FIDEPOC: Consensus on Inspiratory Flow and Lung Deposition as Key Decision Factors in COPD Inhaled Therapy

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Purpose: The pharmacological treatment of chronic obstructive pulmonary disease (COPD) is largely based on inhaled bronchodilators. Inspiratory flow and lung deposition are key parameters to be considered in inhaled therapy; however, the relationship between these two parameters, the patient specificities, and the suitability of the inhaler type for COPD management has not been fully addressed. The present study follows a Delphi Panel methodology to find expert consensus on the role of inspiratory flow and lung deposition as key decision factors in COPD inhaled therapy.

Methods: A two-round Delphi Panel, consisting of 38 statements (items) and completed by 57 Spanish pulmonologists, was carried out to measure the experts’ consensus degree with each item.

Results: A high degree of consensus was reached on most of the items consulted, among these inspiratory flow or inspiratory capacity should be periodically considered when choosing an inhalation device and to ensure the suitability of the inhaler used; the outflow velocity and particle size of the different devices should be considered to ensure adequate lung deposition; an active device (pressurized metered-dose inhalers (pMDI) or soft mist inhalers (SMI)) should be used in patients with low inspiratory flow to achieve adequate lung deposition; and, the use of dry powder inhalers (DPI) should be re-evaluated in patients with severe obstruction and severe exacerbations.

Conclusion: This study shows the relevance of inspiratory flow and the degree of particle deposition in the lung in the choice of an inhalation device for COPD management, as well as the convenience of an SMI type device in cases of low inspiratory flow. Moreover, it highlights the scarcity of information on the specific features of inhalation devices in COPD guidelines.

Keywords: dry powder inhalers, pressurized metered-dose inhalers, soft mist inhaler, inhaled therapy device, exacerbations

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive, life-threatening lung disease that predisposes to exacerbations and other serious diseases1 More than 3 million people die each year from COPD worldwide, accounting for 6% of all deaths globally.2 In recent years, the prevalence of COPD has enlarged dramatically, with an increase of 44.2% between 1990 and 20153- In fact, COPD was the third leading cause of death worldwide in 2019.4 Long-acting bronchodilators are a key component of COPD pharmacological management, either in monotherapy or in combination depending on the patient’s risk level.5 Therefore, the selection of an inhalation device is a crucial step in the therapeutic management of COPD, as it influences drug efficacy and patient adherence to treatment, and consequently long-term outcomes.6 There are different types of inhalation devices, the most frequently used being: pressurized metered-dose inhalers (pMDI), dry powder inhalers (DPI) and soft mist inhalers (SMI).7-11 Two key characteristics of...
an inhaler device are: a high lung deposition, defined as the average probability of an inhaled particle being deposited in the lung, and the correct delivery of the drug despite the presence of a low inspiratory flow. A low inspiratory flow is associated with the presence of pulmonary hyperinflation, which is defined by an increase in functional residual capacity and is the main mechanism explaining dyspnea in COPD patients. Furthermore, COPD exacerbations are associated with a decrease in peak inspiratory flow, that can influence inspiratory flow rate. In fact, COPD exacerbations are also associated with a decrease in peak inspiratory flow. Given the relevance of the inspiratory flow and lung deposition in the therapeutic management of COPD, and the scarcity of information on the relation between these two parameters and the features of each inhaler type on Spanish and international COPD guidelines, it is key to develop a consensus document to help clinicians in the choice of the appropriate type of device.

The present study, named FIDEPOC for its acronym in Spanish, follows a Delphi Panel methodology to find consensus on the role of inspiratory flow and lung deposition as key decision factors in COPD inhaled therapy. The Delphi method consists of a structured process to reach consensus on issues of interest among a group of experts when there is a lack of robust evidence on the topic. This study analyses through the opinion of a Spanish COPD expert pulmonologists panel, the factors that affect inspiratory flow and lung deposition in COPD patients and the features of different inhalation device types (pMDI, DPI and SMI) in relation with these parameters. The FIDEPOC study is the first expert consensus study published to date focusing on inspiratory flow and lung deposition as key decision factors in COPD inhaled therapy.

Materials and Methods

The Delphi Panel

The Delphi Panel employed in this study is characterized by three aspects: anonymity of the answers given by the participants throughout the process, to avoid influences of opinion within the expert group; allowing panel participants to change their opinion from one round of questionnaires or surveys to another (iteration); and controlled feedback, implying that the panelists receive the results of the previous rounds.

According to the selection criteria, the 57 participating experts that constituted the Delphi panel were Spanish practicing pulmonologists with more than 10 years of experience in the management of COPD, 53% of them with a specialized practice on COPD. The experts were contacted by email and were selected based on their experience and with a representation from all over the country (the hospitals are detailed in the acknowledgments). Of the 65 pulmonologists contacted, 8 declined to participate. The 57 experts completed the second round of the survey.

Study Questionnaire and Objectives

Based on the evidence generated in the recent systematic literature review (SLR) on inspiratory flow and lung deposition in COPD patients using different inhaler devices, a questionnaire with a total of 38 items was designed by a panel of 8 COPD experts overseen by a coordinating committee of 2 pulmonologists, and provided to the participating panelists whom, in turn, indicated their degree of agreement or disagreement on the items of the questionnaire in a first consultation round according to a Likert scale (1, fully disagree; 2) partially disagree; 3) doubtful; 4) partially agree; 5, fully agree). Subsequently, a controlled evaluation of the questionnaire results was carried out, the experts’ responses were then analyzed quantitatively and qualitatively, and a second consultation round was performed. In this second round, only the items for which there was weak consensus or disagreement in the first round were subjected to a second consultation. The statements that did not reach this predefined level of agreement were reassessed by the scientific committee, to discern if the lack of consensus was due to the ambiguity of the statement itself, in which case it was reformulated, or due to the asseveration being controversial in the field, in which case the statement remained unchanged in the second.

Delphi Round

The questionnaire was parameterized in a proprietary web tool (Ampersand Consulting) built in PHP (personal home page) and MySQL (My Structured Query Language) database. This Access database allowed results collection and data
export to Microsoft Excel. To avoid the possibility of abstention, the design of the web platform made it mandatory for the experts to indicate a degree of agreement with the items.

The questionnaire was divided into 4 categories according to the study objectives: category 1 - to identify the patient factors, related to inspiratory flow and lung deposition, to be considered in inhaled therapy; category 2 – to identify the characteristics of the devices to be taken into account, related to inspiratory flow and lung deposition in inhaled therapy; category 3 – to establish the relationship between the characteristics of the different types of inhalation devices; and category 4 – to recommend action guidelines in clinical practice for the selection of inhalation devices.

Data Analysis
For data analysis and generation of results, the Likert scale values obtained during the consultation rounds were transformed into 3 categories of agreement (in disagreement -scores 1–2; indifferent - score 3 or in agreement - score 4–5).\(^{18}\) To measure the experts’ degree of agreement, the number of panelists who agreed, were indifferent, or disagreed with each item was transformed into agreement percentages. Consensus for each statement was defined as an agreement percentage of at least 70% of respondents, and consensus was not reached if the sum of responses for negative consensus or positive consensus was <70%.\(^{19}\) Subsequently, the degree of consensus for each item was defined as follows:
- Unanimity, 100% of the expert panelists agree on the same item; -Strong consensus, 80% or more of the experts agree on the same item; -Weak consensus, at least 70% of the experts on the panel agree on the same item without reaching unanimity or strong consensus; -Discrepancy, when 70% agreement among the panelists is not reached.

Results
The 57 participating pulmonologists completed the two rounds of the Delphi panel from December 2020 to March 2021, indicating their degree of agreement with the items proposed, and none of them abstained. The consensus degree reached by the panel in the first and second rounds in relation to the items consulted is shown in Figures 1–5, respectively. The results are shown by questionnaire categories according to the 4 objectives of the study.

The panel reached strong consensus (>80%) in all the items regarding the identification of patient factors, related to inspiratory flow and lung deposition, to be considered in inhaled therapy, except for item 4 (Figure 1). However, despite rephasing item 4 into items 4a and 4b, no consensus was reached on this topic during the second round (Figure 5). Of note, the strong consensus reached for items 5 and 11 indicates disagreement with these statements.

The consensus degree attained by the experts with respect to the identification of characteristics of the different inhalation devices (DPI, pMDI and SMI) related to inspiratory flow and lung deposition is shown in Figure 2. Strong first-round consensus was reached for all items in this category of the questionnaire.

The relationship between the characteristics of the different types of inhalation devices was analyzed in a category of items that deepened in the specific features of DPI, pMDI and SMI device types, that are relevant for their use in the clinical practice, comparing some of them. A strong consensus was reached in the first round for 7 out of 12 statements in this category of the questionnaire (Figure 3). Among these, experts unanimously agreed on item 22. For the remaining 6 items different outcomes were obtained after the second round of consultation (Figure 5). For items 21 and 29 specifically, consensus was attained (strong and weak consensus respectively), after the experts were confronted with these items maintaining the same wording. However, the discrepancies observed in the first round for items 24 and 27 were not solved, despite rephrasing item 24- in 24a and 24b, and presenting item 27 to the panelists during the second round. Finally, item 30- was split in: 30a and 30b, leading to a weak consensus for item 30a and to discrepancy for item 30b.

The degree of consensus on the recommendations for the choice and use of inhaler devices in clinical practice with respect to inspiratory flow and lung deposition in inhaled therapy is shown in Figure 4. The panelists unanimously agreed that it is essential to ensure correct knowledge of the device and the inhalation manoeuvre by the patient before using the device (item 31). The rest of the items in this category obtained a strong consensus, highlighting the need to consider the inspiratory flow or inspiratory capacity, both when the inhalation device is selected and periodically, to ensure its suitability for the patient. Additionally, since item 35 – (DPIs should not be used in patients with low inspiratory flows [<30 L/m]), attained weak consensus in the first round of consultation, it was included in the second one (Figure 5).
Finally, the second round of the Delphi panel led to consensus in 4 items where an agreement below 70% was obtained during the first round (Figure 5). These included items: 21, strong consensus; 29 and 30a, weak consensus; and item 35, strong consensus.

**Discussion**

Current Spanish and international guidelines on COPD (GesEPOC and GOLD; Global Initiative for COPD), devote little attention to the features of inhalation device types in relation with inspiratory flow and lung deposition. Given the absence of previous recommendations and the scarce scientific evidence available on the topic, FIDEPOC, the first study to follow a Delphi methodology with the participation of a broad panel of COPD expert pulmonologists to address this issue was carried out. The FIDEPOC study has identified eight consensus recommendations (items 31–38) for the selection and use of devices for inhalation therapy in COPD patients, considering inspiratory flow and lung deposition.
The experts unanimously recommended the need to ensure correct knowledge of the device and the inhalation manoeuvre by the patient before use (item 31). In this regard and in relation to the presence of comorbidities in COPD patients, specifically the presence of cognitive impairment, the panelists agreed that this difficulty is one of the main limitations of the use of pMDIs devices (item 20), and that the use of inhalation chambers is important to improve lung deposition in patients with coordination difficulties (item 18). Therefore, pMDIs should be used together with a chamber in patients with coordination problems (item 22). In line with the consensus, conventional pMDIs achieve a highly variable pulmonary deposition range from 8% to 53%,\textsuperscript{20–24} that can increase to 11–68% with the use of an inhalation chamber or a spacer.\textsuperscript{22,25–30}

Regarding the identification of characteristics of the different inhalation device types related to inspiratory flow and lung deposition, the panelists agreed that the inhalation devices need an adequate inspiratory flow (specific for each device) to reach maximum lung deposition (item 12), and that the internal resistance of the different devices determines the need for a higher or lower inspiratory flow (item 13). In line with these consensus, inspiratory flow has been related to effective drug deposition in inhaled therapy in the management of other respiratory pathologies such as asthma.\textsuperscript{31} It was thus agreed to recommend that inspiratory flow or inspiratory capacity should be considered in the choice of a particular inhaler device (item 32), and that the inspiratory flow or inspiratory capacity should be assessed periodically to ensure the suitability of the inhaler device used (item 33). In fact, the periodical assessment of these two functional parameters is further supported by the variable progression associated with COPD patients, as some patients follow a relatively stable course, while others experience severe disease progression.\textsuperscript{32}

The experts also agreed to recommend that, in the absence of inspiratory flow or inspiratory capacity measurement, the internal resistance of the devices should be assessed to ensure that it matches the required inspiratory flow needs.
Two factors that would determine the inspiratory flow needed in each inhaler are the internal resistance, which is specific to each device and will generate a specific turbulence, and the unbundling of the drug, in the case of DPIs. Therefore, the patient must generate a certain inspiratory flow to overcome this resistance and achieve adequate inhalation.

According to the expert’s consensus, not all COPD patients are able to generate the minimum inspiratory flow needed (item 28). Therefore, as a guideline for action on the use of DPIs, the expert panelists agreed to recommend the use of active devices (pMDI or SMI) in patients with low inspiratory flow (item 36) and not to use DPI-type devices in these same patients (item 35). Likewise, there was strong consensus with the recommendation, the use of DPIs should be re-evaluated in patients with severe obstruction and severe exacerbations (item 34). In this respect, the panelists also agreed that the need to generate a high inspiratory flow for the activation of certain devices favours the impact of drug particles in the upper airways to the detriment of sedimentation in the peripheral airway (item 14).

Figure 3: Expert consensus on the relationship between the characteristics of the different inhalation devices (DPI, pMDI and SMI). The percentage of agreement among the experts is indicated. Aspects related to the characteristics of the devices produced the greatest disagreement. The concepts of intrinsic resistance and inspiratory flow are likely to lead to some confusion even among expert pulmonologists. Consensus degree is shown as: +++(unanimity, 100% of the experts agreed); ++(strong consensus, >80% of the panelists agreed); +(weak consensus, <80% and >70% agreed); and - (discrepancy, <70% agreed).
The last recommended guideline agreed-upon by the panelists regarding the characteristics of the devices is that the exit velocity and particle size of the different devices should be considered to ensure adequate lung deposition (item 38). As a matter of fact, there is evidence linking airway deposition of inhaled drugs to the patient’s inspiratory flow, aerosol velocity and the particle size of the inhaled drug. On one hand, experts agreed that the higher the emission velocity generated by the devices, the higher the probability of upper airway impact (item 17). In line with this assertion, compared to pMDIs and DPIs, the SMI device generates a fine, slow-moving mist that could reduce oropharyngeal deposition. Indeed, scintigraphic analyses with the SMI device indicated that, compared to a pMDI with a hydrofluoroalkane propellant, lung deposition is higher (up to 50%) and oropharyngeal deposition lower. Furthermore, this slower release rate of around 1.2 seconds in SMI compared to 0.1 seconds in traditional pMDIs could largely reduce the effect of poor coordination between device activation and inhalation. Moreover, the greater stability of cloud emission in SMIs is likely to contribute to easier and more comfortable use for patients. Accordingly, the panelists agreed that an SMI is preferable to a pMDI because of the aerosol exit velocity (slower) and particle size (higher proportion of fine particles) that favour greater lung deposition (item 25). On the other hand, the experts panel agreed that particle size, or MMAD (mass median aerodynamic diameter), is a determining factor in achieving proper lung deposition (item 15), and that particle size greater than 5 µm limits particle deposition to the small airways and alveoli (item 16). In line with the expert consensus, it has been observed that the

Figure 4 Expert consensus on recommended guidelines for the choice and use of inhaler devices in clinical practice with respect to inspiratory flow and lung deposition in inhaled therapy. The percentage of agreement among the experts is indicated. The most clinical-related issues reached strong agreement. Consensus degree is shown as: ++ (unanimity, 100% of the experts agreed); +++ (strong consensus, >80% agreed); and + (weak consensus, <80% and >70% agreed).
distribution of deposition sites of inhaled particles is highly dependent on their aerodynamic diameters.\(^{40}\) According to a recent SLR, MMAD for conventional pMDIs range from 1.22 to 8 μm and from 1.19 to 3.57 μm when using a valved holding chamber or spacer, and from 0.72 to 2.0 μm with Modulite\(^{2}\). The DPIs produce medium particle sizes (1.8–4.8 μm), while with the SMI type 60% of the particles reach an MMAD <5 μm.\(^{2}\)

Finally, although the FIDEPOC study has allowed the definition of eight consensus recommendations for the choice and use of inhaler devices in the management of COPD, it has limitations. First, the wording of some of the items proposed to the experts may have influenced the degree of discrepancy among them due to categorical statements or lack of specificity. Additionally, there are specific concepts related to the pathophysiology of COPD and its influence on inspiratory flow and lung deposition, and the physical characteristics of inhaler devices, that are complex and for which more medical literature and evidence dissemination are needed in national and international COPD management guidelines.

**Conclusion**

First, the high degree of consensus on most of the items included in the FIDEPOC study demonstrates the importance given by COPD pulmonologists to the inspiratory flow and lung deposition in inhaled therapy, and their relevance in the

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**Figure 5** Expert consensus in the second round of the Delphi panel. In the second round, the issues related to the devices continued to maintain some discrepancies. Consensus degree is shown as: ++ (strong consensus, >80% of the experts agreed); +(weak consensus, <80% and >70% agreed); and - (discrepancy, <70% agreed).
choice of inhalation device. Several factors influence inspiratory flow and lung deposition. Among them, the experts highlight COPD pathophysiology, disease course and inhaler device characteristics.

Second, SMI devices would be of choice in patients with lower inspiratory flow due to the combination of a low emission velocity and an adequate particle size which, in turn, would increase lung deposition. In this regard, it is recommended to re-evaluate the use of DPIs, as experts agreed that not all COPD patients are able to generate the minimum inspiratory flow required for the use of these devices. This is especially important in patients with severe exacerbations, as these may affect inspiratory flow and lung deposition.

Finally, the FIDEPOC study has highlighted the absence of recommendations on inhaler devices specificities in national or international COPD management guidelines. To endorse the choice of the best inhaler device in each clinical situation, it would be necessary to generate quality literature on the devices, given that there are notable differences between them which are relevant to COPD management. Therefore, it is highly pertinent to include in COPD guidelines, recommendations regarding: the pathophysiology of COPD and its influence on inspiratory flow and lung deposition, the physical characteristics of inhalation devices and action guidelines for the choice of device according to the severity and phenotype of the patient.

**Ethical Considerations**

Due to the nature of the study that does not include research with people or animals it was not necessary to review by an ethics committee.

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