ventolin HFA, ^c Proventil HFA ^d) LLB (Xopenex HFA ^e)				GLY/FOR (Bevespi Aero- sphere) ^f	FP/SAL (Advair) ^c BUD/FOR Inhalation Aerosol (Symbicort) ^f
DPIs	Aerolizer ^g					FOR (Foradil)		
	Diskus ^c					SAL (Serevent)		FP/SAL (Advair)
	Ellipta ^c				UME (Incruse)		UME/VIL (Anoro)	FF/VIL (Breo)
	HandiHaler ^a				TIO (Spiriva)			FF/UME/ VIL (Trelegy)
	Neohaler ^g				GLY (Seebri)	IND (Arcapta)	GLY/IND (Utibron)	
	Pressair ^f				ACL (Tudorza)			
SIMs	Respimat ^a			IPR/ALB (Combi- vent)	TIO (Spiriva)	OLO (Striverdi)	TIO/OLO (Stiolto)	
Nebulizers*	Breath-enhanced jet (eg, PARI LC Plus ^h)	IPR (Atrovent) ^a	ALB (Proventil ^d , Ventolin ^c) LLB (Xopenex ^e)	IPR/ALB (DuoNeb) ⁱ		ARF (Brovana) ^e FOR (Performo- mist) ^j		
	Breath-actuated jet (eg, AeroEclipse II BAN)							
	Ultrasonic (eg, UltraNeb)							
	Vibrating mesh [†] (eg, AKITA APIXNEB ^k)							

Abbreviations: ACL, aclidinium; ALB, albuterol; ARF, arformoterol; BAN, breath actuated nebulizer; BUD, budesonide; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FDA, US Food and Drug Administration; FF, fluticasone furoate; FOR, formoterol; FP, fluticasone propionate; GLY, glycopyrrolate; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; IND, indacaterol; IPR, ipratropium bromide; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic receptor antagonist; LLB, levalbuterol; MDI, metered-dose inhaler; OLO, olodaterol; SABA, short-acting β_2 -agonist; SAL, salmeterol; SAMA, short-acting muscarinic receptor antagonist; SIM, soft mist inhaler; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.

The SAMA and SABA treatments above are indicated for rescue therapy in patients with COPD. The LAMA, LABA, LAMA/LABA and ICS/LABA treatments are indicated for the maintenance treatment of COPD. Ipratropium (Atrovent) and ipratropium/albuterol (Combivent and DuoNeb) may be used as both a maintenance and rescue therapy.

^aBoehringer Ingelheim; ^bTeva Respiratory; ^cGlaxoSmithKline; ^dSchering; ^eSunovion; ^fAstraZeneca; ^gNovartis; ^hPARI International; ⁱMonaghan Medical Corporation; ^jDeVilbiss Healthcare; ^kActivaero GmbH; [†]Mylan.

*One example of each nebulizer device type provided.

[†]Not yet approved for therapy in patients with COPD.

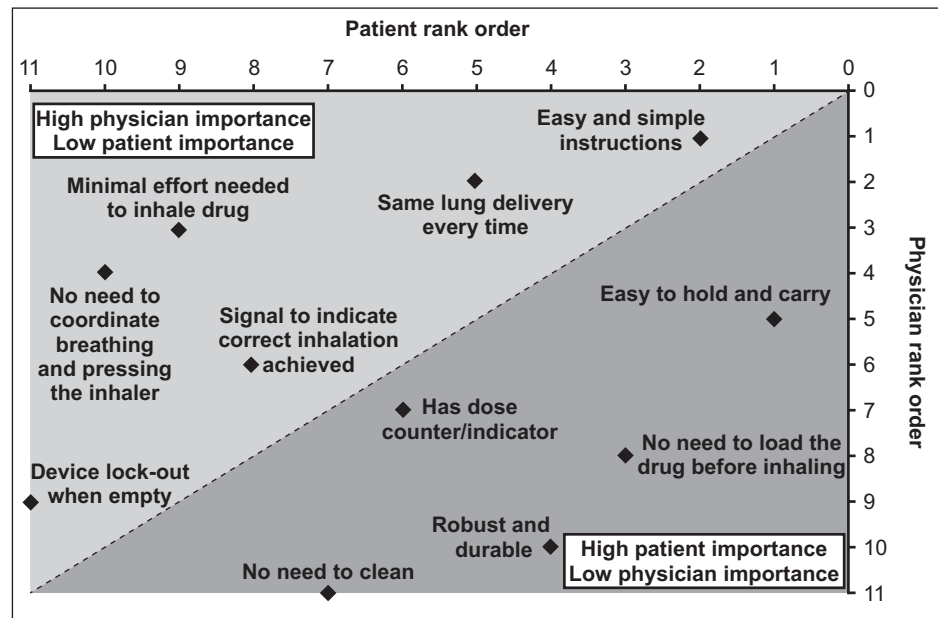
be viewed as a more appropriate option for patients who encounter difficulty in coordinating the inhalation and actuation required for effective operation of a pMDI device. Alternatively, use of a spacer with pMDIs appears to reduce handling errors compared with pMDIs alone, but whether a pMDI plus spacer improves technique versus DPIs remains unclear.^{25,46,47} Lack of device training appears to be a key reason for inhaler handling errors across device types.²⁶

Elderly patients need special consideration when selecting an inhaler and ensuring it is used correctly.⁴⁸ Reduced physical ability and cognitive function due to age-related conditions (eg, dementia, depression, neuromuscular and cerebrovascular diseases) are the main reasons for suboptimal inhaler use in older patients, but other factors may also contribute (eg, multiple comorbid conditions, consequent complicated medication regimens).¹⁵ Older age is strongly associated with inhaler misuse,²⁶ and has also been shown to have a negative correlation with PIF, independent of COPD severity.⁴¹ When compared with younger patients, older patients make more attempts before mastering the inhalation technique for a specific device, and need longer instruction time from trained health care professionals to correct inhaler mishandling.^{49,50} In elderly patients with adequate cognitive and manual ability, the most important factors in selecting a device are availability, convenience, ease of use, patient preference, and cost.^{8,23}

Device continuity is a key consideration when multiple inhaled medications are needed.²³ Lack of continuity of device type for different clinical needs means that patients may need to master the different techniques for each device.³ For instance, a patient may have a pMDI rescue medication, one or more DPIs for their maintenance therapy, and a nebulizer for additional bronchodilation, which may lead to confusion and incorrect device usage. Device continuity has been shown to improve disease control compared with using multiple inhalers in patients with asthma.⁵¹

Economic factors, particularly cost reimbursement in the United States, may influence a patient's ability to access

FIGURE 2 Preferences of patients and physicians regarding different aspects of inhaler device design³⁸



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certain treatments and devices.⁸ Unfortunately, reasonably-priced, effective medication is not currently available for COPD, unlike other conditions such as diabetes. Medication cost has been shown to have a detrimental effect on adherence in patients with COPD.³⁴

A full summary of patient- and physician-related considerations for device selection, along with suggestions for how these can be addressed, is provided in **TABLE 5**.

Inhaler device training for patients and physicians

Comprehensive instruction, including practical demonstration, is important for ensuring patients with COPD use the correct inhaler technique, with regular review and repeated instruction generally needed for continued correct use.^{1,23,32,42} Lack of instruction is significantly associated with inhaler misuse in patients with COPD or asthma.²⁶ Verbal training on inhalation technique increased the number of patients achieving the minimum inhalation flow rate required for a range of different DPIs.³⁹ Similarly, training helped patients using a pMDI to slow their inhalation rate to <90 L/min, as recommended for this type of device.³⁹ The 'teach-back' method, where patients are asked to demonstrate correct usage of their inhaler after instruction from a health care professional,⁵² has shown to be particularly effective in pharmacist-led patient

TABLE 5 Factors affecting inhaler device selection and solutions

	Selection and usage considerations	Measures to address these
Patient-related factors	<ul style="list-style-type: none"> • Understanding of need for inhaler device/medication • Age • Coordination • Manual dexterity • PIF rates • Cognitive impairment • Comorbidities • Patient preference 	<ul style="list-style-type: none"> • Provide adequate training for all patients • Older patients may need additional time for training • Consider using BA devices or spacers if coordination/manual dexterity is poor • DPIs usually require good inspiratory flow; consider other devices if PIF is very low • Consider easier-to-use/passive inhalation devices with cognitive impairment (eg, nebulizers) • Where possible, combine multiple medications in one device, or maintain consistency of device types across medications • Take patient preference/finances into account
System/health care professional factors	<ul style="list-style-type: none"> • Knowledge/training of health care professional • Device availability • Cost (including out-of-pocket cost to patient) 	<ul style="list-style-type: none"> • Provide adequate training to health care professionals as well as patients • Ensure device is available to patient • Evaluate cost vs clinical benefit

Abbreviations: BA, breath-actuated; DPI, dry powder inhaler; PIF, peak inspiratory flow.

device training.⁵³ Educational interventions that incorporated a physical demonstration significantly improved inhaler technique in patients with COPD and asthma compared with patients receiving written and verbal information alone.⁵³ Proper device training in primary care settings should also include education about why the inhaler is needed.³

Face-to-face instruction from trained caregivers for approximately 5 to 10 minutes improves the use of MDIs and DPIs by patients.⁴⁹ However, clinical research indicates that learning correct handling and use may be easier and quicker for some devices than for others.^{31,49} For example, patients naïve to the PulmoJet (a DPI device not currently available in the United States) were found to have fewer serious errors after training than those using Diskus or Turbuhaler devices.²⁴ In another study, it took less time to correct errors in inhaler use with the Diskus compared with the Handi-Haler.⁴⁴ Health care professionals themselves may lack training or knowledge on correct use of inhaler devices,^{35,36,54} with 1 study finding that up to 67% of nurses, doctors, and respiratory therapists were unable to describe or perform critical steps for using inhalers.³⁵

A range of resources is available to aid in training patients and health care professionals in inhaler techniques:

- Tools such as the In-Check DIAL inspiratory flow meter (Clement Clarke International Ltd, Harlow, UK), TurbuHaler Trainer (AstraZeneca, Lund, Sweden), Dis-

kus/Accuhaler Training Device (Vitalograph, Ennis, Ireland), and 2Tone Trainer (Canday Medical Ltd, Newmarket, UK) can be used to evaluate a patient's physical ability to use a specific inhaler.⁵⁵

- The emergence of electronic monitoring devices, such as SmartTrack, SmartTurbo, and SmartMat (all developed by Adherium Ltd, Auckland New Zealand), can provide objective and detailed adherence data to support clinical decision-making.⁵⁶
- It is essential that patients and physicians alike utilize the instructions and video demonstrations available online to understand how to use a device correctly, and avoid errors. These resources can be found on a number of organizations' websites (eg, COPD Foundation, Allergy and Asthma Network, Centers for Disease Control and Prevention, National Jewish Health, Asthma UK, Centre for Pharmacy Postgraduate Education) and on manufacturers' websites for individual inhalers or treatments (eg, <https://www.advair.com/how-to-use-advair.html>, <https://www.incruse.com/how-to-use-incruse.html>, <https://www.mysymbicort.com/copd/taking-symbicort/how-to-use-the-inhaler.html>, <https://www.tudorzhacp.com/tudorza-instructions-dosing.html>, www.us.respimat.com ("How to Use the RESPIMAT Inhaler"), <https://www.utibron.com/how-to-use.html>).

Conclusions

A number of inhalation devices are available for the treatment of COPD. However, incorrect usage or a poor match between the patient and the device may lead to confusion, suboptimal treatment, and increased cost to the patient and health care system. Considering both patient- and health care system-related factors can ensure that appropriate inhaler selection and usage can be optimized. ●

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