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Inhaler Adherence in COPD: A Crucial Step Towards the Correct Treatment

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Abstract: COPD is a typical example of chronic disease. As such, treatment adherence tends to be as low as between 30% and 50%, with specific issues in COPD due to the use of inhaled therapies. Decreased adherence in COPD is associated with worse outcomes, with increased risk for exacerbations and long-term mortality. Factors that impact adherence are multiple, some related to patient, some related to clinicians and finally some related to healthcare system. Among clinician factors, prescription of simplified treatment regimens delivered by an inhaler adapted to the patient's characteristics is crucial. Although it has been observed a huge improvement in the design and usability of inhaler devices for COPD in the last two centuries, there is still a clear gap in this field. Smart inhalers as well as simplified treatment regimens could improve adherence and therefore improve long-term outcomes in COPD.

Plain Language Summary: Treatment adherence in COPD is crucial as in many other chronic diseases, with specific issues due to inhaled route, and many factors involved. Low adherence in COPD has been linked to an increased risk of exacerbations and future mortality. Many interventions have been developed to improve treatment adherence in COPD. This review summarizes the current knowledge and future prospects for this important aspect of COPD treatment.

Keywords: COPD, inhaled therapies, adherence, persistence, posology

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic disease model of our time. It is a frequent disease, with a high prevalence among the adult population close to 10%,[1] which increases with age and is associated with high morbidity and mortality. COPD is the third leading cause of death worldwide, causing more than 3 million deaths in 2019.[2] In addition to the burden that COPD implicates in terms of morbidity and mortality, it is a disease that is frequently underdiagnosed and associated with other comorbidities that make management difficult and usually worsen the prognosis.

Among chronic adult diseases (for example, hypertension or type 2 diabetes mellitus), adherence to treatment is a common clinical problem, since between 30% and 50% of prescribed medications are not taken correctly by patients.[3] Adherence to medication is defined as the process by which patients take their medications as prescribed.[4] Adherence has three components: initiation (when the patient takes the first dose of a prescribed medication), implementation (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen), and discontinuation (when the next dose to be taken is omitted and no more doses are taken thereafter).[5]

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Lack of adherence to treatment is responsible for a high number of hospital admissions and avoidable deaths in patients with chronic diseases, in addition to posing a direct cost to health systems due to the increase in the costs of a given disease and worse clinical outcomes with respect to adherent patients.[6]

Adherence to a prescribed recommendation is a complex problem that involves human behavior and is mediated, among others, by factors of the patient, the clinician and the health system that attends him.[7] Among the patient-dependent factors are the lack of incorporation in decision-making, poor health literacy, personal and societal beliefs about the effectiveness of medication and previous adverse effects with pharmacological treatments. Among the clinician's factors, failure to recognize non-adherence, prescription of complex treatment regimens and compounds of different drugs, ineffective communication of benefits and inadequate communication between prescribers are probably the factors that most increase the risk of non-adherence among patients. Finally, factors related to health systems such as lack of coordination in the transition between hospital and primary care after a hospital admission or the presence of co-payments for certain medications may be responsible for non-adherence. Obviously, in most cases, the lack of adherence to treatment will be a consequence of the sum of several of these factors, which will make the way to approach it more complex.

Treatment adherence in COPD shares many of the abovementioned problems of other chronic diseases with some specific issues derived from the use of inhaled therapies, such as inhalation technique errors, the use of different inhalation devices (each one with different inhaler technique), and complex posologies. Therefore, it is not surprising that despite the advances that have been experienced in the field of pharmacological treatment of COPD in recent decades,[8,9] adherence to inhaled treatment in COPD remains a clinical challenge of the first magnitude. Therefore, this review tries to summarize the evidence regarding adherence to treatment in COPD, the consequences derived from its lack, how to evaluate it in the clinic and, finally, which strategies can help to improve it.

The Impact of Treatment Adherence in COPD Outcomes

The importance of treatment adherence and its association with patient health outcomes was highlighted in a post-hoc analysis of the TORCH study,[10] a 3-year randomized clinical trial with more than 6000 patients designed to assess the impact of different inhaled treatments on mortality. In this post-hoc analysis, 20.2% of patients were non-adherent (defined as those who took less than 80% of the study medication) and this group experienced an increased risk of exacerbation, hospital admission for severe exacerbation and finally an increased risk of death compared to the group of adherent patients (3-year mortality of 11.3% in the group of adherents versus 26.4% in the group of non-adherents) regardless of the treatment arm assigned during the study and after adjusting for confounders.

Low adherence to inhaled treatment is a common finding in different observational studies in COPD, which show that usually after the start of inhaled therapies, more than half of patients will leave such treatment, regardless of the way in which adherence to inhaled treatment is evaluated and with small variations depending on the health system studied.[11–13] In addition, adherence to inhaled therapy is usually associated, as in other chronic diseases, with better clinical outcomes that are of supreme importance in COPD, such as moderate and severe exacerbations.[14] In some cases, an association between improved adherence to inhaled treatment and a lower risk of death in patients with COPD has been demonstrated.[15]

In addition to the health effects of non-adherence to pharmacological treatment in COPD, there is also an increase in costs for health systems. In general, studies carried out from a socio-economic perspective have shown that, although adherent patients have a higher cost in the pharmacy, at a global level the costs derived from non-adherence to treatment are higher due to increased health spending as a result of hospital admissions or emergency care.[16]

Factors Associated with Decreased Adherence in COPD

Several studies have aimed to determine the association between different factors and treatment adherence in COPD patients, although the available evidence presents some limitations, such as the lack of a standardized definition of adherence, and the use of generic questionnaires (eg, Morisky-Green questionnaire) instead of inhaler-specific questionnaires like the Test of the Adherence to Inhalers (TAI).[17,18] Despite the mentioned limitations, the presence of comorbidities, particularly depression, smoking status, the dosing regimen, the complexity of the device, and patient's

self-awareness of the disease are the main factors that negatively impact in treatment adherence. Socioeconomic factors, such as the educational level and income status, have also demonstrated to negatively impact the adherence to inhaled therapy.[17] Other factors that may negatively affect patient's adherence are disease severity and patient's age, although the relation is not yet fully clear.[18,19] Finally, in some patients, adherence is not correct due to difficulties in the inhalation technique, which may be influenced by the presence of cognitive impairment or pulmonary hyperinflation as a marker of disease severity.[20] Aside from that, complex posology (ie: different inhalers in the same patient with overlapping regimens) could decrease the global adherence rates.

Patient education, involvement and self-awareness or perception of the disease are key factors that contribute to medication and adherence. A good understanding of the disease and the prescribed dosing regimen are needed to enhance the adherence to inhaled therapy in COPD. In this sense, patients with psychological comorbidities (eg, anxiety and depression) tend to underestimate treatment efficacy, and polymedicated patients usually do not consider the inhaled therapy as a treatment, negatively affecting the adherence and, consequently, the prognosis of the disease.[21] Thus, in polymedicated patients, the use of simple, comfortable and easy to comply posologies could be an option to increase adherence.

Evaluation of Adherence in COPD

There are different ways to assess adherence to inhaled treatment in COPD, with different properties and weaknesses[19] (Table 1). In general, studies have used general questionnaires, such as those of Morisky-Green or Batalla, which indirectly measure adherence to treatment, or direct measures of adherence to treatment, such as the use of electronic monitors,[20] withdrawals of pharmacy medication or as the percentage of doses taken of the total prescribed doses. Each of these ways of measuring adherence to inhaled treatment in COPD has its advantages and disadvantages, which must be known to be used correctly in research studies. Recently, the TAI questionnaire (*Test de Adherencia a los inhaladores*, Inhaler Adherence Test) has been developed as a questionnaire that allows capturing adherence to inhaled treatment in COPD as well as the causes of non-adherence to treatment.[22,23] This questionnaire consists of 12 questions (10 answered by the patient and 2 by the clinician) and has been validated to assess adherence to inhaled treatment in patients with COPD, with an AUC of 0.7 for the detection of non-adherence. TAI questionnaire identifies types of non-adherence: sporadic, deliberate (which ie could reflect lack of self- awareness of the disease) and unconscious non-compliance (which ie could be due to critical inhaler technique errors).

Interventions to Promote Adherence in COPD

To improve adherence to inhaled therapy and, ultimately, improve symptom control and disease prognosis, it is essential to focus on actionable factors that influence it. The recent update (2023) of GOLD guidelines emphasizes the importance

Table 1 Advantages and Disadvantages of Different Methods to Measure Adherence in COPD

	Advantages	Disadvantages
Direct measurements		
PDC Smart apps	• Easy to use, inexpensive • Provide accurate use and can detect inhaler errors	• Does not always reflect the correct inhalation • Expensive compared to other methods • Need of technology-engaged patients
Pharmacy records	• Provides evidence of drug refill patterns	• Does not always reflect that the patient took the correct dose
Indirect measurements		
Morisky-Green Batalla TAI	• Well validated in COPD • Validated in COPD • Validated in COPD • Specifically designed for inhaled therapies. • Provides information on causes of lack of adherence	• Not specific for inhaled therapies • Reflects patient's understanding of disease • Low AUC for detection of non-adherent patterns

Abbreviations: PDC, proportion of days covered (percentage of taken doses/ doses prescribed); TAI, inhaler adherence test.

of patient's understanding and perception of the disease.[24] Thus, a clear and simple explanation of the disease and the treatment objective and regimen, together with patient involvement in the therapeutic strategy (eg, treatment plan and selection of the inhaler device) would help to improve adherence and to gain trust in physicians. Patient follow-up is another factor that would presumably affect in adherence to inhaled therapy. In this regard, having behavioral interviews and reviewing and training the inhaler technique by nurses or physicians may improve the adherence. However, to timely detect non-adherent patients and to offer a healthcare continuity in COPD, collaboration between different healthcare professionals is a *sine qua non* condition. To this end, and due to the limited time in primary care and pulmonology visits to carry out strict and continuous follow-ups addressing inhaler technique, patient behavior, and adherence, it is essential to involve nursing in the active management of COPD patients. Moreover, the interventions for improving adherence should be multicomponent involving education, motivational or behavioral components delivered by health professionals.[25] However, differences in healthcare system (ie: low- vs high-income countries, overall structure of healthcare system and access to primary care) could limit these interventions and impact the adherence in COPD.

In recent years, smart inhaler apps have been developed that are able to evaluate and increase adherence to inhaled treatment when connected to different inhalation devices.[26,27] These systems usually consist of a sensor that attaches to the inhalation device and detects when the inhalation system is charged or activated.[28] The sensor is usually connected via a bluetooth device to an app that gives information to the user about when the medication should be taken and therefore could help increasing the adherence. Previous studies have shown that this type of device can help increase adherence to treatment in a simple way.[29]

The Effect of the Dosing and Frequency of Administration in Effectiveness and Adherence to Treatment

Inhaled therapy is central to the treatment of COPD patients. However, despite its evolution and the availability of many inhaled devices (ie in Spain, up to May 2023, there are 101 inhaled treatments and 20 devices for COPD) physicians still demand inhaled therapies that provide disease control through better adherence to treatment. On this matter, the dosing regimen is another factor that can affect adherence to inhaled therapy.

Nowadays efficacy treatments with different molecules and dosing regimens are available for the management of COPD patients. Inhaled treatments with the simplest available dosage regimen, once- daily, have demonstrated a long-sustained bronchodilator effect leading an airflow improvement over 24 hours and, therefore, a potential improvement of COPD symptoms during 24 hours after the last inhalation, reducing the potential window of non-protective effect.[30] Regarding the association between the dosing regimen and adherence to treatment, once-daily inhaled therapy has been shown to improve treatment adherence in COPD patients compared to multiple-daily doses requiring 2 or more inhalations per day.[11,31–35] However, this could not be applied to all the long-acting bronchodilators or all the healthcare systems, because some studies suggest that adherence does not change for once-daily LAMA vs twice-daily LAMA.[36] Moreover, although further specific studies would be necessary, available results suggest that COPD patients prefer once-daily dosing regimens due to its simplicity compared to twice-daily regimens.[33] Indeed, there is evidence from randomized-controlled trials that simple, once-daily regimens in triple therapy are more effective controlling symptoms in COPD that open triple therapies.[37] The recent update (2023) of GOLD recommendation note that single inhaler therapy may be more convenient and effective than multiple inhalers.[24] Thus, an inhaled therapy with a demonstrated efficacy profile and simplified dosing regimen (eg, once-daily vs twice-daily, fixed-dose single inhaler vs multiple inhalers) should presumably provide a better control of the disease through enhanced adherence to treatment, which could be especially relevant for those patients at the highest risk of poor outcomes. Moreover, as previously stated, innovation and research has been critical for developing molecules and devices which allows once daily regimens due to a longer effect consequence of a high affinity of the molecules to their receptor and will be needed to improve the pharmacology of inhaled drugs to speciate space time between doses.

The Selection of the Inhaler Device

As it has been previously stated, in chronic diseases, such as COPD, involving the patient in the treatment selection process is crucial since shared decision-making improves outcomes for patients.[3] However, proper use of inhalers has not

improved over the last decades and many healthcare professionals lack education in this field, which translates into barriers for explaining the inhaled therapy for COPD patients.[38] The selection of the dosing regimen and the inhaler device should aim to identify the optimal therapeutic strategy for each individual patient, based on treatment objective, device characteristics (eg, airflow resistance, posology, complexity) and patient's preferences and profile (eg, inspiratory flow, cognitive ability and coordination skills, comorbidities, and treatment complexity).[39–43]

Fortunately, there are many different inhalers available in the market for COPD patients, allowing the clinician to tailor the inhaler for a given patient. This makes it necessary for the physician caring for COPD patients to know the characteristics of the different inhalation devices (DPI- dry powder inhaler; MDI- metered dose inhaler; SMI – soft mist inhaler), their indications and most frequent critical errors. In addition, for each type of inhalation device there are specific medication priming and steps that must also be known. One important factor to consider when prescribing an inhaled therapy for COPD is the peak inspiratory flow, which must be assessed before prescribing a DPI. In this sense, it could be expected that the choice of therapeutic regimens that are simple to comply with in easy-to-use inhaler devices (eg, once-daily fixed-dose in a single device) would improve adherence.[14,15,32,44] Likewise, the transition from one treatment to another pharmacological class could be easier if the inhaler device remains the same, facilitating the comfort and confidence to both healthcare provider and patient.

Final Conclusions

The need to improve adherence to inhaled therapy is an unresolved challenge in COPD which directly affects to the control of symptoms, QoL, use of resources and mortality. The patient profile (eg, presence of comorbidities, smoking status, socioeconomic factors), the dosing regimen, the complexity of the device and patient's perception of the disease are the main factors that influence the adherence to treatment. On this matter, it is important to explain the treatment objective and the expected benefit in a clear and simple way, involving the patient in the therapeutic strategy. Improving adherence in this chronic condition should be based on multicomponent approaches involving different healthcare actors, targeting patient education, behavior, medication management, and pharmacist consultation. Simplifying the dosing regimen using once-daily treatments is another actionable factor that could improve adherence and collaboration between healthcare professionals to continuously address the inhaler technique and patient behavior is also needed to improve adherence and, consequently, the outcomes of COPD patients. More clinical practice-based research on adherence is needed to better understand how the above-mentioned factors impact on adherence to inhaled therapy in COPD and which healthcare strategies would improve it.

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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