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Review article

The role of inspiratory flow in selection and use of inhaled therapy for patients with chronic obstructive pulmonary disease

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ABSTRACT

Inhalation therapy is the mainstay of chronic obstructive pulmonary disease management, and inhaler selection can have a profound impact on drug delivery and medication adherence, as well as on treatment outcomes. Although multiple delivery systems, such as pressurized metered-dose inhalers, dry powder inhalers, slow-mist inhalers, and nebulizers, are available, clinical benefits achieved by patients rely on effective delivery of the inhaled medication to the airways. Among several factors influencing drug deposition, inspiratory flow is one of the most important. Inspiratory flow impacts drug delivery and subsequent clinical efficacy, making it necessary to adequately train patients to ensure correct inhaler use. Peak inspiratory flow is the maximal airflow generated during a forced inspiratory maneuver. Health care professionals need to select the appropriate delivery system after carefully considering patient characteristics, including lung function, optimal inspiratory flow, manual dexterity, and cognitive function. Herein, the role of inspiratory flow in the selection and use of inhaled therapy in patients with COPD is reviewed.

1. Introduction

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 strategy report, pharmacotherapy for chronic obstructive pulmonary disease (COPD) should be individualized based on severity of symptoms and risk of exacerbations [1]. In addition, the patient's response, preference, and ability to use various inhaled delivery systems should be considered [1]. With precision medicine, these and other factors such as genetic, environmental, and lifestyle factors of the individual are taken into account [2].

For health care professionals (HCPs), the decision to prescribe inhaled therapy for COPD is guided primarily by three factors; (1) duration of action of medication: short or long acting, (2) class of medication: β_2-adrenergic agonist bronchodilator, muscarinic antagonist bronchodilator, inhaled corticosteroid, or a combination, and (3) delivery system: pressurized metered-dose inhalers (pMDIs), slow-mist inhalers (SMIs), dry powder inhalers (DPIs), or nebulizers (Table 1).

In a survey of 513 HCPs, 89% of respondents indicated that the specific medication was more important than the delivery system when prescribing inhaled therapy for newly diagnosed patients with stable COPD [11]. This priority may be, in part, because of a lack of understanding about the different features of the four inhalation delivery systems. Furthermore, COPD guidelines and strategy documents do not contain specific recommendations about which delivery system to use in which patient type to achieve optimal benefit [1,12–14].

Inhaler selection can have a profound impact on drug delivery, medication adherence, and treatment outcomes. Choice of the delivery system depends on cost and access, as well as the HCP's familiarity with the device [15]. Further, device-related and patient-related factors should be considered. For inhaled therapy to be successful, for example, the delivery system must generate drug particles of an appropriate size that can reach the lower respiratory tract [9]. Generally, particles >5 μm are deposited in the oropharynx because of impact, whereas those <5 μm (referred to as fine particle fraction [FPF]) have the greatest potential to be deposited in the lungs [9]. Patient-related factors that can impact optimal drug delivery include the patient's inspiratory flow (IF), flow acceleration, time of inhalation, and inhaled volume [16,17]. Instructions for patients on how to inhale from the particular device being used are based on recommended IFs for the different delivery systems. In this review, the role of IF in the selection and use of inhaled therapy in

Abbreviations: COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 s; FPF, fine particle fraction; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HCP, health care professional; HFA, hydrofluoroalkane; IC, inspiratory capacity; IF, inspiratory flow; MDI, metered-dose inhaler; pMDI, pressurized metered-dose inhaler; PIF, peak inspiratory flow; SMI, slow-mist inhaler.

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patients with COPD is considered.

2. pMDI

pMDIs were first introduced in 1956 [18] and since then, remain the most widely prescribed type of inhalation device. Prominent features of pMDIs include their compact size, portability, availability for use with short- and long-acting monotherapy and combination therapy, and the capacity to deliver repeated and consistent drug doses. Despite their use worldwide, errors in use of pMDIs are common among patients [19,20]. A joint task force of the European Respiratory Society and the International Society for Aerosols in Medicine recommended that patients actuate the pressurized canister during a "slow and deep" inhalation to reduce errors [9].

The recommended IF for using pMDIs containing chlorofluorocarbons as a propellant has been 30–60 L/min [21–23]. However, a faster inhalation may be more appropriate based on the aerosol properties of hydrofluoroalkane (HFA), the propellant used in modern pMDIs. For example, Leach [24] demonstrated that beclomethasone dipropionate deposition in the airways with an HFA-metered-dose inhaler (MDI) was consistent across IFs ranging from 26 to 137 L/min, and Biswas and colleagues [25] showed that aerosol lung deposition with an HFA-MDI was consistently higher at an IF of 60–90 L/min than 30 L/min. Based on the characteristics of an HFA propellant, Haidl and colleagues [26] proposed a maximal IF of 120 L/min for HFA pMDIs.

In clinical practice, determining whether or not a patient with COPD is inspiring at an appropriate flow when using a pMDI can be difficult. One approach used commonly by HCPs is to assume correct inhaler technique if the patient reports subjective benefit (i.e., easier to breathe after inhaling a bronchodilator). Valved holding chambers can be used with pMDIs to overcome difficulties in coordinating actuation of the canister and inhalation. Further, some valved holding chambers incorporate a whistle that creates a sound when the IF is too high [26]. Because holding chamber valves have different resistances, optimal IF can vary depending on the specific pMDI and the specific holding chamber. An IF of approximately 30 L/min or less is generally recommended when a pMDI is used with a valved holding chamber [26].

One approach to enhance technique when using a pMDI is to place a cap that provides additional airflow resistance on the mouthpiece [27]. The Flo-Tone (original or Flo-Tone controlled resistance [CR]) cap (Clement-Clarke International Ltd., Harlow, UK) generates a whistle sound when the patient achieves an IF of 30–60 L/min [28]. The patient is instructed to press down on the top of the cannister upon hearing the whistle and to maintain the whistle sound throughout the inhalation. Azouz and colleagues [27] demonstrated that use of the Flo-Tone cap, combined with instructions to prolong inhalation time, decreased mean (±standard deviation [SD]) IF from 156 ± 62 L/min to 74 ± 35 L/min when tested in 71 patients with stable mild-to-moderate asthma. Audio-based devices are being investigated to monitor a patient's IF, as well as adherence, when using a pMDI (Fig. 1) [29].

3. SMI

One SMI, Respimat®, is commercially available. The SMI uses mechanical energy from a coiled spring to generate a slow-moving aerosol [8]. When the dose-release button is pressed, the released coil forces the solution through a fine-nozzle system, producing a mist over a duration of 1.5 s. Similar to pMDIs, the SMI has a very low internal resistance [30], and consistent with instructions for a pMDI [9,31], a slow and deep inhalation lasting at least 1.5 s, followed by a breath hold of 10 s or for as long as possible, is recommended for the SMI [6,32].

Importantly, the aforementioned parameters contribute to optimal lung drug deposition. Brand and colleagues [32] showed that mean ± SD whole lung drug deposition with the SMI was 53% ± 17% of the delivered dose in 13 patients with COPD who were trained to perform the correct technique. In another study of patients with COPD, drug deposition in the lungs was 63% and 60% of the dose delivered with the SMI at IFs of 15 and 30 L/min, respectively [33]. However, lung deposition was reduced to 44% of the dose delivered at an IF of 60 L/min [33]. These data suggest that patients achieve maximum therapeutic benefit with the SMI when they perform "slow and deep" inhalation and maintain IF in the range of 15–30 L/min.

4. DPI

Dry powder medications are often attached to larger carrier particles, such as lactose, in the form of an agglomerate [34]. Optimal use of these medications requires that turbulent energy be generated on inhalation—via patient's inspiratory flow and internal resistance of the inhaler—to separate or disaggregate the medication from the carrier into fine particles and/or to break up the powder pellets [9]. These processes take place inside the DPI and are increased if the flow acceleration is fast at the start of inhalation [35]. Thus, a hard and fast inhalation, followed by a breath hold, is the recommended technique when using a DPI [9].

Table 1
Important characteristics, advantages, and limitations of inhaler devices used in the treatment of COPD [3–10].

Characteristics	pMDI	SMI	DPI	Nebulizer
Formulation	Drug suspended or dissolved in HFA propellant (some contain alcohol and oleic acid)	Aqueous solution or suspension	Drug blended in carrier (most commonly lactose), drug alone, or drug/carrier particles	Aqueous solution or suspension
Metering system	Metering valve and reservoir	Reservoir (cartridge)	Capsule, blister, multi-dose blister pack, or reservoir	Reservoir chamber
Mean velocity of aerosol cloud	2–8.4 m/s	0.8 m/s	NA	NA
Spray duration	0.15–0.36 s	1.5 s	Depends on the patient's inspiratory efforts	Constant
Intrinsic resistance	Very low	Very low	Low to high (0.017–0.058 $kPa^{1/2}/L{\cdot}min^{-1}$)	Minimal
Need for hand-lung coordination	High	Low	Low	NA
Advantages	Reproducible dosing No contamination risk	Slow velocity aerosol Long spray duration High lung deposition Propellant free	Breath-actuated (coordination not required)	No specific inhalation technique required
Limitations	Requires coordination between actuation and inspiration High oropharyngeal deposition	Assembly and priming	Poor dose reproducibility Moisture sensitive	Treatment times can be long Risk of bacterial contamination

COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; HFA, hydrofluoroalkane; NA, not applicable; pMDI, pressurized metered-dose inhaler; SMI, slow-mist inhaler.

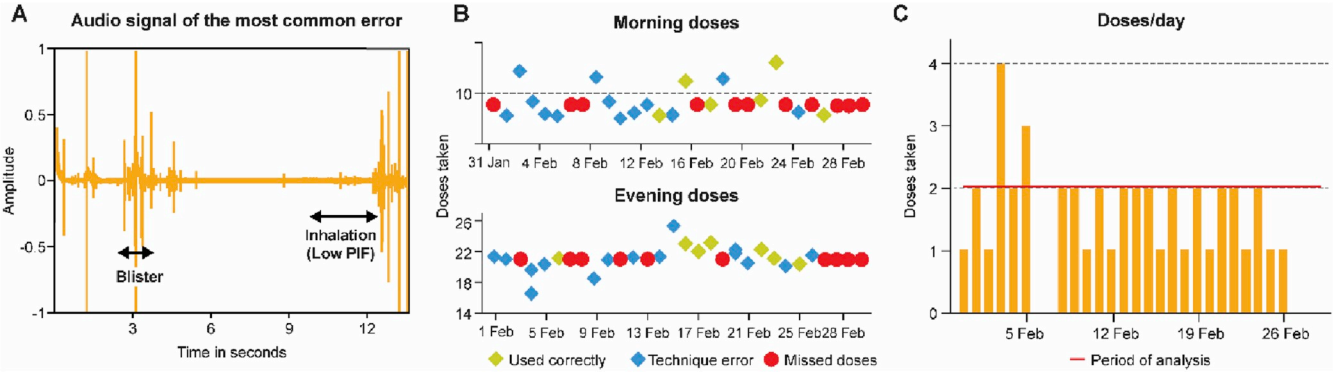

Fig. 1. Audio-based system that illustrates inspiratory flow (labeled PIF) as well as inhaler adherence (doses per day and timing of dosing) [29]. Panel A demonstrates an example of an audio recording of the patient inhaling at an insufficient PIF which is one of the most common technique errors observed. Panel B displays a summary of temporal adherence where each data point represents a dose. Panel C represents the number of doses taken by the patient over the period of one month. Note: Adapted from Taylor TE et al. [29] (copyrights © 2017 American College of Chest Physicians. Published by Elsevier Inc.). PIF, peak inspiratory flow.

All DPIs have an internal resistance, which varies based on the structural design of the device [36]. Generally, the higher the internal resistance of the DPI, the lower the inspiratory flow needed to disaggregate dry powder formulations [34]. Higher inspiratory flows generally increase the dose of the medication reaching the lungs [37]. Pulmonary drug deposition with a DPI can be as low as approximately 15% and as high as 40% of the administered dose, depending on the magnitude of inhalation flow through the device [10]. Poor disaggregation results in larger inhaled particle sizes, leading to greater deposition in the oropharynx [10].

Peak IF (PIF) is the maximal airflow generated during a forced inspiratory maneuver [38]. Measuring PIF against the simulated resistance of a DPI is important for assessing whether or not a patient can achieve optimal drug deposition [39,40]. The In-Check DIAL™ (Clement Clarke International Ltd., Harlow, UK) is widely used to measure PIF. This handheld instrument has an adjustable dial with different sized openings that simulate specific resistances of different DPIs. Magnussen and colleagues [41] demonstrated that a significantly higher PIF against the HandiHaler® DPI was achieved with a "hard and fast" inhalation than a "slow, deep breath" (mean difference in PIF = 13 L/min).

Based on *in vitro* testing, pharmaceutical companies often describe minimal and optimal IFs for specific DPIs. A minimal IF of 30 L/min is required to actuate most DPIs; however, depending upon their structural design, higher IFs might be needed for some inhalers to achieve effective deaggregation [38,42–45]. Further, in *in vitro* studies, higher IFs generated smaller drug particle sizes and enabled greater drug deposition into the lower respiratory tract [39,46]. Although the recommended IF may depend on the specific resistance of the DPI, a PIF of ≥60 L/min is generally considered optimal for DPIs with low to medium high resistances and ≥30 L/min for DPIs with high resistances [39,47,48]. With Turbuhaler®, a high-resistance DPI, an IF of 60 L/min resulted in a much higher total emitted dose of budesonide (64%) than an IF of 30 L/min (38%) [49]. With HandiHaler®, another high-resistance DPI, an IF of 20 L/min produced an FPF of 16.3% and caused the capsule to vibrate; at an IF of 40 L/min, the FPF was 23.4% [43]. With Diskus®, a low-to medium-resistance DPI, the FPF of fluticasone increased from 16% at an IF of 28.3 L/min to 21% at an IF of 60 L/min [50]. These data suggest the potential for greater improvements in lung function in patients with COPD who achieve an optimal PIF with DPIs.

Limited data exist about whether or not a patient with COPD and suboptimal PIF (generally considered < 60 L/min) can achieve clinical benefit using a DPI. In a study of 10 healthy subjects administered radiolabeled budesonide via the Turbuhaler® DPI, drug deposition in the lungs nearly doubled (from 15% to 28%) when PIF increased from 36 to 58 L/min [51]. In a study of 20 patients with COPD, bronchodilation was compared between two long-acting β_2-adrenergic agonists delivered using two different inhalation devices: arformoterol via a nebulizer and salmeterol via the Diskus® DPI [52]. All patients were required to have a PIF of <60 L/min against Diskus® on two separate visits. After a single dose, forced vital capacity (FVC) and inspiratory capacity (IC) were significantly higher at 2 h (peak effect) with nebulized arformoterol than with salmeterol delivered via Diskus® [52]. In a randomized, double-blind, double-dummy, parallel group study, changes in lung function were compared between two different long-acting muscarinic antagonists, again delivered using two different inhalation devices: revefenacin via a nebulizer and tiotropium via the HandiHaler® DPI. All 207 patients with COPD were required to have a PIF of <60 L/min against Diskus® (42 ± 11 L/min) [53]. At 28 days, trough forced expiratory volume in 1 s (FEV_1) was numerically greater with nebulized revefenacin than with tiotropium delivered via HandiHaler® (Δ [adjusted mean difference] = 16 ± 22 mL; p = 0.48). In a prespecified analysis of patients with FEV_1 < 50% predicted, trough FEV_1 (Δ = 49 ± 22 mL; p = 0.02) and trough FVC (Δ = 104 ± 49 mL; p = 0.03) were significantly increased with nebulized revefenacin (n = 80) compared with tiotropium delivered via HandiHaler® (n = 81) [53].

In two observational studies, the potential associations between suboptimal PIF and hospital readmissions were evaluated. In an analysis of 123 hospitalized patients enrolled in an acute exacerbation of COPD care plan, patients with suboptimal PIF had significantly higher rates of 90-day COPD readmissions [54]. However, in another study with 268 patients, all-cause rehospitalizations up to 180 days were comparable between the normal and suboptimal PIF cohorts [55]. More prospective studies are needed to better establish the relationship between PIF and clinical outcomes, such as hospital readmission.

Overall, the prevalence of suboptimal PIF in COPD ranges from 19% to 100% in stable outpatients (Table 2) and from 32% to 52% among those hospitalized for an exacerbation (Table 3). Note, in these studies subjects performed PIF effort after a complete exhalation except for the study by Loh and colleagues [54] in which subjects exhaled to functional residual capacity. The wide ranges in prevalence values reflect data obtained for specific DPIs (including low to high internal resistance DPIs), as well as different patient populations. Common (i.e., observed in at least two studies) characteristics of patients with COPD and suboptimal PIF include age, female sex, and reduced inspiratory capacity (IC) (Table 4). Advanced age [56] and female sex [57] are expected because these variables predict lower lung function. Reduced IC is a marker of lung hyperinflation that adversely affects respiratory muscle strength and, therefore, the ability to generate PIF [58].

5. Nebulizer

Normal tidal breathing is recommended for inhaling aerosol medications from a nebulizer [9]. As such, IF is not an influencing factor for

Table 2
Prevalence of suboptimal PIF (<60 L/min) against simulated resistances of DPIs in stable outpatients with COPD.

Study	Patients, n	FEV_1% predicted (mean ± SD)	DPI	PIF (L/min)	
				Mean ± SD	<60
Chodosh et al., 2001 [43]	26	30[a]	HandiHaler®	30[a]	100%
Al-Showair et al., 2007 [39]	163	48 ± 22	Diskus®	58 ± 18	53%
			Turbuhaler®	48 ± 15	84%
			HandiHaler®	29 ± 10	100%
Janssens et al., 2008[c] [48]	26	49 ± 20	Aerolizer®	NA	27%
			Diskus®	NA	36%
			Turbuhaler®	NA	78%
Malmberg et al., 2010 [59]	93	51 (18–96)[b]	Easyhaler®	54 (26–95)[b]	NA
Mahler et al., 2013 [60]	213	37 ± 9	Diskus®	71 ± 18	19%
Azouz et al., 2015[c] [61]	50	52 ± 22	Turbuhaler®	50 ± 16	84%
Duarte et al., 2019 [62]	303	54 ± 20	Diskus®	NA	20%

COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 s; NA, not available; PIF, peak inspiratory flow; SD, standard deviation.
[a] Median value.
[b] Mean (range).
[c] Data extrapolated from Figure 3 of the reference.

Table 3
Prevalence of suboptimal PIF (<60 L/min) against simulated resistances of DPIs in patients hospitalized for a COPD exacerbation.

Study	Patients, n	FEV_1% predicted (mean ± SD)	DPI	PIF (L/min)	
				Mean ± SD	<60
Broeders et al., 2004 [63]	15*	48 ± 25	Turbuhaler®	59 ± 5	40%
			Diskus®	86 ± 5	NA
Loh et al., 2017 [54]	123	42 ± 15**	No resistance	66 ± 26[#]	52%
Sharma et al., 2017 [55]	268	46 ± 19[†]	Diskus®	71 ± 22	32%

COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 s; NA, not available; PIF, peak inspiratory flow; SD, standard deviation. *Includes five patients with asthma. **n = 96. [#] = PIF was performed at functional residual capacity (FRC). [†]n = 68.

this delivery system. However, Wise and colleagues [65] suggested to consider nebulized long-acting β_2-adrenergic agonists in patients with COPD who are "unable to generate adequate inspiratory force" (i.e., PIF too low for a DPI).

6. Discussion

β_2-adrenergic agonists and muscarinic antagonists are available in all four delivery systems. Inhaled corticosteroids are available as a solution for use in a nebulizer; as monotherapy in pMDIs and DPIs; and as combination therapy in pMDIs and DPIs but not in SMIs. Therefore, selection of the most appropriate delivery system for the individual patient presents a major decision for HCPs.

An initial approach is to consider which of the three handheld devices (pMDIs, SMIs, or DPIs) is appropriate for use by the patient. An algorithm for this approach is proposed in Fig. 2. To make this decision, HCPs should address three clinical questions. First, does the patient have sufficient **cognitive function** to follow instructions? Cognitive function is required to use a handheld device correctly. Patients must understand

Table 4
Features of patients with COPD and a PIF of <60 L/min.

Feature	Study	Subjects, n	p value
Older age	Janssens et al., 2008 [48]	26	0.014[a]
	Malmberg et al., 2010 [59]	93	0.022[a]
	Sharma et al., 2017 [55]	268	0.006
Female sex	Malmberg et al., 2010 [59]	93	0.010
	Mahler et al., 2013 [60]	213	<0.001
	Taylor et al., 2015 [64]	16	<0.05
	Sharma et al., 2017 [55]	268	0.014
Low inspiratory capacity (% predicted)	Broeders et al., 2004 [63]	15	<0.001
	Mahler et al., 2013 [60]	213	0.007

COPD, chronic obstructive pulmonary disease; PIF, peak inspiratory flow.
[a] A multiple regression was performed to investigate independent predictors of suboptimal PIF.

that they have to exhale completely before inhaling through the inhaler mouthpiece, inhale at the recommended IF based on instructions of "slow and steady" for pMDIs and the SMI, and "hard and fast" for DPIs, and then hold their breath as directed [9,66]. Simple screening tests are available to assess cognitive function in individuals at clinic visits and in the hospital. Second, does the patient have sufficient **manual dexterity** to use the handheld device correctly? For example, comorbidities like arthritis, muscle weakness, and neuromuscular disease are common in patients with COPD and may affect their ability to manipulate the device as instructed. One or both hands are required to press the canister of a pMDI, to insert the cartridge into the base of an SMI and press the dose-release button, and to activate a DPI by moving a lever or mouthpiece cover and/or to place a capsule into the base of a DPI and press the side to pierce the capsule. Simple tests can be performed to

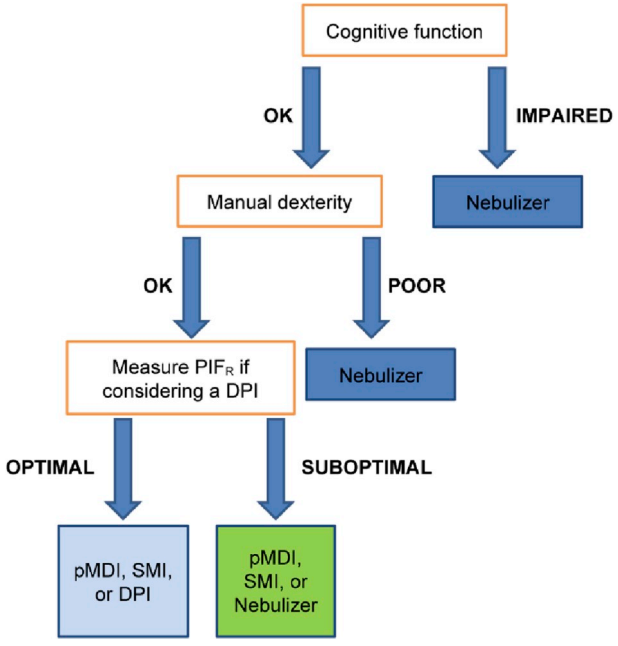

Fig. 2. Algorithm for assessing the ability of a patient to use a hand-held inhaler. DPI, dry powder inhaler; PIF_R, peak inspiratory flow against the simulated resistance (R) of a specific DPI; pMDI, pressurized metered-dose inhaler; SMI, slow-mist inhaler.

assess dexterity and sensory skills of the hand. Third, does the patient have an **optimal PIF** to use a specific DPI? Measuring PIF with the In-Check DIAL™, or a similar instrument, against the simulated resistance of the DPI being considered provides guidance. Of note, PIF measured against the internal resistance of a specific DPI has been proposed as an emerging biomarker in COPD to predict patients who are less likely to respond optimally to a dry powder medication, although additional evidence is needed to establish broad clinical application [67]. For patients who exhibit a suboptimal PIF (<60 L/min for a low-to a medium-high resistance DPI or < 30 L/min for a high resistance DPI), HCPs should consider one of the three other delivery systems given the goal of inhaler therapy to provide optimal benefit for each individual patient.

With DPIs, the patient should produce a fast flow acceleration to generate turbulent energy inside the device to break up the powder. Pharmaceutical companies have performed *in vitro* testing to assess FPF with their DPIs at different IFs. FPF has the greatest clinical relevancy because fine drug particles are deposited in the lower respiratory tract [50]. Minimal and optimal PIFs are typically presented relative to a specific DPI. Of note, the minimal PIF is the inspiratory flow required to actuate the DPI, whereas the optimal PIF provides the best or greatest effect based on *in vitro* modeling. Ideally, each patient should generate an optimal PIF with the use of a specific DPI to achieve the greatest benefit. Additional investigations are needed to assess the magnitude of response with a dry powder bronchodilator in patients with COPD and suboptimal PIF.

This approach incorporates the principle of precision medicine—the tailoring of medical treatment to the individual characteristics of each patient. After an HCP has selected the medication and delivery system, the patient should be instructed on correct use of the chosen delivery system. Instructions may be provided by an HCP demonstrating the use of the actual or placebo device one-on-one with the patient in the office, handing out written instructions for the patient to take home with diagrams to emphasize "key" inhalation maneuvers, and/or presenting website information to view online guidance, as well as videos, on delivery system use. Specific inhalation instructions for each of the four delivery systems, along with corresponding IFs, are provided in Table 5. These instructions, and the teach-back approach, should be repeated at follow-up appointments to reinforce the correct steps and to minimize errors [68]. Expectations of specific inhalation profiles for different inhalers reinforce the need for HCPs to regularly check and train patients on correct inhaler technique, as outlined in the GOLD 2020 report [1].

Supplementary video related to this article can be found at https://doi.org/10.1016/j.rmed.2019.105857

7. Summary

Recommended inhalation techniques, along with corresponding optimal IF for the four delivery systems, are provided in Table 5. Of importance, inhalation time and volume also affect optimal drug delivery into the lower respiratory tract. "Accessories" are available for use with pMDIs to estimate IF. Some valved holding chambers that are used with pMDIs produce a whistle sound if the patient is inhaling too fast (i.e., IF is too high). In addition, measurement of PIF against the simulated resistance of a specific DPI enables HCPs to know whether or not a patient has optimal ability to disaggregate the powder and inhale the fine particles deep into the lungs.

Audio-based systems that use data collection/interpretation software should enable HCPs and health care systems to objectively assess a patient's inhaler technique. As illustrated in Fig. 1, these monitoring systems can be used to evaluate adherence (doses per day and timing of dosing), as well as an inhalational profile that includes IF.

Table 5
Recommended inhalation techniques along with the corresponding optimal IF [9,24–26,33,39,47,48].

Delivery system	Inhalation	Recommended optimal IF
pMDI	Slow and steady[a]	30–60 L/min[a]
SMI	Slow and steady	15–30 L/min
DPI	Hard and fast	R1-R4: ≥60 L/min[b] R5: ≥30 L/min[b]
Nebulizer	Normal tidal breathing	Breathe in and breathe out normally

DPI, dry powder inhaler; HFA, hydrofluoroalkane; IF, inspiratory flow; pMDI, pressurized metered-dose inhaler; SMI, slow-mist inhaler.
[a] A faster inhalation and higher IF may be appropriate based on the aerosol properties of HFA as the propellant in pMDIs.
[b] R1-R4 include DPIs with low to medium high resistances and R5 includes DPIs with high resistances as specified for the use of In-Check DIAL™.

Guarantor

Donald A. Mahler is the guarantor of the manuscript and is responsible for the manuscript content.

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Declaration of competing interest

Donald A. Mahler has participated in advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sunovion, and Theravance. He is on the speakers' bureau for AstraZeneca, Boehringer Ingelheim, and Sunovion. He has received royalties from Hillcrest Media for COPD: Answers to Your Question, 2015; CRC Press for Dyspnea: Mechanisms, Measurement, and Management, 3rd edition, 2014; and pharmaceutical companies for use of the baseline and transition dyspnea indexes.

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