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ORIGINAL RESEARCH

The importance of inhaler devices: the choice of inhaler device may lead to suboptimal adherence in COPD patients

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Josep Darbà[1]
Gabriela Ramírez[2]
Antoni Sicras[3]
Pablo Francoli[4]
Saku Torvinen[5]
Rainel Sánchez-de la Rosa[4]

[1]Department of Economics, Universitat de Barcelona, [2]BCN Health Economics and Outcomes Research SL, [3]Dirección de Planificación, Badalona Serveis Assistencials, SA, Barcelona, [4]Medical Department, TEVA Pharmaceutical, Madrid, Spain; [5]Market Access Department, TEVA Pharmaceutical Europe BV, Amsterdam, the Netherlands

Objective: This study aims to identify factors associated with poor adherence to COPD treatment in patients receiving a fixed-dose combination (FDC) of inhaled corticosteroids and long-acting β_2-agonist (ICS/LABA), focusing on the importance of inhaler devices.

Methods: We conducted a retrospective and multicenter study based on a review of medical registries between 2007 and 2012 of COPD patients (n=1,263) treated with ICS/LABA FDC, whose medical devices were either dry powder inhalers (DPIs) or pressurized metered-dose inhalers (pMDI). Medication adherence included persistence outcomes through 18 months and medication possession ratios. Data on exacerbations, comorbidities, demographic characteristics, and health care resource utilization were also included as confounders of adherence.

Results: The analyses revealed that COPD patients whose medication was delivered through a DPI were less likely to have medication adherence compared to patients with pMDI, after adjusting for confounding factors, especially active ingredients. Younger groups of patients were less likely to be adherent compared to the oldest group. Smoker men were less likely to be adherent compared to women and non-smokers. Comorbidities decreased the probability of treatment adherence. Those patients that visited their doctor once a month were more likely to adhere to their medication regimen; however, suboptimal adherence was more likely to occur among those patients who visited more than three times per month their doctor. We also found that worsening of COPD is negatively associated with adherence.

Conclusion: According to this study, inhaler devices influence patients' adherence to long-term COPD medication. We also found that DPIs delivering ICS/LABA FDC had a negative impact on adherence. Patients' clinic and socioeconomic characteristics were associated with adherence.

Keywords: adherence, inhaler technique, medication possession ratio (MPR), dry powder inhalers (DPIs), pressurized metered-dose inhalers (pMDIs), persistence

Introduction

COPD causes specific inflammatory cell types and structural changes in the airways that determine the severity of this condition. In Spain, chronic lung diseases were the fourth leading cause of mortality in 2008.[1] Furthermore, recent studies have reported that ~10.2% of Spanish population between 40 and 80 years have COPD,[2] but its under-diagnosis is frequent, and it is estimated that 73% of COPD cases have not been diagnosed.[3] These characteristics make COPD already a very costly condition, which is estimated to be equivalent to 0.2% of Spanish gross domestic product.[2]

Pharmacological treatment should adjust to each patient, guided by severity of symptoms, risk of exacerbations, and patient's response. Maintenance treatment

Correspondence: Josep Darbà
Department of Economics, Universitat de Barcelona, Diagonal 690, 08034 Barcelona, Spain
Email darba@ub.edu

of COPD relies on inhaled agents to control symptoms and/or complications of the disease and to prevent exacerbations.[1] Although these effects are required, inhaled pharmacological treatment depends on the efficacy of inhaler devices, patient's ability, and precision for using it;[4,5] the reliability of devices for delivering the medicine directly to patients' lungs;[6,7] and patient's compromise to comply timing, dosage, and frequency of medication taking.[8,9] Suboptimal adherence within chronic conditions has been largely documented.[10,11] Specifically, the lack of adherence toward medication regime can cause progression of COPD, more severity of symptoms and exacerbations, hospitalization, and detriment of the quality of life among COPD patients.[12–14] Medication adherence is a complex issue that can be defined as the degree to which a patient's medication-taking behavior and/or executing lifestyle changes correspond with agreed recommendations from a health care professional with respect to timing, dosage, and frequency.[8,11] Over the last few years, researchers from several disciplines raised that adherence is an important problem given that is influenced not only by the increasingly complexity of lifelong therapy regimens but also by multiple clinical and nonclinical factors, to which we have to add the sociodemographic changes of a population aging.[15] These aspects represent a challenge for national health care systems worldwide that should be analyzed from a multidisciplinary perspective.[4,6,13,14]

Although inhaled corticosteroids and long-acting β_2-agonist (ICS/LABA) fixed-dose combinations (FDCs) have shown to relieve COPD symptoms similarly, recent research has shown that inhaler technique might affect adherence and hence efficacy of pharmacological treatment.[2–4] Inhaler technique is different between dry powder inhalers (DPIs) and pressurized metered-dose inhalers (pMDIs). Each of the devices is associated with procedure, which is also affected by the ability of patients to handle it. The aim of this study was to examine medication adherence in COPD patients, focusing on the associations between adherence with COPD medication and inhaler devices, such as DPI and pMDI, while adjusting for the potential effect of the active ingredients. Moreover, some other factors that could be affecting medication adherence, such as clinical or socioeconomic characteristics of patients, were also analyzed.

Materials and methods

Study sample

We conducted a retrospective and multicenter study based on a review of medical registries of COPD patients treated with ICS/LABA FDC, whose inhaler devices were either DPIs or pMDIs. Diagnosis was spirometry based, which was useful to classify patients into three categories: mild, moderate, and severe. Criteria were always the doctor's opinion. The study population included patients attending primary care centers, whose population was mostly urban, with a low-to-medium socioeconomic level.

The study sample comprised all COPD patients, who initiated their treatment with ICS/LABA FDC between January 1, 2007 and June 30, 2014. Moreover, patients fulfilled the following characteristics: 1) aged ≥35, 2) time of diagnosis >3 years, and 3) were required to have registries with regular monitoring for 18 months (ie, those who were part of the long-term prescription program to obtain prescriptions with a confirmed record of the daily dosage, time interval, and duration of each treatment) (n=1,645). We excluded patients who were transferred outside the area, patients permanently institutionalized, patients who died during the period of analysis (n=382), and patients who presented clinical history of pulmonary emphysema, bronchiectasis, cystic fibrosis, and bronchial neoplasia.

Data source and variables

This retrospective study used integrated medical and pharmacy claims' data to identify the impact of inhaler technique toward adherence outcomes. Database contains information on COPD treatments with ICS/LABA FDC according to the Anatomical Therapeutic Chemical Classification System. We linked each treatment to its inhaler device, which could be a DPI or a pMDI. Thus, within DPIs were included Turbuhaler®, Accuhaler®, and NEXThaler® that delivered formoterol/budesonide, salmeterol/fluticasone, and formoterol/beclomethasone, respectively. pMDIs delivered either formoterol/beclomethasone or salmeterol/fluticasone. Database is managed by Badalona Serveis Assitencials, which provides services to ten primary care centers, one hospital, and one sociohealth center. Ethics approval for the database to be used for research was granted by the Ethics Committee of the Hospital Universitari Germans Trías i Pujol.

Information on persistence was obtained for 1 year and half, indicating whether patient kept taking that treatment (persistence) at the third, sixth, 12th, and 18th months (Figures 1 and 2). Information on medication possession was also obtained by patient's refill count as well as data on duration by the number of days patient should be consuming the medication. Demographic characteristics of

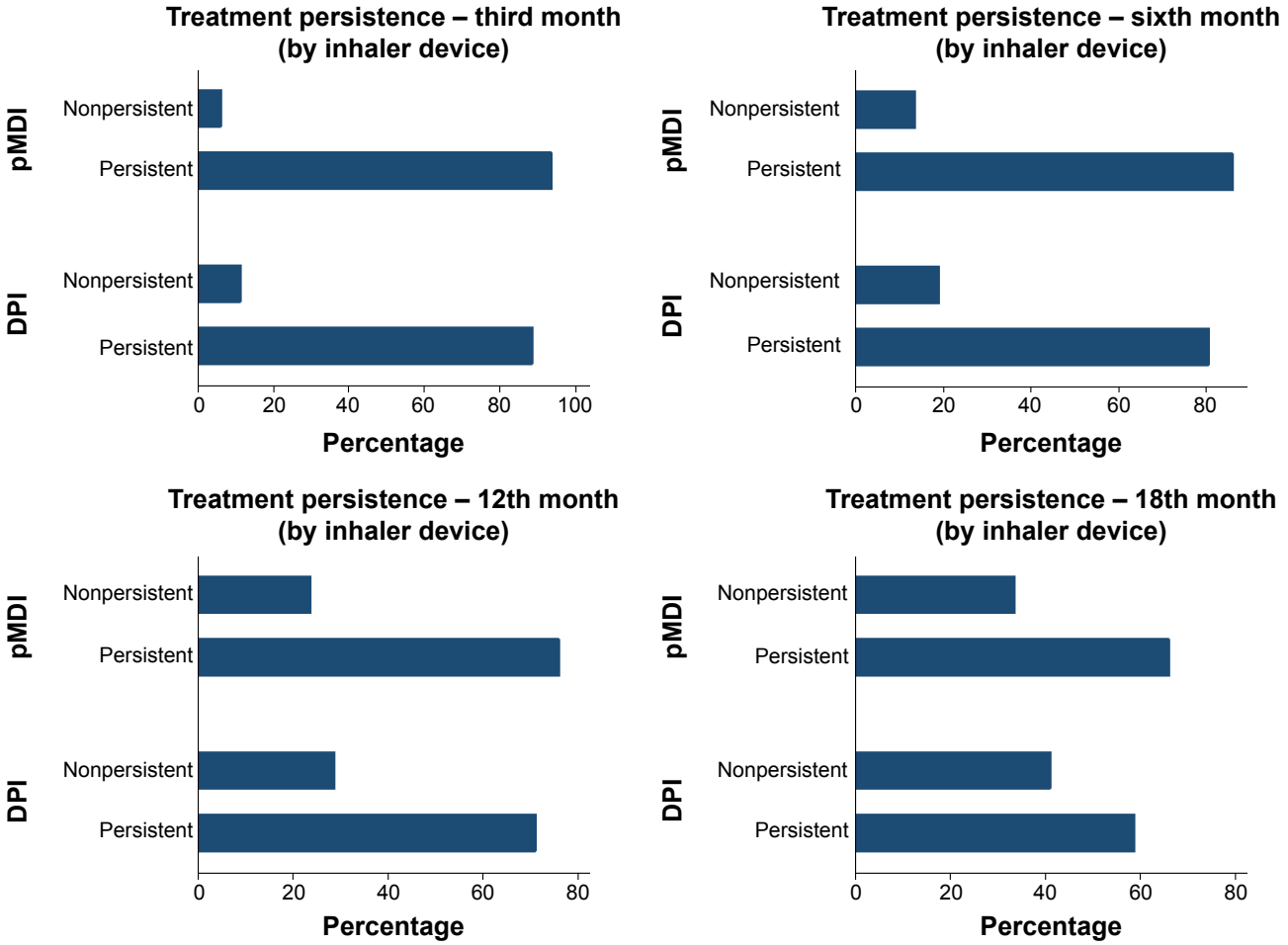

Figure 1 Percentage of persistent patients at the third, sixth, 12th, and 18th months.
Abbreviations: pMDI, pressurized metered-dose inhaler; DPI, dry powder inhaler.

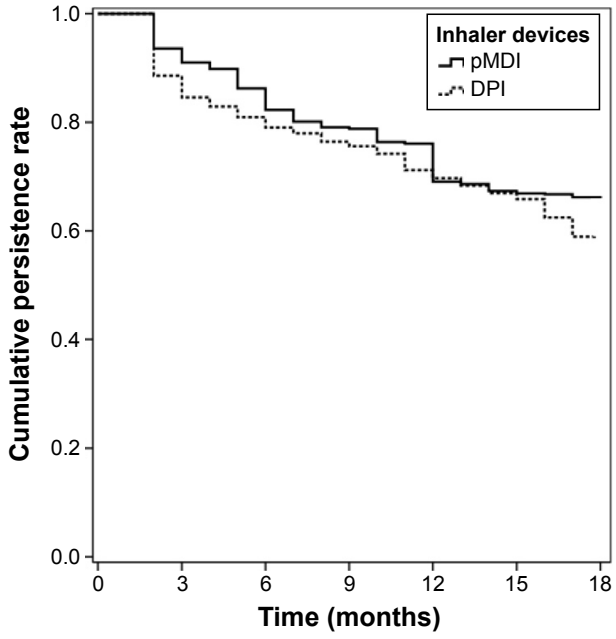

Figure 2 Medication persistence.
Abbreviations: pMDI, pressurized metered-dose inhaler; DPI, dry powder inhaler.

this sample were age, sex, and whether the patient was retired or not.

Furthermore, we gathered data of other potential confounders of medication adherence. A number of mild/moderate exacerbations and acute events, defined by the GesEPOC recommendations,[2] were collected. Medications, such as oral corticosteroids, systemic antibiotics, short-acting β_2-agonist, short-acting anticholinergic, and systemic β_2-agonists, to treat the symptoms and complications of COPD were available. Clinical data on comorbidities were included. Basically, it was indicated whether the patients suffered from simultaneous conditions, such as hypertension, diabetes, dyslipidemia, arthritis, osteoarthritis, depression, and dementia. Also severe events, including failures, ischemic heart disease, cerebrovascular diseases, and neoplasm, were indicated. Behavior attitudes that could derive to higher risk of developing a disease, for instance, obesity, smoking habit, and alcoholism, were also included as comorbidities. We had also access to number of visits to

the physician during the period of study. Pharmacy administrative database also stores gross amount of pharmaceutical expenditure per patient. Data were adapted into our model by obtaining patient's average cost per month because Spanish patients have low co-payment levels for their medication; we approximated the potential cost that patients could face each month.

Calculation of patient's medication adherence

To calculate adherence, we utilized the medication possession ratio (MPR), which is calculated by dividing the number of days supplied for a given medication by the number of days in the study, and persistence data.[16] Persistence is defined as the duration of time from initiation to discontinuation of therapy. Clinical outcomes are affected not only by how well patients take their medication but also by how long they take them, so the effect on how well patients take ICS/LABA FDC can be observed without being disturbed by discontinuation. First, we identified patients who last 18 months with their medication, which implied that they were persistent. These patients were analyzed to obtain adherence by using the MPR. Therefore, within these persistent patients, we applied a cut-point of 90% to the MPR. Since MPR tends to be overestimated,[9,17] we also increased the limit to consider medication adherence. We had an ordered categorical variable, which showed to be very useful to identify persistence and adherence patterns: patients first need to be persistent with their treatment, and then they need to comply with their prescriptions.[4,9] This variable reflects patients who are not neither persistent nor adherent, patients who are persistent but nonadherent, and patients who are persistent and showed adherence to their medication (Figure 3). Finally, to check the robustness of our findings, we decided to use the most common cut-point that is 80% to the MPR.[13,18] This analysis focuses on factors that diminish medication adherence.

Analysis

To illustrate the distribution of patient's adherence within each medical device (DPI or pMDI), we tabulated sample characteristics for patients using either a DPI or a pMDI (Table 1). Univariate associations between medication adherence, medical device, and several confounders, such as age, comorbidities, exacerbations, severity of COPD, medication to treat COPD, and drug cost, were analyzed (Table 2). To perform basic analysis, we only included statistically significant variables from the univariate analysis into the first specification (Table 3).

With reference to health care utilization, visits to physicians were categorized in order to explore the association of having, on average, none or one visit per month, between one and three visits per month, and more than three visits per month (baseline will be none or one visit per month). We considered a variable for comorbidity status, which was categorized as having one, two, or more than three conditions, besides COPD.

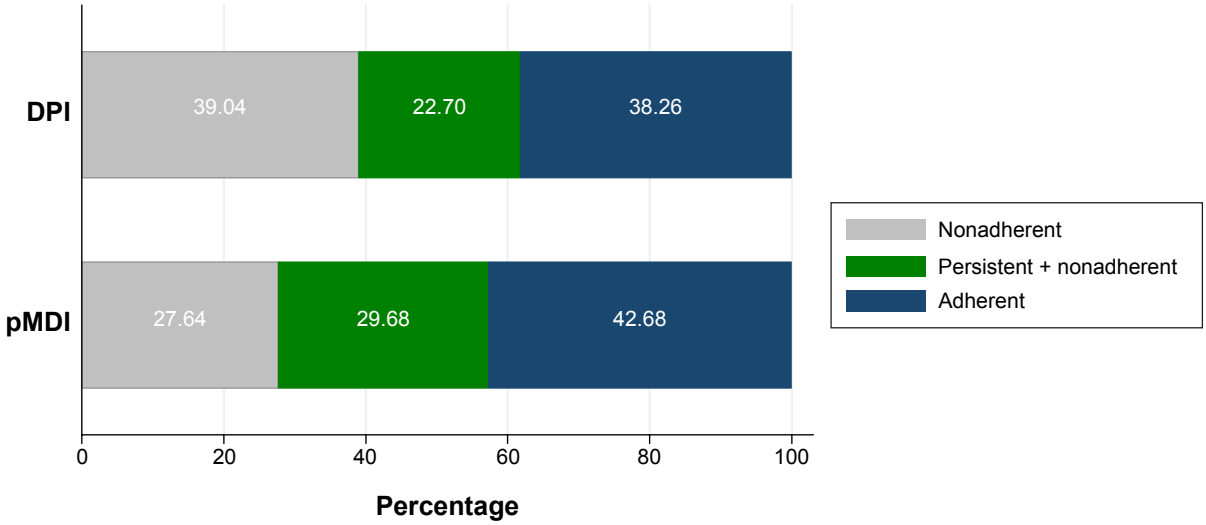

Figure 3 Percentage of adherent patients by each inhaler device (n=1,263).
Notes: Nonpersistent patient = patient who discontinued their therapy before the 18th month, persistent + nonadherent patient = patient who did not discontinue therapy but was <90% of the MPR, and adherent patient = patient who did not discontinue their therapy but was >90% of the MPR.
Abbreviations: pMDI, pressurized metered-dose inhaler; DPI, dry powder inhaler; MPR, medication possession ratio.

Table 1 Characteristics of COPD patients according to the type of inhaler device: DPI or pMDI

Characteristics	pMDI (n=492)	DPI (n=771)	Total (n=1,263)	*P*-value
Male (%)	38.95	61.04	83.45	0.735
Age, mean (SD) (years)	70.54 (10.37)	70.66 (9.91)	70.61	0.326
39–50	5.28	3.50	4.20	–
51–61	12.40	13.75	13.22	–
62–71	33.54	32.68	33.02	–
72–83	40.04	40.73	40.46	–
84–97	8.74	9.34	9.11	–
Retired status (%)	87.2	89.23	88.44	0.966
Time since COPD was diagnosed, mean (SD) (years)	15.0 (5.19)	15.44 (5.04)	15.38 (5.10)	0.994
Severity of COPD (%)				
Mild	17.89	14.79	15.99	–
Moderate	77.85	80.80	79.65	–
Severe	4.27	4.41	4.35	–
FEV_1, mean (SD)	76.6 (9.9)	79.1 (9.9)	79.2 (9.9)	0.256
ICS/LABA FDC (%)				
Formoterol/beclomethasone	24.59	17.12	20.03	–
Formoterol/budesonide	0.0	51.88	31.67	–
Salmeterol/fluticasone	75.41	31.00	48.30	–
Exacerbations (%) (binary on whether patients suffered an exacerbation or not)	36.99	42.15	40.14	0.068
Moderate	31.5	36.96	34.84	<0.001
Acute	16.06	14.92	15.36	0.630
Comorbidities (%)				
Obesity	38.62	40.86	39.98	0.650
Smoking	21.14	19.58	20.19	0.743
Alcoholism	6.91	6.10	6.41	0.891
Cerebrovascular disease	34.15	35.80	35.15	0.948
Hypertension	59.35	60.57	60.10	0.650
Diabetes	28.66	28.40	28.50	0.732
Dyslipidemia	52.44	49.68	50.75	0.518
Osteoarthritis	8.40	6.28	7.17	0.099
Arthritis	20.42	21.16	20.73	0.714
Stroke	23.78	25.42	24.78	0.510
Ischemic heart disease	16.06	15.30	15.60	0.948
Failures	25.20	27.11	26.37	0.987
Dementia	6.50	6.87	6.73	0.964
Depression	24.19	26.72	25.73	0.855
Neoplasm	16.26	17.12	16.79	0.846
Other medication to treat COPD (%)	84.76	84.95	84.88	–
Oral corticosteroids	8.54	8.17	8.31	0.856
Systemic antibiotics	2.7	7.0	5.9	<0.05
SABA	80.3	80.4	80.3	0.862
Short-acting anticholinergic	57.72	55.12	56.14	0.364
Number of visits to doctor, mean (SD)	18.99 (13.28)	21.99 (14.24)	20.82 (13.94)	<0.001
Average cost per month, mean (SD) (Euros)	64.95 (43.54)	62.75 (44.10)	63.60 (43.88)	0.3852
Mean of total health care cost per patient, mean (SD) (Euros)	1,920.99 (1,427.22)	2,013 (1,716.5)	1,977 (1,716.5)	0.3527

Note: Patients' characteristics who visited their primary care center between January 2007 and June 2014.
Abbreviations: DPI, dry powder inhaler; pMDI, pressurized metered-dose inhaler; SD, standard deviation; FEV_1, forced expiratory volume in 1 second; ICS/LABA, inhaled corticosteroids and long-acting β_2-agonist; FDC, fixed-dose combination; COPD, chronic obstructive pulmonary disease; SABA, short-acting β_2-agonist.

Moreover, to consider the potential heterogeneity sources across age groups, the continuous variable age was split into five groups. Utilization of medication to treat COPD, besides ICS/LABA FDCs, was combined in a single variable that captures number of medication took per patient during the period of study. We did not analyze each pattern by itself because we are interested on adherence patterns in patients attempting to take ICS/LABA FDC chronically. Tables 2–4 contain results expressed in percentage points (pp) and odd ratios.

Table 2 Univariate analysis of each potential confounders of adherence

Explanatory variables	Category	Adherence (n=1,263)			
		Percentage points	Odds ratios	95% CI	*P*-value
Medical device DPI (baseline pMDI)		−7.85	0.72	0.583–0.8686	0.002
ICS/LABA FDC (baseline formoterol/beclometasone)	Formoterol/budesonide	−3.58	0.858	0.640–1.150	0.308
	Salmeterol/fluticasone	2.98	1.13	0.860–1.487	0.378
Therapy line (baseline first line)	Second line	16.55	1.96	1.363–2.814	0.000
	Third line	24.75	2.75	1.222–6.186	0.011
Age		−0.35	0.98	0.975–0.995	0.004
Sex (baseline men)		6.29	1.30	0.985–1.715	0.063
Retired status		−3.14	0.87	0.638–1.204	0.417
Obesity		4.61	1.21	0.985–1.493	0.069
Smoking		7.63	1.37	1.066–1.777	0.014
Stroke		−6.73	0.75	0.594–0.957	0.020
Cerebrovascular disease		−6.72	0.75	0.608–0.935	0.010
Hypertension		0.89	1.04	0.843–1.278	0.724
Diabetes		−1.80	0.93	0.738–1.164	0.517
Dislipemia		−1.89	0.92	0.753–1.133	0.448
Osteoarthritis		0.87	1.03	0.808–1.330	0.775
Arthritis		−0.31	0.98	0.654–1.489	0.951
Alcoholism		6.51	1.31	0.863–1.993	0.203
Ischemic cardiomyopathy		−0.83	0.96	0.730–1.277	0.807
Failures		2.89	1.12	0.895–1.421	0.306
Dementia		−9.18	0.68	0.446–1.309	0.075
Depression		−2.07	0.92	0.727–1.156	0.465
Neoplasm		3.93	1.17	0.896–1.548	0.239
Number of exacerbations		4.48	1.21	1.114–1.311	0.000
Number of severe exacerbations		−9.41	0.91	0.684–1.210	0.518
Number of mild/moderate exacerbations		5.77	1.28	1.165–1.403	0.000
Severity of COPD (baseline mild)	Moderate	4.80	1.23	0.930–1.619	0.148
	Severe	22.15	2.47	1.374–4.459	0.003
Time since COPD was diagnosed		−1.72	0.93	0.909–0.947	0.000
Other medication to treat COPD		5.66	1.27	1.181–1.375	0.000
	Oral corticosteroids	11.32	1.61	1.307–1.990	0.000
	Systemic antibiotics	14.83	1.87	1.444–2.430	0.000
	SABA	16.95	2.06	1.629–2.604	0.000
	Short acting anticholinergic	7.83	1.388	1.130–1.707	0.002
	β_2 Agonists (systemic)	6.82	1.33	0.903–1.956	0.149
Long acting anticholinergic agents		13.56	1.77	1.393–2.260	0.000
Cost		−0.25	0.98	0.986–0.991	0.000
Visits to doctor		0.41	1.017	1.009–1.25	0.000

Abbreviations: CI, confidence interval; DPI, dry powder inhaler; pMDI, pressurized metered-dose inhaler; ICS/LABA, inhaled corticosteroids and long-acting β_2-agonist; FDC, fixed-dose combination; COPD, chronic obstructive pulmonary disease; SABA, short-acting β_2-agonist.

Results

Clinical and demographic characteristics

Persistence rates were diminishing throughout 18 months and were similar among inhaler devices at the 18th month (Figures 1 and 2). We could identify the final proportion of adherent patients on the basis of methodology described in the "Calculation of patient's medication adherence" section. Remarkably higher rates of discontinuation were observed in patients using a DPI. However, patients who have medication adherence were similar in both groups (Figure 3). Sociodemographic and clinical characteristics of 1,263 COPD patients tabulated by an inhaler device are shown in Table 1. A total of 38.95% of patients used a pMDI and 61.05% used a DPI during the time of study. The mean age of patients was 71 years, most of them were retired (88.44%), and 83.45% of them were men. Time since diagnosis (in years) was similar in both groups. The most frequent comorbidity observed in this sample was hypertension (60.1%), followed by dyslipidemia (50.75%), which were very similar in both groups. Patients with moderate COPD represent 79.65%, and the distribution

Table 3 Multivariate results of potential confounders of adherence

Explanatory variables (McFadden's R^2=0.0711)	Adherence (n=1,263)					
	Without active ingredients			Controlling for active ingredients		
	Percentage points	Odd ratios	95% CI	Percentage points	Odd ratios	95% CI
Medical device DPI (baseline pMDI)	–9.95*	0.60*	0.481–0.750	–9.57*	0.61*	0.467–0.802
ICS/LABA FDC (baseline formoterol/beclometasone)						
Formoterol/budesonide	–	–	–	2.07	1.11	0.798–1.556
Salmeterol/fluticasone	–	–	–	3.37	1.19	0.893–1.586
Severity of COPD (baseline mild)						
Persistent moderate	11.22*	1.91**	1.323–2.766	11.65*	1.89*	1.311–2.741
Persistent severe	7.08	1.49	0.645–3.484	6.74	1.47	0.632–3.426
Time since COPD was diagnosed	–1.15*	0.942	0.917–0.968	–1.14*	0.94*	0.918–0.968
Therapy line						
Second	10.13**	1.637**	1.125–2.380	10.21**	1.64**	1.130 – 2.390
Third	20.45**	2.624**	1.077–6.361	20.14**	2.58*	1.063–6.305
Age	–0.11	0.994	0.979–1.009	–0.12	0.99	0.978–1.009
Sex	4.02	1.23	0.161–0.921	0.41	1.23	0.923–1.644
Obesity	2.12	1.11	0.894–1.391	1.94	1.10	0.885–1.379
Smoking	4.63	1.268	0.958–1.677	4.50	1.260	0.952–1.667
Stroke	–3.34	0.842	0.588–1.206	–3.21	0.848	0.592–1.214
Cerebrovascular disease	–3.84	0.821	0.551–1.222	–3.85	0.821	0.551–1.222
Exacerbations	–6.20**	0.72**	0.529–1.001	–6.57**	0.714**	0.517–0.984
Mild/moderate exacerbations	10.22**	1.69**	1.188–2.400	10.62**	1.72**	1.210–2.457
Long-acting anticholinergic agent	2.77	1.15	0.838–1.584	2.73	1.150	0.836–1.582
Pharmacological cost	–0.21*	0.989*	0.986–0.992	–0.21**	0.989**	0.986–0.992
Visits to doctor	0.24**	1.012**	1.004–1.021	0.24**	1.012**	1.004–1.021

Notes: *$P<0.001$ and **$P<0.05$.
Abbreviations: CI, confidence interval; DPI, dry powder inhaler; pMDI, pressurized metered-dose inhaler; ICS/LABA, inhaled corticosteroids and long-acting β_2-agonist; FDC, fixed-dose combination; COPD, chronic obstructive pulmonary disease.

of disease severity is very similar across clusters. It is worth mentioning that the use of ICS/LABA FCD in COPD subjects is limited to severe or moderate-to-severe obstruction and common exacerbations; however, we observed patients classified as mild who use these therapies. Furthermore, one DPI included does not have indication for COPD in Spain but our sample shows that currently is being used with such a propose, which might be explained by a certain freedom to prescribe off-label. Almost half of the patients (40.79%) experienced at least one exacerbation.

Table 2 contains results of univariate regressions. DPI utilization was negatively correlated with adherence; on the contrary, the effect of active ingredients was not statistically significant. Clinical characteristics, such as COPD severity, time since diagnosis, number of mild and moderate exacerbations, and some comorbidities, such as smoking and cerebrovascular diseases, were negatively correlated with adherence, except for moderate exacerbations that were positively correlated with it. None of the diseases that are mobility limiting were significant. Long-acting anticholinergic agents were positively correlated with adherence as well as most of the medication to treat COPD, except for systemic administration of β_2-adrenoceptor agonists that were not statically significant. Pharmaceutical costs were negatively correlated with adherence, and visits to physician were positively correlated with it.

Inhaler technique and other confounders affecting patient's adherence to the COPD treatment

Results are shown in Table 3 with and without active ingredient variable. Remarkably, variable for inhaler devices increased its significance ($P<0.001$), and the probability of adherence by a patient using a DPI would be diminished by almost 10 pp compared to that of a patient using pressurized inhalers. These measures were adjusted for confounders, and some of them were significant. For instance, time since diagnosis is negatively associated with medication adherence. In case of moderate exacerbations, the link is positive. Regarding health care resources, the coefficient of pharmaceutical cost would have a small negative impact on medication adherence, while the effect of doctor's visit is positive.

In Table 4, we present the results of the regression that provided the adjusted measures of association between the

Table 4 Final specification: results of multivariable analysis examining the associations between inhaler devices for ICS/LABA FDC and adherence

Explanatory variables (McFadden's R^2=0.2898)	Adherence (n=1,263)		
	Percentage points	Odds ratio	95% CI
Medical device DPI (baseline pMDI)	−5.38*	0.71*	0.521–0.970
ICS/LABA FDC (baseline formoterol/beclomethasone)			
Formoterol/budesonide	−0.38	0.97	0.661–1.440
Salmeterol/fluticasone	3.07	0.72	0.241–2.174
Severity of COPD (baseline moderate)			
Mild	−9.81*	0.53*	0.300–0.960
Severe	−5.15	0.72	0.241–2.174
Time since COPD was diagnosed	−0.78*	0.95*	0.923–0.981
Therapy line (baseline first line)			
Second line	−1.27	0.92	0.603–1.413
Third line	1.69	1.11	0.437–2.823
Sex (baseline men)	3.01	1.21	0.816–1.782
Age (as a continuous variable)	−1.23**	0.96**	0.887–0.966
Age groups (baseline 87–97)			
39–51	−34.04**	0.99*	0.169–0.578
51–61	−29.69**	0.13*	0.036–0.501
61–71	−23.04**	0.212*	0.081–0.552
72–83	−16.62**	0.32**	0.173–0.599
Retired status	5.05	1.37	0.736–2.563
Number of comorbidities			
2	−0.74	0.95	0.662–1.374
3	−10.96*	0.49*	0.282–0.864
Obesity	6.26	1.47	0.975–2.231
Smoking	14.52*	2.248*	1.105–5.587
Smoking men	−28.73**	0.167**	0.034–0.800
Hypertension	6.29*	1.48*	1.085–2.018
Diabetes	5.00	1.36	0.981–1.902
Acute exacerbation	−8.36*	0.59*	0.378–0.933
Moderate exacerbation	2.20	1.14	0.914–1.438
Long-acting anticholinergic agents	5.23	1.37	0.928–2.050
Other medication to treat COPD	2.44	1.16	0.995–1.362
Additional visit to the doctor	2.15**	1.14**	1.122–1.165
Visits to doctor			
Two times per month (on average)	−33.88**	0.11**	0.797–0.165
Three times per month (on average)	−67.25**	0.0028**	0.009–0.007
Average pharmacological cost per month	0.04	1.00	0.999–1.006

Notes: *$P<0.05$ and **$P<0.001$.

Abbreviations: ICS/LABA, inhaled corticosteroids and long-acting β_2-agonist; FDC, fixed-dose combination; CI, confidence interval; DPI, dry powder inhaler; pMDI, pressurized metered-dose inhaler; COPD, chronic obstructive pulmonary disease.

inhaler technique and medication adherence and showed to fit the data better than previous models. This analysis revealed that patients treated with ICS/LABA FDC delivered by a DPI were less likely to adhere to their COPD treatment compared to patients that used a pMDI. By contrast, the variable that captures the association between ICS/LABA and adherence was not significant. Regarding disease severity, worsening of COPD is not negatively associated with adherence. This effect is not consistent with the coefficient of time since the diagnosis, which implies that the probability of medication adherence would decrease by 0.7 pp, for an extra year with COPD.

The categorical variable for the number of comorbidities shows that having more than three multiple conditions would impact negatively on medication adherence, despite most of the comorbidities in the previous regressions were not statistically significant. Regarding comorbidities, we found that hypertension was positively correlated with adherence as well as smoking. Regarding patients' characteristics, age appeared to be determinant, affecting adherence to treatment negatively. However, this effect becomes smaller as we moved to older age groups.

An additional acute exacerbation for COPD patients was negatively associated with medication adherence, but

number of medication to treat COPD, besides ICS/LABA FDC, showed to be not significant. An additional visit to the doctor was positively associated with medication adherence. Conversely, more than one physician visit per month is negatively associated with adherence. Some other potential confounders, such as sex, concomitant medication, and moderate exacerbations, were not statistically significant for explaining adherence with COPD medication. Additionally, results of the interaction term of sex and smoking suggest that the probability of medication adherence was reduced for smoking men compared to smoking women and nonsmokers. Regarding health care resources, cost was not significant. Robustness check confirmed our results, and the effect of inhaler technique increases its significance toward suboptimal adherence ($P<0.001$).

Discussion

These analyses revealed that after adjustment for confounding variables, especially the active agents, patients treated with ICS/LABA FCD delivered using a DPI (Accuhaler®, NEXThaler®, and Turbuhaler®) were less likely to show adherence compared to patients treated with ICS/LABA FCD delivered using a pMDI. Results are striking because, despite the inclusion of several confounders of adherence, there was still a statistically significant coefficient of the variable of inhaler devices' utilization, suggesting that factors related only to inhaler devices might weaken probability of medication adherence. We can find critical errors of DPIs in the literature. The most frequently reported flaw is failure to exhale before inhaling and in consequence, failure to use a forceful and deep inhalation.[19] Moreover, DPIs included in our analysis present errors regarding the metering of the dose and positioning the inhaler.[19] Suboptimal adherence limits the efficacy of inhalation therapy, since there are negative impacts in outcomes as survival and cost as well as clinical outcomes.[20,21] Although there is not an agreement on the situation that predisposes to inhaler misuse, the identification of associations between inhaler technique and patients' adherence shed some light on reasons why suboptimal adherence has become a major problem.[3,18,22,23]

Our results are consistent with the previous analyses that described several factors affecting medication adherence negatively.[8,24,25] In our analysis, we identified factors that affect adherence of long-term inhalation therapy in COPD patients. Age was negatively associated with adherence.[26] This effect is consistent with time since diagnosis, which indicates a negative in adherence as time passes toward adherence to long-term therapy. However, the effect decreases along with age.[27,28] Hypertension patients were more likely to medication adherence, which is plausible because these patients might be also more controlled due to high blood pressure, and adherence in hypertension is higher compared to COPD, which could also influence adherence for COPD.[29] Conversely, arthritis and osteoarthritis have not shown to be statistically significant, although these conditions contribute to an inability of device utilization.[30] These results are likely to be explained by the constrained subsample size of these comorbidities; hence, further research is needed in this area.

Some patients failed to comply with physician's recommendations since they did not quit smoking (19% of the sample). Smoking cessation is the most effective way of slowing the progression of this disease.[12] Therefore, it is plausible to think that patients are also nonadherent to their medication.[31] Indeed, our results suggest that the smoking men's probability of medication adherence decreased by 30 pp. Although sex was not crucial for explaining adherence, the negative effect of the interaction term between smoking status and men is considerable. The sample was mostly composed of men, who represent the common COPD patient.[2] However, this pattern is changing since incidence of smoking, main cause of COPD, has increased in women, which have now greater health risks.[2]

Regarding health care utilization, we identified two effects of visiting the doctor. The effect of doctor visit would increase the probability of medication adherence.[18] Conversely, patients who have visited their doctor more than three times per month were more likely to have suboptimal adherence. Results are feasible since health care professional interventions are consistently positive for adherence and compliance.[32] However, many visits to the doctor negatively associated might indicate serious problems and patients are pushed to visit several times their physician.[14,15,33] Cost was not finally statistically significant toward adherence. This is plausible since Spanish patients do not bear 100% of the pharmaceutical costs directly.[34]

These results should be interpreted within the context of study limitations. First, this is a retrospective study, which is vulnerable to bias. For instance, we could identify endogeneity in results for exacerbations, since it is likely that the causal direction goes from medication adherence toward exacerbations and not vice versa.[13,35] Second, this study was conducted in a single health system; thus, results may not be extrapolate to other populations. However, trends are similar to previous research.[17,20,23] Third, the assumption that obtaining prescription was equivalent to taking the medication, which might not be completely true. Moreover, our study approach to quantify adherence was done by using the MPR, which has

been reported to be biased upward by previous research.[9,14] Nevertheless, we tried to correct this by elevating the cut-point, so fewer patients would be seen as adherent, and testing robustness of estimates due to this cut-point confirmed our findings. Actually since we obtain the persistence to COPD long-term medication, our estimates could be more accurate than those of few others who also used MPR without taking into account persistence. It is also true that tracking adherence patterns may imply to have data across time, which can be accomplished by analyzing adherence prospectively as well as analyzing other issues related with poor adherence that were not measured, such as intentional and nonintentional nonadherences, patients' preferences, and specific steps that the patients fail to complete within the process of taking their medicine.[5,36,37] The fact that NEXThaler® was introduced in 2012 could limit our study, but dataset provides a sufficient number of cases using NEXThaler® in order to be included within the DPI group. Finally, we could not obtain some patients' characteristics, such as race, level of education, type of job, and few others. This problem of data limitation also restricts our outcomes.

Conclusion

Medication adherence in COPD is crucial for optimizing clinical outcomes, and there are several factors that condition it. Inhaler devices are expected to help optimization of active ingredients. However, we found that DPIs included in our analysis (Turbuhaler®, Accuhaler®, and NEXThaler®) delivering ICS/LABA FDCs had a negative effect on patients' medication adherence compared to pMDIs. The findings reviewed here suggest that the pharmacological effectiveness of the FDC, which seemed to be very promising in the beginning, might be conditioned by the inhaler technique associated with inhaler devices. The special feature of our findings is that we adjusted for the effects of the active ingredients in order to explore the specific effect of inhaler technique toward adherence. We have also corroborated that patients' clinic and demographic characteristics are associated with adherence.

Suboptimal adherence is a major problem in long-term therapies, such as COPD treatment. The consideration of incidence trends and risk factors related to COPD, in addition to the aging of population, makes very relevant to overcome barriers to treatment adherence in order to avoid progression of the disease and waste of resources because patients cannot obtain the maximum efficacy of their treatment, even among those who want to take their medicine correctly. Overcoming barriers passes through the innovation of inhaler devices. Instead of attributing all the responsibility of poor utilization due to human errors, more intuitive and simple designs are needed.

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