

Identification of factors involved in medication compliance: incorrect inhaler technique of asthma treatment leads to poor compliance

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Objective: To identify the impact of delivery device of inhaled corticosteroids and long-acting β_2 -agonist (ICS/LABA) on asthma medication compliance, and investigate other factors associated with compliance.

Materials and methods: We conducted a retrospective and multicenter study based on a review of medical registries of asthmatic patients treated with ICS/LABA combinations ($n=2,213$) whose medical devices were either dry powder inhalers (DPIs, such as Accuhaler[®], Turbuhaler[®], and NEXThaler[®]) or pressurized metered-dose inhalers (pMDI). Medication compliance included persistence outcomes through 18 months and medication possession ratios. Data on potential confounders of treatment compliance such as asthma exacerbations, comorbidities, demographic characteristics, and health care resource utilization were also explored.

Results: The probability of asthma medication compliance in case of DPIs was lower compared to pMDIs, which suggests that inhaler devices influence inhalation therapies. There were additional confounding factors that were considered as explanatory variables of compliance. A worse measure of airflow obstruction (forced expiration volume in 1 second), comorbidities and general practitioner (GP) consultations more than once per month decreased the probability of compliance. Within comorbidities, alcoholism was positively associated with compliance. Patients of 29–39, 40–50, and 51–61 age groups or suffering from more than two exacerbations during the study period were more likely to comply with their medication regime. The effects of DPIs toward compliance varied with the different DPIs. For instance, Accuhaler[®] had a greater negative effect on compliance compared to Turbuhaler[®] and Nexthaler[®] in cases of patients who suffered exacerbations. We found that GP consultations reduced the probability of medication compliance for patients treated with formoterol/budesonide combination. For retired patients, visiting the GP increased the probability of medication compliance.

Conclusion: We concluded that inhaler devices influence patients' compliance for long-term asthma medication. The impact of Accuhaler[®], Turbuhaler[®], and NEXThaler[®] on medication compliance was negative. We also identified some confounders of medication compliance such as patient's age, severity of asthma, comorbidities, and health care costs.

Keywords: adherence, inhaler devices, medication possession ratio, dry powder inhalers, pressurized metered-dose inhalers, persistence

Introduction

Asthma is characterized by the inflammation of respiratory airway, hypersensitivity of airway path, and the variable airflow limitation during short periods of time. A controller medication is daily medication that is used to prevent or improve asthma symptoms in patients who experience them frequently. The medical decision to use a controller medication for a patient with asthma is based on the frequency and type of daytime or

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nighttime symptoms, frequency of medical visits for asthma, frequency of requiring asthma rescue medications, frequency of oral steroid use, impact of asthma symptoms on daily life, and breathing tests for asthma. Inhalation therapy presents advantages in respect to oral or parenteral treatment such as easy access of the medication to the bronchoalveolar system and lower dosage.¹ However, these attributes are diminished due to a poor compliance associated with deficient inhaler technique.²⁻⁵ Although inhaled corticosteroids and long-acting β_2 -agonist (ICS/LABA) fixed-dose combinations have shown to relieve asthma symptoms, similarly,^{6,7} there is increasing research that claims that inhaler technique might affect compliance and hence, efficacy of pharmacological treatment.^{8,9}

Several studies reported a critical problem of patients' compliance in chronic airway conditions.^{2,10,11} Noncompliance with drug treatment continues to be a significant barrier to asthma control, which contributes to costly exacerbations and worsening of the disease over time.¹² Medication compliance implies that the patient follows doctor's orders and patient's medication-taking behavior corresponds with doctor's recommendations with respect to timing, dosage, and frequency.¹³⁻¹⁵ Over the past few years, researchers from several disciplines raised that poor compliance is an important problem for the national health care system around the world and should be treated from a multidisciplinary perspective.^{9,12,13}

The aim of this study was to examine medication compliance in asthmatic patients, focusing on the associations between compliance with asthma medication and inhaler devices such as dry powder inhaler (DPI) or pressurized metered-dose inhaler (pMDI). Moreover, some other confounders of compliance were analyzed, which were beyond clinical aspects.

Materials and methods

Study sample

We conducted a retrospective and multicenter study based on review of medical registries of asthmatic patients treated with ICS/LABA combinations, whose medical devices were either DPIs (such as Accuhaler[®], Turbuhaler[®], or NEXThaler[®]) or pMDI. The study population included patients attending primary care centers, whose population was mostly urban, with a low-to-medium socioeconomic level.

The study sample was comprised of all asthmatic patients who started taking ICS/LABA delivered by a DPI or pMDI between 2007 and 2014. Moreover, patients needed to fulfill the following characteristics: 1) aged 18 and over; 2) time of diagnosis >3 years; 3) patients were required to have registries with regular monitoring for 18 months (ie, those who were part of the long-term prescription program to

obtain drugs with a confirmed record of the daily dosage, time interval, and duration of each treatment). We excluded patients who were transferred outside the area and patients permanently institutionalized.

Data source

Patient compliance for each medication was tracked for 1.5 years using persistence and adherence information. We obtained information on asthma treatment with ICS/LABA combination accordingly, with the Anatomical Therapeutic Chemical Classification System. Moreover, we linked each ICS/LABA combination to its medical device: Accuhaler[®], Turbuhaler[®], NEXThaler[®], or pMDI. Data on diagnoses for a given individual were linked to medication associated with asthma using pharmacy administrative database and clinical visit data from electronic patient records. These databases are managed by Badalona Serveis Assistencials, which provides services to ten primary care centers, one hospital, and one socio-health center. Ethics approval for the database to be used for research was granted by the Hospital Germans Triás i Pujol Ethics Committee. No consent form from patients or caregivers was required for this study because data included in this database went through an anonymization process for patients' information, guaranteed by the Badalona Serveis Assistencials S.A. organization that had access to the data.

Data on persistence of each patient at the 3rd, 6th, 12th, and 18th month were obtained (Figures 1 and 2) as well as information on medication possession, by patient's refill count, and duration, by the number of days the patient should be consuming the medication. Other potential explanatory variables of compliance were considered after literature review and most of them were available in electronic patient reports. Number of exacerbations per patient during the study period was collected and more specifically data on number of mild/moderate exacerbations and acute events. These acute exacerbations implied hospitalizations patients could not control the exacerbation at home. We also gathered data on additional medication. However, we did not analyze compliance toward this medication since we were interested on compliance patterns in patients attempting to take ICS/LABA fixed dose combinations chronically.

Clinical data on comorbidities were included.¹⁶ It was indicated whether the patient suffered simultaneous condition such as hypertension, diabetes, dyslipidemia, depression, and dementia. We also decided to indicate severe events including organ failures, ischemic heart disease, stroke, cerebrovascular disease, and neoplasm. Behavior attitudes that could result in higher risk of for instance obesity, smoking habit, and alcoholism were also included as comorbidities.¹⁷

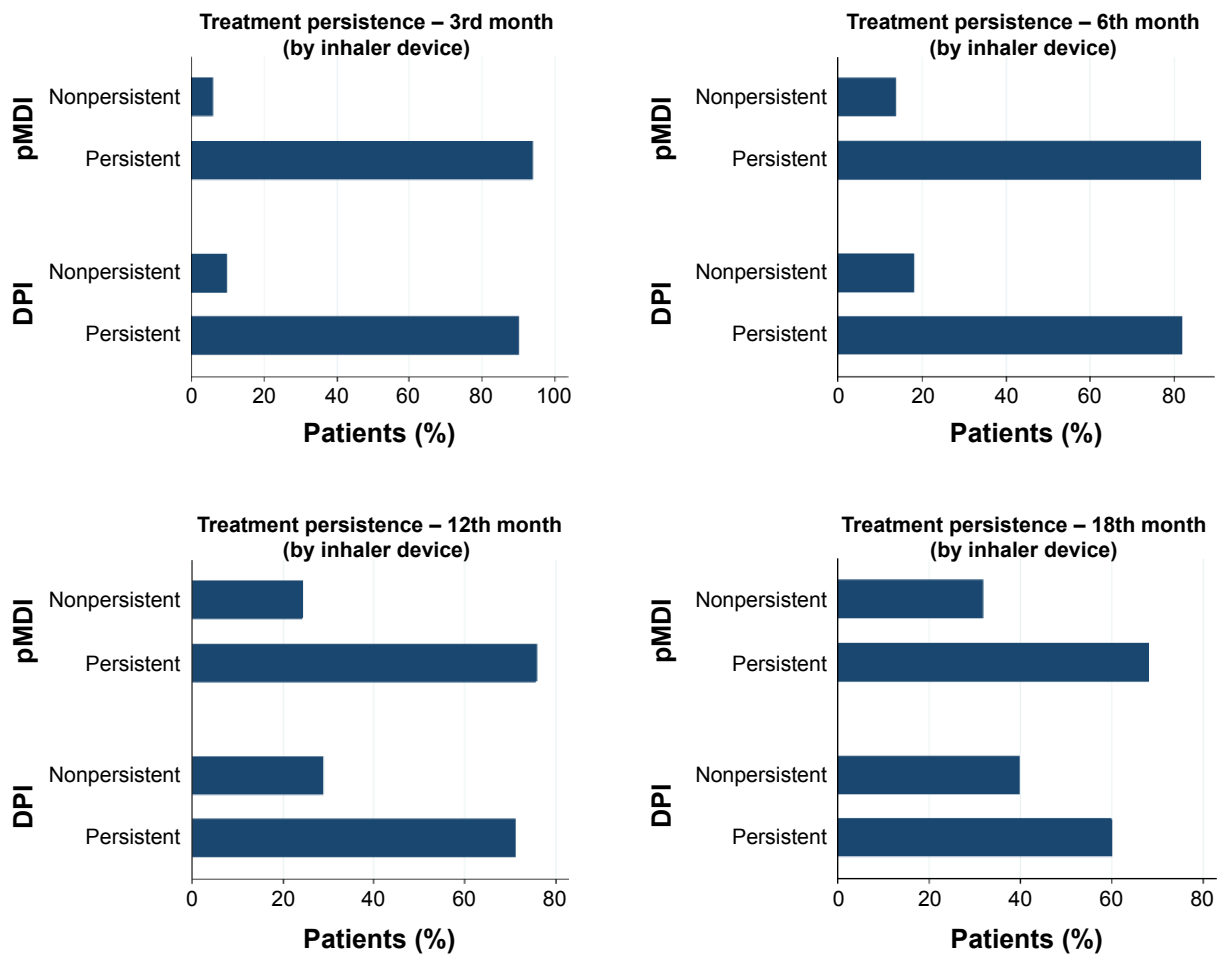


Figure 1 Percentage of persistent patients at the 3rd, 6th, 12th, and 18th month. **Abbreviations:** DPI, dry powder inhaler; pMDI, pressurized metered dose inhaler.

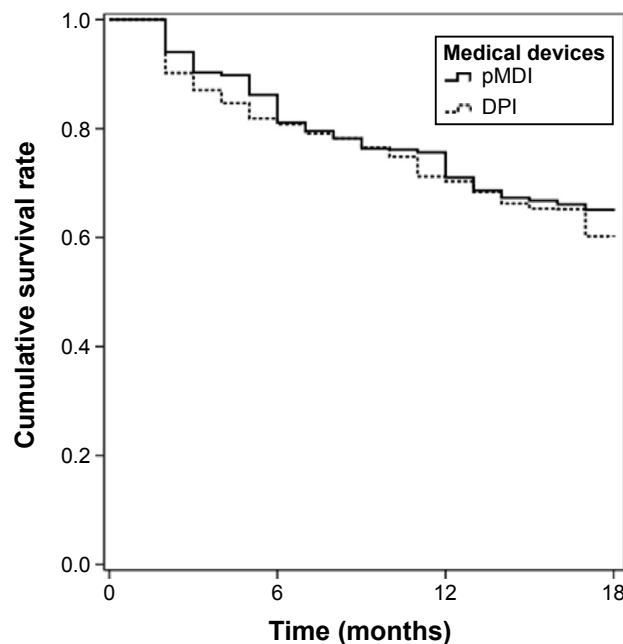


Figure 2 Medication compliance. **Abbreviations:** DPI, dry powder inhaler; pMDI, pressurized metered dose inhaler.

Moreover, we considered the number of visits in primary care centers for general practitioner (GP) consultation, hospital emergency visits, and we had access to pharmacy registries that gather the gross amount of pharmaceutical expenditure. Amounts were adapted into our model by obtaining patient’s average cost per month, and because Spanish patients have low co-payment levels, this proxy might be more accurate than the gross amount. Sick leave days were also gathered.¹⁸ Demographics of this sample were age, sex, and whether the patient was retired or not.^{19,20}

Calculation of patient’s medication compliance

To calculate compliance, 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.²¹ First, we identified persistent patients as those who used their medication for 18 months. These patients were analyzed

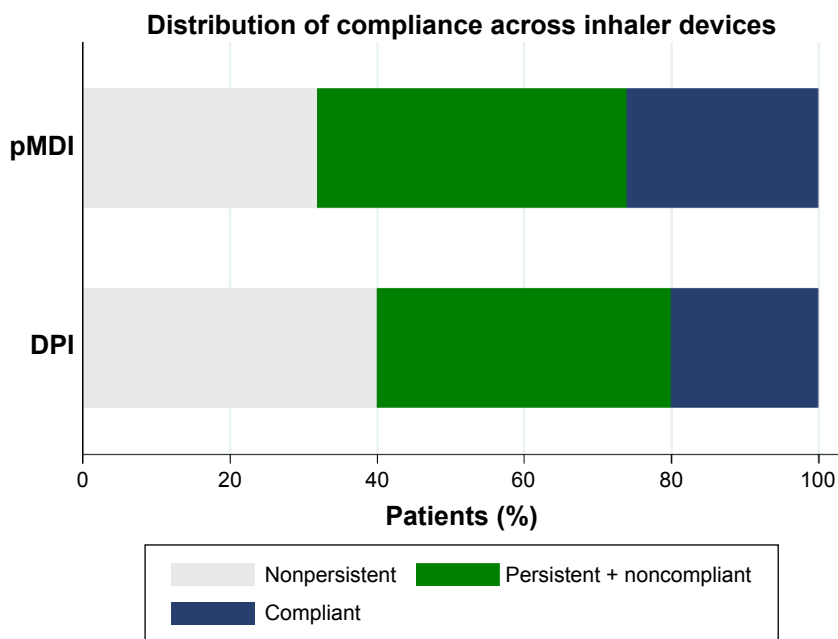


Figure 3 Percentage of patients' compliance for each inhaler device (n=2,213).
Abbreviations: DPI, dry powder inhaler; pMDI, pressurized metered dose inhaler.

to obtain compliance by using the MPR. Therefore, within these persistent patients we applied a cut-point of 95% to the MPR, which tends to be overestimated,^{9,22} thus we also increased the limit to where patients were considered actively compliant. In the end, we had an ordered categorical variable, which showed to be very useful to identify persistence and compliance patterns, since patients first need to be persistent with their treatment and then they need to comply with their prescriptions.^{9,13} This variable reflects patients who are not either persistent or compliant, patients who are persistent but noncompliant, and patients who are persistent and showed compliance 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.^{14,23}

Analysis

To describe the distribution of patient's compliance within each medical device (DPI or pMDI), we tabulated sample characteristics for patients using either a DPI or a pMDI. Univariate associations between drug compliance, medical device, and several confounders such as age, comorbidities, exacerbations, severity of asthma, concomitant and rescue medication, and drug cost were analyzed.

In order to determine a specification that provides a better fit of the data for explaining compliance outcomes, interaction terms between the proxy of inhaler technique and the confounders of interest were also included. The impact of exacerbations relative to each inhaler device toward adherence

was captured by computing the probability of having an exacerbation for each device of interest. The effect of severity of asthma for each type of DPIs was also examined.

With reference to health care utilization, visits to the GP were categorized in order to explore the association of having, on average: none or one visit per month, one to two visits per month, and more than three visits per month. Further, patients' visits to their GP were computed per active substance. The effect of GP consultation for retired patients was also obtained. We considered a variable for comorbidity status, which was categorized as having 1, 2, 3, or more than 4 conditions.

Additionally, having an acute event (ischemic heart disease, organ failures, stroke, or cerebrovascular diseases) was added into the regression. Moreover, to consider the potential heterogeneity sources across age groups, the continuous variable age was split into seven groups. Finally, the effect of cost toward adherence for each age group was introduced in order to approximate the effect of socioeconomic status.²⁰

Results

Clinical and demographic characteristics

Characteristics of underlying populations of DPI users (73.2%) and pMDI users (26.8%) are presented in Table 1. Asthmatic patients (n=2,213) were predominantly female (61.46%), working-age (59.69%), and age distribution was very similar among the sample except for the oldest age group (5.60%) in which patients were 83–96 years old. Time

Table 1 Characteristics of COPD patients according to type of inhaler device used

Characteristics	pMDI n=593 (26.8%)	DPI n=1,620 (73.2%)	Total N=2,213	P-value
Female, %	60.9%	61.7%	61.5%	0.735
Age mean (SD), years	52.3 (19.6)	53.2 (18.8)	52.9 (18.5)	0.326
18–28	15.85%	7.78%	9.94%	NA
29–39	15.17%	18.14%	17.35%	NA
40–50	14.84%	21.19%	20.02%	NA
51–61	17.03%	19.19%	18.62%	NA
62–72	17.53%	16.29%	16.63%	NA
73–83	16.02%	10.31%	11.84%	NA
83–96	3.54%	6.36%	5.60%	NA
Retirement status	40.5%	40.6%	40.6%	0.966
Time since diagnosis (SD), years	13.0 (5.3)	13.0 (4.2)	13.0 (4.5)	0.994
Asthma classification				
Mild intermittent	19.7%	19.4%	19.5%	NA
Mild persistent	31.0%	30.5%	30.6%	NA
Moderate persistent	46.5%	47.3%	47.1%	NA
Severe persistent	2.7%	2.7%	2.7%	0.990
FEV ₁ (SD)	76.6 (9.9)	79.1 (9.9)	79.2 (9.9)	0.256
Allergy	43.84%	49.13%	47.72%	0.892
ICS/LABA combination				
Formoterol/beclomethasone	31.2%	14.4%	18.9%	NA
Formoterol/budesonide	0.0%	60.6%	44.4%	NA
Salmeterol/fluticasone	68.8%	25.0%	36.7%	NA
Exacerbations	14.7%	22.8%	20.7%	<0.001
Moderate	11.6%	22.0%	19.2%	<0.001
Acute	5.2%	6.7%	6.3%	0.199
Comorbid conditions				
Obesity	27.7%	28.0%	27.9%	0.650
Smoking	21.8%	22.4%	22.2%	0.743
Alcoholism	2.7%	2.6%	2.6%	0.891
Cardiovascular event	9.8%	9.7%	9.7%	0.948
Hypertension	25.6%	24.7%	24.9%	0.650
Diabetes	14.3%	13.8%	13.9%	0.732
Dyslipidemia	38.8%	37.3%	37.7%	0.518
Cerebrovascular events	7.4%	6.7%	6.9%	0.570
Ischemic heart disease	4.4%	4.3%	4.3%	0.948
Organ failures	12.3%	12.3%	12.3%	0.987
Dementia	2.2%	2.2%	2.2%	0.964
Depression	18.5%	18.2%	18.3%	0.855
Neoplasm	9.8%	9.5%	9.6%	0.846
Additional medication				
Oral corticosteroids	14.7%	22.8%	20.7%	<0.001
Systemic antibiotics	2.7%	7.0%	5.9%	<0.001
SABA	80.3%	80.4%	80.3%	0.958
Number of visits to GP, (SD)	12.5 (11.3)	17.0 (14.0)	15.8 (13.5)	<0.001
Mean of number of visits to the emergency room, (SD)	0.1 (0.3)	0.2 (0.5)	0.2 (0.5)	<0.001
Mean of cost of pharmacological treatment (SD), Euros	502.0 (510.4)	407.0 (407.8)	432.4 (439.5)	<0.001
Days off from work (SD)	2.5 (18.4)	3.2 (22.2)	3.1 (21.2)	0.444
Mean of total health care cost per patient (SD), Euros	1,261 (2,093.8)	1,520 (2,562.9)	1,449.9 (2,448.4)	0.024

Note: Patients' characteristics of those who visited their primary care center between January 2007 and June 2014.

Abbreviations: COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FEV₁, forced expiratory volume in the first second; GP, general practitioner; ICS/LABA, inhaled corticosteroid and long-acting β_2 -agonist; NA, not applicable; pMDI, pressurized metered dose inhaler; SABA, short-acting β_2 -agonist; SD, standard deviation.

since asthma was diagnosed (in years) was similar in both groups, however, its distribution varies widely and it goes from 3 years to 76.13 years. The most frequent comorbidity observed in this sample is dyslipidemia (37.7%), followed

by obesity (27.9%), and diabetes (24.9%), which were very similar in both groups. Nearly half of the patients had moderate persistent asthma. It was interesting to note that 79.35% of the sample did not experience any exacerbation event.

Across clusters, DPI users had higher rate of exacerbations compared to pMDI users ($P<0.001$) and severe exacerbations were more prevalent for DPI users ($P<0.001$).

Table 2 contains estimates of the univariate analysis and significance levels. At a first glance, having DPIs was negatively associated with compliance. Regarding active substances, patients taking salmeterol/fluticasone combination tend to have higher compliance compared to patients taking formoterol/beclomethasone combinations; in contrast

the coefficient for the variable of salmeterol/fluticasone combination was not statistically significant. Most of the comorbidities were not statistically significant and only hypertension and organ failures correlated positively with compliance. Number of exacerbations and most specifically moderate exacerbations were positively correlated with better compliance outcomes. Mild, moderate, and severe persistent asthma were correlated with better compliance compared to intermittent asthma. Regarding utilization of health care

Table 2 Univariate analysis of potential confounders of compliance

Category	Compliance		
	Percentage points	Odds ratio	95% CI
Explanatory variables			
DPI compared to pMDI	-5.89	0.706	(0.593–0.841)
ICS/LABA (baseline formoterol/beclomethasone)			
Formoterol/budesonide	-0.37	0.976	(0.789–1.207)
Salmeterol/fluticasone	5.99**	1.409**	(1.131–1.755)
Therapy line (baseline first line)			
Second line	17.47*	2.441*	(1.848–3.224)
Third line	68.98*	31.384*	(11.00–89.52)
FEV ₁ measure	-0.41	0.97	(0.968–0.983)
Age	0.11**	1.007**	(1.002–1.011)
Male	1.50	1.092	(0.932–1.281)
Retired	4.17**	1.278**	(1.090–1.498)
Obesity	1.73	1.108	(0.932–1.317)
Smoking	-4.15**	0.783**	(0.648–0.945)
Stroke	2.52	1.160	(0.839–1.602)
Cerebrovascular disease	3.23	1.210	(0.923–1.584)
Hypertension	3.64*	1.239*	(1.035–1.484)
Diabetes	-2.53	0.861	(0.685–1.082)
Dyslipidemia	-0.57	0.994	(0.847–1.167)
Alcoholism	6.18	1.439	(0.905–2.290)
Ischemic heart disease	2.77	1.177	(0.801–1.731)
Organ failures	6.29**	1.449**	(1.139–1.843)
Dementia	-4.29	0.777	(0.450–1.341)
Depression	-1.75	0.902	(0.737–1.035)
Neoplasm	0.36	1.021	(0.781–1.335)
Allergy	3.84**	1.255**	(1.074–1.465)
Number of exacerbations	2.01**	1.126**	(1.018–1.245)
Number of acute exacerbations	0.76	1.046	(0.761–1.438)
Number of mild/moderate exacerbations	2.77**	1.178**	(1.047–1.325)
Severity of asthma (baseline intermittent)			
Mild persistent	8.40*	1.857*	(1.480–2.327)
Moderate persistent	13.52*	2.473*	(2.000–3.057)
Severe persistent	17.85*	3.064*	(1.865–5.032)
Time from diagnosis	0.26	1.01	(0.999–1.033)
Oral corticosteroids	2.91	1.187	(0.982–1.435)
Systemic antibiotics	8.40**	1.642**	(1.187–2.274)
SABA	6.96*	1.509*	(1.240–1.836)
Visits to GP	0.21*	1.012*	(1.006–1.018)
Emergency visits	2.05	1.12	(0.962–1.323)
Sick leave	-0.04	0.99	(0.993–1.001)
Cost	-0.11*	0.994*	(0.991–0.996)

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

Abbreviations: CI, confidence interval; DPI, dry powder inhaler; FEV₁, forced expiratory volume in the first second; GP, general practitioner; ICS/LABA, inhaled corticosteroid and long-acting β_2 -agonist; pMDI, pressurized metered dose inhaler; SABA, short-acting β_2 -agonist; SD, standard deviation.

resources, an extra visit to the GP was positively linked to compliance, while cost was negatively correlated with it. Patient characteristics such as age, retirement status, and allergy were positively correlated with compliance.

Inhaler technique and other confounders affecting patient's compliance to the asthma treatment

The patterns of the relationship from the multivariate ordered logistic regression model matched some of those of the univariate results (Table 3). Indeed, the probability of having more negative compliance is larger for DPI users compared to patients using pMDI. These patterns also fit for severity of asthma, allergy, acute exacerbations, and cost. In contrast, age, comorbidities, moderate exacerbations, and retirement were not statistically correlated with compliance. After controlling for the ICS/LABA combination, which became statistically significant, the magnitude of DPIs' effect on compliance in comparison with pMDI outcomes decreased.

The final specification showed to fit the data better for explaining compliance patterns (Table 4). Having a DPI would decrease the probability of asthmatic patients to comply with their treatment compared to pMDI. Moreover,

deterioration of forced expiratory volume in the first second measure by 1 unit and having ≥ 3 comorbidities would decrease the probability of medication compliance. More than one doctor's consultation per month was associated with worse adherence. Patients who belonged to 29–39, 40–50, and 51–61 age groups were more likely to be adherent compared to the oldest group, as well as those who suffered more than two moderate exacerbations compared to those who did not experience any exacerbation. An additional doctor visit was associated with better adherence. Alcoholism, which was the only comorbidity statistically significant, was positively associated with compliance. Again, active substance categorical variable was not statistically significant.

The introduction of interaction terms revealed interesting results. The effect of exacerbations varies across inhaler devices and the probability of being a compliant patient with Accuhaler[®] who suffered an exacerbation is lower compared to the rest of DPI users. However, as asthma gets worse, Accuhaler[®] devices have a small but positive effect toward compliance compared to the pMDI. Estimates of the other DPIs were not statistically significant. In the case of healthcare utilization, the patient's probability of medication compliance would be lower for those who visited their GP

Table 3 Multivariate results of potential confounders of compliance

McFadden's $R^2=0.029$	Compliance					
	Without active substance			Controlling for active substances		
	Percentage points	Odds ratio	95% CI	Percentage points	Odds ratio	95% CI
Explanatory variables						
Medical device DPI	-6.46*	0.69*	(0.575–0.841)	-4.48**	0.77**	(0.617–0.972)
ICS/LABA						
Formoterol/budesonide	–	–	–	1.02	1.065	(0.830–1.368)
Salmeterol/fluticasone	–	–	–	5.78**	1.398**	(1.104–1.770)
Severity						
Persistent mild	11.02*	2.22*	(1.737–2.834)	10.81*	2.188*	(1.712–2.796)
Persistent moderate	15.42*	2.82*	(2.203–3.610)	15.26*	2.791*	(2.180–3.575)
Persistent severe	24.08*	4.26*	(1.994–9.124)	24.41*	4.322*	(2.017–9.260)
Therapy line						
Second	14.04*	2.10*	(1.558–2.831)	13.69*	2.07*	(1.535–2.791)
Third	65.53*	29.0*	(9.794–85.92)	65.20*	28.43*	(9.575–84.45)
Age	0.13	1.008	(0.999–1.016)	0.12	1.007	(0.999–1.015)
Retired	2.96	1.188	(0.843–1.597)	2.97	1.190	(0.885–1.601)
Smoker	-1.74	0.902	(0.733–1.109)	-1.87	0.894	(0.727–1.100)
Hypertension	-0.95	0.946	(0.748–1.194)	-0.95	0.945	(0.748–1.194)
Organ failures	3.06	1.195	(0.896–1.595)	2.93	1.187	(0.889–1.585)
Allergy	3.70**	1.24**	(1.045–1.474)	3.96**	1.261**	(1.061–1.497)
Acute exacerbations	-8.02*	0.626*	(0.417–0.938)	-8.61**	0.604**	(0.402–0.907)
Mild/moderate exacerbations	0.67	1.040	(0.868–1.245)	0.746	1.04	(0.871–1.252)
Pharmacological cost	-0.170*	0.988*	(0.986–0.992)	-0.179*	0.989*	(0.986–0.992)
Visit to GP	0.04	1.002	(0.995–1.009)	0.04*	1.002*	(0.995–1.009)

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

Abbreviations: CI, confidence interval; DPI, dry powder inhaler; GP, general practitioner; ICS/LABA, inhaled corticosteroid and long-acting β_2 -agonist; pMDI, pressurized metered dose inhaler; –, not considered within the regression.

Table 4 Final specification: ordered logistic regression analysis: predicting compliance for asthmatic patients

McFadden's $R^2=0.239$	Compliance		
	Percentage points	Odds ratio	95% CI
Explanatory variables			
DPI compared to pMDI	-10.67**	0.457**	(0.229-0.909)
ICS/LABA compared to formoterol/beclomethasone			
Formoterol/budesonide	7.75	1.761	(0.837-3.706)
Salmeterol/fluticasone	3.37	1.309	
FEV ₁	9.78*	0.977*	(0.959-0.996)
Therapy line			
Second line	0.75	1.056	(0.755-1.475)
Third line	52.7*	27.09*	(8.657-84.78)
Age groups compared to the oldest group			
18-28	6.25	2.236	(0.841-6.427)
29-39	15.64**	3.625**	(1.375-9.547)
40-50	12.68**	2.961**	(1.150-7.634)
51-61	13.59**	3.154**	(1.368-7.727)
62-72	-4.59	1.496	(1.496-3.141)
73-83	-9.38	1.598	(0.738-3.460)
Retirement	1.71	1.342	(0.540-2.379)
Allergy	1.76	1.138	(0.937-1.381)
Number of comorbidities			
1	-1.86	0.877	(0.665-1.157)
2	-4.82	0.704	(0.488-1.017)
3	-7.52**	0.566**	(0.367-0.874)
>4	-7.16**	0.584**	(0.505-1.557)
Acute event/condition	1.08	1.082	(0.796-1.471)
Obesity	2.69	1.218	(0.933-1.591)
Alcoholism	7.98**	1.795**	(1.013-3.179)
Smoking	0.58	1.043	(0.788-1.381)
Acute exacerbation	-1.60	0.886	(0.505-1.557)
Moderate (compared with no exacerbation)			
1 moderate exacerbation	15.03	2.736	(1.003-6.463)
≥2 moderate exacerbations	20.35**	3.726**	(1.111-10.49)
Visit to the emergency room	-8.20	0.517	(0.235-1.134)
Additional visit to the GP	1.98*	1.156*	(1.137-1.175)
Visiting a GP			
Two times per month (on average)	-25.83*	0.094*	(0.674-0.131)
Three times per month (on average)	-39.12*	0.025*	(0.001-0.005)
Average pharmacological cost per month	0.22	1.016	(0.998-1.035)
Day lost due to some event related with asthma	-0.81	0.941	(0.680-1.300)
Potential underlying mechanism			
Severity related to DPI			
Severity/Accuhaler®	4.98**	1.441**	(1.049-1.978)
Severity/Turbuhaler®	4.98	1.037	(0.812-1.324)
Severity/NEXThaler®	2.64	1.214	(0.877-1.680)
Exacerbations related to each inhaler			
Accuhaler®	-21.98*	0.199*	(0.074-0.532)
Turbuhaler®	-9.84	0.482	(0.193-1.203)
NEXThaler®	-15.25**	0.326**	(0.107-0.995)
pMDI	-14.24**	0.351**	(0.139-0.886)
Visit to GP related to each ICS/LABA			
Salmeterol/fluticasone	-65.84*	0.008*	(0.001-0.498)
Formoterol/budesonide	-90.17*	0.0013*	(0.001-0.009)
Formoterol/fluticasone	-65.43*	0.008*	(0.001-0.055)
Visit to GP for retired patient	4.15**	1.356**	(0.992-0.055)
Costs for each age group (baseline 83-97 group)			
18-28	-0.37**	0.973**	(0.948-0.998)

(Continued)

Table 4 (Continued)

McFadden's $R^2=0.239$	Compliance		
	Percentage points	Odds ratio	95% CI
29–39	–0.29**	0.978**	(0.958–0.998)
40–50	–0.22	0.983	(0.964–1.003)
51–61	0.29**	0.978**	(0.962–0.994)
62–72	0.007	1.005	(0.987–1.015)
73–83	0.003	1.002	(0.987–1.010)

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

Abbreviations: CI, confidence interval; DPI, dry powder inhaler; FEV₁, forced expiratory volume in the first second; GP, general practitioner; ICS/LABA, inhaled corticosteroid and long-acting β_2 -agonist; pMDI, pressurized metered dose inhaler; SD, standard deviation; –, not considered within the regression.

more than 3 times and were treated with Formoterol/Budesonide combination compared to patients taking the other ICS/LABA combinations, although the common effect of visiting their GP was observed to be a positive association with compliance (see previous paragraph). The effect of GP visits toward compliance was greater for retired patients compared to working-age patients and retired ones who did not visit the GP during the study period. The negative effect of cost through age affected mostly younger patients and became not statistically significant for older age groups.

Robustness check confirmed our results, which implied that inhaler technique associated with DPIs would decrease the probability of patients to adhere to asthma medication ($P < 0.001$).

Discussion

Our study shows that the inhaler technique associated with inhaler devices can affect compliance of asthmatic patients. In fact, findings are consistent with previous literature that shows patient's compliance as a real and latent problem within chronic conditions.¹² In our case, we explored the problem of compliance toward asthma medication while controlling for potential confounders. We controlled for the effect of active substance toward the probability to stick to the treatment,²⁴ so we could obtain the potential effect of the inhaler device. Interestingly, findings suggest that ICS/LABA combinations would not impact on the probability of being adherent, which is reasonable since medicines are 100% effective but the inhalation technique is the key for better clinical outcomes.^{1–3,7}

Along with inhaler technique, different confounders of patient's compliance were explored. Univariate results determined that only a few variables were associated with medication compliance. The proxy for inhaler technique was statistically significant; in contrast, patients' characteristics, comorbidities, and health outcomes that were significant in the univariate analysis became nonstatistically significant in the basic multivariate specification. However, in our last

specification we identified confounders of compliance from the interaction between variables. This indicates that a basic analysis was not enough to identify factors affecting compliance outcomes, and as it has been reported, adherence and compliance are a more complex topic.²⁵ According to our results, having more than three conditions simultaneously would impact negatively on the likelihood of medication compliance. Suffering from a disease is a burden for patients, and it is reported that there is a substantial burden on patients having more than three simultaneous conditions, which starts to affect their compliance to asthma treatment (as we have observed in our results), and may require more complex health management strategies.^{26,27} Remarkably, unhealthy behaviors of patients were not statistically significant in compliance. However, we identified a scope for improvement since we detected that 22% of the sample were smokers despite their asthmatic condition.

Despite the positive effect of GP consultation for compliance, a high number of visits per month to health care professionals was negatively correlated with it. Indeed, greater number of visits was associated with worse compliance outcomes, which is consistent with previous literature that reported reductions in health care utilization due to good compliance with asthma treatment.²⁸ Further, the effect of visits for retired patients is positive for compliance compared to active patients and retired patients who did not visit their GP during the time they were persistent with their medication. This is consistent with previous findings that suggest for elderly, GP consultation should be encouraged in order to maintain patient's compliance to medication in the long term.²⁹

Accordingly with our results, younger age groups were more likely to be compliant patients.¹⁹ However, this effect might be offset due to the effect of costs toward compliance. Our results for the interaction between age and cost suggest pharmacological cost for younger groups would decrease the probability of being compliant. It may be that the effect of bearing some part of the pharmaceutical cost

for patients whose salary was not very high represented an economic burden that influences compliance to a treatment. In contrast, cost for older groups was not statistically significant; this is reasonable since elderly Spanish patients have access to pharmaceutical treatment without co-payments.³⁰

There are limitations to these estimates besides the fact that this is a retrospective study, which is vulnerable to bias. First, this study was conducted in a single health system, thus results may not be extrapolated to other populations. However, trends are similar to previous research.^{22,23,25} Second, the assumption that obtaining a prescription was equivalent to taking the medication might not be completely accurate. Moreover, the study approach to quantify compliance was done by using the MPR, which has been reported to be biased upwards.^{9,14} Nevertheless, we tried to correct for this by elevating the cut-off point so fewer patients were seen as compliant with their medication. Robustness test of estimates confirmed our findings. Actually, our estimates could be considered accurate, since we used persistence to asthma treatment data. It is also true that tracking compliance patterns may imply having data across time; however, this could be only possible by assessing compliance prospectively.

It is worth mentioning that physicians have been aware that the majority of patients cannot use their prescribed pMDI correctly,³¹ and DPIs included in this study were seen as an effective alternative to solve problems related to inhaler technique. However, our results suggest that there is still a crucial barrier to avoid the loss of pharmacological efficacy due to the inhaler technique associated with DPIs included in this analysis, which determines compliance of long-term medication in asthmatic patients. Finally, we could not obtain some patients' characteristics such as race, level of education, type of job, and some clinical confounders such as lung function. This problem of data limitation also restricts our outcomes.

Conclusion

The effect of inhaler technique associated with DPIs included in this analysis (Accuhaler[®], nexThaler[®], and Turubhlaer) was negative towards compliance for long-term asthma medication. In contrast, the active substance was not significant in exploring compliance patterns. Furthermore, we identified some other confounders of patient's compliance such as severity of asthma, comorbidities, cost, age, and health care utilization. Associations between exacerbations and patient's compliance have shown to be divergent across inhaler devices.

Treatment noncompliance is a real and damaging problem for patients and for the Spanish National Healthcare System. The quantification of compliance and persistence is always an issue in current literature, which can limit results; identification of potential factors affecting compliance is necessary in order to guide actions to attenuate the problem of poor compliance in asthma patients. This study assessing treatment compliance across asthma inhaler devices for ICS/LABA combinations confirms that inhaler devices play an important role in asthma management by conditioning compliance, which is consistent with prior research.^{1-9,17,23} The special feature of our findings is that we adjusted for the effects of the active substances in order to explore the effect of inhaler technique toward compliance, which has shown to be influenced also by patients' demographic characteristics and clinical aspects. Helping patients to properly use their inhaler devices, has shown to be the key for better compliance outcomes, as we observed that inhaler technique might be diminishing the efficacy of pharmacological treatment.

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