Real-world outcomes in patients with chronic obstructive pulmonary disease initiating long-acting mono bronchodilator therapy

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Abstract

Background: Randomized clinical trials have shown long-acting mono bronchodilator therapy to be efficacious in improving lung function and dyspnea, while reducing exacerbations; however, less is known regarding the effectiveness in routine clinical practice. This study examined treatment patterns, rescue medication use, healthcare resource utilization and costs, and exacerbations in patients with chronic obstructive pulmonary disease (COPD) who initiated long-acting mono bronchodilator therapy in real-world settings.

Methods: This retrospective study used US claims data from adult patients with COPD initiating long-acting mono bronchodilator therapy between 1 January 2008 and 31 January 2015. Patients were required to have continuous health plan enrollment 12 months prior to (baseline period) and 12 months following therapy initiation (follow-up period). Outcomes, including treatment patterns, rescue medication use, exacerbations, and healthcare utilization and costs, were measured until the earliest of treatment augmentation or discontinuation, death, health plan disenrollment, or the end of the study period. Results were analyzed descriptively for all measures. Baseline and follow-up measures of all-cause and COPD-related healthcare costs and exacerbations [per patient per month (PPPM)] were compared using paired *t* tests.

Results: Among 27,394 patients with a mean follow up of 6.3 months, 18.2% augmented, 74.2% discontinued, and 7.6% continued long-acting mono bronchodilator therapy. Rescue medication use was prevalent during the follow-up period, with an average of 1.0 short-acting β agonist (SABA) fills/month and 0.8 short-acting muscarinic antagonist (SAMA) fills/month , among patients with at least one fill for the medication of interest. PPPM mean number of exacerbations was more than triple (0.17 *versus* 0.05, $p < 0.001$) and PPPM exacerbation-related costs were more than double over the follow-up period compared with baseline ($1070 *versus* $485). COPD-related costs accounted for 50% of all-cause costs during the follow-up period and were significantly higher compared with baseline ($1206 *versus* $592, $p < 0.001$).

Conclusions: Patients initiating long-acting mono bronchodilator therapy had high rates of medication discontinuation or augmentation. Patients used more rescue medications and experienced significantly more COPD exacerbations with higher healthcare costs compared with baseline. Further research is warranted to determine whether more aggressive initial therapy would result in symptom improvement.

Keywords: chronic obstructive pulmonary disease, exacerbation, long-acting β agonist, long-acting muscarinic antagonist, utilization

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by an irreversible and progressive decline in lung function and is the third leading cause of death in the US, affecting an estimated 24 million Americans.[1] Medical costs attributable to COPD were estimated at $32.1 billion in the US in 2010, with a projected rise to $49 billion by 2020.[2] The largest proportion of the COPD cost burden is due to exacerbations.[3,4] Annual healthcare costs in patients with acute COPD exacerbations are reportedly 10 times greater than costs for patients with COPD without exacerbations.[5]

The goal of pharmacologic therapy for COPD is to reduce symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and quality of life.[3] Inhaled long-acting bronchodilators (β agonists and anticholinergics) are the mainstays of pharmacologic therapy in COPD symptom management.[3] Randomized controlled trials (RCTs) have shown long-acting mono bronchodilator therapy to be effective in improving lung function, dyspnea, and health-related quality of life, while reducing exacerbations and the need for hospitalization compared with placebo.[6–9] RCTs have documented the efficacy of tiotropium monotherapy, a commonly prescribed long-acting muscarinic antagonist (LAMA), over placebo in improving health-related quality of life and dyspnea, and reducing exacerbations and exacerbation-related hospitalizations.[8] In the ATTAIN and ACCORD studies, the LAMA, aclidinium bromide, significantly improved lung function,[10,11] reduced COPD symptoms,[10,11] and reduced the number of exacerbations compared with placebo.[12,13] Toward a Revolution in COPD Health (TORCH), the largest trial of the long-acting β agonist (LABA), salmeterol, reported a significant decrease in exacerbation rate and improved lung function compared with patients randomized to placebo.[14]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) categorizes patients based on symptoms and risk of exacerbation. Based on data from RCTs, the GOLD treatment guidelines recommend LAMA monotherapy as the initial treatment for patients categorized in group C, whereas LABA or LAMA monotherapy is advised for group B patients.[3,15] Treatment augmentation to dual therapy (LAMA/LABA) is recommended in group B patients who remain symptomatic, and inhaled corticosteroid (ICS)/LABA or LAMA/LABA therapy in group C patients with continuing exacerbations despite the use of long-acting mono bronchodilators. Group D patients are recommended to initiate dual therapy, preferably a LAMA/LABA combination, and augment to triple therapy (ICS/LABA + LAMA) if exacerbations continue on dual therapy. Newer fixed-dose combination (FDC) LAMA/LABAs have been shown to significantly improve lung function, inspiratory capacity, dyspnea, and health status, and reduce rescue medication use compared with individual drugs alone.[16–19]

It has been suggested that real-world treatment prescribing patterns for COPD may not align with recommended GOLD guidelines, particularly with regard to ICS use.[20–25] In several US-based studies, real-world GOLD-adherent prescribing ranged from 36% to 56% among patients with COPD.[20–22] Few real-world studies have been conducted to examine health outcomes of patients with COPD initiating long-acting mono bronchodilator therapy in this treatment landscape. Describing the patient population and their treatment patterns and outcomes in a real-world setting will provide insights into the management and control of COPD in patients receiving monotherapy. The purpose of this study is to examine treatment patterns, COPD exacerbations, and all-cause and COPD-related healthcare resource utilization and costs in patients who initiated long-acting mono bronchodilator therapy.

Methods

Study design and data source

This was a retrospective cohort database study using administrative claims from the Optum Research Database (ORD). The ORD includes enrollment information and medical and pharmacy claims for approximately 14 million enrollees in commercial plans and 3 million enrollees in Medicare Advantage with Part D (MAPD) plans annually. The ORD is geographically diverse and representative of the US commercially insured population. Medical claims included International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, Current Procedural Terminology codes, Healthcare Common Procedure Coding System codes, revenue codes,

and site of service codes. Outpatient pharmacy claims included National Drug Codes for filled prescriptions, dosage form, fill date, days' supply, and deidentified patient and prescriber codes. Linked sociodemographic data were available for a subset of patients in the database. No identifiable protected health information was extracted or accessed during this study, therefore Institutional Review Board approval or a waiver of authorization was not required.

Study population

The study population included adult commercial and Medicare Advantage health plan enrollees who initiated long-acting mono bronchodilator therapy between 1 January 2008 and 31 January 2015 (identification period). The index date was defined as the date of the first pharmacy fill for a LABA (i.e. arformoterol, formoterol, salmeterol, olodaterol, indacaterol) or LAMA (i.e. tiotropium, aclidinium, umeclidinium, glycopyrrolate) during the identification period. To be eligible for study participation, patients were at least 40 years of age as of the index year and had evidence of COPD (at least two nondiagnostic medical claims 30 days or more apart with a COPD diagnosis code in any position; at least one COPD diagnosis code was required to occur prior to or on the index date). Patients were also required to have continuous health plan enrollment 12 months prior to the index date (baseline period) and 12 months following the index date (follow-up period). Patients with at least one pharmacy fill for a LAMA, LABA, or ICS in the baseline period or a diagnosis of cystic fibrosis (at least one medical claim with ICD-9-CM code: 277.0x; ICD-10-CM codes: E849, E840, E8419, E848 in any position) at any time during the study period were excluded from the study. Patients were also excluded if they had evidence of ICS use on the index date. Patient observation began on the index date and lasted until the earliest of treatment augmentation, discontinuation of long-acting bronchodilator therapy, death, disenrollment from the health plan, or the end of the study period (31 January 2016).

Study measures

Demographic and clinical characteristics. Characteristics assessed during the baseline period included age in the index year, sex, insurance type, geographic region, race/ethnicity, education level, urbanicity,[26] comorbidity based on the Charlson index,[27,28] and oxygen therapy use. The top five comorbid conditions among patients with COPD were also identified.

Follow-up long-acting mono bronchodilator treatment patterns. The proportion of patients who augmented or discontinued their long-acting mono bronchodilator therapy was measured during the follow-up period. Augmentation was defined as intensification to dual (i.e. ICS/LABA or LAMA/LABA) or triple (i.e. ICS/LABA + LAMA) therapy based on pharmacy fills on the date of the first augmentation, while discontinuation was defined as a gap in mono bronchodilator therapy of at least 60 days following depletion of days' supply. The date of discontinuation was defined by the run out of days' supply of the last prescription filled prior to the gap in therapy, corrected for any inpatient stays (it was assumed that medication was supplied during the stay). The time to long-acting mono bronchodilator therapy augmentation or discontinuation from the index date was also calculated. In patients with no evidence of augmentation or discontinuation, the time from the index date to the end of follow up (i.e. death, disenrollment in the health plan, or the end of the study period) was calculated.

Baseline and follow-up rescue medication and systemic corticosteroid use. Among patients who used rescue medication [short-acting muscarinic antagonists (SAMAs) or short-acting β agonists (SABAs)] or systemic corticosteroids during the baseline or follow-up periods per patient per month (PPPM) total days' supply and number of prescription fills were calculated. The number of prescription fills was counted among patients with at least one fill and only one fill per national drug code (NDC) per day. If there were multiple fills with the same NDC on the same day, the fill with the longest days' supply was retained.

COPD exacerbations and related costs. The PPPM mean number of exacerbations and associated costs were calculated for the baseline and follow-up periods. It was possible for each exacerbation episode to contain multiple exacerbation events. The exacerbation episode ended when 14 days had passed without an exacerbation event. An exacerbation event was defined as an inpatient hospitalization with a primary diagnosis of COPD (start and end date of exacerbation defined as the inpatient hospitalization admission and discharge

dates, respectively); an emergency room (ER) visit with a diagnosis in any position for COPD (start and end date of the exacerbation defined as the ER service date); or an ambulatory visit with a COPD diagnosis in any position and a procedure code for a steroid or antibiotic administration during the visit, or a pharmacy claim for an oral corticosteroid or antibiotic on the same day or within 10 days following the ambulatory visit (start and end date of the exacerbation defined as the ambulatory visit service date). Exacerbations requiring hospitalization or an ER visit were considered severe, while exacerbations with an associated ambulatory visit and a pharmacy claim for a steroid or antibiotic on the same day or within 10 days following the ambulatory visit were considered moderate. PPPM COPD-related exacerbation costs were calculated during the time period between the exacerbation start date and within 7 days following the exacerbation end date and adjusted to 2015 US$ using the annual medical care component of the Consumer Price Index (CPI).[29,30] Costs were stratified by severe and moderate exacerbations.

Healthcare resource utilization and costs. All-cause and COPD-related healthcare utilization was calculated during the baseline and follow-up periods; the PPPM mean number of inpatient stays, ER visits, or ambulatory visits were reported. Visits were considered COPD related if they had a COPD diagnosis code in any position on the claim. All-cause and COPD-related healthcare costs were calculated in the baseline and follow-up periods as the 2015 CPI-adjusted PPPM combined health plan and patient-paid amounts. Total costs comprised inpatient costs, ER costs, ambulatory costs, pharmacy costs, and other costs.

Statistical analyses

All study variables were analyzed descriptively. Numbers and percentages were calculated for dichotomous and polychotomous variables, and means and standard deviations (SDs) were calculated for continuous measures. Patients were censored at the earliest of treatment augmentation, discontinuation of long-acting bronchodilator therapy, death, health plan disenrollment, or the end of the study period. PPPM values were reported as appropriate to account for the variable follow-up period. Baseline and follow-up measures of PPPM all-cause and COPD-related healthcare costs and PPPM COPD exacerbations were compared using paired *t* tests.

Results

Study sample and baseline characteristics

Of 27,394 eligible patients with COPD (Figure 1), 95.2% initiated treatment with a LAMA and the remaining 4.8% initiated LABA therapy. Mean age was 68.4 years, approximately half of the population was male (50.1%), and the majority were white (76.4%) (Table 1). Patients were most frequently enrolled in Medicare Advantage (60.0%) and resided in the South (46.1%) or Midwest (30.1%), with almost all (94.3%) residing in an urban area. The mean Charlson comorbidity index score was 2.1. Almost all patients (92.1%) had evidence of at least one comorbid condition, most commonly hypertension (73.8%), atherosclerotic cardiovascular disease (35.9%), and anxiety or depression (26.5%) (data not shown).

Long-acting mono bronchodilator treatment patterns

Over a mean follow-up duration of 6.3 ± 10.1 months, 18.2% of patients augmented, 74.2% of patients discontinued, and 7.6% of patients continued their long-acting mono bronchodilator therapy (Table 2). Patients who augmented remained on monotherapy for a mean duration of 5.8 ± 9.3 months before augmentation and most (75.5%) intensified to triple therapy. Among patients who discontinued, the mean time to discontinuation was 4.3 ± 6.6 months. The small percentage of patients who remained on long-acting mono bronchodilator therapy had an average follow-up duration of 27.6 ± 14.9 months.

Rescue medication and systemic corticosteroid use

Among patients with at least one fill for the medication of interest (i.e. SABA, SAMA, or SAMA/SABA) during the 12-month baseline period, the mean number of fills in the baseline period was 0.3 for both SABAs and SAMAs, with a mean days' supply of 6.6 and 7.1, respectively (Table 3). Among patients with at least one fill for the medication of interest, the mean days' supply for SABAs and SAMAs was 14.4 and 12.6, respectively, with a mean of 1.0 SABA fills/month and 0.8 SAMA fills/month in the follow-up period. The number of SABA doses used per day was calculated as 1.0 dose/day during the baseline period compared with 3.7 doses/day during the follow-up period.

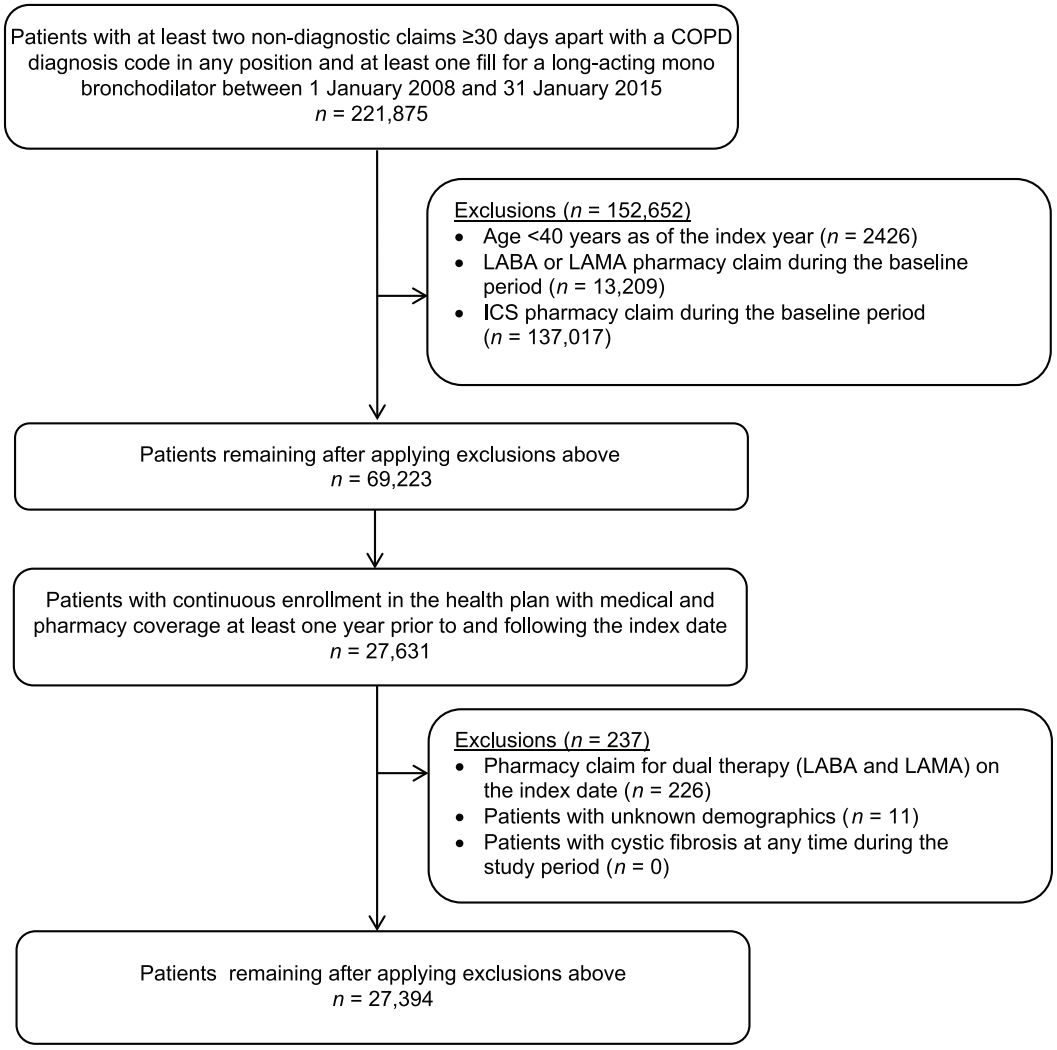

Figure 1. Patient sample selection.
COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β agonist; LAMA, long-acting muscarinic antagonist.

Almost one quarter of patients (24.1%) had evidence of systemic corticosteroid use in the follow-up period. Among patients with at least one fill, the mean number of fills was 0.9 fills/month in the follow-up period, compared with 0.2 fills/month among the 8,937 patients with at least one fill during the baseline period.

COPD exacerbation and exacerbation-related costs

Compared with baseline, the PPPM mean number of exacerbations was more than triple (0.17 *versus* 0.05, $p < 0.001$) and PPPM costs related to exacerbations were more than double ($1070 *versus* $485) during the follow-up period (Table 4). Although the PPPM mean number of severe exacerbations was only slightly higher during follow up than during the baseline period (0.02 *versus* 0.01), PPPM costs related to severe exacerbations were more than three times higher ($3398 *versus* $1051).

Healthcare resource utilization and costs

Compared with baseline, the average follow-up numbers of PPPM visits were higher, with 0.05 inpatient stays (*versus* 0.04 stays during the baseline period), 0.12 ER visits (*versus* 0.10 visits during the baseline period), and 2.8 ambulatory visits (*versus* 1.8 visits during the baseline period) (Table 5).

Table 1. Baseline characteristics of patients with COPD initiating long-acting mono bronchodilator therapy.

	Overall *n* = 27,394
Age, years, mean (SD)	68.4 (10.3)
Male sex, *n* (%)	13,728 (50.1)
Insurance type, *n* (%)*	
Commercial	10,971 (40.1)
Medicare advantage	16,423 (60.0)
Geographic region, *n* (%)*	
Northeast	3568 (13.0)
Midwest	8254 (30.1)
South	12,639 (46.1)
West	2932 (10.7)
Other	1 (0.0)
Race, *n* (%)	
White	20,936 (76.4)
Black/African American	2646 (9.7)
Hispanic	819 (3.0)
Asian	313 (1.1)
Missing/unknown/other/no data available	2680 (9.8)
Education level, *n* (%)	
Less than high school graduate	416 (1.5)
High school graduate	13,447 (49.1)
College or Associate's degree	10,257 (37.4)
Bachelor's degree or higher	1496 (5.5)
Missing/unknown/no data available	1778 (6.5)
Urbanicity[$]	
Urban	25,798 (94.3)
Rural	1556 (5.7)
Missing/unknown	2 (0.0)
Charlson comorbidity score, mean (SD)	2.1 (1.8)
Oxygen therapy, *n* (%)	4952 (18.1)

*Totals do not equal 100% due to rounding.
[$]Based on the US Census Bureau Core Based Statistical Area.
COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Table 2. Treatment patterns among patients with chronic obstructive pulmonary disease (COPD) initiating long-acting mono bronchodilator therapy.

	Overall ***n*** **= 27,394**
Observation time*, months, mean (SD)	6.3 (10.1)
Augmentation of long-acting mono bronchodilator therapy[$], *n* (%)	4973 (18.2)
Months to augmentation of mono long-acting bronchodilator therapy, mean (SD)	5.8 (9.3)
Intensification to dual therapy (ICS/LABA, LAMA/LABA, or ICS + LAMA), *n* (%)	1221 (24.6)
Intensification to triple therapy (ICS/LABA + LAMA), *n* (%)	3752 (75.5)
Continued mono long-acting bronchodilator therapy through end of study/ continuous enrollment, *n* (%)	2092 (7.6)
Months to end of observation, mean (SD)	27.6 (14.9)
Discontinuation of mono long-acting bronchodilator therapy[‡], *n* (%)	20,329 (74.2)
Months to mono long-acting bronchodilator therapy discontinuation[‡], mean (SD)	4.3 (6.6)

*Time from index date to earliest of treatment augmentation, discontinuation of long-acting bronchodilator monotherapy, health plan disenrollment, death, and study end (31 January 2016).
[$]Augmentation was defined as intensification to dual (i.e. ICS/LABA, LAMA/LABA, or ICS + LAMA) or triple (i.e. ICS/LABA + LAMA) therapy, based on pharmacy fills on the date of first augmentation.
[‡]Defined as a gap in monotherapy of ⩾60 days following depletion of days' supply.
COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation.

Due to the higher PPPM healthcare resource utilization in the follow-up period, all-cause PPPM costs were significantly higher in the follow-up period compared with baseline ($2402 *versus* $1543, $p < 0.001$) (Figure 2). PPPM costs related to COPD were also significantly higher in the follow-up period than during baseline ($1206 *versus* $592, $p < 0.001$). COPD-related costs made up approximately 38% of the all-cause costs in the baseline period and 50% of the all-cause costs in the follow-up period. The largest increases in PPPM COPD-related costs from the baseline to the follow-up period were among ambulatory ($56 *versus* $190) and pharmacy ($12 *versus* $384) costs.

Discussion

This was a retrospective claims data study of 27,394 patients with COPD who initiated treatment with a long-acting mono bronchodilator. In patients initiated on (mostly LAMA) mono bronchodilator therapy, high rates of therapy discontinuation or augmentation were observed, with 74.2% of patients discontinuing therapy, and 18.2% augmenting therapy. Most patients augmenting therapy progressed to a triple combination regimen that incorporated an ICS and LABA.

These findings are consistent with reports from other studies; a real-world investigation in the US found that 25% of patients with COPD discontinued their LAMA therapy beyond their initial prescription at baseline, and 13% had only one prescription within the study's 24-month follow-up period.[31] A study in an Italian cohort of patients with COPD reported similar high rates of discontinuation after initiation of long-acting bronchodilator therapy, with 67% of patients discontinuing after just 6 months, and 80% discontinuing after 1 year.[32] Further, a study of German patients with COPD found that 67% did not continue long-acting bronchodilator therapy beyond 1 year.[33] Two real-world studies in patients with COPD found similar rates of augmentation to those reported in this study, with 19% and 28% switching or augmenting their long-acting mono bronchodilator therapy within 12 months of initiation, respectively.[31,34]

Table 3. PPPM baseline and follow-up rescue medication and systemic corticosteroid use in patients with COPD initiating long-acting bronchodilator monotherapy[$].

	Baseline ***n*** **= 27,394**	**Follow-up** ***n*** **= 27,394**
Any SABA use*, *n*	11,823	11,999
Days' supply[$], mean (SD)	6.6 (7.6)	14.4 (10.1)
Number of fills[$], mean (SD)	0.3 (0.3)	1.0 (2.6)
Any SAMA use[‡], *n*	4351	2716
Days' supply[$], mean (SD)	7.1 (7.9)	12.6 (10.2)
Number of fills[$], mean (SD)	0.3 (0.3)	0.8 (2.2)
Any systemic corticosteroid use[§], *n*	8937	6608
Days' supply[$], mean (SD)	2.8 (5.5)	7.0 (8.4)
Number of fills[$], mean (SD)	0.2 (0.2)	0.9 (2.7)

[$]Only among patients with at least one fill for the medication of interest.
*Any SABA includes SABA and SABA/SAMA fills.
[‡]Any SAMA includes SAMA and SABA/SAMA fills.
[§]Rescue medication and systemic corticosteroid use were observed during the 12 months prior to long-acting bronchodilator monotherapy initiation (baseline) and from long-acting bronchodilator monotherapy initiation until the earliest of treatment augmentation, discontinuation of long-acting bronchodilator therapy, death, disenrollment from the health plan, or the end of the study period (31 January 2016).
COPD, chronic obstructive pulmonary disease; FDC, fixed-dose combination; PPPM, per patient per month; SABA, short-acting β agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

The need to augment therapy can be partially explained by disease progression, which is associated with increasing symptoms; however, lung function decline may not completely elucidate the observed escalation of therapy, since lung function decline is typically slow, and symptoms would be expected to remain stable for a longer period. In this study and others, augmentation tended to occur within 1 year of initiating mono long-acting bronchodilator therapy, which is before significant lung function decline would be expected to occur. For example, a 3-year longitudinal study of over 2000 patients with COPD demonstrated a mean decline in forced expiratory volume in the first second (FEV_1) of only 33 ml, well below the minimally clinical important difference for FEV_1 of 100 ml.[35] This suggests that other factors besides lung function decline, for example disease severity at medication initiation, may contribute to the need for additional therapy in patients with COPD.

Our study also demonstrated very high rates of medication discontinuation. Almost three quarters of patients discontinued their long-acting bronchodilator therapy, with a mean time to discontinuation of 4.3 ± 6.6 months. Due to the definition used for discontinuation in this study, it is possible that some patients who were extremely nonadherent may have been inaccurately identified as a discontinuer; regardless, these patients effectively stopped taking their long-acting bronchodilator medication.

Among patients who used rescue medication, use was higher in the follow-up period than in the baseline period. Mean SABA and SAMA PPPM fills were approximately 3.3 and 2.7 times greater, respectively, during the follow-up period than during the baseline period. The increase in the number of short-acting bronchodilator fills suggests that patients continued to experience COPD symptoms.

Recurrent COPD exacerbations are associated with an accelerated decline in lung function,[35,36] reduced physical activity,[37] poor quality of life, and increased risk of hospitalization and death.[38] During follow up, the mean PPPM number of COPD exacerbations was 0.17, which was significantly higher than baseline (0.05 PPPM). These real-world results

Table 4. PPPM COPD exacerbations and PPPM costs by exacerbation severity level among patients with COPD initiating long-acting mono bronchodilator therapy.

	Baseline ***n*** **= 27,394**	**Follow up** ***n*** **= 27,394**
Any COPD exacerbation*		
Mean (SD)	0.05 (0.08)	0.17 (0.99)
Exacerbation costs[$,‡,§], mean (SD)	$485 ($1169)	$1070 ($3841)
Severe exacerbation		
Mean (SD)	0.01 (0.04)	0.02 (0.2)
Severe exacerbation costs[$,‡,§], mean (SD)	$1051 ($1603)	$3398 ($6080)
Moderate exacerbation		
Mean (SD)	0.04 (0.1)	0.15 (1.0)
Moderate exacerbation costs[$,‡,§], mean (SD)	$151 ($544)	$440 ($2018)

*Each COPD exacerbation is classified as severe or moderate based on site of care. COPD exacerbation episodes with a COPD-related hospitalization or a COPD-related ER visit are classified as severe and COPD exacerbation episodes with a COPD-related ambulatory visit and with a procedure code for administration of or a pharmacy claim for a steroid or antibiotics on the same day or within 10 days following the ambulatory visit are classified as moderate.
$Among patients with COPD exacerbations costs >$0 within 7 days following the exacerbation end date.
‡The start and end date of an exacerbation were defined as the inpatient hospitalization admission and discharge dates for a hospitalization, the date of service for an emergency room or urgent care visit, and the date of service for an office visit with a steroid or antibiotic within 10 days; costs within 7 days following the exacerbation end date are included in the COPD-related exacerbation costs.
§Costs were adjusted to 2015 US$ using the annual medical care component of the Consumer Price Index to reflect inflation between the earliest and latest year of data. Healthcare costs are combined health plan and patient paid amounts.
COPD, chronic obstructive pulmonary disease; ER, emergency room; PPPM, per patient per month; SD, standard deviation.

Table 5. PPPM healthcare resource utilization in patients with COPD initiating long-acting mono bronchodilator therapy.

	All cause		**COPD related**	
	Baseline ***n*** **= 27,394**	**Follow up** ***n*** **= 27,394**	**Baseline** ***n*** **= 27,394**	**Follow up** ***n*** **= 27,394**
Inpatient visits, mean (SD)	0.04 (0.08)	0.05 (0.24)	0.03 (0.06)	0.04 (0.22)
Emergency visits, mean (SD)	0.10 (0.22)	0.12 (0.53)	0.02 (0.06)	0.04 (0.32)
Ambulatory visits, mean (SD)	1.80 (1.51)	2.82 (3.99)	0.21 (0.26)	0.82 (2.54)

COPD, chronic obstructive pulmonary disease; PPPM, per patient per month; SD, standard deviation.

contrast with those reported previously in two RCTs. In these trials, current or former treatment with LABA monotherapy was associated with an 18% reduction in the rate of exacerbation requiring hospitalization compared with placebo[14] and LAMA monotherapy was associated with a 14% reduction in the relative risk of exacerbation in patients with moderate or severe COPD compared with placebo.[39] A study by Herland and colleagues found that only 7.2% of real-world patients with COPD would meet the strict inclusion criteria for most COPD clinical trials,[40] thus the difference in trial results from those found in our study likely reflect the differences in patient populations (e.g. comorbidities, lung function, smoking history) and the additional monitoring in clinical trials.

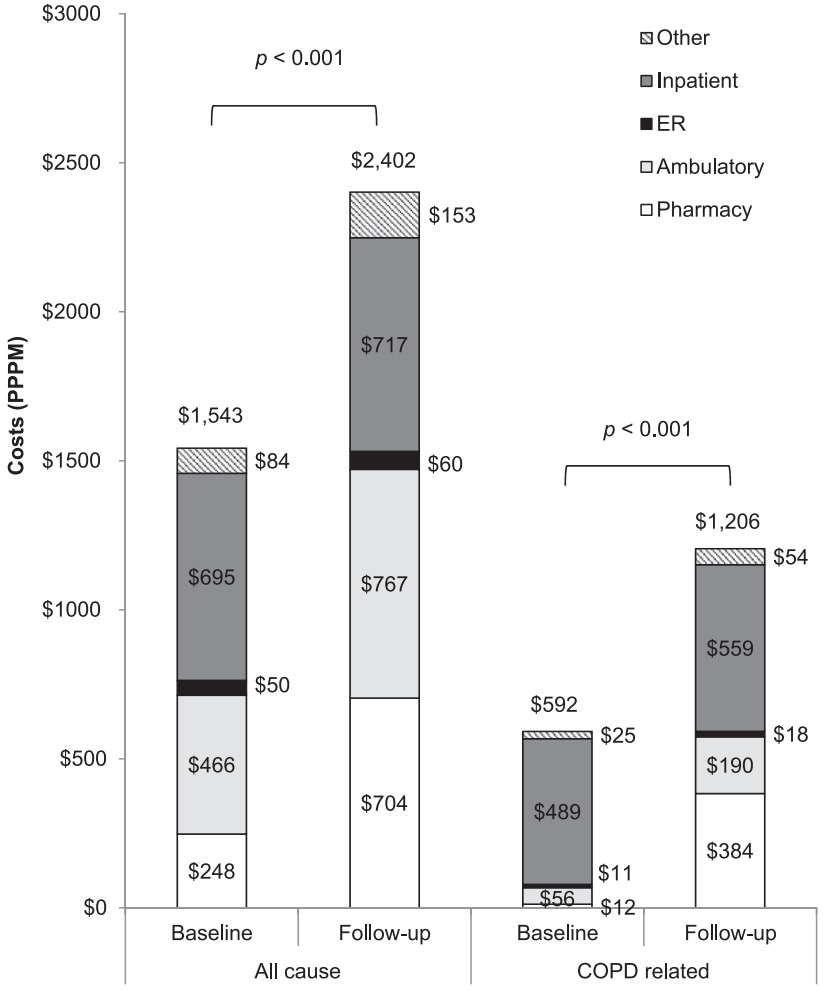

Figure 2. Healthcare costs in patients with COPD on long-acting bronchodilator monotherapy (per patient per month).
COPD, chronic obstructive pulmonary disease; ER, emergency room; PPPM, per patient per month.

Significant COPD healthcare resource use was observed in the study. Costs associated with COPD exacerbations were particularly high; in the current study, the mean PPPM cost related to severe exacerbations was $3398. The high costs associated with exacerbations have been documented in several studies. Yu and colleagues found that in 2004–2008, the cost for patients with a severe exacerbation was $7014 per quarter compared with $658 for patients with no exacerbation[41]; Pasquale and colleagues documented 2007–2009 annual costs for patients with a severe exacerbation to be $12,765, compared with $1425 for those with no exacerbations.[42] Exacerbations are a major driver of COPD-related healthcare costs, and reducing the number and severity of exacerbations is key to reducing these costs. Given the known benefits of long-acting mono bronchodilators in controlling exacerbations, it is possible that the high rates of medication discontinuation by symptomatic patients with COPD may have left them unprotected from acute exacerbations. Lowering the rates of long-acting maintenance discontinuation could help decrease the rates of COPD exacerbations and their associated COPD-related healthcare resource use.

Rates of medication discontinuation and adherence are affected by multiple factors, including a patient's perception of treatment benefit, and symptom relief due to their medication.[43] A lack of perceived treatment benefit has been associated with medication discontinuation among patients with COPD.[44,45] It is possible that high rates of mono bronchodilator discontinuation despite continued rescue medication use was related to

patients not obtaining sufficient symptom relief to perceive a benefit; however, other patient factors including a general low adherence with therapy may impact the high rates of monotherapy discontinuation. Further studies are needed to determine whether more aggressive initial therapy would result in better adherence, and consequently lead to symptom improvement. Also, additional studies are needed to better understand the factors influencing patients' adherence and discontinuation of mono bronchodilation therapy in light of rescue medication use.

Physicians are faced with an array of treatment options for patients with COPD. Clinical evidence has shown the greatest level of improvement among patients treated with newer combination therapy compared with the individual drugs alone, specifically in patients with more severe COPD, such as those prone to exacerbation.[3,46–48] GOLD guidelines recommend mono bronchodilator therapy as the initial treatment in group B and C patients with COPD; however, there are no data available regarding how often patients should be reassessed and when therapy should be augmented. Several studies have reported that many patients with moderate COPD remain symptomatic despite treatment with long-acting mono bronchodilators.[49–52] This is aligned with the findings of our study, which reported high rates of rescue medication use, treatment augmentation, and an increased number of COPD exacerbations and healthcare resource utilization and costs in patients who initiated long-acting mono bronchodilator therapy; however, it is unknown whether these findings were a result of monotherapy inadequacy. The persistent COPD-related healthcare costs observed in our study prior to therapy discontinuation again raises the possibility that some patients may not have perceived sufficient benefit from inhaled mono bronchodilator therapy to encourage continued use. Further research is required to understand the reasons for discontinuation and the lack of improved outcomes in patients with COPD initiating long-acting mono bronchodilator therapy and to determine whether these outcomes differ between patients who augmented, discontinued, or persisted on their monotherapy.

Claims data provide a powerful method to examine treatment patterns and healthcare utilization and costs in a real-world setting. These data offer the advantage of large sample sizes with diverse medical histories; however, the study findings should be interpreted with the following limitations in mind. First, this study is largely descriptive in nature, thus restraint should be used in drawing conclusions based on numerical differences in the baseline and follow-up periods when statistical testing was not performed. Second, the factors that led to patients' discontinuation or augmentation are unknown. Third, long-acting mono bronchodilator use was identified by pharmacy fills. Although repeat fills for a medication suggest continued use, they do not prove the medication was taken as prescribed. It is possible that asthma was misdiagnosed as COPD, particularly among elderly patients, or that some patients included in the study may have had asthma–COPD overlap syndrome (ACOS). Such patients would require the addition of an ICS with or without a second bronchodilator to achieve adequate disease control. The possibility of under recognition of asthma or ACOS in this population is consistent with a lack of perceived symptom relief with mono bronchodilator therapy alone resulting in discontinuation. Fourth, COPD exacerbations were defined using proxies in claims data and may not be consistent with definitions used in clinical practice. Fifth, the data used for this analysis came from a commercial and Medicare Advantage population; therefore, results of this analysis are primarily applicable to insured patients with COPD on similar therapies in stable managed care settings. Further, almost half of patients had an associate degree or higher, which may not be representative of all patients with COPD. Finally, certain limitations are inherent in all studies that rely on secondary claims data, including potential coding errors, incomplete data, pharmacotherapy misclassification due to low-cost generics (if patients pay out of pocket rather than submit an insurance claim), and the inability to observe over-the-counter medications, medications administered as part of a clinical trial, or free samples given to patients by physicians.

Conclusion

Patients who were initiated on long-acting mono bronchodilator therapy had high rates of medication discontinuation (74%) or treatment escalation (18%). During follow up, rescue medication use was considerable and patients had significantly increased healthcare costs and number of COPD exacerbations compared with baseline.

Continued rescue medication use, exacerbations, and healthcare resource utilization suggest that treatment discontinuation occurred despite continued COPD symptoms and disease activity. Reasons for treatment discontinuation require further study and may include multiple factors, including a lack of patient perception of sufficient treatment benefit and overall low adherence to controller therapy. Further studies should also evaluate whether more complete resolution of symptoms with initial treatment is associated with improved perceptions of clinical effectiveness by patients, better adherence and medication persistence, and improved clinical outcomes.

Authors' Note

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Conflict of interest statement

LB and JM are employees of Optum, and were funded by AstraZeneca Pharmaceuticals to conduct the study. MD was an employee of AstraZeneca and KF was a contractor with AstraZeneca during the time the study was conducted.

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