ORIGINAL RESEARCH

Impact of Nonadherence to Inhaled Corticosteroid/LABA Therapy on COPD Exacerbation Rates and Healthcare Costs in a Commercially Insured US Population

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BACKGROUND: Evidence of poor patient adherence to medications for chronic obstructive pulmonary disease (COPD) is well-documented, but its impact on disease exacerbation rates and associated healthcare costs remains unclear.

OBJECTIVE: To assess the association between adherence levels to different inhaled corticosteroid/long-acting β_2-adrenergic agonist (LABA) and COPD exacerbation rates and costs in a commercially insured population.

METHODS: In this observational cohort study, patients with COPD (aged ≥40 years) who were treatment-naïve to inhaled corticosteroid/LABA and were initiating budesonide plus formoterol or fluticasone plus salmeterol between March 1, 2009, and January 31, 2014, were identified in a national representative claims database and were followed for up to 12 months. The date of the first prescription fill for either drug was defined as the index date. Patients were divided into 4 cohorts based on adherence to the index therapy, which was measured by proportion of days covered (PDC); the cohorts were classified as adherent (PDC ≥0.8), mildly nonadherent (0.5 ≤ PDC <0.8), moderately nonadherent (0.3 ≤ PDC <0.5), and highly nonadherent (PDC <0.3). Each nonadherent group was matched in a 1:1 ratio to the adherent group independently, based on prognostically important variables, using propensity score analyses. Exacerbation rates and healthcare costs were analyzed for 1 year after treatment initiation.

RESULTS: During the study period, 13,657 eligible patients with COPD initiated inhaled corticosteroid/LABA; of these, only 1898 (13.9%) patients were adherent during follow-up. Group matching resulted in 1572 patients per group for comparison 1 (adherent vs mildly nonadherent), 1604 patients for comparison 2 (adherent vs moderately nonadherent), and 1755 patients for comparison 3 (adherent vs highly nonadherent). The moderately and highly nonadherent cohorts had higher exacerbation rates than the adherent patients (comparison 2: rate ratio [RR], 1.11; 95% confidence interval [CI], 1.01-1.21; P = .03; comparison 3: RR, 1.11; 95% CI, 1.01-1.21; P = .02). Adherent patients incurred significantly lower healthcare costs than all the nonadherent groups (comparison 1, $22,671 vs $25,545; P <.01; comparison 2, $22,508 vs $24,303; P <.01; comparison 3, $22,460 vs $25,148; P <.01).

CONCLUSIONS: Patients adhered to their inhaled corticosteroid/LABA treatments had lower COPD exacerbation rates and lower healthcare costs compared with the moderately and highly nonadherent patients. Better adherence to maintenance therapies may help to reduce the clinical and economic burdens of COPD.

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KEY WORDS: adherence, COPD, cost, disease exacerbation, economic burden, inhaled corticosteroid/LABA, nonadherence, propensity score matching, proportion of days covered

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Chronic obstructive pulmonary disease (COPD) is characterized by declining lung function attributable to a combination of airway obstruction and inflammation. COPD mainly includes 2 chronic lower respiratory disease disorders—emphysema and chronic bronchitis.[1] Approximately 14.8 million people in the United States have been diagnosed with asthma/COPD.[2] The condition is associated with substantial disability and was the third leading cause of death in the United States in 2011.[3] The annual economic burden of asthma/COPD was estimated to be approximately $68 billion in 2008, including $53.7 billion in direct healthcare and $14.3 billion in indirect mortality costs.[2]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines highlight the prevention and treatment of exacerbations as primary objectives for COPD management, underscoring the deleterious effects of exacerbations on patients and the care delivery system.[4,5] Recent treatment guidelines (ie, GOLD 2016) suggest initiating controller medications in accordance with patients' history of exacerbations and symptoms.[6] For patients with a history of COPD exacerbations, treatment with inhaled corticosteroid/long-acting β_2-adrenergic agonist (LABA) combination therapies is the recommended option; the use of a LABA or an inhaled corticosteroid individually as monotherapy is not recommended.[6] To date, the US Food and Drug Administration–approved inhaled corticosteroid/LABA combination medications for COPD maintenance therapy include budesonide plus formoterol (160/4.5 µg),[7] fluticasone plus salmeterol (250/50 µg),[8] and fluticasone furoate plus vilanterol (100/25 µg).[9]

The clinical efficacy and safety of inhaled corticosteroid/LABA combination therapy have been demonstrated in several randomized clinical trials (RCTs).[10,11] However, one of the characteristics of RCTs is the requirement for high adherence rates among patients who are assigned treatments that are under investigation. This differs substantially from how patients adhere to their prescribed medication regimens in real-world settings, and limits the utility of extracting healthcare utilization data and the resulting economic impact on a system of care within the constraints of most RCTs. Restrepo and colleagues suggested that, based on self-reports, only an average of 40% to 60% of patients with COPD adhere to the prescribed medication.[12] Systematic reviews have emphasized the inadequacy of medication adherence among patients with COPD, resulting from reasons such as medication delivery mechanisms, cost burden, and clinicians' preferences.[13-16]

To date, no retrospective observational study has examined the impact of adherence on outcomes for patients with COPD. The objective of this study was to evaluate the association between different levels of adherence to fixed-dose inhaled corticosteroid/LABA therapy and exacerbation rates and healthcare costs in a cohort of commercially insured patients with COPD receiving usual care in real-world settings in the United States.

KEY POINTS

- COPD causes substantial disability and death, yet COPD-related exacerbation rates and healthcare costs are not well-documented.
- This study included 13,657 patients with COPD who were treatment-naïve to inhaled corticosteroid/LABA and initiated budesonide plus formoterol or fluticasone plus salmeterol therapy.
- Patients were placed into 4 cohorts based on adherence as measured by proportion of days covered—adherent, mildly nonadherent, moderately nonadherent, and highly nonadherent.
- The moderately and highly nonadherent cohorts had more exacerbations than adherent patients, resulting from increased hospitalizations and emergency department visits.
- Adherent patients had lower healthcare costs than the nonadherent groups (comparison 1: $22,671 vs $25,545; comparison 2: $22,508 vs $24,303; comparison 3: $22,460 vs $25,148).
- These findings suggest that there are missed opportunities to obtain optimal clinical benefits from maintenance therapies for COPD, improve adherence, and potentially reduce the economic burden associated with this disease.

Methods

Data Source and Study Design

Data for this observational cohort study were drawn from a commercially insured population residing in 50 states whose administrative claims are curated in the HealthCore Integrated Research Database. The data cover claims from 14 commercial health plans in which Medicare supplemental coverage and commercially managed Medicare Advantage plans are included, which constituted a small portion of the study population. However, federal Medicare and state Medicaid claims are not captured in this database. Medical and pharmacy claims data were queried to identify patients with COPD (≥40 years) who had not received any inhaled corticosteroid/LABA combination therapy during the 12 months before initiating budesonide plus formoterol (160/4.5 µg) or fluticasone plus salmeterol (250/50 µg) therapy between March 1, 2009, and January 31, 2014. Fluticasone furoate plus vilanterol (100/25 µg) therapy was not tar-

geted in this study because of the small sample size during the study period. Strict compliance with applicable Health Insurance Portability and Accountability Act rules was exercised related to the data throughout the study. The study data were kept anonymous to preserve patient confidentiality, and researchers' access did not include individual patient identifiers. This nonexperimental study was conducted under the Research Exception provisions of the Privacy Rule, 45 CFR 164.514(e), and was exempt from Institutional Review Board review.

Inclusion Criteria

The study patients had ≥1 prescription fills for budesonide plus formoterol (160/4.5 µg) or fluticasone plus salmeterol (250/50 µg) between March 1, 2009, and January 31, 2014, and the first observed prescription fill date for either drug was considered the index date. Patients were included in the study if they were aged ≥40 years as of the index date. Inclusion also required a diagnosis of COPD (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 491.xx, 492.xx, 496.xx) and ≥1 prescription fills for a short-acting $ß_2$-adrenergic agonist (SABA), short-acting muscarinic antagonist (SAMA), and/or the combination of SABA and SAMA during the 12-month preindex period. All patients were required to have ≥12 months of continuous health plan enrollment before and after the index date.

Exclusion Criteria

Patients with ≥1 prescription fills for any inhaled corticosteroid/LABA combination therapy (including all strength forms of budesonide plus formoterol, fluticasone plus salmeterol, fluticasone furoate plus vilanterol, and mometasone furoate plus formoterol) during the 12-month preindex period were excluded from the analysis. Also excluded were patients who filled budesonide plus formoterol (160/4.5 µg) and fluticasone plus salmeterol (250/50 µg) on the index date, and long-term users for any oral corticosteroids (≥180 days of total length of therapy) during the 12-month preindex period. Patients with ≥2 diagnoses for the same type of cancer within 60 days of each other during the 12-month preindex period were also excluded.

Postindex Follow-Up

The patients were followed for up to 12 months after the index date. If they filled an inhaled corticosteroid/LABA medication different from their index therapy (switching therapy) during the 12-month period, their postindex follow-up was censored at the time of the switch.

Study Cohorts

The study patients were stratified into 4 cohorts based on their medication adherence levels—which was measured by the proportion of days covered (PDC)[17,18]—to the index therapy during the 12-month postindex period. The PDC was calculated as the number of days a patient had index inhaled corticosteroid/LABA therapy on hand, divided by the number of health plan enrollment days during the postindex follow-up. The PDC ranged from 0 to 1, with a higher number indicating better adherence. A PDC >0.5 means that the patient had at least a 6-month supply for the index medication over 12 months of observation. The patients were classified as adherent (PDC ≥0.8), mildly nonadherent (0.5 ≤ PDC <0.8), moderately nonadherent (0.3 ≤ PDC <0.5), or highly nonadherent (PDC <0.3).

Group Matching

To create comparable cohorts, each nonadherent group was matched to the adherent group independently (1:1) based on demographic and preinitiation clinical characteristics using propensity scores that were calculated from logistic regression models.[19,20] The outcome variable in the model was dichotomous, indicating whether a patient was adherent (1) to the index inhaled corticosteroid/LABA combination therapy or nonadherent (0). The goal was to have a similar distribution of patient characteristics between the matched cohorts. Unadjusted bivariate tests were conducted, with $\alpha = 0.05$, to determine whether the groups were well-balanced. All the following variables were required to be balanced after matching: the number of preindex hospitalizations with a primary diagnosis of COPD; the number of preindex emergency department visits with a primary or secondary diagnosis of COPD; the number of preindex oral corticosteroids, antibiotics, SABA, SAMA, SABA/SAMA, LABA, and long-acting muscarinic antagonist prescription fills; comorbidities; age; sex; and preindex asthma diagnosis.

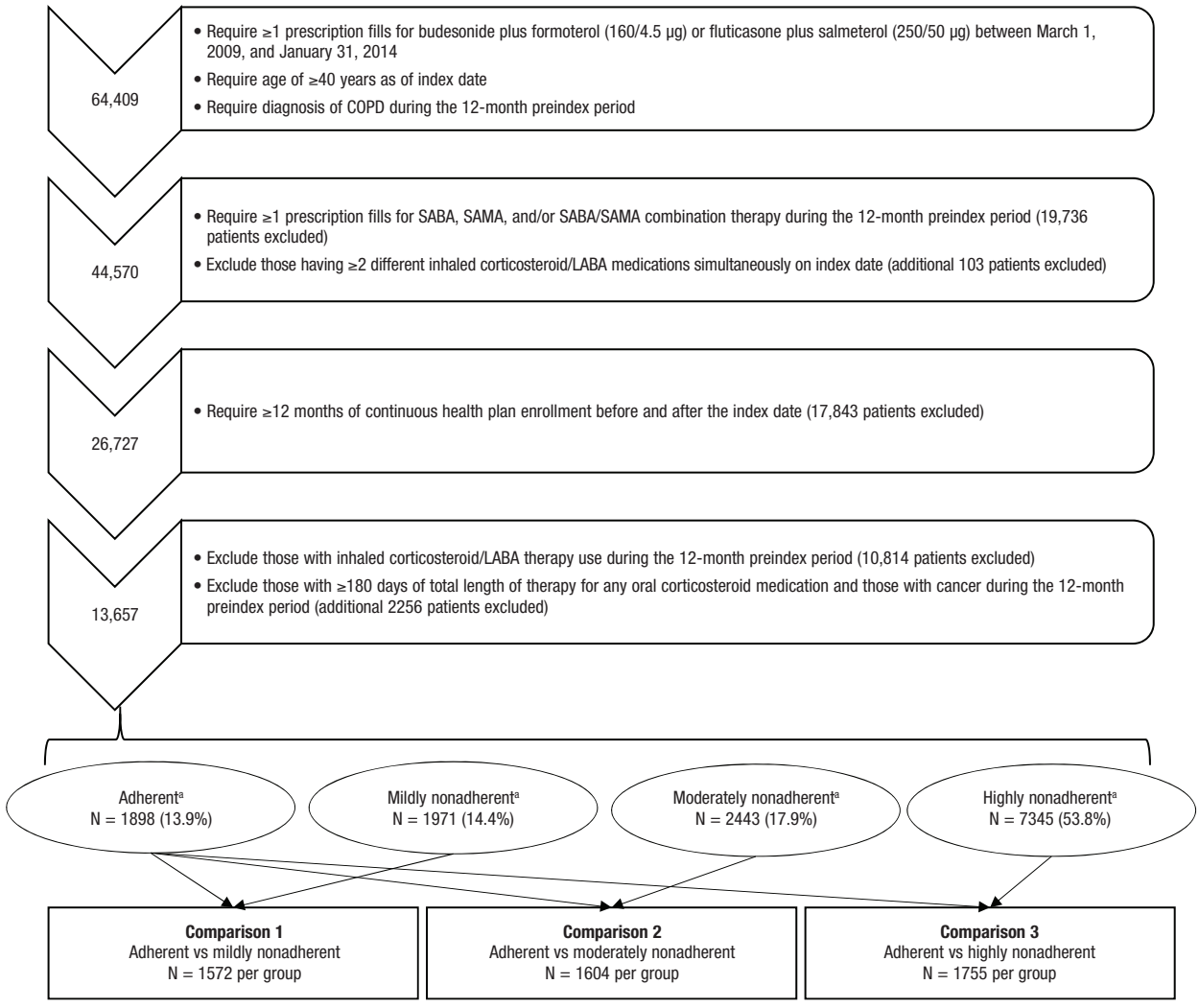
Outcome Measures

Exacerbation rates and all-cause and COPD-related (medical claims with a COPD diagnosis and pharmacy claims for COPD medication) healthcare costs (adjusted to 2014 US dollars) during the 12-month postindex period were compared between the adherent and nonadherent cohorts, independently. Exacerbation events included hospitalizations with a primary diagnosis of COPD, emergency department visits with a primary or secondary diagnosis of COPD, and outpatient visits with a diagnosis of COPD and oral corticosteroids and/or an antibiotic medication fill on the same day of, or within 10 days after, the outpatient visit.

Statistical Analysis

The exacerbation rates were evaluated with general-

Figure 1 Medication Nonadherence in Patients with COPD



[a]Adherent, proportion of days covered (PDC) ≥0.8; mildly nonadherent, 0.5 ≤ PDC <0.8; moderately nonadherent, 0.3 ≤ PDC <0.5; highly nonadherent, PDC <0.3.

COPD indicates chronic obstructive pulmonary disease; LABA, long-acting β_2-adrenergic agonist; SABA, short-acting β_2-adrenergic agonist; SAMA, short-acting muscarinic antagonist.

ized linear models (GLMs) with a negative binomial distribution and log link function. The costs were estimated with GLMs with a gamma distribution and log link weighted by the length of follow-up. The models controlled for all unbalanced preindex factors and the analogous preindex variable (eg, when analyzing the number of COPD-related hospitalizations postindex, the model controlled for the number of preindex COPD-related hospitalizations). All statistical analyses were performed with SAS version 9.4 (SAS Institute, Inc; Cary, NC).

Results

Among the total 13,657 eligible patients with COPD who initiated prespecified inhaled corticosteroid/LABA fixed-dose combination therapy, 1898 (13.9%) patients were adherent to their treatment during the 12-month postindex period. A total of 1971 (14.4%) patients were mildly nonadherent, 2443 (17.9%) patients were moderately nonadherent, and 7345 (53.8%) patients were highly nonadherent. Group matching resulted in 1572 patients per group for comparison 1 (adherent vs mildly nonadherent), 1604 patients per group for comparison 2 (adherent vs moderately nonadherent), and 1755 patients per group for comparison 3 (adherent vs highly nonadherent; **Figure 1**).

The cohorts were well-balanced in age (mean, 67 years), sex (51%-53% female), previous COPD-related

Table Baseline Demographics and Clinical Characteristics of Patients with COPD Initiating Budesonide plus Formoterol (160/4.5 µg) or Fluticasone plus Salmeterol (250/50 µg)

Parameter	Comparison 1 (N = 1572 each)		Comparison 2 (N = 1604 each)		Comparison 3 (N = 1755 each)	
	Adherent[a]	Mildly nonadherent[a]	Adherent	Moderately nonadherent	Adherent	Highly nonadherent[a]
Demographics						
Age, mean (SD)	67.0 (11.0)	67.1 (11.0)	67.2 (10.9)	67.2 (11.1)	67.2 (10.9)	67.3 (11.1)
Female, N (%)	833 (53.0)	821 (52.2)	838 (52.2)	841 (52.4)	898 (51.2)	900 (51.3)
COPD severity						
Previous COPD inpatient visits, mean (SD)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.2 (0.5)
Previous COPD emergency department visits, mean (SD)	0.2 (0.6)	0.2 (0.6)	0.2 (0.6)	0.2 (0.6)	0.2 (0.6)	0.3 (0.7)
Previous oral corticosteroid fills, mean (SD)	1.4 (1.7)	1.3 (1.7)	1.3 (1.7)	1.3 (1.7)	1.3 (1.7)	1.3 (1.8)
Previous antibiotic fills, mean (SD)	2.6 (2.8)	2.7 (3.0)	2.7 (3.0)	2.6 (2.8)	2.7 (3.0)	2.8 (3.1)
COPD medications						
Previous SABA, SAMA, or SABA/SAMA fills, mean (SD)	5.3 (5.7)	5.2 (5.7)	4.8 (4.9)	4.7 (5.1)	5.2 (5.3)	5.1 (5.8)
Previous LABA fills, mean (SD)	0.3 (1.6)	0.3 (1.6)	0.2 (1.3)	0.2 (1.3)	0.3 (1.5)	0.3 (1.4)
Previous LAMA fills, mean (SD)	1.8 (3.3)	1.8 (3.3)	1.6 (3.1)	1.7 (3.1)	1.7 (3.2)	1.7 (3.1)
Comorbid conditions, N (%)						
Hypertension	1095 (69.7)	1104 (70.2)	1139 (71.0)	1142 (71.2)	1244 (70.9)	1243 (70.8)
Depression or psychotropic drug use	813 (51.7)	795 (50.6)	822 (51.2)	813 (50.7)	890 (50.7)	896 (51.1)
Asthma	541 (34.4)	550 (35.0)	548 (34.2)	538 (33.5)	601 (34.2)	605 (34.5)
Coronary artery disease	466 (29.6)	474 (30.2)	476 (29.7)	489 (30.5)	531 (30.3)	518 (29.5)
Pneumonia	347 (22.1)	364 (23.2)	375 (23.4)	363 (22.6)	409 (23.3)	420 (23.9)
Diabetes	333 (21.2)	323 (20.5)	341 (21.3)	335 (20.9)	368 (21.0)	356 (20.3)
Congestive heart failure	304 (19.3)	290 (18.4)	306 (19.1)	302 (18.8)	325 (18.5)	326 (18.6)
Anxiety	238 (15.1)	227 (14.4)	239 (14.9)	226 (14.1)	258 (14.7)	283 (16.1)
Pulmonary hypertension	108 (6.9)	107 (6.8)	107 (6.7)	103 (6.4)	120 (6.8)	123 (7.0)
Chronic respiratory failure	95 (6.0)	91 (5.8)	94 (5.9)	95 (5.9)	108 (6.2)	112 (6.4)
Stroke	51 (3.2)	50 (3.2)	48 (3.0)	49 (3.1)	51 (2.9)	60 (3.4)
Left ventricular failure	23 (1.5)	27 (1.7)	28 (1.7)	31 (1.9)	28 (1.6)	29 (1.7)

[a]Adherent, proportion of days covered (PDC) ≥0.8; mildly nonadherent, 0.5 ≤ PDC <0.8; moderately nonadherent, 0.3 ≤ PDC <0.5; highly nonadherent, PDC <0.3.

COPD indicates chronic obstructive pulmonary disease; LABA, long-acting β_2-adrenergic agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β_2-adrenergic agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

medication use, healthcare utilization, and comorbid conditions (**Table**).

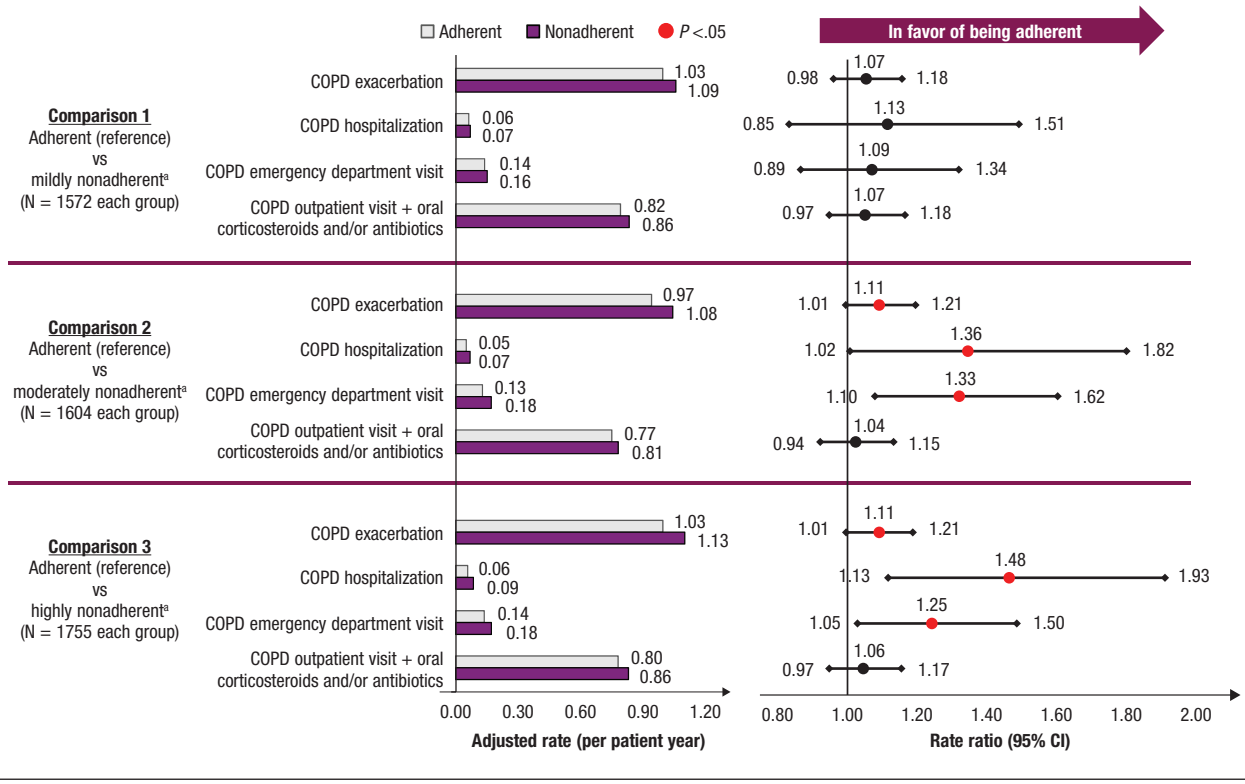
Exacerbation Rates

During follow-up, no significant difference in COPD exacerbation rate was seen between the adherent and mildly nonadherent cohorts (rate ratio [RR], 1.07; 95% confidence interval [CI], 0.98-1.18; *P* = .14; **Figure 2**). The moderately nonadherent and highly nonadherent cohorts had significantly higher rates of COPD exacerbations compared with the adherent cohort (comparison 2: RR, 1.11; 95% CI, 1.01-1.21; *P* = .03; comparison 3: RR, 1.11; 95% CI, 1.01-1.21; *P* = .02), which was mainly driven by higher rates of COPD-related hospitalizations (comparison 2: RR, 1.36; 95% CI, 1.02-1.82; *P* = .03; comparison 3: RR, 1.48; 95% CI, 1.13-1.93; *P* <.01) and COPD-related emergency department visits (comparison 2: RR, 1.33; 95% CI, 1.10-1.62; *P* <.01; comparison 3: RR, 1.25; 95% CI, 1.05-1.50; *P* = .01).

Healthcare Costs

As shown in **Figure 3**, during the 12-month follow-up, adherent patients incurred significantly lower mean all-cause healthcare costs than nonadherent patients for the 3 comparisons (comparison 1, unadjusted mean $22,671 vs $25,545; adjusted mean difference,

Figure 2 Association Between Nonadherence to First-Year Fixed-Dose Combination Inhaled Corticosteroid/LABA Therapy and COPD Exacerbations Rate



[a]Adherent, proportion of days covered (PDC) ≥0.8; mildly nonadherent, 0.5 ≤ PDC <0.8; moderately nonadherent, 0.3 ≤ PDC <0.5; highly nonadherent, PDC <0.3.
CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; LABA, long-acting β_2-adrenergic agonist.

$1653; *P* <.01; comparison 2, $22,508 vs $24,303; adjusted mean difference, $2001; *P* <.01; comparison 3, $22,460 vs $25,148; adjusted mean difference, $1854; *P* <.01), which was mainly driven by lower hospitalization and outpatient costs, despite the higher pharmacy costs. Although COPD-related hospitalization costs were lower in adherent patients, as shown in **Figure 4**, the higher COPD-related pharmacy costs resulted in significantly higher mean total COPD-related healthcare costs for adherent patients (comparison 1, unadjusted mean, $8149 vs $7053; adjusted mean difference –$712; *P* <.01; comparison 2, $7997 vs $6623; adjusted mean difference –$1282; *P* <.01; comparison 3, $8080 vs $5644; adjusted mean difference –$2639; *P* <.01).

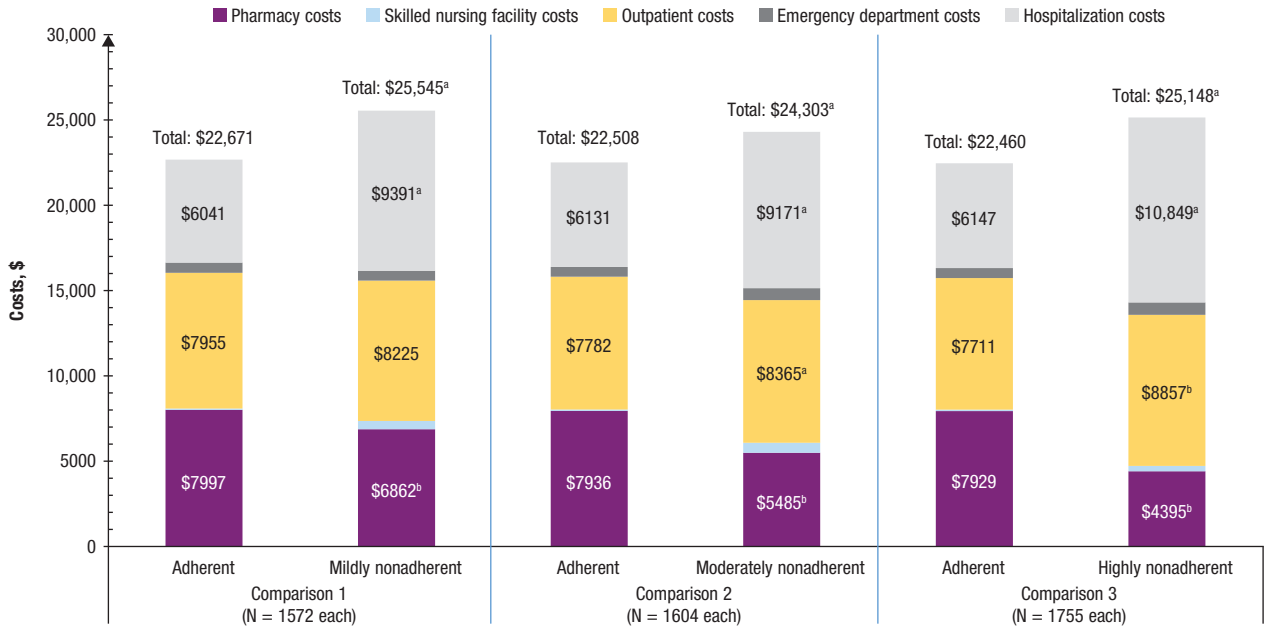
Discussion

The disease exacerbation rates were significantly higher among moderately and highly nonadherent patients compared with adherent patients, although they were not different between the adherent and mildly nonadherent cohorts in this study. This finding points to an association between poor adherence and increased rates of COPD exacerbations during the 12-month follow-up period in this cohort of patients with COPD. Consistent with previous literature that showed suboptimal adherence to COPD medication,[12,14-16] we found that the majority of patients with COPD had poor adherence to fixed-dose combination inhaled corticosteroid/LABA therapy, which suggests lost opportunities in usual care settings to optimize the benefits of this maintenance therapy.

This study's findings show that better treatment adherence to fixed-dose combination inhaled corticosteroid/LABA therapy was associated with significantly lower all-cause healthcare costs during the 12-month period after treatment initiation, which was mainly driven by the lower all-cause hospitalization and outpatient costs. Notably, patients adherent to treatment had fewer all-cause hospitalizations and intensive care unit stays relative to each of the 3 nonadherent groups.

One explanation for this observation is that adherence to fixed-dose combination inhaled corticosteroid/LABA therapy could indicate better adherence to medications for comorbid conditions. Although not assessed

Figure 3 Postindex All-Cause Healthcare Costs Among Patients with COPD



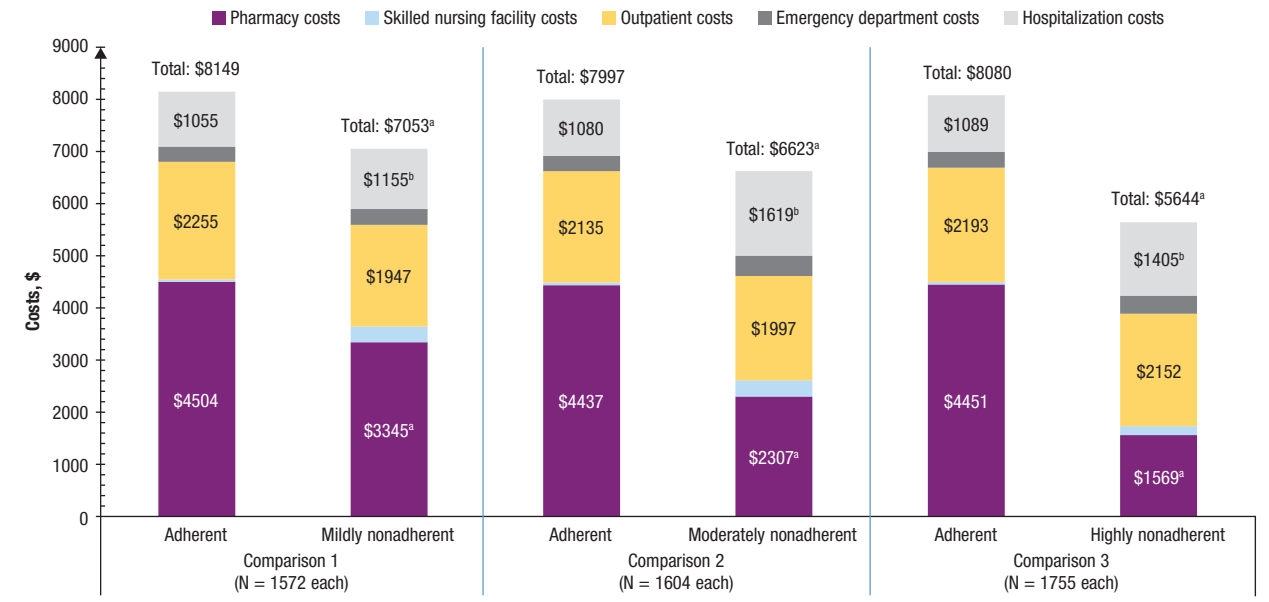
NOTE: Values for emergency department costs and SNF costs are not shown in the figure because of their relatively small amount. Adherent, proportion of days covered (PDC) ≥0.8; mildly nonadherent, 0.5 ≤ PDC <0.8; moderately nonadherent, 0.3 ≤ PDC <0.5; highly nonadherent, PDC <0.3.

[a]*P* <.05, in favor of being adherent.

[b]*P* <.05, in favor of being nonadherent.

COPD indicates chronic obstructive pulmonary disease.

Figure 4 Postindex COPD-Related Healthcare Costs Among Patients with COPD



NOTE: Values for emergency department costs and skilled nursing facility costs are not shown in the figure because of their relatively small amount. Adherent, proportion of days covered (PDC) ≥0.8; mildly nonadherent, 0.5 ≤ PDC <0.8; moderately nonadherent, 0.3 ≤ PDC <0.5; highly nonadherent, PDC <0.3.

[a]*P* <.05, in favor of being nonadherent.

[b]*P* <.05, in favor of being adherent.

COPD indicates chronic obstructive pulmonary disease.

in this study, overall medication adherence might have contributed to the reduced healthcare utilization for conditions other than COPD and might have subsequently led to lower overall healthcare costs. With regard to COPD-specific healthcare costs, we found that adherent patients incurred significantly higher COPD-related pharmacy costs that were not completely offset by savings from reduced COPD-related inpatient hospitalization costs, thereby leading to higher overall COPD-related healthcare costs compared with nonadherent patients. However, this study was not designed to evaluate the impact of COPD maintenance therapy nonadherence on COPD-related costs beyond 1 year.

In a review of some of the important factors contributing to medication nonadherence, Restrepo and colleagues noted that progress in COPD management has been stymied by poor medication adherence.[12] The authors reported that adherence rates among patients with COPD averaged 40% to 60%. Treatment efficacy, side effects, ease of medication administration, medication cost, clinician's preference, and patient's belief were potential factors contributing to suboptimal medication adherence. Assigning responsibility to patients and to providers, Restrepo and colleagues suggest that current attempts to educate patients are not yielding the desired results.[12]

The findings in our study have important implications for all stakeholders—patients, providers, and payers—who are engaged with the management of COPD. With the potential to realize substantial clinical and economic benefits from the effective use of maintenance therapies, initiatives, including greater emphasis on patient education and on the benefits of medication adherence among patients with COPD, should be developed. These initiatives could include educational programs for physicians to raise awareness and encourage the assessment of adherence to medications, and to counsel patients on the importance of complying with the recommendations regarding prescribed treatment regimens. Finally, technologies could be better utilized to facilitate real-time communication between patients and providers to proactively collect patient feedback, monitor medication adherence, and send refill reminders.

We also acknowledge that there is a fundamental difference between patient self-reported outcomes and claims-based measures. The adherence rate reported by Restrepo and colleagues was measured using medication adherence report scales,[12] which, like other frequently used patient self-reporting techniques, tend to overestimate adherence.[21] By contrast, claims-based measures tend to underestimate adherence, because prescriptions paid for by cash over the counter, those administered in the hospital, and free samples are usually not captured in claims. Therefore, each technique has its limitation.

In addition, the adherence reported by Restrepo and colleagues refers to the overall COPD medications,[12] whereas our study only focused on inhaled corticosteroid/LABA combination therapy, which may have lower adherence because of the complexity of the delivery device and the high cost.

Limitations

This study has some limitations that should be considered. One of the most salient limitations is that adherence to therapy and outcomes were measured during the same time period. It was unclear whether poor therapy adherence led to the outcomes, or the occurrence of outcomes led to poor adherence. We recognize that adding and analyzing another year of data after the 1-year postindex data could provide the basis to reexamine this relationship; however, that step was outside the scope of this study. As a result, no causal implication can be concluded in this study, and it is not possible to claim that greater adherence to fixed-dose combination inhaled corticosteroid/LABA therapy leads to lower rates of COPD exacerbation or reduced costs over time.

The prescription claim date is the date a medication was filled, and is not necessarily the date of treatment administration, as is assumed in this study. Furthermore, this study was not designed to indicate how patients took their medication, as is typical in studies using secondary data sources. Thus, prescription refill is only a surrogate marker for medication adherence. Any inpatient-administered medications were not present in these claims data and were not included in any of the analyses.

It was also not possible to determine the primary reason for outpatient visits, including emergency department visits, via claims data. Although a COPD diagnosis code was indicated for visits, these visits could have been for routine follow-up or non–COPD-related reasons and not necessarily because of a COPD exacerbation. Important risk factors, such as smoking status, were not captured in the administrative claims data; thus, this study was not able to address such unmeasured confounding factors. Furthermore, these results may have limited generalizability to a non–commercially insured population.

Finally, the intention of excluding long-term users for any oral corticosteroids was to exclude "very sick" patients who may be managed differently with various adherence behaviors. These patients were likely to be the cost outliers that would confound the study results. Because we did not compare the adherence rate between these sicker patients with other healthier patients, we do not know if the exclusion could lead to a bigger or smaller differential between the adherence subtypes. However, it is an appropriate topic for future researchers to explore.

Conclusions

This study shows the presence of suboptimal adherence to fixed-dose combination inhaled corticosteroid/LABA therapy in a majority of patients with COPD. Poor adherence was associated with an increased rate of COPD exacerbations and higher overall all-cause healthcare costs. These findings point to missed opportunities to realize optimal clinical benefits from these maintenance therapies. Furthermore, improving adherence may help to reduce the economic burden associated with COPD. ■

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Author Disclosure Statement

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References

1. National Heart, Lung, and Blood Institute. COPD: Learn More Breathe Better. NIH Publication No 07-5840. September 2013. www.nhlbi.nih.gov/files/docs/public/lung/copd-atrisk.pdf. Accessed March 15, 2017.
2. National Heart, Lung, and Blood Institute. *Morbidity and Mortality: 2009 Chart Book on Cardiovascular, Lung, and Blood Diseases*. February 2012. www.nhlbi.nih.gov/files/docs/research/2012_ChartBook.pdf. Accessed March 15, 2017.
3. Hoyert DL, Xu J. Deaths: preliminary data for 2011. *Natl Vital Stat Rep*. 2012;61:1-51.
4. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2013;187:347-365.
5. Mannino DM, Homa DM, Akinbami LJ, et al. Chronic obstructive pulmonary disease surveillance--United States, 1971-2000. *MMWR Surveill Summ*. 2002;51:1-16.
6. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2016. http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/. Accessed January 22, 2016.
7. Symbicort (budesonide and formoterol fumarate dihydrate) inhalation aerosol [prescribing information]. Wilmington, DE: AstraZeneca; February 2016.
8. Advair Diskus (fluticasone propionate and salmeterol) inhalation powder [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; April 2016.
9. Breo Ellipta (fluticasone furoate and vilanterol) inhalation powder [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; April 2015.
10. Dong YH, Lin HH, Shau WY, et al. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. *Thorax*. 2013;68:48-56.
11. Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. *Cochrane Database Syst Rev*. 2014:CD010844.
12. Restrepo RD, Alvarez MT, Wittnebel LD, et al. Medication adherence issues in patients treated for COPD. *Int J Chron Obstruct Pulmon Dis*. 2008;3:371-384.
13. Albertson TE, Harper R, Murin S, Sandrock C. Patient considerations in the treatment of COPD: focus on the new combination inhaler umeclidinium/vilanterol. *Patient Prefer Adherence*. 2015;9:235-242.
14. Ágh T, Inotai A, Mészáros Á. Factors associated with medication adherence in patients with chronic obstructive pulmonary disease. *Respiration*. 2011;82:328-334.
15. Bryant J, McDonald VM, Boyes A, et al. Improving medication adherence in chronic obstructive pulmonary disease: a systematic review. *Respir Res*. 2013;14:109.
16. Lareau SC, Yawn BP. Improving adherence with inhaler therapy in COPD. *Int J Chron Obstruct Pulmon Dis*. 2010;5:401-406.
17. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother*. 2006;40:1280-1288.
18. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. *Am J Manag Care*. 2005;11:449-457.
19. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Stat Med*. 2008;27:2037-2049.
20. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol*. 2010;172:1092-1097.
21. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther*. 1999;21:1074-1090.

STAKEHOLDER PERSPECTIVE

When an Outcome Is Overdetermined: Nonadherence, Utilization, and the Impetus for Research in COPD

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In an era in which observational and randomized controlled trials (RCTs) proceed in tandem toward drug registration, Davis and colleagues provide a superb example of observational research impacting clinical development program design for investigational drugs, as well as healthcare delivery options for approved therapies in chronic obstructive pulmonary disease (COPD).[1] Richly annotated, with informative tables, figures, and measured conclusions, this retrospective, observational cohort study provides estimates of healthcare utilization and expenditures based on levels of treatment adherence in a commercially insured population in 50 states from 14 commercial plans. Study methodology can serve as a primer on methods for administrative claims data analysis, while highlighting limitations and opportunities for additional research. Details regarding disease presentation, healthcare utilization patterns, and methods of analysis place the results in context and pique the interest of diverse stakeholders.

RESEARCHERS: This report excels in its descriptions of cohort eligibility, time frames sampled before and after the initiation of the inhaled corticosteroid/long-acting $ß_2$-adrenergic agonist combination, and stratification with group-matching techniques using propensity scores.[1] Outcome measures (ie, exacerbation rates) are operationally defined, and potential confounders are acknowledged. Particularly laudable is the use of confidence intervals to illustrate comparisons between the groups, a technique that facilitates an intuitive evaluation of the potential clinical importance for differences that could exist within the population.[2]

Limitations noted by the authors in the study data include the absence of important risk factors (eg, smoking status) and inpatient-administered medication, the use of prescription refills as a surrogate for adherence, and a study design that may conflate the measurement of adherence and outcomes occurring in the same interval.[1] An inability to parse the differences in utilization resulting from COPD exacerbation versus comorbidities invokes the possibility for a "healthy adherer effect," in which adherence to fixed-dose combination therapy becomes a surrogate for overall healthy behavior, entangling cause and effect and precluding causal implications.

Propensity score matching techniques adjust for the differences between adherent and nonadherent groups based on observed variables. However, the parameters extracted from the administrative claims data in some indications may incompletely map into patient characteristics in clinical trials[3] and jeopardize generalizability. Other techniques for accounting for unmeasured confounders are comparably limited[4] and reinforce the importance of developing health economic data "piggybacked" onto registration studies, despite the recognized limitations.[5] Comorbidity cost drivers have been reported to be comparable between clinical trials and observational studies in patients with COPD,[6] suggesting that a rapprochement is possible in well-designed clinical development programs in which observational trials and RCTs serve complementary and mutually supportive objectives.

PAYERS: An ability to influence adherence in COPD requires the accommodation of regional heterogeneity in provider and patient characteristics and methods of care. Regional variations exist in healthcare utilization for COPD within the United States, particularly for hospitalization rates, which are a key driver of healthcare expenditures.[7] Local, more extensive, and detailed group-, pharmacy-, service-, and patient-level data would be informative. Indeed, programs to enhance adherence tailored to "microenvironments" may be more effective given the interplay of patient and provider characteristics and physician–patient interactions dictating adherence.[8] Nesting substudies within an RCT protocol to address hypotheses of local interest offers 1 pathway for highly granular data acquisition.

Designing programs to enhance adherence based exclusively on data from administrative claims analyses has limitations.[9] Indeed, incorporating physician prescriptions from electronic health records into estimates for claims-based adherence can significantly change conclusions (thus actionable information), regardless of the method initially employed for calculating adherence based on administrative claims.[10]

STAKEHOLDER PERSPECTIVE *Continued*

The results from the research by Davis and colleagues do not permit inferences that greater adherence to COPD medication yields overall reduced cost for COPD-related healthcare, although intuitively plausible. A repartition of cost across inpatient and outpatient services is noted based on adherence strata, but in a direction that is clinically intuitive. Stakeholders, therefore, will perceive implications differently and qualify conclusions based on setting, measurements, comorbidities (eg, cardiovascular disease, diabetes),[11] and disease severity in the absence of standard nomenclature and measures.

PATIENTS: The determinants of adherence cluster within 5 World Health Organization dimensions with 13 discrete parameters, many of which are modifiable by educational programs for providers and patients.[12] The frequency and quality of physician contact and reciprocal physician–patient engagement are influential, measurable, and modifiable, and suggests additional dimensions of assessments that could be incorporated into program design as part of the registration process.[13] Self-management interventions in COPD that impact utilization for respiratory-related and all-cause hospital admissions show promise, although common elements in effective program design remain elusive,[14] and effects of interactions with pharmacotherapy are not systematically explored. ■

1. Davis JR, Wu B, Kern DM, et al. Impact of nonadherence to inhaled corticosteroid/LABA therapy on COPD exacerbation rates and healthcare costs in a commercially insured US population. *Am Health Drug Benefits*. 2017;10(2):92-102.
2. Ranstam J. Why the P-value culture is bad and confidence intervals a better alternative. *Osteoarthritis Cartilage*. 2012;20:805-808.
3. Austin PC, Mamdani MM, Stukel TA, et al. The use of the propensity score for estimating treatment effects: administrative versus clinical data. *Stat Med*. 2005;24:1563-1578.
4. Johnson ML, Crown W, Martin BC, et al. Good research practices for comparative effectiveness research: analytic methods to improve causal inference from nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force report—part III. *Value Health*. 2009;12:1062-1073.
5. O'Sullivan AK, Thompson D, Drummond MF. Collection of health-economic data alongside clinical trials: is there a future for piggyback evaluations? *Value Health*. 2005;8:67-79.
6. Miravitlles M, Price D, Rabe KF, et al. Comorbidities of patients in tiotropium clinical trials: comparison with observational studies of patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2015;10:549-564.
7. Holt JB, Zhang X, Presley-Cantrell L, Croft JB. Geographic disparities in chronic obstructive pulmonary disease (COPD) hospitalization among Medicare beneficiaries in the United States. *Int J Chron Obstruct Pulmon Dis*. 2011;6:321-328.
8. Restrepo RD, Alvarez MT, Wittnebel LD, et al. Medication adherence issues in patients treated for COPD. *Int J Chron Obstruct Pulmon Dis*. 2008;3:371-384.
9. Fairman KA, Curtiss FR. Still looking for health outcomes in all the wrong places? Misinterpreted observational evidence, medication adherence promotion, and value-based insurance design. *J Manag Care Pharm*. 2009;15:501-507.
10. Zhao B, Wong EC, Palaniappan L. Estimating patient adherence to medication with electronic health records data and pharmacy claims combined. Paper presented at the SAS Global Forum; April 28-May 1, 2013; San Francisco, CA. Paper 167-2013.
11. Simon-Tuval T, Scharf SM, Maimon N, et al. Determinants of elevated healthcare utilization in patients with COPD. *Respir Res*. 2011;12:7.
12. Hovstadius B, Petersson G. Non-adherence to drug therapy and drug acquisition costs in a national population—a patient-based register study. *BMC Health Serv Res*. 2011;11:326.
13. Fuertes JN, Mislowack A, Bennett J, et al. The physician–patient working alliance. *Patient Educ Couns*. 2007;66:29-36.
14. Zwerink M, Brusse-Keizer M, van der Valk PD, et al. Self management for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2014:CD002990.