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REVIEW

Lung Deposition and Inspiratory Flow Rate in Patients with Chronic Obstructive Pulmonary Disease Using Different Inhalation Devices: A Systematic Literature Review and Expert Opinion

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Background: Our aim was to describe: 1) lung deposition and inspiratory flow rate; 2) main characteristics of inhaler devices in chronic obstructive pulmonary disease (COPD).

Methods: A systematic literature review (SLR) was conducted to analyze the features and results of inhaler devices in COPD patients. These devices included pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and a soft mist inhaler (SMI). Inclusion and exclusion criteria were established, as well as search strategies (Medline, Embase, and the Cochrane Library up to April 2019). In vitro and in vivo studies were included. Two reviewers selected articles, collected and analyzed data independently. Narrative searches complemented the SLR. We discussed the results of the reviews in a nominal group meeting and agreed on various general principles and recommendations.

Results: The SLR included 71 articles, some were of low–moderate quality, and there was great variability regarding populations and outcomes. Lung deposition rates varied across devices: 8%–53% for pMDIs, 7%-69% for DPIs, and 39%–67% for the SMI. The aerosol exit velocity was high with pMDIs (more than 3 m/s), while it is much slower (0.84–0.72 m/s) with the SMI. In general, pMDIs produce large-sized particles (1.22–8 μm), DPIs produce medium-sized particles (1.8–4.8 μm), and 60% of the particles reach an aerodynamic diameter <5 μm with the SMI. All inhalation devices reach central and peripheral lung regions, but the SMI distribution pattern might be better compared with pMDIs. DPIs' intrinsic resistance is higher than that of pMDIs and SMI, which are relatively similar and low. Depending on the DPI, the minimum flow inspiratory rate required was 30 L/min. pMDIs and SMI did not require a high inspiratory flow rate.

Conclusion: Lung deposition and inspiratory flow rate are key factors when selecting an inhalation device in COPD patients.

Keywords: COPD, lung deposition, inspiratory flow, inhalation devices, systematic literature review

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a persistent airflow limitation that is usually progressive, according to guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[1] In recent years, the prevalence of COPD has dramatically increased, growing by 44.2% from 1990 to 2015.[2] The impact on patients, society, and health systems is correspondingly

huge. More than 3 million people die of COPD worldwide each year, accounting for 6% of all deaths worldwide.[3] In 2010, the cost of COPD in the USA was projected to be approximately US $50 billion.[4]

One of the primary treatment modalities for COPD is medications that are delivered via inhalation devices. Currently, in clinical practice, a variety of devices are available for the treatment of these patients, including pressurized metered-dose inhalers (pMDIs), which are used with or without a valved holding chamber or spacer, as well as dry powder inhalers (DPIs) and the soft mist inhaler (SMI). Inhaler devices vary in several ways, including how the inhaler dispenses the drug, whether the treatment is passively or actively generated (using propellant, mechanical, or compressed air), and the drug's formulation (solution, dry powder, or mist).

The selection of an inhalation device is a key point in COPD because it impacts patient adherence, the drug's effectiveness, and long–term outcomes.[5] A range of studies have assessed which factors/characteristics should be considered when selecting the most appropriate device.[6–8] Interestingly, according to many expert opinions, the most important factors involved in achieving optimal disease outcomes are the generation of high lung deposition and correct dispensation with low inspiratory flow rates.[9] Other relevant factors include inhalation technique, potential difficulties with the device, and patient preferences.

On the other hand, data regarding lung deposition and inspiratory flow rates across inhalation devices in COPD patients are usually described and evaluated as absolute, static numbers. However, a theoretical framework and pathophysiological and clinical evidence all suggest that both are influenced by several factors that relate to the patients and their COPD, all of which can change over time.[6,10–17] Therefore, analyzing lung deposition and inspiratory flow rates in COPD patients who use inhalation devices requires a more careful, holistic, and dynamic approach.

Considering all the aspects described above, we performed a systematic literature review (SLR) and a narrative review to assess lung deposition and inspiratory flow rates, as well as data related to these inhalation devices in COPD patients. Using this information, we propose related conclusions and recommendations that can contribute to the selection of inhalation devices. We are confident that this information will be very useful for health professionals who are involved in the care of patients with COPD.

Methods

This project consisted of an SLR, a narrative review, and an expert opinion based on a nominal group meeting. A nominal group meeting is a structured method for brainstorming that encourages contributions from everyone and facilitates quick agreement on the relative importance of issues, problems, or solutions.

Experts' Selection

We first established a group of 10 pneumologists (two of us were project coordinators). We are all specialized in COPD with demonstrated clinical experience (a minimum of 8 years and ≥5 publications and members of the Sociedad Española de Neumología y Cirugía Torácica (SEPAR). Besides, we are located in different parts of Spain. Then, we defined the project's objectives, established the protocol of the SLR, and decided that this would be complemented by a narrative review.

Systematic Literature Review

The SLR was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective of the SLR was to analyze lung deposition, inspiratory flow, and other characteristics of different inhaler devices (pMDIs, DPIs, and SMI) in both COPD patients and healthy subjects. Studies were identified using sensitive search strategies in the main medical databases. For this purpose, an expert librarian checked the search strategies (Tables 1–7 of the Supplementary material). Disease- and inhaler device-related terms were used as search keywords, which employed a controlled vocabulary, specific MeSH headings, and additional keywords. The following bibliographic databases were screened up to April 2019: Medline (PubMed) and Embase from 1961 to April 2019, and the Cochrane Library up to April 2019. Retrieved references were managed in Endnote X5 (Thomson Reuters). Finally, a manual search was performed by reviewing the references of the included studies and all the publications, as well as other information provided by the authors. Retrieved studies were included if they met the following pre-established criteria: Patients had to be diagnosed with COPD, aged 18 or older, and treated with an inhaler device, and studies had to include outcomes related to lung deposition and inspiratory flow, including the rate of lung deposition, the particles' mass median aerodynamic diameter (MMAD) expressed as μm (micrometer), the aerosol exit velocity

(AEV) in meter per second (m/s), the lung distribution pattern, the inspiratory flow rate expressed as liter per minute (L/min), or the device's intrinsic resistance. Other variables, such as safety, were also considered. Only SLRs, meta-analyses, randomized controlled trials (RCTs), observational studies, and in vitro studies in English, French, or Spanish were included. Animal studies were excluded. The screening of studies, data collection (including the evidence tables), and analysis were independently performed by two reviewers. In the case of a discrepancy between the reviewers, a consensus was reached by including a third reviewer. The 2011 levels of evidence from the Oxford Center for Evidence-Based Medicine (OCEBM)[18] were used to grade the quality of the studies.

Narrative Review

To supplement the SLR, additional searches were performed specifically to explore the basis of lung deposition and inspiratory flow, including their determinants and the effect of COPD on these aspects. For this purpose, apart from the results of the SLR, we performed different searches in Medline using PubMed's Clinical Queries tool and small search strategies using MeSH and text–word terms (Table 8 of the Supplementary material).

Nominal Group Meeting

The results of the SLR and narrative searches were presented and discussed in a guided nominal group meeting. In this meeting, we agreed on a series of general conclusions and clinical recommendations.

Results

The SLR retrieved 3064 articles, of which 979 were duplicates. A total of 120 articles were reviewed in detail, as well as a further 20 articles that were retrieved using the manual search. Eventually, 75 articles were excluded (Table 9 of the Supplementary material), most of them due to lack of relevant data, and 71 were included, 24 were in vitro studies. Some of the included articles were of low–moderate quality (due to the study design, and poor description of the methodology, especially for the articles published before the 1990s). We found great variability regarding study designs, populations, outcomes, and measures. There were 24 in vitro studies,[16,17,19–40] and the rest of the articles comprised one SLR[41] and several RCTs and cross-sectional studies. The studies analyzed more than 1600 COPD patients, most of whom were men, with age ranges from 27 to 89 years, and with forced expiratory volume in 1 second from 25% to 80%. Many of these studies assessed one type of inhalation device, but others compared pMDIs and DPIs,[19,20,30,33,37,40–46] pMDIs and SMI,[47–49] or DPIs and SMI.[17,27,28] One study also evaluated the three inhalation devices.[17] The narrative searches found almost 1000 articles.

Here, we summarize the main results of the SLR and narrative review, according to the project's objectives (lung deposition, inspiratory flow rate, and data regarding these aspects for different inhaler devices). We also present the general conclusions and recommendations. Tables 1–3 show the main characteristics of the inhalation devices.

Lung Deposition

Different factors have been associated with lung deposition, some of which relate to the patient's features (eg, airway geometry, inspiratory capacity, inhalation technique, breath–hold time, etc.) and to COPD (eg, exacerbations or hyperinflation).[10–12,50–52] In fact, it has been shown during COPD exacerbations patients present decreased lung function and respiratory muscle strength that eventually influence on lung deposition.[53] However, other factors are connected to the inhaler device (eg, the aerosol-generating system, speed of the aerosol plume, intrinsic resistance, inhaled carrier gas, oral/nasal inhalation, etc.), formulation (eg, the particle charge, lipophilicity, hygroscopicity, etc.), inhaled particle (eg, MMDA, its effect on lung distribution, etc.), and inhalation pattern (eg, the inspiration flow rate, volume, breath–hold time, etc.).[52,54]

With regards to the lung deposition (in relation to the emitted dose) across inhaler devices, data from in vitro and in vivo studies have estimated that 10%–20% of the delivered dose reaches the airways.[54–56]

Lung deposition rates (from individual studies) ranging from 8% to 53% have been reported for pMDIs.[49,54,56–59] However, this rate increased to 11%–68% with the addition of a valved holding chamber or spacer[31,35,46,59–63] and to 50%–60% with press-and-breathe actuators.[64] More specifically, when Modulite® was used, lung deposition could reach up to 31%–34%.[65,66] The K–haler® has a reported lung deposit of 39%.[67] As exposed before, different factors might be contributing to these rate variability.

The studies included that analyzed DPIs have shown that the lung deposition rate is low, at around 20%,[68] which is negatively influenced by a suboptimal inspiratory flow rate, humidity, and changes in temperature.[69] Furthermore, clear differences in lung deposition were not observed when patients

Table 1 Main Characteristics of Pressurized Metered-Dose Inhalers

Formulation	Drug Suspended or Dissolved in Propellant (With Surfactant and Cosolvent)
Metering system	Metering valve and reservoir
Propellant	HFA or CFC
Dose counter	Sometimes
Priming	Variable priming requirements
Temperature dependence	Low
Humidity dependence	Low
Actuator orifice	The design and size of the actuator significantly influences the performance of pMDIs
Lung deposition	8%-53%
MMDA	1.22 μm-8 μm
Aerosol exit velocity	High (more than 3 m/s)
Lung distribution	Central and peripheral regions
Intrinsic resistance	Low
Inspiratory flow rate	~ 20 L/min
Advantages	Compact and portable, consistent dosing, and rapid delivery
Disadvantages	Not breath-actuated, require coordination

Abbreviations: pMDI, pressurized metered-dose inhaler; HFA, hydrofluoroalkane; CFC, chlorofluorocarbon; MMAD, mass median aerodynamic diameter; m/s, meter per second; μm, micrometer; L/min, liter per minute.

Table 2 Main Characteristics of Dry Powder Inhalers

Formulation	Drug/Lactose Blend, Drug Alone, Drug/Excipient Particles
Metering system	Capsules, blisters, multi-dose blister packs, reservoirs
Propellant	No
Dose counter	Yes
Priming	Variable priming requirements
Temperature dependence	Yes
Humidity dependence	Yes
Actuator orifice	Does not apply
Lung deposition	~ 20%
MMDA	1.8 μm–4.8 μm
Aerosol exit velocity	Depends on inspiratory flow rate
Lung distribution	Central and peripheral regions
Intrinsic resistance	Low/medium/high
Inspiratory flow rate	Minimum of 30 L/min to > 100 L/min
Advantages	Compact and portable Some are multi-dose devices. Do not require coordination of inhalation with activation or hand strength
Disadvantages	Require a minimum inspiratory flow Patients with cognitive or debilitating conditions might not generate sufficiently high inspiratory flows Most are moisture-sensitive

Abbreviations: DPI, dry powder inhaler; MMAD, mass median aerodynamic diameter; m/s, meter per second; μm, micrometer; L/min, liter per minute.

performed inhalation correctly.[68] For the main DPI devices, the published lung deposition rates from individual studies (without direct comparisons) are as follows: Accuhaler® 7.6%,[70] Aerolizer® 13%–20%,[34,71] Breezhaler® 26.8%–39%,[24,29] Easyhaler® 18.5%–31%,[71,72] Genuair® 30.1%–51.1%,[27,73,74] Handihaler® 9.8%–46.7%,[19,24,71] Ingelheim inhaler® 16%–59%,[75] NEXThaler® 39.4%–56%,[11,76] Spinhaler® 11.5%,[75] Turbuhaler® 14.2%–69.3%,[21,42,77–79] and Twisthaler® 36%–37%.[80] Similarly to all inhaler devices, other factors are probably influencing the lung deposition rate.[81] Although some studies have compared lung deposition in pMDIs and DPIs, their results are contradictory.[19,33]

Respimat® (SMI) has largely exhibited high lung deposition rates that range from 39.2% to 67%,[27,38,48,49,74,82–84] with different inspiratory flow rates (high and low) and irrespective of humidity.[85] Compared with other devices, SMI showed higher lung deposition than pMDIs (including those with a chamber or spacer) or DPIs.[27,48,74,83,86]

We also evaluated the AEV. Inhalation devices with a high AEV might have a short spray duration and vice versa. With pMDIs, the aerosol exits through a nozzle at

Table 3 Main Characteristics of the Soft Mist Inhaler

Formulation	Aqueous Solution or Suspension
Metering system	Reservoirs
Propellant	No
Dose counter	Yes
Priming	Actuate the inhaler toward the ground until an aerosol cloud is visible and then to repeat the process three more times
Temperature dependence	No
Humidity dependence	No
Actuator orifice	–
Lung deposition	39.2%–67%
MMDA	~ 3.7 μm
Aerosol exit velocity	0.72–0.84 m/s
Lung distribution	Central and peripheral regions
Intrinsic resistance	Low/none
Inspiratory flow rate	Independent
Advantages	Portable and compact. Multi-dose device. Reusable. Compared with dry powder inhalers, a considerably smaller dose of a combination bronchodilator results in the same level of efficacy and safety
Disadvantages	Needs to be primed if not in use for over 21 days

Abbreviations: SMI, soft mist inhaler; MMAD, mass median aerodynamic diameter; m/s, meter per second; μm, micrometer; L/min, liter per minute.

a very high rate of more than 3 m/s.[87] However, the AEV of the SMI is much slower, at 0.84–0.72 m/s, and the aerosol cloud lasts longer.[88–90]

It has also been observed that the distribution of the deposition sites of inhaled particles is strongly dependent on their aerodynamic diameters.[69] This SLR found that pMDIs generally produce at least medium-sized particles, with a significant rate of extrafine particles. The observed MMAD of conventional pMDIs varies from 1.22 to 8 μm,[35,91,92] from 1.19 to 3.57 μm when a valved holding chamber or spacer is used,[31,35,93] and from 0.72 to 2.0 μm with Modulite®.[65,66] Regarding particle size data for DPIs, depending on the device and drug, MMDAs vary from 1.40 to 4.8 μm.[11,19,21,24,27–29,36,37,74,76] Conversely, SMI

Table 4 Main Factors Associated to Inspiratory Flow Rate

Patient-related
Inspiratory capacity
Inspiratory effort
Comorbidities
Inhalation technique
COPD-related
Severity
Hyperinflation
Exacerbations
Respiratory muscle alterations
Inhalation device-related
Internal resistance
Disaggregation of the powdered drug dose (DPIs)

Abbreviations: COPD, chronic obstructive pulmonary disease; DPIs, dry powder inhalers.

generates a cloud that contains an aerosol with a fine particle fraction of around 3.7 μm.[74] It is estimated that 60% of the particles reach a MMAD <5 μm with SMI.[85] The reported rate with pMDIs and DPIs (indirect comparison) is not that high.[27,28,74,94]

Another relevant outcome when using inhalation devices is the lung distribution pattern (through the central and peripheral regions). All inhalation devices have been shown to reach both central and peripheral areas. SMI data suggest that lung distribution pattern might be better than pMDIs, with a higher distribution in bronchial trees and peripheral regions.[11,28,49,60,65,66,73,74,82,95,96] More specifically, a comparative study found mean peripheral, intermediate and central lung deposition, and peripheral zone/central zone ratio of 5.0%–9.4%, 4.8%–11.3%, 4.5%–10.4%, 1.01–1.16 with Respimat® vs 3.8%, 4.9%, 5.6%, 1.36 with pMDIs, respectively.[49] Comparative data between pMDIs and DPIs are conflicting.[33,46]

Inspiratory Flow Rate

The other main focus of this project was the inspiratory flow rate. First, it is important to consider the factors associated with inspiratory flow rate (Table 4). Similar to lung deposition, some of these factors relate to the patient's and COPD's characteristics, while other factors relate to the inhaler device, such as the intrinsic resistance.[6,10,13–17,43,45,97,98]

Overall, two main driving forces can affect the performance of DPIs: the inspiratory flow generated by the patient and the turbulence produced inside the device, the latter of which solely depends on the original technical

characteristics of the device, including the intrinsic resistance. These two parameters affect the disaggregation of the drug dose, the diameter of the particles to inhale, the lung distribution of the dose, and eventually, the efficacy of the delivered drug. Essentially, a higher intrinsic resistance results in the patient needing to generate a higher inspiratory flow.

In general, although variable, DPIs' intrinsic resistance is higher than that of pMDIs or SMI, which are relatively similar and low. Therefore, pMDIs and SMI do not require the patient to generate a high inspiratory flow (and inspiratory effort).

According to the results of the SLR, pMDIs require low inspiratory flow rates of around 20 L/min (59, 70, 132) to achieve an adequate lung deposition.[10,17,43,45,57,82,99–101] There were no major differences between the use of one propellant and another.[57] In order to generate the correct inspiratory airflow and lung deposition with this type of inhalation device, it is recommended the patients start breathing from their functional residual capacity, then they should activate the inhalation device and start inhalation using an inspiratory flow rate that is below 60 L/min. Then, at the end of inspiration, patients should hold their breath for around 10 seconds.[100] Consequently, patients need a correct inhalation technique and coordination. The K-haler® is triggered by an inspiratory flow rate of approximately 30 L/min.[67]

Inhaler devices are many times classified as low- (30 L/min or below), medium– (~30–60 L/min), and high-resistance (>60 L/min) devices.[10,17] DPIs with low intrinsic resistance include Aerolizer®, Spinhaler®, and Breezhaler®; DPIs with medium resistance include Accuhaler®/Diskhaler®, Genuair®/Novolizer®, and NEXThaler®; DPIs with medium/high resistance include Turbuhaler®; and DPIs with high resistance include Easyhaler®, Handihaler®, and Twisthaler®. The estimated inspiratory flow rates required thus vary across devices, from a minimum of 30 L/min to more than 100 L/min.[6,26,32,43,45,101–108]

Based on the information presented above, when using a high-resistance DPI, the disaggregation and micro-dispersion of the powdered drug are relatively independent of the patient's inspiratory effort because the driving force depends on the intrinsic resistance of the DPI itself, which is able to produce the turbulence required for effective drug micro-dispersion. However, when a low-resistance device is used, the only force that can generate turbulence is the patient's inspiratory airflow, which should be high.

Finally, the studies showed that the SMI inhalation device uses mechanical energy (from a spring) to generate a fine, slow–moving mist from an aqueous solution, which is independent of the patient's inspiratory effort. Therefore, the required inspiratory flow rate and/or effort are less relevant than with DPIs.[83,88,89,109] Moreover, the inhalation maneuver with SMI is more similar to physiological inhalation. One study observed that drug delivery to the lungs with SMI was more efficient than with pMDIs, even with poor inhalation technique.[82]

General Conclusions and Recommendations

The experts discussed the results of the reviews, and, based on the evidence, they formulated a series of general conclusions and recommendations that are outlined in Tables 5 and 6. In summary, health professionals involved in the management of COPD patients should be aware of all factors involved in adequate drug distribution when using inhalation devices. Two main objective factors emerged at this point: lung deposition and the required inspiratory flow rate. Both of these factors are highly influenced by patient, COPD, and inhaler device characteristics. Moreover, COPD is a heterogeneous and dynamic chronic disease, in which lung deposition and inspiratory flow rates vary across patients and also within the same patient.

Thus, it is strongly recommended that, in addition to the standard variables for COPD, inspiratory flow rate and the patient's inspiratory capacity are evaluated (on a regular basis), and the selection of an inhaler device should be based on the COPD patient's features, needs, and clinical situation. This selection should consider the different characteristics of the devices to ensure physicians choose the device that best matches that patient's needs.

Finally, we considered it important to systematically review the patient's inhalation maneuver,[110] see Tables 3 and 6. This should be checked during every visit, so that errors can be resolved, and inhalers can be checked and even changed, where necessary. The same way, before considering a change in the patient's treatment, possible errors with the inhalation maneuver should be evaluated.

Discussion

We have presented a critical and detailed review of data related to lung deposition and inspiratory flow rates in COPD patients across different inhalation devices, while

Table 5 General Conclusions Regarding Lung Deposition and Inspiratory Flow Rate in Chronic Obstructive Pulmonary Disease

#	Conclusion
1	The lung deposition profile and required inspiratory flow rate are key factors to be considered when selecting an inhalation device
2	COPD is a progressive disease with specific pathophysiological features that impact patients' lung deposition and inspiratory flow rate
3	In COPD patients, obstruction severity and especially hyperinflation are decisive pathophysiological factors
4	During the course of COPD, some situations, notably exacerbations, impact the inspiratory flow rate
5	An homogeneous drug distribution through the airways is essential, not only because of the COPD pathophysiology but also because of the different distribution of cholinergic and β2 receptors
6	COPD treatment requires inhalation devices capable of delivering particles with a MMAD comprised between 0.5 and 5 µm to achieve high lung deposition
7	The patients' ability to perform a correct inhalation maneuver (inspiratory effort, coordination, etc.) is decisive to achieve an adequate inspiratory flow rate and lung deposition
8	Inhalation maneuvers that are similar to physiological/standard inspiratory flow are more likely associated with reduced oropharyngeal deposition and therefore increased lung deposition
9	Inhalation devices present different characteristics that define the required inspiratory flow rate and influence lung deposition
10	The inspiratory flow rate required for drug dispersion with a given DPI is inversely proportional to the intrinsic resistance of the DPI
11	The faster the exit speed of the drug delivered from the device (initial acceleration of the inhalation maneuver by the patient or directly by the device), the greater the risk of oropharyngeal deposition and the lesser the lung deposition
12	The SMI requires a low inspiratory flow rate. Therefore, compared with other inhaler devices, when performing a correct maneuver, oropharyngeal deposition is lower and lung deposition is higher

Abbreviations: COPD, chronic obstructive pulmonary disease; MMAD, mass median aerodynamic diameter; µm, micrometer; DPI, dry powder inhaler; SMI, soft mist inhaler.

also taking into account all the factors and bases that determine the effectiveness of the inhaled route of administration.

Table 6 Experts' Recommendations for the Selection of the Appropriate Inhalation Device in Chronic Obstructive Pulmonary Disease

#	It is Strongly Recommended to …
1	Consider COPD pathophysiological aspects as well as patients' clinical status and disease severity/evolution when selecting an inhalation device
2	Take into account the specific characteristics of each inhalation device
3	Assess patients' ability to perform a correct inhalation maneuver and the specific requirements for each inhalation device
4	Evaluate patients' inspiratory flow rate or inspiratory capacity before selecting an inhalation device
5	Take into account patients' history of exacerbations or other events that may affect their ability to perform adequate inhalation
6	Regularly review patients' inhalation maneuver and check whether the inhalation device meets their needs
7	Use an active inhalation device, such as pMDI or SMI, in patients with reduced inspiratory capacity
8	Consider using a valved holding chamber with SMI or pMDI devices in fragile patients with inspiratory and/or coordination difficulties
9	Use inhalation devices that generate a low oropharyngeal and high lung deposition
10	Check patients' inhalation maneuver during every visit and, where necessary, resolve errors or even change the inhaler

Abbreviations: COPD, chronic obstructive pulmonary disease; pMDI, pressurized metered-dose inhaler; SMI, soft mist inhaler.

The delivery of drugs by inhalation is an integral component in the treatment of COPD. A growing number of inhalation devices, whose designs and characteristics vary, have been engineered in recent years to treat COPD and other respiratory diseases.[111] Therefore, selecting the most appropriate device that meets each individual patient's needs is vital in clinical practice. Several factors have been proposed that should be considered when choosing an inhalation device. These include the patient's lung function, device handling, inhalation technique, and preferences.[8] However, according to a published expert opinion, the two most important characteristics for an inhaler used by patients with COPD are that the device permits a high pulmonary deposition of the drug and allows its delivery at low inspiratory flows.[9]

With regards to lung deposition, the selected inhalation device should guarantee the maximum lung deposition and distribution of the drug in the context of a given patient. At this point, we would like to highlight that it is extremely relevant to consider that COPD presents specific pathophysiological features that (negatively) impact a patient's lung deposition, especially hyperinflation.[10–12,50,51] Moreover, COPD is considered a progressive disease that carries the risk of clinical exacerbation, suggesting that the impact on lung deposition might also change during the disease course. Similarly, a wealth of evidence indicates that patient-related factors, such as the inhalation technique and the presence of debilitating conditions, influence lung deposition.[112] Finally, lung distribution is also important because β2 and cholinergic receptors are present in both central and peripheral areas.[113,114] It is important to bear in mind that the receptors are present in different amounts in the central and peripheral areas, so ideally the active ingredients should also be delivered to the appropriate area in correspondence with the receptor concentrations.

Data from the SLR show that the lung deposition rate (of the emitted dose) of pMDIs is generally low, although it can be increased with the addition of a valved holding chamber or spacer or with the use of Modulite®.[49,54,56–59] Data for DPIs vary depending on the device, but lung deposition rates are quite low and negatively influenced by different factors.[69] Individual studies and comparisons with pMDIs and DPIs indicate that SMI generates higher lung deposition rates, irrespective of other factors, such as inspiratory flow or humidity.[27,38,48,49,74,82–86] We also found that AEV is high with pMDIs,[87] compared to SMI, the latter of which is distinctly slower and produces a longer-lasting aerosol cloud.[88–90] Further research is necessary to corroborate individual (and some comparative results) that suggest that SMI also generates a higher rate of fine particle fraction.[27,28,74,85,94] It is well established that the generation of particles with smaller diameters is essential for passing the mouth–throat region.[69] Finally, all inhalation devices can reach both central and peripheral airways.

Inspiratory flow rate analysis also generated interesting data. We have identified several factors that are associated with the inspiratory flow rate, of which physicians should be aware. Some of these factors relate to the patient and COPD, such as inspiratory capacity and hyperinflation.[6,10,13–17,43,45,97,98] However, other factors relate to the inhalation device's characteristics, including its intrinsic resistance.

Most DPIs require a high inspiratory flow to overcome the device's resistance and to achieve effective drug delivery. Therefore, the inspiratory airflow generated by the patient represents the only active force that can produce the disaggregation of the powdered drug for inhalation. This point is critical because many patients with COPD, especially those with severe COPD (but also many patients with less severe disease), might not achieve the required inspiratory flow. It has been described that up to 20% of patients with severe COPD are not able to generate the required inspiratory flows with some DPIs (126). Similarly, it is estimated that 30% of elderly patients with COPD and 40% of patients hospitalized for COPD exacerbations do not achieve required inspiratory flows with Turbuhaler®.[44,102] However, we also found the opposite situation, in which an excessive inspiratory flow rate that overcomes the resistance might lead to an increased oropharyngeal deposition.[6] Thus, DPIs might not be the best option when the required inspiratory rate cannot be assured.

Conversely, pMDIs and SMI require low inspiratory effort.[10,17,43,45,57,82,99–101] However, the pMDI's inhalation technique is quite complex, compared to the SMI inhalation maneuver, which is similar to physiological inhalation. Moreover, SMI generates a fine, slow-moving mist that might reduce oropharyngeal deposition, when compared with pMDIs.[82] This finding has implications for clinical practice. For example, patients with difficulties between breathing and actuation of the device may be unable to effectively use a pMDI. In these cases, SMI or DPIs might be more appropriate.

We would also like to note some limitations of the SLR, the first of which is the great heterogeneity regarding the studies' designs, populations, and outcomes. This could have limited comparability across inhalation devices. Furthermore, the quality of many of the studies was low or moderate. As previously mentioned, some studies were published more than 20 years ago. Consequently, it was quite difficult to draw robust conclusions. The recommendations were also not formally evaluated using a Delphi process. However, we agree that the recommendations reflect general but objective facts.

Conclusions

The choice of inhalation devices for COPD patients depends on a combination of factors, but lung deposition and inspiratory flow rate are key aspects of this selection process. When selecting an inhalation device, all health

professionals who are involved in the care of patients with COPD must consider the basis of lung deposition and inspiratory flow rate, among other aspects. The clinician can then select the most adequate inhalation device, depending on the patient, their COPD, and the inhalation device's characteristics, which will ultimately achieve the maximum lung deposition and distribution.

Abbreviations

COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; GOLD, Global Initiative for Chronic Obstructive Lung Disease; L/min, liter per minute; MMAD, mass median aerodynamic diameter; m/s, meter per second; OCEBM, Oxford Centre for Evidence-Based Medicine; pMDI, pressurized metered-dose inhaler; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; SLR, systematic literature review; SMI, soft mist inhaler; µm, micrometer; USA, United States of America.

Data Sharing Statement

The tables and datasets analysed during the current systematic review are available from the corresponding author on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest.

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