

Medication management patterns among Medicare beneficiaries with chronic obstructive pulmonary disease who initiate nebulized arformoterol treatment

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Purpose: Global evidence-based treatment strategies for chronic obstructive pulmonary disease (COPD) recommend using long-acting bronchodilators (LABDs) as maintenance therapy. However, COPD patients are often undertreated. We examined COPD treatment patterns among Medicare beneficiaries who initiated arformoterol tartrate, a nebulized long-acting beta₂ agonist (LABA), and identified the predictors of initiation.

Methods: Using a 100% sample of Medicare administrative data, we identified beneficiaries with a COPD diagnosis (ICD-9 490–492.xx, 494.xx, 496.xx) between 2010 and 2014 who had ≥1 year of continuous enrollment in Parts A, B, and D, and ≥2 COPD-related outpatient visits within 30 days or ≥1 hospitalization(s). After applying inclusion/exclusion criteria, three cohorts were identified: (1) study group beneficiaries who received nebulized arformoterol (n=11,886), (2) a subset of the study group with no LABD use 90 days prior to initiating arformoterol (n=5,542), and (3) control group beneficiaries with no nebulized LABA use (n=220,429). Logistic regression was used to evaluate predictors of arformoterol initiation. Odds ratios (ORs), 95% confidence intervals (CIs), and *p* values were computed.

Results: Among arformoterol users, 47% (n=5,542) had received no LABDs 90 days prior to initiating arformoterol. These beneficiaries were being treated with a nebulized (50%) or inhaled (37%) short-acting bronchodilator or a systemic corticosteroid (46%), and many received antibiotics (37%). Compared to controls, beneficiaries who initiated arformoterol were significantly more likely to have had an exacerbation, a COPD-related hospitalization, and a pulmonologist or respiratory therapist visit prior to initiation (all *p*<0.05). Beneficiaries with moderate/severe psychiatric comorbidity or dual-eligible status were significantly less likely to initiate arformoterol, as compared to controls (all *p*<0.05).

Conclusion: Medicare beneficiaries who initiated nebulized arformoterol therapy had more exacerbations and hospitalizations than controls 90 days prior to initiation. Findings revealed inadequate use of maintenance medications, suggesting a lack of compliance with evidence-based treatment guidelines.

Keywords: long-acting beta₂-agonists, arformoterol, nebulized therapy, COPD, Medicare, treatment patterns

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Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States (US),^{1,2} affecting 16 million people,^{1,3} and accounting for more than \$32.1 billion in medical costs.⁴ By 2020, the economic burden of COPD is

projected to increase to \$49 billion.⁴ To better manage the clinical spectrum of COPD, US and international guidelines recommend the use of maintenance therapy with long-acting bronchodilators (LABDs).^{5–7} Despite these guidelines, adequate management of COPD remains a challenge, as does curtailing its rising economic toll.^{8,9}

Past studies on COPD treatment patterns have revealed that health care providers do not consistently prescribe medications in accordance with evidence-based strategies.^{10–16} The Global Initiative for Chronic Obstructive Lung Disease (GOLD) therapeutic strategy sheds light on this issue by highlighting that two out of three COPD patients receive pharmacotherapy that is inconsistent with evidence-based guidelines.⁵ A closer examination of these inconsistencies reveals that patients are often undertreated with LABDs, despite exacerbations and multiple hospitalizations.^{15,17–20} A recent study conducted on commercially insured patients found that 55% of the members diagnosed with COPD did not receive guideline-recommended maintenance medications.¹⁸ In that study, only 64% of COPD patients with a history of exacerbations received a prescription for maintenance medication. Similar findings of undertreatment of COPD have been documented in managed Medicare populations where research has shown 40% to 71% receive no maintenance treatment, including almost 69% with moderate to severe COPD.¹³ Additional studies on medication adherence patterns among Medicare beneficiaries with COPD have documented that 40% to 50% fail to use any maintenance medications.^{21,22} Although maintenance medication use by Medicare beneficiaries has improved over time,²³ suboptimal disease management continues to be a persistent clinical challenge.^{23,24}

Given that 12% of all Medicare beneficiaries and 17% of dual-eligible beneficiaries (ie, Medicare and Medicaid recipients) suffer from COPD,²⁵ it is imperative to better understand specific medication treatment patterns to improve care management. The primary objective of our study was to examine COPD medication management patterns among Medicare beneficiaries who initiated nebulized arformoterol tartrate (neb arformoterol), a long-acting beta₂ agonist (LABA), for maintenance therapy. Our secondary objective was to identify the predictors associated with initiating neb arformoterol.

Methods

Data source

Our study used a 100% sample of Medicare administrative data from the Chronic Condition Warehouse at the Centers for Medicare and Medicaid Services (CMS). All data were

obtained from Master Beneficiary Summary Files. Information specific to hospitalizations (including skilled nursing facility) was extracted from MedPar files. Data regarding outpatient services were extracted from Carrier and Outpatient (OP) files. Home health care utilization was obtained from Home Health (HH) files. Medication use was extracted from Part D and Durable Medical Equipment (DME) files. The data were analyzed on the secure Virtual Research Data Center (VRDC) provided by CMS. All individual Medicare beneficiaries were provided a unique identifier for this study. No identifying information such as name, social security number, and Medicare number were used. The Human Research Protections Program at the University of California San Diego approved our study which was subject to a data use agreement with CMS.

Sample and cohort selection

Our primary study population was 10,371,035 Medicare beneficiaries who had a COPD-related claim (ie, International Classification of Disease, 9th Revision, Clinical Modification codes 490.xx, 492.xx, 494.xx, 496.xx) between 2010 and 2014 and a COPD diagnosis before January 1, 2013 (Figure 1). Our study sample was further refined to 3,642,497 beneficiaries who met the inclusion criteria of having continuous coverage under Medicare Parts A, B, and D. Among these beneficiaries, 106,442 used nebulized LABA therapy during 2010 and 2014 and 3,536,055 beneficiaries did not use nebulized LABA therapy during this time period.

To support the analyses described below, a start date was randomly assigned to control group beneficiaries consistent with the distribution of initiation dates for nebulized LABA therapy in the study group. Both samples (study group and controls) were limited to beneficiaries: (a) with a diagnosis of COPD for at least one year, (b) with at least 2 office claims with COPD 30 days apart or one hospitalization for COPD in the prior year, (c) without an admission to a skilled nursing facility, (d) who used COPD medication(s), and (e) without end-stage renal disease who survived for at least 364 days following initiation of nebulized LABA therapy or their assigned start date. We further limited the sample of users of nebulized LABA therapy to those using arformoterol only. As a final restriction, we limited both samples to beneficiaries who did not use any LABD medication in the 90 days prior to initiation of nebulized LABA therapy or their assigned start date. After applying these criteria, the following three cohorts of Medicare beneficiaries were identified: (1) a study group of beneficiaries who were treated

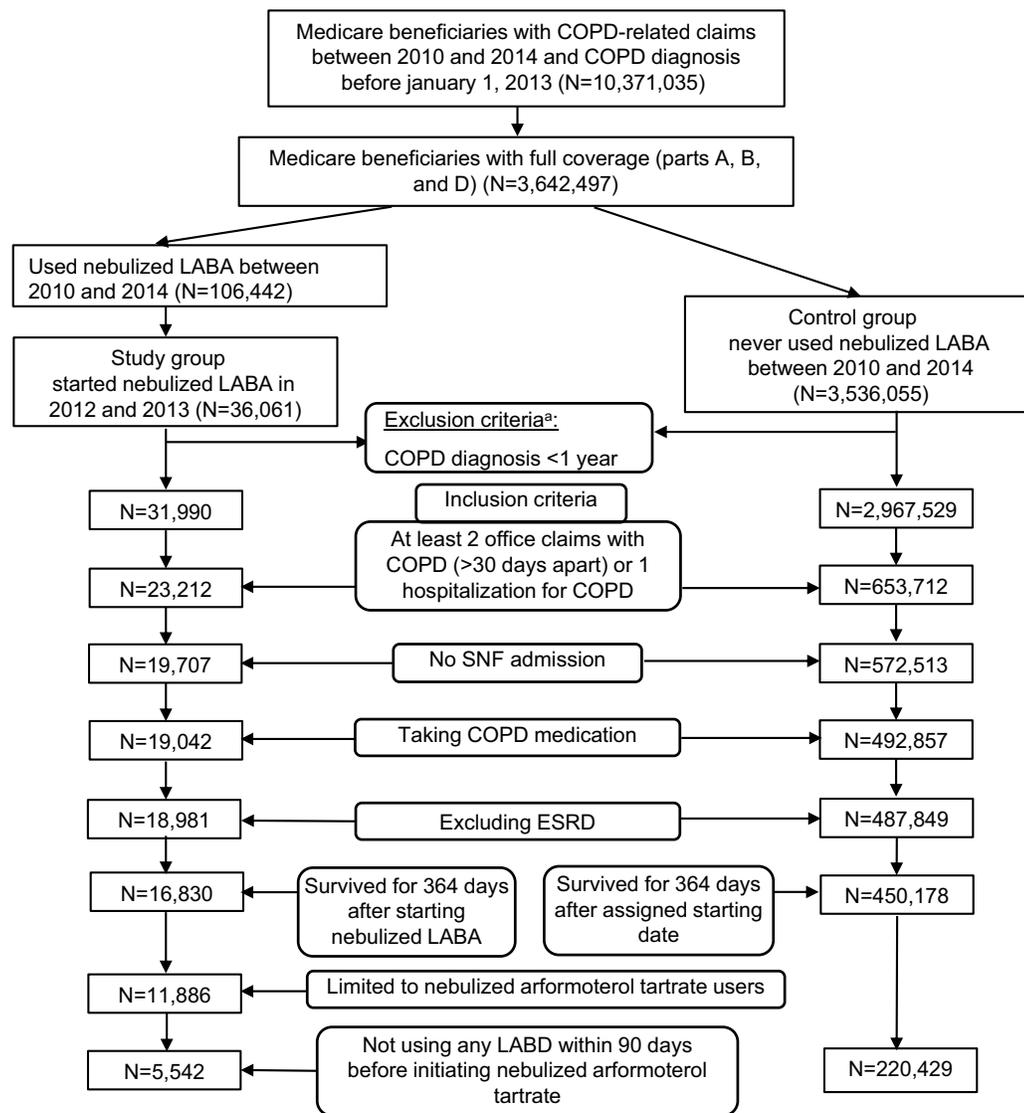


Figure 1 Flow chart depicting selection of sample and study cohorts. ^aFull coverage and COPD diagnosis <1 year prior to first nebulized LABA claim. Excluded deaths before first nebulized LABA claims.

Abbreviations: COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; LABA, long-acting beta₂ agonist; LABD, long-acting bronchodilators; SNF, skilled nursing facility.

with neb arformoterol (n=11,886), (2) a subset of the study group who had no use of LABD in the 90 days prior to initiating neb arformoterol (n=5,542), and (3) a control group of beneficiaries who had no claims for a nebulized LABA between 2010 and 2014 and no use of LABD in the 90 days prior to their assigned start date (n=220,429).

Measures

The following measures were extracted from Medicare files: (a) demographic characteristics such as age, gender, and race; (b) dual-eligibility status; (c) comorbidities as measured by the Chronic Illness and Disability

Payment System diagnostic classification;²⁶ (d) COPD medications based on drug refill rates specific to short-acting bronchodilators (SABDs) which included short-acting muscarinic antagonists (SAMAs) and short-acting beta-agonists (SABAs), LABAs, long-acting muscarinic antagonists (LAMAs), inhaled corticosteroids (ICS), systemic corticosteroids (CS), methylxanthines, phosphodiesterase (PDE4) inhibitors, non-specific PDE inhibitors, and mucolytics; (e) antibiotic use; (f) oxygen use; (g) frequency of exacerbations; and (h) health resource utilization (HRU) including medical equipment use, hospitalizations (all cause and

COPD-specific), intensive care unit stays, pulmonary specialist visits (inpatient and outpatient), emergency department (ED) visits, use of skilled nursing facilities, and home health care visits.

Data analysis

Univariate and bivariate analyses were conducted to examine beneficiary characteristics and treatment patterns including computing comparative means, frequencies, and proportions. Cell sizes below 11 were suppressed per CMS' requirements. Logistic regression analysis was used to evaluate the predictors associated with initiation of neb arformoterol. Odds ratios (ORs), 95% confidence intervals (CIs), and *p*-values were computed. *p*<0.05 denoted statistical significance. All analyses were performed using SAS Enterprise Guide 7.1.

Results

Sociodemographic characteristics

The majority of Medicare beneficiaries were ≥ 70 years old, female, non-Hispanic white, and from either the southern or Midwest region of the US. In addition, more than one-third of the beneficiaries were dual-eligible (Table 1).

Clinical characteristics and medication management patterns

Among beneficiaries who initiated neb arformoterol (*n*=11,886), the most frequent comorbidities were cardiovascular, musculoskeletal, gastrointestinal, and psychiatric disease (Table 2). Medication treatment patterns revealed that 47% (*n*=5,542) of beneficiaries had received no LABDs 90 days prior to initiating neb arformoterol, and 55% had received no SABDs (Figure 2).

Table 1 Sociodemographic characteristics of study cohorts

Characteristic, n (%)	Nebulized arformoterol Users (N=11,886)	Received no LABDs 90 Days prior to initiating nebulized arformoterol (N=5,542)	Received no LABDs and did not initiate nebulized arformoterol (N=220,429)
Age, years			
<55	739 (6.2)	302 (5.4)	21,463 (9.7)
55 to 64	1,528 (12.9)	619 (11.2)	32,075 (14.6)
65 to 69	1,809 (15.2)	809 (14.6)	29,081 (13.2)
70 to 74	2,833 (23.8)	1,340 (24.2)	44,598 (20.2)
75 to 79	2,242 (18.9)	1,098 (19.8)	37,946 (17.2)
80 to 84	1,548 (13.0)	773 (13.9)	28,605 (13.0)
≥ 85	1,187 (10.0)	601 (10.8)	26,661 (12.1)
Sex			
Male	4,738 (39.9)	2,293 (41.4)	89,216 (40.5)
Female	7,148 (60.1)	3,249 (58.6)	131,213 (59.5)
Race			
Non-Hispanic White	10,804 (90.9)	5,078 (91.6)	187,529 (85.1)
Hispanic	336 (2.8)	153 (2.8)	9,538 (4.3)
African-American	573 (4.8)	242 (4.4)	17,983 (8.2)
Asian/Pacific Islander	58 (0.50)	25 (0.5)	2,959 (1.3)
Other	115 (0.97)	44 (0.8)	2,420 (1.1)
Dual-eligible			
Yes	4,337 (36.5)	1,645 (29.7)	99,751 (45.3)
No	7,549 (63.5)	3,897 (70.3)	120,678 (54.8)
US region			
Midwest	3,505 (29.5)	1,681 (30.3)	57,854 (26.3)
Northeast	1,517 (12.7)	592 (10.7)	35,529 (16.1)
South	5,393 (45.4)	2,571 (46.4)	98,947 (44.9)
West	1,474 (12.4)	698 (12.6)	28,099 (12.8)

Abbreviation: LABDs, long-acting bronchodilators.

Table 2 Comorbidities and types of COPD medications filled by Medicare beneficiaries 90 days before initiating nebulized arformoterol by (N=11,886)

Most frequent comorbidities ^a , n (%)	LABAs	LAMAs	ICS/Nebulized CS	LABAs+LAMAs	No LABDs
Cardiovascular	2,119 (89)	1,630 (90)	1,060 (91)	1,884 (87)	3,923 (90)
Psychiatric	753 (32)	541 (30)	336 (29)	695 (32)	1,266 (29)
Musculoskeletal	1,190 (50)	890 (49)	551 (47)	1,078 (50)	2,215 (51)
CNS	660 (28)	482 (27)	309 (26)	576 (27)	1,298 (30)
Gastrointestinal	1,171 (49)	890 (49)	579 (49)	1,092 (51)	2,177 (50)
Diabetes	791 (33)	573 (32)	398 (34)	676 (31)	1,564 (36)
Skin	422 (18)	291 (16)	189 (16)	398 (18)	838 (19)
Renal	571 (24)	459 (25)	333 (28)	491 (23)	1,240 (28)
Cancer	426 (18)	359 (20)	243 (21)	380 (18)	895 (20)
Developmental disability	12 (1)	<11 ^b	12 (1)	12 (1)	17 (0)
Genital	377 (16)	231 (13)	198 (17)	288 (13)	628 (14)
Metabolic	616 (26)	449 (25)	292 (25)	573 (27)	1,185 (27)
Eye	864 (36)	711 (39)	488 (42)	748 (35)	1,537 (35)
Cerebrovascular	113 (5)	80 (4)	63 (5)	84 (4)	243 (6)
Infectious	333 (14)	296 (16)	167 (14)	387 (18)	589 (13)
Hematological	170 (7)	135 (7)	102 (9)	144 (7)	364 (8)
Total	2,374	1,811	1,171	2,159	4,371

Notes: Percentages presented are not based on mutually exclusive categories. ^aComorbidities present 12 months prior to initiating nebulized arformoterol treatment. ^bCell blinded due to small sample size per Centers for Medicare and Medicaid Services.

Abbreviations: COPD, chronic obstructive pulmonary disease; LABAs, long-acting beta₂ agonists; LAMAs, long-acting muscarinic antagonists; ICS, inhaled corticosteroids; CS, corticosteroids; LABDs, long-acting bronchodilators; CNS, central nervous system.

The most common COPD treatments received by beneficiaries before initiating neb arformoterol were inhaled (49%) or nebulized (45%) SABDs, systemic CS (48%), followed by LABA/ICS combination therapy (37%), and monotherapy LAMAs (33%) (Figure 3). Many beneficiaries (38%) were also receiving antibiotics. Most of the beneficiaries who had received no LABDs prior to initiating neb arformoterol were being treated with a nebulized (50%) or inhaled (37%) SABD, or a systemic CS (46%) (Figure 4).

The following changes in medication patterns were observed 90 days after initiation of neb arformoterol: (a) reduced use of inhaled SABDs (45% vs 38%), systemic CS (48% vs 37%), LABA/ICS (37% vs 19%), LAMAs (33% vs 28%), and antibiotics (38% vs 30%), and (b) increased use of nebulized SABD (49% vs 53%) and nebulized CS (13% vs 63%) (Figure 3).

The most noticeable change was an increase in concomitant neb arformoterol + nebulized CS (63%), a substitution for the observed decrease in inhaled LABA + ICS dual therapy. Other common concomitant therapies included neb arformoterol + nebulized SABD (53%) or inhaled SABD (38%), neb arformoterol + systemic CS (37%), and neb arformoterol + inhaled LAMA (28%).

Predictors associated with initiating arformoterol treatment among beneficiaries who received no LABDs 90 days prior

A comparison of the treatment characteristics between the subsample of beneficiaries from the study group who had received no LABDs 90 days prior to initiating neb arformoterol (n=5542) and controls revealed that a significantly higher proportion of study group beneficiaries received nebulized SABDs (22.7 vs 10.8%, respectively; $p<0.05$), antibiotics (36.5 vs 22.8%, respectively; $p<0.05$), and systemic (46.5 vs 24.1%, respectively; $p<0.05$) or nebulized CS (16.7 vs 3.5%, respectively; $p<0.05$) (Table 3). In addition, more study group beneficiaries received spirometry tests than control beneficiaries (9.7 vs 4.2%, respectively; $p<0.05$).

After adjusting for potential confounders (eg, age, gender), the results revealed that the strongest predictors of neb arformoterol initiation were receiving outpatient care from a pulmonologist (OR 2.36, 95% CI 2.22, 2.51) or a respiratory therapist (OR 1.80, 95% CI 1.43, 2.27), having had an exacerbation (OR 1.72, 95% CI 1.59, 1.86), use of a systemic CS (OR 1.68, 95% CI 1.58, 1.78), and having had a COPD-related hospitalization (OR 1.54, 95% CI 1.37, 1.74) (Table 4).

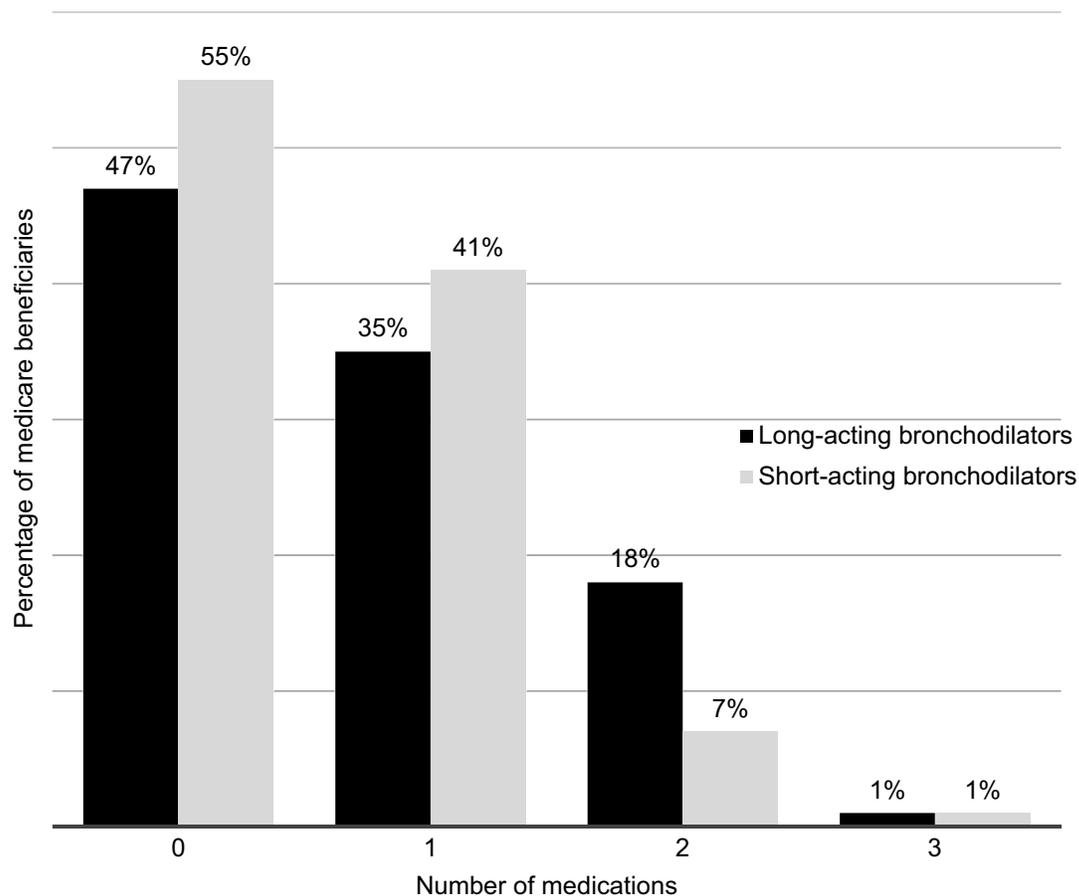


Figure 2 Number of long-acting and short-acting bronchodilators filled by Medicare beneficiaries 90 days before initiating nebulized arformoterol (N=11,886). With the exception of beneficiaries taking 0 medication, no other categories are mutually exclusive (ie, categories refer to taking at least 1, 2, or 3 therapeutic agents).

By contrast, predictors that were strongly associated with a reduced likelihood of initiating neb arformoterol included presence of a severe infection (OR 0.31, 95% CI 0.14, 0.65), having acquired immunodeficiency syndrome (OR 0.37, 95% CI 0.21, 0.66) or a severe psychiatric comorbidity (OR 0.56, 95% CI 0.44, 0.72), being dual-eligible (OR 0.69, 95% CI 0.64, 0.73), and using an ICS (OR 0.74, 95% CI 0.65, 0.84). Racial/ethnic minorities (ie, Asian/Pacific Islanders, African Americans, and Hispanics) were also significantly less likely to receive neb arformoterol as compared with Caucasian beneficiaries (Table 4).

Discussion

To our knowledge, this is the first study in the literature to examine COPD treatment patterns among Medicare beneficiaries who initiated neb arformoterol and to identify the key predictors of initiation. We found several emerging themes with important implications for clinical practice. First, nearly 1 in 2 Medicare beneficiaries had received no LABDs for

maintenance treatment 90 days prior to initiating neb arformoterol. Instead, these beneficiaries were primarily being treated with short-acting agents (ie, a nebulized or inhaled SABD). Our findings are consistent with previous reports that 40% to 50% of Medicare beneficiaries with COPD receive no maintenance medications.^{21,22} Patients with mild COPD are generally not candidates for maintenance therapy. Our findings that 50% of the Medicare beneficiaries in our sample had experienced an exacerbation, 23% had an ED visit, and 10% had a COPD-related hospitalization in the 90 days prior to initiating neb arformoterol suggest that these beneficiaries had more advanced COPD.^{5,27} It is concerning that maintenance therapy was not initiated among apparently sicker beneficiaries earlier in their treatment regimen, suggesting undertreatment of COPD consistent with previous studies.^{27–30} These results also indicate a lack of compliance with GOLD therapeutic strategies, indicating the need for continued education to increase physician awareness about the importance of following recommended guidelines to lower the risk of exacerbations and hospitalizations.^{5,31,32}

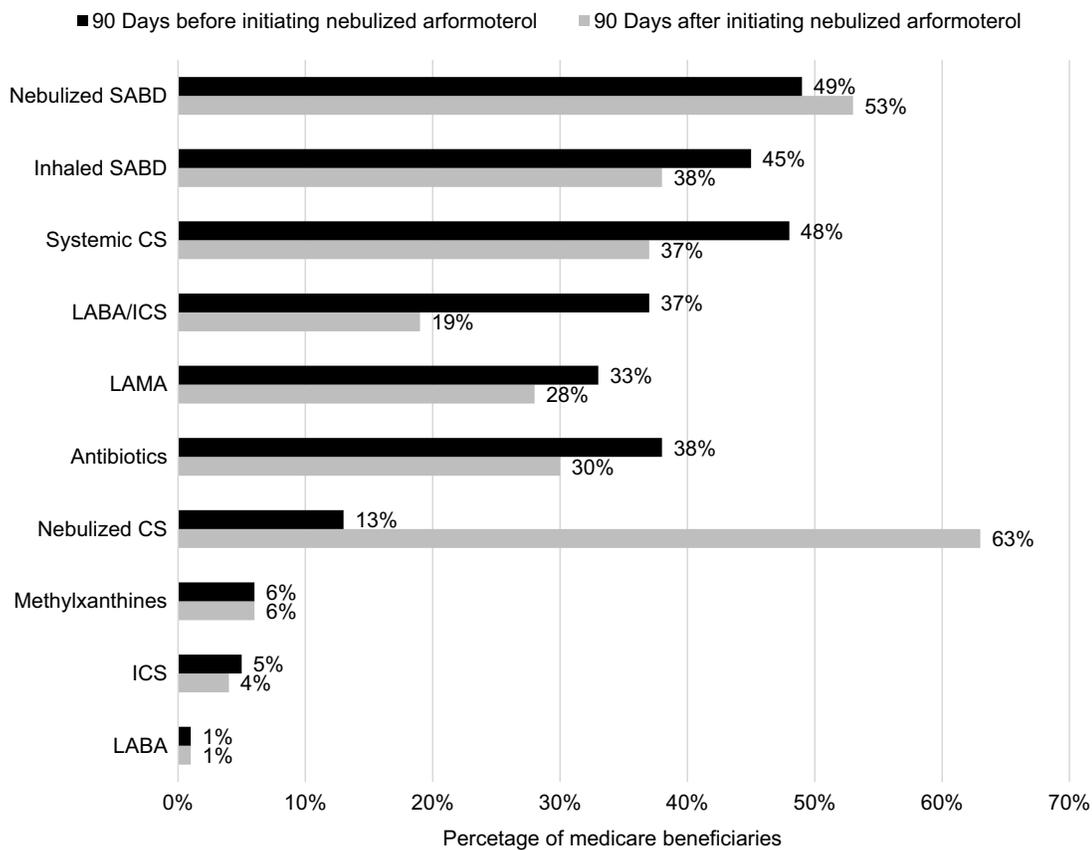


Figure 3 Medication use by Medicare beneficiaries 90 days before and after initiating nebulized arformoterol (N=11,886). Percentages are not mutually exclusive. **Abbreviations:** CS, corticosteroid; LABA, long-acting beta₂ agonist; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; SABD, short-acting bronchodilator.

A second emerging theme from our study was that concomitant therapy with neb arformoterol was common including dual therapy with a CS, SABD, or LAMA. Once arformoterol was initiated, treatment with a nebulized CS and SABD increased, but the use of all other concomitant medications decreased. The GOLD therapeutic strategy recommends combination therapy for COPD patients with moderate to severe airflow limitation.^{5,33} Whether the use of neb arformoterol was administered as a primary or augmented therapy was unclear since 19% of the beneficiaries were using a handheld inhaler for LABA + ICS inhaler in conjunction with neb arformoterol 90 days after initiation. One potential explanation could be that these beneficiaries may have had difficulty using a handheld device, leading to a prescription for a nebulizer as a strategy to improve disease management.^{27,33} Another possibility could be that beneficiaries wanted to have the flexibility of a portable handheld inhaler in addition to a nebulizer to use at home.

An unexpected but illuminating finding was that moderate to severe psychiatric comorbidity was negatively

associated with neb arformoterol initiation among beneficiaries who had received no LABDs 90 days prior to starting arformoterol. This result was counterintuitive. In Medicare populations, concurrent COPD and psychiatric conditions, such as depression and anxiety, have been associated with increased exacerbations, HRU, and costs.^{34–36} Furthermore, among these beneficiaries, low adherence to COPD maintenance medications is common.^{21,22,36,37} Given the relative ease of using a nebulizer (eg, requires fewer steps to administer medications than most handheld inhalers), increasing reliance on nebulization may improve adherence to prescribed regimens by lowering the procedural burden associated with inhaler use.^{21,38,39}

Another key finding of our study was that dual-eligible beneficiaries who had not received a LABD for maintenance treatment were less likely to initiate neb arformoterol when compared to controls. This result is concerning because dual-eligible beneficiaries with COPD tend to be sicker, have higher rates of

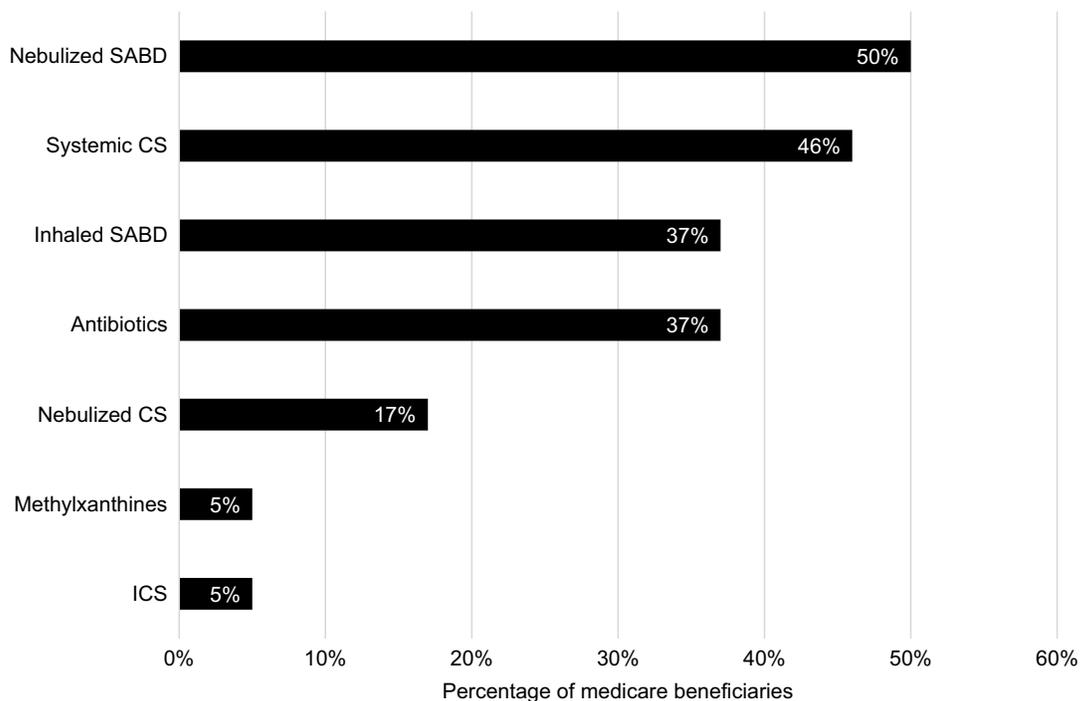


Figure 4 COPD medication patterns 90 days before initiating nebulized arformoterol among Medicare beneficiaries who received no long-acting bronchodilators (N=5,542). Percentages are not mutually exclusive.

Abbreviations: CS, corticosteroid; ICS, inhaled corticosteroid; SABD, short-acting bronchodilator.

Table 3 Treatment characteristics of Medicare beneficiaries who received no long-acting bronchodilators 90 days before initiating nebulized arformoterol compared with controls

Treatment, n (%)	Initiated nebulized arformoterol (N=5,542)	Controls (N=220,429)
Oxygen	0 (0)	0 (0)
Respiratory therapy	87 (1.6)	956 (0.4)
Spirometry tests	538 (9.7)	9,346 (4.2)*
Antibiotics	2,025 (36.5)	50,190 (22.8)*
Methylxanthines	291 (5.3)	6,762 (3.1)
Nebulized SABDs	1,256 (22.7)	23,839 (10.8)*
Inhaled SABDs	2,037 (36.8)	68,796 (31.2)
Inhaled CS	274 (4.9)	13,729 (6.2)
CS	2,577 (46.5)	53,189 (24.1)*
Nebulized CS	925 (16.7)	7,769 (3.5)*

Note: * $p < 0.05$.

Abbreviations: SABDs, short-acting bronchodilators; ICS, inhaled corticosteroids; CS, corticosteroids.

exacerbations and hospitalizations, more comorbidities, higher HRU, and a greater cost burden to treat.^{40–46} Our finding is also somewhat perplexing. Nebulized medications are covered under Medicare Part B as a durable medical equipment benefit, whereas other drugs are covered under Medicare Part D.⁴⁷ For full-benefit dual-eligible individuals who represent the vast majority of beneficiaries (>70%), Part D covers the costs of nebulized therapy and does not require beneficiary cost-

sharing.^{48,49} Since we found that dual eligibility was a negative predictor of neb arformoterol initiation and most of these beneficiaries would have had no out-of-pocket cost, our results suggest a potential lack of access to nebulized therapy in this patient population. Given that dual-eligible beneficiaries tend to be more medically needy,^{40,42–44} addressing the potential lack of adequate maintenance therapy in this population should become a priority.^{32,50}

Table 4 Predictors associated with initiating nebulized arformoterol among Medicare beneficiaries who received no long-acting bronchodilators 90 days prior (N=5,542) compared with controls (N=220,429)

Predictor	Odds ratio 95% CI	
Sociodemographic		
Asian/Pacific Islander	0.43	(0.29–0.65)*
African American	0.60	(0.52–0.68)*
Hispanic	0.75	(0.63–0.88)*
Dual-eligible	0.69	(0.64–0.73)*
Region		
US Northeast region	0.67	(0.61–0.73)*
US Midwest region	1.15	(1.08–1.22)*
US West region	1.09	(1.00–1.19)*
Clinical		
Very severe pulmonary disease	1.42	(1.31–1.54)*
COPD exacerbation	1.72	(1.59–1.86)*
Acquired immune deficiency syndrome	0.37	(0.21–0.66)*
Severe infection	0.31	(0.14–0.65)*
Severe psychiatric morbidity	0.56	(0.44–0.72)*
Treatment		
Antibiotic therapy	1.24	(1.16–1.32)*
ICS	0.74	(0.65–0.84)*
Inhaled SABDs	1.31	(1.24–1.39)*
Methylxanthines	1.30	(1.15–1.47)*
Spirometry	1.40	(1.27–1.54)*
Systemic CS	1.68	(1.58–1.78)*
Health resource utilization		
COPD-related hospitalization	1.54	(1.37–1.74)*
Emergency department visit	0.88	(0.82–0.96)*
Home health visit	1.11	(1.01–1.21)*
Pulmonologist inpatient visit	1.20	(1.07–1.34)*
Pulmonologist outpatient visit	2.36	(2.22–2.51)*
Respiratory therapist visit	1.80	(1.43–2.27)*

Note: * $p < 0.05$.

Abbreviations: CI, confidence interval; SABDs, short-acting bronchodilators; CS, corticosteroids; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids.

The rationale for using neb arformoterol has been well described in the literature.²⁸ In two 12-week, double-blind randomized controlled trials that compared neb arformoterol to placebo, patients treated with arformoterol had improved and sustained lung function and lower exacerbation rates.^{51,52} In another 52-week trial, neb arformoterol treated patients were found to have greater improvements in health status and health-related quality-of-life than patients who received placebo.^{53,54} Research comparing nebulized LABA therapies has shown that patients treated with arformoterol have fewer exacerbations, lower inpatient costs, and lower COPD-related costs (primarily related to

hospitalizations) when compared with patients treated with formoterol.^{55,56} In Medicare populations, LABA therapy has been shown to significantly lower the risk of hospitalizations, resulting in fewer inpatient days and lower total health care utilization when compared with SABA therapy.^{57–59} Research specific to medication adherence has found significantly lower risk of hospitalizations and decreased health care costs among Medicare beneficiaries who adhere to COPD maintenance medication regimens as compared to beneficiaries who discontinue maintenance therapy.^{36,60,61} Because 69% of the COPD patients who are hospitalized (mainly due to exacerbations) are primarily insured through Medicare,⁶² preventing acute exacerbations and subsequent hospitalizations through timely LABD maintenance therapy would be consistent with Medicare's Hospital Readmission Reduction Program in the era of value-based health care.^{63–67}

The findings of the current study must be viewed in light of limitations inherent to retrospective observational studies that rely on administrative claims data. There was no information available on certain factors that may have influenced medication management such as cognitive impairment, limited hand-breath coordination abilities, poor dexterity, or patient preferences.^{27,68–72} In addition, no direct assessment of COPD severity, such as measures of lung function, was available. However, our inclusion criteria required a COPD diagnosis of ≥ 1 year, and studies have shown that by the time a COPD diagnosis is given, most patients are beyond mild disease.^{1,2,73–75} Moreover, COPD patients typically receive a handheld inhaler as the first line of treatment and switching to or receiving augmented therapy with a nebulizer is often due to poor symptom control.^{31,76} Furthermore, the use of ICD-9 codes to classify beneficiaries with psychiatric disorders may have underrepresented the true prevalence of these conditions given that clinicians often fail to recognize mental illness.^{77,78}

Conclusion

In this study, we found that 47% of the Medicare beneficiaries with COPD who initiated neb arformoterol had received no LABDs 90 days prior, despite multiple comorbidities, exacerbations, and hospitalizations. Furthermore, beneficiaries with moderate to severe psychiatric comorbidity and those who were dual-eligible were less likely to receive neb arformoterol when compared with controls, implying the need to increase access to nebulized maintenance therapy for these

more vulnerable populations. Taken together, our findings suggest that clinical practice is not yet well aligned with current GOLD therapeutic strategies for COPD care management.

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Author contributions

BRC, MN, ZX, SCR, CD, and TPG all made substantial contributions to the conception, design, and/or interpretation of data. ZX and TPG were responsible for data acquisition and data analysis. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

BRC received consultation remuneration as a member of the Medical Advisory Board at Advance Health Solutions, LLC. He has also been an expert pulmonologist consultant for Glaxo Smith Kline, Boehringer-Ingelheim, Astra Zeneca, Novartis, and Pulmonix. He reports personal fees from Boehringer Ingelheim, Glaxo Smith Kline, Astra Zeneca, Novartis, and Chiesi, outside the submitted work. MN and SCR are employed by Advance Health Solutions, LLC which received funding from Sunovion Pharmaceuticals Inc. to oversee this study. ZX and TPG are employed by the University of California San Diego which received a grant from Advance Health Solutions, LLC to conduct this study. CD is employed by Sunovion Pharmaceuticals Inc. The authors report no other conflicts of interest in this work.

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