Economic Impact of Low Adherence to COPD Management Guidelines in Spain

Marc Miravitlles 1
Alexandra Solé 2
Helena Aguilar 3
Ana Ampudia 2
Jaume Costa-Samarra 4
Maria Mallén-Alberdi 4
Diana Nieves 4
1 Pneumology Department, Vall d’Hebron University Hospital, Vall d’Hebron Research Institute (VHIR), Vall d’Hebron Barcelona Hospital Campus, CIBER for Respiratory Diseases (CIBERES), Barcelona, Spain; 2 Market Access Department of Boehringer Ingelheim SA, Barcelona, Spain; 3 Medical Department of Boehringer Ingelheim SA, Barcelona, Spain; 4 Oblikue Consulting SL, Barcelona, Spain

Objective: The objective of this study was to assess the non-adherence level of Spanish clinical practice to guideline recommendations for the treatment of chronic obstructive pulmonary disease (COPD) and to estimate the potential impact on pharmaceutical expenditure resulting from transitioning current treatment patterns according to guidelines.

Methods: A model was developed to compare current prescribing patterns with two alternative scenarios: the first aligned with the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2020) recommendations, and the second with the Spanish Guidelines for COPD (GesEPOC 2017). Current treatment practice was obtained from publications that describe treatment patterns by pulmonary departments in Spain. The economic impact between patterns was calculated from the perspective of the Spanish National Health System (NHS), considering the annual pharmacological costs of COPD inhaled maintenance therapy. Two additional analyses were performed: one that included current prescribing patterns of patients managed by pulmonology and primary care centers in Spain (published aggregated data); and another that only considered the appropriate use of inhaled corticosteroids (ICS) treatment according to guidelines.

Results: It was estimated that 54% and 38% of patients were not treated in line with GOLD and GesEPOC recommendations, respectively, mainly due to a broader use of ICS-based therapies. Adapting treatment to recommendations could provide a potential annual cost-saving of €17,792,022 (according to GOLD) and €5,881,785 (according to GesEPOC). In scenario analysis 1, a 26% of non-adherence to GesEPOC guideline was observed with a potential annual pharmacological cost-saving of €2,707,554. In scenario analysis 2, considering only inappropriate use of ICS treatment, an annual cost-saving of €17,863,750 (according to GOLD) and €9,904,409 (according to GesEPOC) was calculated.

Conclusion: More than a third of treatments for COPD patients in Spain are not prescribed in accordance with guideline recommendations. The adaptation of clinical practice to guideline recommendations could provide important cost-savings for the Spanish NHS.

Keywords: cost, chronic obstructive pulmonary disease, Spanish, treatment, recommendations

Introduction

Chronic obstructive pulmonary disease (COPD) affects 11.8% of the Spanish population aged 40 years or older. 1 Although it has an irreversible component, an early diagnosis and appropriate guideline based treatment can modify the prognosis of its clinical evolution. 2,3 However, it is an under-diagnosed disease with high morbidity and mortality and it constitutes a major public health problem. 4

Recommendations for the management of patients with COPD suggest an individualized approach to treatment according to patient characteristics, based primarily on symptom burden and risk of exacerbations. 5–7
pharmacological therapy for the management of COPD is to reduce the symptoms, frequency and severity of exacerbations, as well as to improve the prognosis of the disease.5,8

Similar to the ABCD groups of the classification according to the GOLD strategy,5 four phenotypes are defined in the GesEPOC 2017 guidelines: patients with ≤1 exacerbation/year without hospitalization belong to the non-exacerbator phenotype, in patients with ≥2 exacerbations/year or ≥1 hospitalizations a distinction is made between exacerbator with emphysema phenotype and exacerbator with chronic bronchitis phenotype and, finally, a fourth phenotype is defined, the asthma and COPD overlapping (ACO) phenotype.5

Bronchodilator therapy is the main initial and maintenance treatment for stable COPD in patients not at increased risk of exacerbations.5–7 According to several observational studies conducted in Spain, these patients represent around 60% of all COPD patients.9–11 Bronchodilator therapy may consist of a long-acting muscarinic antagonist bronchodilator (LAMA) or a long-acting β2 adrenergic agonist (LABA), in monotherapy or in combination. These therapies combined with inhaled corticosteroid (ICS) are recommended in patients with a history of previous exacerbations (2 or more moderate or 1 or more leading to hospitalization), especially if blood eosinophils are elevated – according to Global Initiative for Chronic Obstructive Lung Disease (GOLD)5,12 –, or triple therapy (LAMA/LABA/ICS) in uncontrolled high risk patients with exacerbations treated with LAMA/LABA – according to Spanish Guidelines for the diagnosis and treatment of COPD patients (GesEPOC)5, as well as in patients with overlapping asthma and COPD (asthma-COPD overlap).6,13,14

Several studies carried out in Spain have reported a lack of adherence of clinical practice to guideline recommendations, both in the primary care setting9,10,15,16 and in specialized care.9,10,17,18 The lack of adherence is mainly due to inadequate evaluation and segmentation of COPD patients, a low use of spirometry and a high use of ICS in patients with mild-moderate COPD and without exacerbations.16,18,19 Different studies have found that more than 60% of patients with mild COPD receive ICS therapy, often at high doses.18,20

The correct evaluation of COPD patients and the optimization of pharmacological treatment in accordance with guideline recommendations could result in a clinical benefit for patients21–24 plus cost-savings for the Spanish National Health Service (NHS).25–28

This study aims to assess the degree of adherence of clinical practice to guideline recommendations for COPD in Spain, and estimate the potentials savings derived from the optimization of drug treatment to guideline recommendations.

Methods

Model

A model was developed to compare current prescribing patterns with two alternative patterns in line with the recommendations of: (1) international GOLD 2020 document5 and (2) Spanish-level reference guide GesEPOC 2017.6

In the model, the natural history of COPD was not simulated, only the COPD population and associated pharmacological treatments. Costs have been estimated considering a time horizon of a year, 100% adherence to medications and no change in treatment over that period.

Two COPD studies conducted in Spain with a detailed description of COPD population and pharmacological treatment were identified during the literature review. These studies provide detailed information regarding the distribution of the COPD population according to the GOLD and/or GesEPOC classification criteria (ABCD GOLD groups and GesEPOC phenotypes), and the pharmacological treatment used in each group of patients:

1. Multicenter observational study conducted in pulmonology departments with classification of patients according to GOLD groups and according to GesEPOC phenotypes,17 used in the base case analysis of this study.
2. Multicenter observational epidemiological study (FENEPOC study) conducted in primary care and pulmonology services (aggregated data), with classification of patients according to GesEPOC phenotypes.9 This study was used in scenario analysis 1, considering an alternative source of current treatment patterns in Spain.

Base Case Analysis

Population and Classification

The model considered the Spanish population aged 40 years or older1 with diagnosed1 and treated COPD,30 with a total of 365,142 patients (Figure 1).

The classification of patients by group was based on the data from the study conducted in the field of pulmonology (Figure 2),17 with distribution based on: (1) GOLD...
Figure 1 Spanish population ≥ 40 years with diagnosed and treated COPD.
Notes: *National data, for the analysis by Autonomous Communities, the population in said region was considered.
Abbreviation: COPD, chronic obstructive pulmonary disease.

Figure 2 Distribution of patients considered in each GOLD group and GesEPOC phenotype in the base case analysis (A and B) and scenario analysis 1 (C), based on literature 17. (A) Distribution of patients according to the GOLD strategy used in the base case analysis.17 (B) Distribution of patients according to the GesEPOC guide used in the base case analysis.17 (C) Distribution of patients to each GesEPOC phenotype used in scenario analysis 1.9
Notes: *The current treatment prescription patterns only take into account patients treated with the main treatments (LAMA, LABA, LAMA/LABA, LABA/ICS and LAMA/LABA/ICS).
Abbreviations: ACO, asthma-COPD overlap; COPD, chronic obstructive pulmonary disease; GesEPOC, Spanish Guidelines for Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; ICS, inhaled corticosteroids; LABA, long-acting β2 adrenergic agonists; LAMA, long-acting muscarinic antagonists.
classification according to four groups (ABCD, according to symptoms and history of exacerbations) and (2) GesEPOC classification according to four phenotypes of high-risk patients (non-exacerbator phenotype, exacerbator with emphysema, exacerbator with chronic bronchitis and ACO [asthma-COPD overlap]; according to clinical profile).

Based on the GOLD 2020 strategy, peripheral eosinophilia is a determining clinical parameter for selecting ICS treatment. According to recently published data, in Spain 28.4% of the patients have blood eosinophilia levels $>$300 cell/µL. It was assumed this proportion of patients in GOLD groups C and D had high blood eosinophils.

**Drug Treatment Patterns**
The model used a treatment-mapping matrix to hypothetically redistribute patients with COPD undergoing long-acting inhaler therapy from their current treatment pathway (actual prescribing patterns) to one of two alternative treatment pathways, which represents treatment optimization with prescribing in accordance with GOLD strategy and GesEPOC guideline (Figure 3).

**Current Treatment**
The current drug treatment patterns used for each of the GOLD groups and GesEPOC phenotypes were obtained from the same observational study in pulmonology (Figure 3). The therapies considered were the inhaled therapies LAMA, LABA, LAMA/LABA, LABA/ICS and LAMA/LABA/ICS.

**Treatment Proposal According to Guideline Recommendations**
Two patterns were mapped for the analysis of adherence to guidelines: (1) the recommendations of the GOLD 2020 strategy and (2) the recommendations of the Spanish GesEPOC 2017 guidelines (Figure 3).

**Costs**
The impact on pharmaceutical expenditure as a result of changing the current treatments that did not follow guideline recommendations to the appropriate therapies according to guidelines was estimated. The impact was conducted from the perspective of the Spanish NHS in 2020.

The annual pharmacological costs by therapeutic group (LAMA, LABA, LAMA/LABA, LABA/ICS and LAMA/LABA/ICS) were considered based on the public price including (PPI) Value Added Tax (VAT) (PPI VAT), applying the deductions of Royal Decree Law (RDL) 8/2010, the recommended dosage of each drug according to the summary of product characteristics and weighting the cost of each pharmacological option according to its consumption in Spain (Table 1). All patients treated with dual or triple therapies were assumed to use fixed-dose combination inhalers. Likewise, when calculating the annual pharmacological cost of LAMA and LABA/LABA, specifically for tiotropium and tiotropium/olodaterol Respimat® reusable, due to the fact that the same inhaler can be used with up to 6 cartridges, a maximum use of refills was assumed (annual prescription of 2 packs of the reusable inhaler plus cartridge and 10 refill cartridges).

**Analysis in Autonomous Communities**
The distribution of the economic impact for the 17 individual budget holding Autonomous Communities of Spain was estimated, as they are individually responsible for providing healthcare services. To this end, the population $\geq$40 years of age with diagnosed COPD and treated was estimated in each autonomous community. The same classification of patients and distribution of treatments by group/phenotype were applied as in the total Spanish population, since no published data were identified at the Autonomous Community level.

The annual pharmacological costs per therapeutic group were weighted based on the pharmacological consumption of each region.

**Scenario Analyses**
Two scenario analyses were performed.

- **Scenario analysis 1**

This scenario included prescribing patterns of COPD patients who attended pulmonology and primary care centers in Spain (aggregated data).

For the calculation, the distribution of patients and the detail of current prescription patterns was considered according to the four phenotypes of the GesEPOC guidelines based on the FENEPOC study (Figure 2; Annex 1).

The treatment changes used in this analysis were those recommended by the GesEPOC 2017 guideline, shown in Annex 1.

- **Scenario analysis 2**

Here the focus was limited to the economic impact as a result of aligning ICS treatment with guideline recommendations. The population distribution and current COPD treatment used were those used in the base case analysis.
The estimated recommended treatment was based on the appropriate use of ICS treatment where its use is not recommended in certain populations according to GOLD 2020\(^5\) and GesEPOC 2017,\(^6\) without modifying the rest of the non-recommended therapeutic options that did not include ICS.

### Results

#### Base Case Analysis

**Analysis According to GOLD Recommendations**

It was observed that 54% of patients managed in pulmonology departments were not treated in line with GOLD recommendations for their GOLD category (Table 2).
Table 1 Annual Pharmacological Cost Considered by Each Therapeutic Group

| Therapeutic Group | Annual Drug Cost per Patient $^a,b$ |
|-------------------|-------------------------------------|
| LAMA              | €490.97                             |
| LABA              | €426.51                             |
| LAMA/LABA         | €770.49                             |
| LABA/ICS          | €327.91                             |
| LAMA/LABA/ICS     | €952.07                             |

Notes: $^a$Values in PPI + VAT, considering the deduction of RDL 8/2010. $^b$For the data on drugs with dual indication (COPD and asthma), it is assumed that 75% of the total sales of LAMA and 64% of the total sales of LABA (with or without ICS) correspond to COPD.15

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting β2 adrenergic agonists; LAMA, long-acting muscarinic antagonists; PPI + VAT, public price including VAT; RDL, royal decree law; VAT, value added tax.

The lack of adherence to guideline recommendations in current practice was mainly due to a broader use of ICS-based therapies. Ninety-nine percent (195,051 of the 196,164 patients who were not treated in accordance with recommendations) of patients were inappropriately treated with LABA/ICS or LAMA/LABA/ICS, and the remaining 1% of patients treated with LABA not in accordance with guidelines (Table 2).

In analyzing the results according to patient type, 46% and 65% of patients in population GOLD groups A and B (low risk of exacerbations), respectively, were not treated in line with the recommended pharmacological treatment. Additionally, groups C and D (high exacerbation risk) amounted to 49% and 57% of patients, respectively (Table 2; Figure 3).

If patients undergoing long-acting inhaler therapy from their current treatment pathway are hypothetically redistributed to treatment aligned with GOLD recommendation, it could result in potential cost-savings on the NHS of €17,792,022 (Figure 4).

Analysis According to GesEPoC Guideline

This analysis showed that the patterns of treatment from 38% of patients managed in the pulmonology setting were not prescribed in line with recommendations of GesEPoC guidelines for their specific phenotype (Table 2).

Lack of adherence to guideline recommendations in current practice was mainly due to a broader use of ICS-based therapies. Ninety-four percent of patients (128,929 of the 137,464) who were not treated in accordance with the Spanish guideline were treated with ICS-based therapies, as opposed to the remaining 6% who were treated with bronchodilator therapy (Table 2).

Regarding the different phenotypes, it was observed that half of the patients with the non-exacerbator phenotype were not treated according to GesEPoC recommendations because they were treated with ICS (Table 2; Figure 4).

Table 2 COPD Patients Not Adherent to GOLD Recommendations and GesEPoC Guidelines in Pulmonology Units (Base Case Analysis)

| Patients (%) Non-Adherent to Recommendations | Current Treatment in Clinical Practice |
|---------------------------------------------|--------------------------------------|
|                                             | LAMA | LABA | LAMA/LABA | LABA/ICS | LAMA/LABA/ICS | Total     |
| GOLD                                       |      |      |           |         |              |          |
| Group A (N = 141,309)                      | 0    | 0    | 0         | 21,326 | 44,321        | 65,648   |
| Group B (N = 75,476)                       | 0    | 0    | 0         | 8,716  | 40,242        | 48,958   |
| Group C (N = 41,540)                       | 0    | 556  | 0         | 4,294  | 15,435        | 20,285   |
| Group D (N = 106,817)                      | 0    | 556  | 0         | 7,049  | 53,669        | 61,747   |
| Total (N = 365,142)                        | 0    | 1,113| 0         | 41,385 | 153,667       | 196,164  |
| GesEPoC                                   |      |      |           |         |              |          |
| Non-exacerbator (N = 213,742)              | 0    | 0    | 0         | 24,491 | 83,864        | 108,355  |
| Exacerbator with emphysema (N = 34,510)    | 2,041| 186  | 0         | 6,308  | 0             | 8,535    |
| Exacerbator with chronic bronchitis (N = 87,204) | 2,226| 371  | 0         | 8,535  | 0             | 11,132   |
| ACO (N = 29,686)                           | 742  | 928  | 0         | 5,731  | 0             | 9,441    |
| Total (N = 365,142)                        | 5,010| 1,484| 0         | 45,065 | 83,864        | 137,464  |

Notes: Lack of adherence to the guidelines: patients who change treatment due to its adequacy according to guideline recommendations.

Abbreviations: ACO, asthma-COPD overlap; COPD, chronic obstructive pulmonary disease; GesEPoC, Spanish Guidelines for Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; ICS, inhaled corticosteroids; LABA, long-acting β2 adrenergic agonists; LAMA, long-acting muscarinic antagonists.
Figure 4 Pharmaceutical expenditure and annual savings in patients treated in exclusively pulmonology services (base case analysis) (A and B) or pulmonology and primary care (scenario analysis) (C). (A) Following recommendations of the GOLD strategy (base case). (B) Following recommendations of the GesEPOC guide (base case). (C) Following the recommendations of the GesEPOC guide (scenario analysis).

Abbreviations: GesEPOC, Spanish Guidelines for Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; ICS, inhaled corticosteroids; LABA, long-acting β2 adrenergic agonists; LAMA, long-acting muscarinic antagonists.
In 25% of patients with exacerbator phenotype with emphysema and in 13% of patients with exacerbator phenotype with chronic bronchitis, the change to dual-bronchodilator treatment should be considered (Table 2; Figure 3). Patients with ACO phenotype should all be treated with ICS-based therapies (Figure 3); however, 32% of ACO patient therapies were not prescribed in line with guideline recommendations (Table 2).

The model showed that if patients are hypothetically redistributed to treatment in accordance with GesEPOC guideline recommendations, it could provide potential cost-savings of €5,881,785 on the NHS (Figure 4).

Analysis of Savings by Autonomous Communities
Additionally, the potential savings were calculated by autonomous community. The factors with the greatest impact on savings were the population size and the prevalence of diagnosed and treated COPD in each region. The Community of Madrid, Catalonia, and Andalusia were the autonomous communities with the greatest potential savings, as a result of realigning current treatment to GOLD and GesEPOC guidelines (Figure 5).

Scenario Analyses
In scenario analysis 1, it was observed that 26% of patients were not treated in line with GesEPOC recommendations

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**Figure 3** In 25% of patients with exacerbator phenotype with emphysema and in 13% of patients with exacerbator phenotype with chronic bronchitis, the change to dual-bronchodilator treatment should be considered (Table 2; Figure 3). Patients with ACO phenotype should all be treated with ICS-based therapies (Figure 3); however, 32% of ACO patient therapies were not prescribed in line with guideline recommendations (Table 2).

**Figure 4** The model showed that if patients are hypothetically redistributed to treatment in accordance with GesEPOC guideline recommendations, it could provide potential cost-savings of €5,881,785 on the NHS.

**Figure 5** Base case analysis: annual savings in pharmaceutical expenditure in patients treated in pulmonology services distributed by Autonomous Community according to the GOLD (A) and GesEPOC (B) guidelines. (A) Following GOLD strategy recommendations. (B) Following GesEPOC guideline.

Notes: The sum of the costs of the regions does not correspond to the total Spanish cost (Figure 4) as the pharmacological costs have been weighted according to their sales in each region.

Abbreviations: GesEPOC, Spanish Guidelines for Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease.
for their specific phenotype (Table 3). The lack of adherence was most prominent in the inappropriate use of ICS in most COPD phenotypes; 94% of the total number of patients not treated in accordance with recommendations were treated with an ICS therapy, compared with 6% that were inappropriately treated with bronchodilators (Table 3; Annex 1).

Forty-four percent of the patients with a non-exacerbator phenotype were treated with ICS, while they should not have received ICS according to GesEPOC guidelines (Table 3; Annex 1). Among exacerbating patients, 12% of patients with emphysema and 7% with chronic bronchitis were treated with another option than recommended according to GesEPOC guidelines (Table 3; Annex 1). Patients with ACO phenotype should all be treated with ICS-based therapies; however, 28% of these patients were not prescribed in line with guideline recommendations (Table 3; Annex 1).

The model also showed a potential reduction in annual pharmaceutical expenditure resulting from alignment of treatment to the GesEPOC guidelines of €2,707,554 (Figure 4), equivalent to 0.9% of the 2020 pharmaceutical expenditure on COPD in Spain.

In scenario analysis 2, it was observed that adapting clinical practice regarding the management of ICS-based therapies to guideline recommendations would lead to savings in pharmaceutical expenditure of €17,863,750 and €9,904,409 according to the GOLD and GesEPOC recommendations for the Spanish NHS, respectively.

**Discussion**

This study illustrates the low adherence of Spanish clinical practice in the management of stable COPD to GOLD strategy and GesEPOC guidelines. According to guidelines, the population who can benefit from ICS, in addition to long-term bronchodilator therapy, are those with a history of exacerbations and elevated blood eosinophil levels, as well as the population with a history of asthma. However, the present analysis demonstrates a broader inappropriate use of ICS being the main reason for the low adherence to guidelines.

This trend in the use of ICS has also been observed in other Spanish studies. In particular, in the field of pulmonology, the EPOCONSUL clinical audit revealed that more than 60% of patients with a phenotype other than ACO were treated with ICS. Likewise, the results of the COACH clinical audit, carried out in primary care centers, showed up to 55% of COPD patients without a history of exacerbations followed treatment regimens that included ICS.

More recently, a big data analysis has been published with data from patients from Castile La Mancha, in which 68% of COPD patients were receiving ICS, mostly in the form of triple therapy.

Given the high use of ICS, the GOLD strategy recommends a periodic review of treatment and proposes an assessment of ICS withdrawal in patients who experience an ICS-related adverse effect (such as pneumonia), inappropriate original indication, and/or lack of response to ICS. Although the current analysis did not follow individual patients over time, it can be observed that any de-escalation of treatment was taken into account, as the gradual withdrawal of ICS in patients treated with LAMA/LABA/ICS does not increase the risk of exacerbation, and may reduce the risk of adverse events, such as pneumonia.

In this respect, and based on all the available evidence, the European Respiratory

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**Table 3 COPD Patients Treated Without Following GesEPOC Guidelines in Pulmonology and Primary Care Units (Scenario Analysis 1)**

| GesEPOC Phenotype | Current Treatment in Clinical Practice |
|-------------------|---------------------------------------|
|                   | LAMA | LABA | LAMA/LABA | LABA/ICS | LAMA/LABA/ICS | Total    |
| Non-exacerbator (N = 167,357) | 0    | 0    | 0         | 13,140 (7.9%) | 60,857 (36.4%) | 73,997 (44.2%) |
| Exacerbator with emphysema (N = 65,698) | 692 (1.1%) | 0    | 0         | 6,916 (10.5%) | 0    | 7,607 (11.6%) |
| Exacerbator with chronic bronchitis (N = 105,808) | 1,383 (1.3%) | 692 (0.7%) | 0         | 5,532 (5.2%) | 0    | 7,607 (7.2%) |
| ACO (N = 26,279) | 1,383 (5.3%) | 0    | 1,383 (5.3%) | 4,576 (17.4%) | 0    | 7,343 (27.9%) |
| Total (N = 365,142) | 3,458 (0.9%) | 692 (0.2%) | 1,383 (0.4%) | 30,164 (8.3%) | 60,857 (16.7%) | 96,554 (26.4%) |

**Notes:** Lack of adherence to guidelines: patients who change treatment due to an adaptation to guideline recommendations.

**Abbreviations:** ACO, asthma-COPD overlap; COPD, chronic obstructive pulmonary disease; GesEPOC, Spanish Guidelines for Chronic Obstructive Pulmonary Disease; ICS, inhaled corticosteroids; LABA, long-acting β2 adrenergic agonists; LAMA, long-acting muscarinic antagonists.
Society (ERS) has recently issued a conditional recommendation of ICS withdrawal in patients with blood eosinophils <300 cel/µL and no history of frequent exacerbations.37

In contrast, the present study shows that 13% of patients with an ACO phenotype are not treated with ICS, despite GesEPOC recommendations. These results were similar to EPOCONSUL, where a quarter part of ACO patients were not receiving ICS.18

From an economic perspective, the model showed that treating patients in accordance with guideline recommendations could lead to a 6.3% (according to GOLD) and 2.1% (according to GesEPOC) reduction in pharmaceutical spending on COPD in Spain in 2020 (total cost of €282 million [Figure 4]).

Overall, the degree of adherence to recommendations was higher for the GesEPOC guideline compared with the GOLD strategy. Consequently, regarding the economic implications, the appropriateness of clinical practice to the GOLD recommendations would entail an additional pharmacological saving of €11,910,237, compared with the potential savings generated by aligning with GesEPOC guidelines. The main reason for these differences observed from GOLD in comparison with GesEPOC, is associated with the more restrictive recommendations regarding the use of ICS in the GOLD strategy. Likewise, the decrease in the use of triple therapy in line with the recommendations also contributed to savings over GesEPOC. On the other hand, the GesEPOC guideline recommends dual bronchodilator therapy as the main treatment in high-risk patients, reserving the LABA/ICS combination as initial therapy only for patients with ACO phenotype. This implies scaling up the treatment of patients treated with less costly therapies (such as bronchodilator monotherapy or LABA/ICS) to more expensive ones (such as dual bronchodilation), adding an additional pharmacological cost. These additional costs, however, are offset by a reduction of the use of triple therapy (a more costly therapy), generating overall savings for the NHS.

In scenario analysis 1, a higher adherence of treatment patterns to GesEPOC guidelines was observed than in the base case analysis. The low adherence was mainly due to the broader use of ICS-based therapies, including patients with a non-exacerbator phenotype.

In scenario analysis 2, it was observed that the pharmacological savings resulting from limiting re-alignment to ICS-based therapies alone, were higher than observed in the base case analysis. The savings derived from switching from more expensive therapies (such as triple therapy) to less costly treatments (such as monotherapy or double bronchodilation) offset the additional pharmacological costs derived from switching away from less costly therapies (such as LABA/ICS) to LAMA/LABA. This suggests that a correct evaluation of ICS treatment use could be an effective cost-reducing strategy.

These data are consistent with those of a Spanish study which analyzed 10,711 patients with COPD in the primary care setting and showed that 34.5% received ICS and in 18.2% of them the use was inappropriate according to the GOLD strategy.25 Patients who received ICS treatment not aligned with the recommendations had a poorer quality of life and generated higher direct costs (€1,590/patient per year if the use of ICS was inappropriate vs. €1,157 if they followed the recommendations, p <0.05). In addition, a recent study performed in primary care in Spain showed that from more than 34,000 patients initiating triple therapy, 70% were GOLD A or B and up to 54% were non exacerbators, showing again a broader use of ICS, not aligned with current guidelines.38

A number of limitations in the current analysis should be noted. First, the use of fixed-dose combination inhalers was assumed in all patients treated with double or triple therapies. This simplified approach led to an underestimation of the costs of the combinations, since the pharmacological costs of the fixed-dose combinations are lower than the sum of the cost of the single components taken separately.

Another limitation was that this study only considers the costs associated with the pharmacological treatment of stable COPD. Thus, the potential variations in other direct or indirect costs in patients derived from low adherence to the recommendations have not been quantified, and the clinical side effects produced by the drugs have not been included.

On the other hand, the prescribing patterns of clinical practice in the scenario of patients classified according to GOLD groups of the base case analysis have been obtained from a study that was based on the version of the GOLD strategy from 2013,39 where obstruction level was considered in the classification of patients and, instead, the proposed treatment has been determined based on the recommendations of the 2020 version. This may lead to some patients not belonging to the same ABCD group in both versions of the guideline, specifically some patients from D group according to 2013 version may be classified as B group in the updated version.
In addition, another limitation is that the assumption of the number of patients with elevated eosinophils used for the estimations comes from a different study.\textsuperscript{31}

Finally, in the autonomous communities analyses it was not possible to use regional data on patient distribution by typology and drug prescription, as there was no data published, so model projections are simplifications of reality.

The current analysis demonstrates the potential savings to the Spanish NHS as a result of aligning treatment with international and national guidance. However, any change in treatment should be evaluated by the clinician and agreed with the patient, in particular when the disease is not well controlled.\textsuperscript{8,40} In line with guidelines recommendations, a review of the diagnosis, management of comorbidities, history of symptoms and exacerbations, inhalation technique and adherence to medication should be included. However, it has been identified the potential economic benefits for the Health System to consider when assessing the risks and benefits of therapies, particularly those containing ICS for their COPD patients.

\textbf{Conclusion}

The results of this analysis show that more than a third of the patients with COPD in Spain are not treated in line with national and international clinical recommendations.

The adherence of clinical practice to COPD treatment recommendations, and the reduction in the use of ICS-based therapies in patients in whom their use is not recommended, could provide significant cost-savings for the Spanish NHS. These findings encourage the need for establishing strategies for adapting the management of stable COPD in Spanish clinical practice to guideline recommendations, thus optimizing health outcomes for patients and reducing the pharmaceutical expenditure of the Spanish NHS.

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