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Treatment of COPD: Relationships between daily dosing frequency, adherence, resource use, and costs

Edmond L. Toy [a], Nicolas U. Beaulieu [b], Joshua M. McHale [b], Timothy R. Welland [a], Craig A. Plauschinat [c], Andrine Swensen [c], Mei Sheng Duh [b,*]

[a] Analysis Group, Inc., 225 Union Blvd., Suite 600, Lakewood, CO 80228, USA
[b] Analysis Group, Inc., 111 Huntington Ave., Tenth Floor, Boston, MA 02199, USA
[c] Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936, USA

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KEYWORDS
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Summary
Background: Medication adherence is important in managing COPD. This study analyzed real-world use of inhaled medications for COPD to characterize relationships between daily dosing frequency, adherence, healthcare resource utilization, and cost.
Methods: This retrospective study used a large administrative claims database covering 8 million insured lives in the US from 1999 to 2006. Patients were stratified based on the recommended daily dosing frequency of their first COPD drug claim following COPD diagnosis. Adherence was measured using proportion of days covered (PDC) over 12 months following treatment initiation. Healthcare resource use included inpatient, outpatient, and emergency room visits. A multivariate regression model assessed the relationship between adherence and one-year healthcare resource use, controlling for demographics, comorbidities, and baseline resource use. Unit healthcare costs were obtained from the 2005 Medical Expenditure Panel Survey, adjusted to 2008 dollars.
Results: Based on a sample of 55,076 COPD patients, adherence was strongly correlated with dosing frequency. PDC was 43.3%, 37.0%, 30.2% and 23.0% for QD, BID, TID, and QID patient cohorts, respectively. Regression analysis showed that one-year adherence was correlated with healthcare resource utilization. For 1000 COPD patients, a 5% point increase in PDC reduced the annual number of inpatient visits (−2.5%) and emergency room visits (−1.8%) and slightly increased outpatient visits (+.2%); the net reduction in annual cost was approximately $300,000.

* Corresponding author. Tel.: +1 617 425 8131; fax: +1 617 425 8001.
E-mail address: mduh@analysisgroup.com (M.S. Duh).

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Conclusion: COPD patients who initiated treatment with once-daily dosing had significantly higher adherence than other daily dosing frequencies. Better treatment adherence was found to yield reductions in healthcare resource utilization and cost.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized as a chronic airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to gaseous or particulate irritants.[1] Although COPD is under-diagnosed in the US, the prevalence of the disease in the US has been estimated at 23.6 million adults (about 13.9% of the adult population), and within the next decade COPD is expected to become the third leading cause of death.[2] The economic burden of COPD is also substantial. In 2007, the total cost of COPD in the United States was approximately $42.6 billion, including $26.7 billion incurred in direct healthcare expenditures, $8 billion in indirect morbidity costs, and $7.9 billion in indirect mortality costs.[3]

Although pharmacotherapies have not been shown to modify the long-term decline of lung function in COPD patients, a variety of effective medications are available to prevent and control symptoms, improve health status, and reduce the occurrence of COPD exacerbations.[1] A central part of COPD management is the use of bronchodilators, which includes beta-agonists, anti-cholinergics, and methylxanthines. Regular use of long-acting beta-agonists (LABAs), short-acting anti-cholinergics (SAACs), and long-acting anti-cholinergics (LAACs) has been shown to improve health status. Orally administered methylxanthines are another type of bronchodilator, but current guidelines note a preference for inhaled bronchodilators (e.g., beta-agonists and anti-cholinergics), which have less potential for toxicity.[1] Glucocorticosteroids are anti-inflammatory agents that are also used to manage COPD. These drugs are often used to treat exacerbations of COPD, as their use in the management of stable COPD is limited to specific indications.[1] More recently, therapies that combine multiple bronchodilators or that combine a bronchodilator and glucocorticosteroid together in a single inhaler have been developed. For example, a combination of a LABA and inhaled glucocorticosteroid has been shown to be more effective than each individual drug.[1]

COPD is a chronic disease in which effective management requires long-term adherence to pharmacotherapies. Although researchers have used a variety of different definitions, patient adherence to treatment generally relates to the extent to which a patient obtains and consumes his or her medication as prescribed. Non-adherence is a significant risk factor for mortality, morbidity, hospitalizations, and reduced quality of life.[4,5] Adherence levels observed in clinical trials may be around 70—90%, but in real-life clinical practice, observed levels of adherence are typically far lower (e.g., 10—40%).[6] Research suggests that many factors influence adherence to therapy. These factors are patient's age, co-payment, type of prescriber, comorbidities, concomitant medications, knowledge about and faith in the treatment, and complexity of the treatment regimen.[7—10] Research also suggests that the lengthier and more complicated the treatment regimen, the greater the likelihood of non-adherence, and that patients prefer once-daily COPD therapy over therapies that require multiple dosings per day.[11,12]

This study examines adherence levels among patients prescribed inhaled COPD medications. Using data from real-world clinical practice, the study investigates the relationship between adherence and daily dosing frequency, as well as the healthcare resource utilization and cost implications of higher adherence.

Methods

Data sources

This study used an administrative claims database consisting of de-identified, Health Insurance Portability and Accountability Act (HIPAA)-compliant medical and prescription drug dispensing claims from employees and retirees (including their spouses and dependants) of 40 self-insured Fortune 500 companies located throughout the United States, between 1999 and 2006. Together these companies cover a broad array of industries and job classifications (e.g., financial services, manufacturing, telecommunications, energy, utilities, airline, railroad, entertainment, pharmaceutical, and food and beverage). It contains enrollment records and complete medical and pharmacy claims for approximately 8.4 million beneficiaries: about 7.6 million beneficiaries less than 65 years of age (non-Medicare) and approximately 800,000 beneficiaries over the age of 65.

Because of possible Medicare dual coverage for patients above the age of 65, the administrative claims database was not used as the source of cost data. To estimate healthcare costs experienced by these patients, unit costs for inpatient and outpatient services were obtained from the 2005 survey of the Medical Expenditure Panel Survey (MEPS). MEPS is a nationally representative large-scale survey of families and individuals (non-institutionalized), their medical providers, and employers across the United States that has been ongoing since 1996. It provides cost information at the patient level compiled from both patient payments for services and insurance payments. The data available from MEPS are considered to be the one of the most complete sources of national data on the cost and use of healthcare and health insurance coverage.[13] In order to have a more accurate cost estimate on the national level, patient data were weighted to compensate for over-sampling of certain populations and non-response to the survey.[13] All costs from the 2005 survey were adjusted to

2008 dollars using the Medical Care Consumer Price Index (Medical CPI).[14]

Study population

The study focused on patients who were naïve users of commonly used, inhaled COPD medications. The COPD drugs of interest included LABAs and LAACs. Although SAACs can be used on an as-needed basis, these drugs are also used as regular, maintenance therapy and thus were also included. Patients taking combinations of these aforementioned drugs were also eligible.

Patients were included in the study if they satisfied the following inclusion criteria. First, patients had to have been diagnosed with COPD, based on the presence of at least one claim with a diagnosis code for COPD (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for chronic bronchitis, emphysema, chronic obstructive asthma, and chronic airway obstruction not elsewhere classified: 491, 492, 493.2, and 496). Second, patients were required to have at least two pharmacy claims for a COPD drug of interest following a diagnosis of COPD. The index date was defined as the date of a patient's first prescription claim for a COPD drug of interest. Third, patients needed to have continuous eligibility for 6 months prior to (i.e., baseline period) and 1 year after the index date. Fourth, patients who received one of the COPD drugs of interest in a non-pharmacy setting (i.e., in a physician's office or hospital setting) were excluded as it was not possible to determine the specific drug information about the dose and days supply of drug provided to the patient.

All medical, prescription medication, and eligibility records were extracted for the baseline period (i.e. 6 months preceding the index date) and the one-year study period (i.e., 12 months following the index date) for each patient. Patients were categorized into separate cohorts based on the daily dosing frequency of the COPD drug prescription that was filled on the index date. Drugs were classified as once-daily (QD), twice-daily (BID), three times daily (TID), or four times daily (QID) primarily using the dosing frequency recommended in FDA-approved prescribing information labels (See Table 1).[15]

Table 1 Drugs included in each daily dosing frequency.

Daily Dosing Frequency[a,b]	Active Ingredient
QD	tiotropium
BID	salmeterol + fluticasone combination
	formoterol + budesonide combination
	formoterol
	salmeterol
TID	ipratropium bromide (nasal spray form)[c]
QID	ipratropium bromide (nasal spray form)[c]
	ipratropium bromide (nebulizer form)
	albuterol + ipratropium combination

[a] Based on FDA-approved prescribing information.
[b] QD = Once-Daily, BID = Twice-Daily, TID = Three Times Daily, and QID = Four Times Daily.
[c] Atrovent HFA®, an ipratropium bromide inhalation aerosol, was classified QID. All other ipratropium bromide nasal sprays were classified TID.

Study outcomes

Patient adherence was measured using the proportion of days covered (PDC), defined as the proportion of days in a given time interval that a patient had a drug available.[6,16] This study considered PDC measured over a one-year interval: the sum of all the days supply for all prescriptions with the daily dosing frequency of the initial drug was divided by 365 days. As a sensitivity analysis, PDC was also calculated for shorter intervals (9, 6, and 3 months).

Healthcare resource utilization outcomes included the number of inpatient visits, the number of inpatient days, and the number of outpatient visits and emergency room (ER) visits over 365 days of observation following the index date. Utilization of healthcare resources was based on medical claim type and place of service. Utilization was not restricted to that associated with COPD diagnoses; all-cause utilization was measured in this study to capture complications associated with COPD that may not have been explicitly billed under COPD. The cost associated with each healthcare utilization visit (inpatient, outpatient, and ER visits) was taken from estimates produced by the Agency for Healthcare Research and Quality using cost adjusted MEPS data.

Statistical analyses

Comparisons of demographic baseline variables and PDC between COPD patients in each daily dosing frequency group were performed using Wilcoxon tests for continuous outcomes and Chi-square tests for categorical outcomes.

Resource utilization was analyzed using negative binomial regression to control confounding factors. Covariates in the model included age, gender, PDC (over 12 months), and baseline resource utilization (inpatient, outpatient and ER visits). The model also adjusted for the presence of comorbidities during the 6 months pre-index period, including Charlson comorbidity index (CCI), depression/anxiety, diabetes, coronary artery disease, renal failure, liver failure, hypertension, asthma, pneumonia, influenza, and emphysema. The Charlson comorbidity index is a score of 17 comorbid diseases that are weighted for disease severity.[17] In addition, variables related to the baseline severity of COPD were included (claims for oxygen therapy, spirometry tests, pulmonologist visits, and glucocorticosteroid use).[18] These surrogates for COPD severity were used because direct measures of COPD severity (i.e., forced expiratory volume in 1 s, FEV_1) were not available in the claims data. To analyze the relationship between adherence level and healthcare resource use and cost, the estimated regression model was used to predict the effect of improving adherence. Holding all other patient characteristics constant, the measured PDC value for each patient was increased by five percentage points to calculate the predicted utilization and costs associated with this hypothetical improvement in adherence. The difference between the predicted and actual observed utilization is interpreted as the incremental effect of a five percentage

point increase in adherence. The outcomes were expressed as annual resource use and costs for a hypothetical cohort of 1000 patients with COPD. The cost impacts associated with the predicted changes in utilization were calculated by applying unit cost estimates from MEPS. All statistical analyses were carried out using SAS v9.2 software (SAS Institute, Cary, NC).

Results

Baseline patient characteristics

A total of 55,076 patients met the criteria for inclusion in the study. The most frequent daily dosing frequency class of the initial drug taken as of the index date was BID, which accounted for 45.4% of the population, followed by QID (39.7%), TID (8.3%), and QD (6.7%). As shown in Table 2, patients in the QD class were more often male ($p < .0001$). The average age of patients was approximately 69 years, with the exception that patients in the BID cohort were younger ($p < .0001$). In general, QD and QID patients tended to have non-respiratory comorbidities more often. However, there was no clear relationship between daily dosing frequency class and respiratory comorbidities. Patients in the QD class had more severe COPD, as evidenced by the higher fraction of patients in that class who had claims for oxygen therapy, spirometry tests, and pulmonologist visits; these differences compared to the other daily dosing frequency classes were statistically significant ($p < .0001$). Glucocorticosteroid use was highest among patients in the BID class.

Adherence

During the 12 month study period, patients initiated on QD treatment had an average PDC of 43.3% (Table 3). There was a consistent trend of PDC declining as the frequency of dosing increased: the PDC for BID, TID, and QID was 37.0%, 30.2%, and 23.0% ($p < .0001$), respectively. As a sensitivity analysis, PDC was also calculated for intervals of 9, 6, and 3 months post index date. Adherence levels were consistently higher for QD.

Utilization and cost

The multivariate regression model found that higher adherence was correlated with reduced urgent care usage (i.e., the annual number of inpatient days, inpatient visits, and ER visits). As expected, patients who were adherent to their COPD therapy had a tendency to utilize more routine

Table 2 Baseline characteristics of COPD patients stratified by dosing class of first COPD treatment.

	QD ($N = 3678$)		BID ($N = 25{,}011$)		p-value[a]	TID ($N = 4544$)		p-value[a]	QID ($N = 21{,}843$)		p-value[a]
Age, years (Mean, SD)	69.0	11.01	64.0	14.21	<.0001	69.0	11.58	(.53)	68.9	12.38	.66
Seniors, age ≥65 (n,%)	2407	65.4%	12,762	51.0%	<.0001	3018	66.4%	.35	14,084	64.5%	.26
Male (n, %)	1960	53.3%	10,742	43.0%	<.0001	2172	47.8%	<.0001	10,557	48.3%	<.0001
Region (n, %)											
Northeast	984	26.8%	6175	24.7%	.01	1065	23.4%	.001	4708	21.6%	<.0001
Midwest	1006	27.4%	6890	27.6%	.80	1406	30.9%	<.0001	7190	32.9%	<.0001
South	1445	39.3%	9521	38.1%	.16	1600	35.2%	<.0001	8486	38.9%	.61
West	243	6.6%	2425	9.7%	<.0001	473	10.4%	<.0001	1459	6.7%	.87
Charlson Comorbidity Index - CCI (Mean,SD)[8]	1.83	(1.65)	1.50	(1.50)	<.0001	1.72	(1.64)	<.0001	1.85	(1.82)	(.05)
Comorbid Conditions (n,%)[b]											
Depression/Anxiety	122	3.3%	1011	4.0%	.04	187	4.1%	.06	1105	5.1%	<.0001
Diabetes Mellitus	629	17.1%	3392	13.6%	<.0001	654	14.4%	.001	3635	16.6%	.49
Coronary Artery/Heart Disease	915	24.9%	4331	17.3%	<.0001	968	21.3%	<.0001	5191	23.8%	.14
Renal Failure	156	4.2%	681	2.7%	<.0001	163	3.6%	.13	1144	5.2%	.01
Liver Failure	73	2.0%	365	1.5%	.02	69	1.5%	.11	440	2.0%	.91
Hypertension	882	24.0%	4877	19.5%	<.0001	961	21.2%	.002	5143	23.6%	.57
Respiratory Comorbidities (n, %)[b]											
Asthma	497	13.5%	7626	30.5%	<.0001	693	15.3%	.03	3013	13.8%	.65
Pneumonia and Influenza	496	13.5%	2703	10.8%	<.0001	538	11.8%	.03	4068	18.6%	<.0001
Emphysema	436	11.9%	1532	6.1%	<.0001	413	9.1%	<.0001	1750	8.0%	<.0001
Oxygen Therapy (n, %)[b]	400	10.9%	1209	4.8%	<.0001	308	6.8%	<.0001	1544	7.1%	<.0001
Spirometry Test (n, %)[b]	1399	38.0%	7290	29.2%	<.0001	878	19.3%	<.0001	4288	19.6%	<.0001
Pulmonologist Visit (n, %)[b]	1211	32.9%	5151	20.6%	<.0001	730	16.1%	<.0001	4421	20.2%	<.0001
Glucocorticoid Use (n, %)[b]											
Inhaled Glucocorticoid	790	21.5%	21,548	86.2%	<.0001	1290	28.4%	<.0001	4434	20.3%	.10
Systemic Glucocorticoid	690	18.8%	5805	23.2%	<.0001	957	21.1%	.01	5435	24.9%	<.0001

[a] *P*-values are for comparison of QD vs. BID, QD vs. TID, and QD vs. QID. Wilcoxon test is used for continuous outcomes and Chi-square test for categorical outcomes.

[b] The CCI, all comorbidities, oxygen therapy, spirometry tests, pulmonologist visits, and glucocorticosteroid use are measured during the 6 month period preceding the index date.

Table 3 Proportion of days covered[a] (PDC) for COPD patients at twelve, nine, six, and three month intervals stratified by dosing class of first COPD treatment.

	QD	BID	TID	QID
After Twelve Months				
N	3678	25,011	4544	21,843
Mean PDC	43.3%	37.0%	30.2%	23.0%
St. Dev.	.32	.29	.28	.24
p-value[b]	N/A	<.0001	<.0001	<.0001
After Nine Months				
N	4418	26,757	4700	23,613
Mean PDC	46.7%	40.1%	33.4%	25.4%
St. Dev.	.32	.29	.28	.24
p-value[b]	N/A	<.0001	<.0001	<.0001
After Six Months				
N	5195	28,575	4900	25,615
Mean PDC	52.8%	45.6%	38.4%	30.1%
St. Dev.	.31	.29	.29	.25
p-value[b]	N/A	<.0001	<.0001	<.0001
After Three Months				
N	6056	30,814	5097	28,159
Mean PDC	67.6%	60.9%	51.6%	42.6%
St. Dev.	.29	.29	.31	.27
p-value[b]	N/A	<.0001	<.0001	<.0001

[a] PDC is defined as the ratio of the days supply a given drug during the observation period to the total number of days in the observation period.
[b] *P*-values are for comparison of QD vs. BID, QD vs. TID, and QD vs. QID. Wilcoxon test is used for continuous outcomes and Chi-square test for categorical outcomes.

care services (i.e., outpatient visits). Table 4 shows that for a cohort of 1000 patients with COPD, a five percentage point increase in adherence level would lead to a 2.5% reduction in inpatient visits on average. On a percentage basis, a smaller reduction for emergency room visits and a slight increase in outpatient visits was predicted.

These predicted changes in healthcare utilization were analyzed with respect to cost. Based on MEPS data, average unit healthcare costs were assumed to be $9124 for a hospital visit, $110 for an outpatient visit, and $505 for an ER visit; the average cost per inpatient day was unavailable in MEPS. On an aggregate basis for 1000 COPD patients, the predicted change in healthcare utilization would result in an estimated cost decrease of $296,598 for inpatient visits and $7410 for ER visits, with a slight cost increase of $3219 for outpatient visits; the net effect would amount to a reduction in total annual medical costs of $300,789, or about a 2.2% reduction.

Discussion

COPD is a chronic disease that, for most patients, typically necessitates the regular use of pharmacotherapies to control symptoms and improve quality of life. Accordingly, COPD treatment regimens that increase the likelihood of higher medication adherence levels would be expected to contribute to improved disease management. This study used a large, retrospective administrative claims database to measure the relationships between the daily dosing frequency of commonly used COPD medications, adherence, healthcare resource use, and costs.

In a sample of 55,076 patients initiating drug treatment for COPD, we found that adherence level was strongly associated with daily dosing frequency. COPD drugs with QD dosing had the highest adherence level, and adherence declined consistently with BID, TID, and QID dosings.

This finding is consistent with the literature. Iskedjian et al. conducted a meta-analysis of adherence to a variety of hypertension drugs and found that QD regimens had higher adherence levels than regimens with more frequent daily dosings.[19] Claxton et al. reviewed studies across a variety of therapeutic areas that measured adherence using electronic monitoring techniques and likewise found that adherence declined with medications that required more frequent dosing.[20] Several studies have also examined adherence in the context of COPD treatment. Bender et al. measured adherence to a combination fluticasone-salmeterol drug and found one-year PDC levels at approximately 22%; they noted that this adherence was substantially lower than that estimated from clinical trials and markedly discrepant with practice guidelines.[21] Cramer [7] and Breekveldt-Postma et al.[6] reported that adherence to tiotropium (QD dosing) was higher than for ipratropium (QID) and for drugs that were dosed as two or more times daily (i.e., LABA, LABA + inhaled glucocorticosteroids). However, these COPD-related studies did not focus specifically on the relationship between adherence and dosing frequency.

Table 4 The effect of increasing PDC on predicted 12 month mean healthcare resource use and cost based on 1000 COPD patients.

	Resource Use			Cost[a]		
Utilization	Baseline PDC	Baseline PDC + 5 Percentage Points	Difference (%)	Baseline PDC	Baseline PDC + 5 Percentage Points	Difference (%)
Hospital Visits	1275	1243	−33 (−2.6%)	$11,635,099	$11,338,501	-$296,598 (−2.6%)
Inpatient Days[b]	5906	5720	−186 (−3.1%)	—	—	—
Outpatient Visits	16,981	17,010	29 (−.2%)	$1,867,863	$1,871,082	$3219 (−.2%)
ER Visits	817	802	−15 (−1.8%)	$412,658	$405,248	-$7410 (−1.8%)

[a] The average costs using MEPS data were $9124 for a hospital visit, $110 for an outpatient visit, and $505 for an ER visit.
[b] Average cost per inpatient day was unavailable from MEPS.

A second finding of this study was that higher adherence levels were associated with lower healthcare resource utilization and cost in the year after initiating treatment for COPD. The study population was modeled using a multivariate regression model that controlled for various factors that may influence adherence, such as age, gender, respiratory and non-respiratory comorbidities, and surrogates for COPD severity.[10,18] The regression model was then used to predict the effect of a five percentage point increase in PDC, holding all other factors constant. In a hypothetical population of 1000 COPD patients, this improvement in adherence was predicted to reduce the annual number of hospitalizations by approximately 2.5%. There were minor predicted changes to the number of outpatient visits (slight increase) and emergency room visits (slight decrease), but as the cost of COPD care is driven by hospitalizations,[3] the predicted change in net costs was about 2.2%.

The relationship between adherence and healthcare resource utilization and cost has been analyzed elsewhere. A review by Muszbek et al. reported that in 23 studies covering treatment of diabetes, hypertension, heart disease/failure, and dyslipidemia, higher adherence was generally found to be associated with lower overall healthcare cost.[22] The present study extends this literature to show that the inverse relationship between adherence and utilization and cost is observed in the context of COPD treatments.

This study suggests that the effective management of COPD can be aided by consideration of the dosing frequency of drug treatments prescribed to patients. Drugs with fewer daily dosings are associated with improved adherence, which in turn are associated with lower healthcare resource use and cost. This is consistent with the general findings of studies in other therapeutic areas. Much of this literature examined oral medications,[22] and this study confirms that there are similar patterns in the context of inhaled medications.

Several limitations exist in this study. First, adherence to COPD treatments was measured using administrative claims data. A claim for a prescription refill does not necessarily mean that a patient is taking the medication as prescribed, as some patients may obtain refills before a prescription runs out, or in the case of the medications examined in the present study, patients may not be using inhalers correctly. While techniques such as electronic monitoring may offer a more accurate method of measuring adherence, these data are not readily available and where data are available sample sizes are small; using claims data provides a larger study population. Although different approaches exist to measure adherence, we are not aware of factors that would differentially affect treatment patterns across daily dosing frequency classes and therefore bias the comparisons of the daily dosing frequency classes. Claims data also are subject to coding errors or incomplete records. Second, COPD severity could not be measured directly (i.e., based on spirometry tests), as claims databases typically do not contain such information. COPD severity is correlated with resource utilization, adherence, and treatment choice, and therefore can act as a confounding factor in the analysis. However, the regression analysis of resource utilization included a variety of covariates that are indirect measures for COPD severity. This statistical approach reduces the potential for bias. Our understanding of this topic would be enhanced by future research utilizing more detailed clinical and spirometric data. Third, our analysis is limited to patients that are initiating treatment of COPD and therefore is unlikely to include patients with severe COPD. These results may not be generalized to other settings or patient groups. As patients gain more experience with inhaled medications or as the frequency and severity of symptoms change over time, the relationships between daily dosing frequency, adherence, resource use, and cost may differ from that observed among treatment-naïve patients. Fourth, complete data on costs were not available in the claims database. The cost analysis therefore relied on a unit cost approach using data from the MEPS database, which may not accurately reflect the actual costs experienced by the patients in the sample.

Conclusions

This study found that adherence to the initial drug treatment of COPD was associated with dosing frequency, with QD dosing having the highest adherence levels relative to BID, TID or QID. In addition, improved adherence was associated with a reduction in healthcare resource utilization and cost. A five percentage point increase in PDC was estimated to reduce annual healthcare resource use and costs by approximately 2.2%. This study suggests that dosing frequency should be an important consideration in developing effective strategies for managing COPD.

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Conflict of interest statement

Toy, Beaulieu, McHale, Welland, and Duh are employees of Analysis Group, Inc., which received research funds from Novartis. Plauschinat and Swensen are employees and stockholders of Novartis, which develops products in the area of COPD.

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