Use and Outcomes Associated with Long-acting Bronchodilators among Patients Hospitalized for Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: Long-acting β -adrenergic agonists and long-acting anticholinergic agents are recommended for the management of patients with stable chronic obstructive pulmonary disease (COPD); however, their role in the acute setting is uncertain.

Objectives: To describe the use and outcomes associated with long-acting bronchodilator therapy (LABD) among patients hospitalized with exacerbations of COPD.

Methods: We conducted a retrospective cohort study at 421 U.S. hospitals of patients hospitalized with exacerbations of COPD between January 1, 2010, and June 30, 2011. We used propensity score methods to compare the risk of a composite measure of treatment failure, length of stay, and hospital costs in patients who were treated with an LABD to those who did not receive treatment.

Measurements and Main Results: Of the 77,378 patients included in the analysis, 31,725 (41%) were treated with an LABD on Hospital Day 1 or Day 2, including 15,356 (48.4%) who received a long-acting β -agonist, 6,665 (21%) who received a long-acting

anticholinergic, and 9,704 (30.6%) who received both. When compared with patients who were not treated with an LABD, treated patients tended to be younger and had a modestly lower comorbidity burden but were more likely to have had prior admission for COPD and to be treated with inhaled corticosteroids. The incidence of treatment failure was similar among those who were or were not treated with LABDs (13.1 vs. 13.6%, $P = 0.06$). In propensity-matched analyses we found no difference in the risk of treatment failure associated with exposure to LABDs (relative risk [RR], 1.00; 95% confidence interval [CI], 0.96–1.04), minimal differences in hospital cost (RR, 1.02; 95% CI, 1.01–1.03), and no difference in length of stay (RR, 1.01; 95% CI, 1.00–1.02).

Conclusions: Despite a lack of evidence, LABDs are commonly prescribed to patients hospitalized for exacerbations of COPD but are not associated with better clinical or economic outcomes. Clinical trials are needed to determine the optimal use of these medications in the acute care setting.

Keywords: bronchodilator agents; chronic obstructive pulmonary disease; retrospective studies; lung diseases; inpatients

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Chronic obstructive pulmonary disease (COPD) affects as many as 24 million individuals in the United States and is

responsible for 800,000 annual hospitalizations and more than \$3.8 billion in hospital care expenditure (1, 2). Among

Medicare beneficiaries, the mortality rate within 30 days of hospital admission is 8.6%, and approximately 23% of patients

are rehospitalized within 1 month of discharge (3, 4). In addition to supplemental oxygen, conventional therapy for hospitalized patients consists of short-acting bronchodilators (SABDs; short-acting β_2 -adrenergic agonists and short-acting anticholinergic agents) and systemic glucocorticoids. Most hospitalized patients are also treated with antibiotics.

Over the past decade, long-acting β_2 -adrenergic agonists and tiotropium, a long-acting anticholinergic agent, have emerged as invaluable medications for the treatment of stable COPD. They improve lung function and reduce the risk of exacerbation and hospitalization, and guidelines recommend them as first-line pharmacotherapy for most patients (5–10). Although long-acting bronchodilators (LABDs) are widely prescribed in ambulatory care, their role in the acute setting is uncertain, and guidelines highlight the lack of evidence about their benefit. Although SABD remain the standard of care for the management of acutely ill patients, the addition of an LABD could extend the period of bronchodilation and reduce the

need for acute symptom control using short-acting agents. With this in mind, pilot studies have reported that patients treated with LABDs showed improved lung function and reduced need for short-acting agents and had shorter length of stay compared with patients who did not receive LABDs (11, 12). In light of the large number of hospitalizations each year, we sought to describe the use and outcomes associated with LABD therapy among patients admitted for exacerbations of COPD.

Methods

Design, Setting, and Subjects

We conducted a retrospective cohort study of patients hospitalized between January 1, 2010 and June 30, 2011 at 421 structurally and geographically diverse U.S. hospitals that participate in the Premier Inpatient Database, which is used to support quality improvement activities at member institutions (Premier Healthcare Informatics, Charlotte, NC). In addition to the information contained in the uniform

bill (i.e., UB-04), the database contains a date-stamped log of all items and services charged to the patient or his/her insurer, including individual item costs. Data are electronically collected from participating sites and audited to ensure validity. The database represents approximately 15% of all annual U.S. hospital admissions and has been extensively used in comparative effectiveness research in COPD (13–17).

We included all patients 40 years and older who received a principal discharge diagnosis (*International Classification of Disease, 9th Revision, Clinical Modification code*, [ICD-9-CM]) consistent with an acute exacerbation of COPD (AECOPD; 491.21, 492.22, 491.8, 491.9, 492.8, 496) or a secondary diagnosis of COPD when accompanied by a principal diagnosis of acute respiratory failure (518.81, 518.82, 518.84) and who were treated with at least 20 mg (in prednisone equivalents) of systemic glucocorticoids on the first or second hospital day (18, 19). Patients were excluded from the study if they were transferred from or to another acute care facility, their length of stay was less than 2

Figure 1. Study recruitment. COPD = chronic obstructive pulmonary disease; DRG = diagnosis-related group.

Table 1. Characteristics of patients included in the study

	Overall, n (%)	No Long-Acting Bronchodilator, n (%)	Treated with Long-Acting Bronchodilator, n (%)	P Value
Age, median (Q1–Q3), yr	70 (61–79)	70 (61–79)	69 (61–77)	<0.001
Sex				
Female	44,722 (57.8)	26,237 (57.5)	18,485 (58.3)	0.03
Race/ethnicity				
White	59,574 (77.0)	34,902 (76.5)	24,672 (77.8)	<0.001
Black	6,750 (8.7)	4,137 (9.1)	2,613 (8.2)	
Hispanic	2,112 (2.7)	1,465 (3.2)	647 (2.0)	
Other	8,942 (11.6)	5,149 (11.3)	3,793 (12.0)	
Marital status				
Married	28,397 (36.7)	16,697 (36.6)	11,700 (36.9)	<0.001
Single	43,097 (55.7)	25,781 (56.5)	17,316 (54.6)	
Other/missing	5,884 (7.6)	3,175 (7.0)	2,709 (8.5)	
Insurance payor				
Medicare	56,141 (72.6)	33,163 (72.6)	22,978 (72.4)	<0.001
Medicaid	6,887 (8.9)	4,024 (8.8)	2,863 (9.0)	
Private	9,869 (12.8)	5,517 (12.1)	4,352 (13.7)	
Uninsured	3,021 (3.9)	2,044 (4.5)	977 (3.1)	
Other	1,460 (1.9)	905 (2.0)	555 (1.7)	
Indicator of COPD severity				
Admission for COPD in past year	14,307 (18.5)	7,446 (16.3)	6,861 (21.6)	<0.001
Noninvasive ventilation in past year	7,209 (9.3)	3,977 (8.7)	3,232 (10.2)	<0.001
Invasive mechanical ventilation in past year	3,677 (4.8)	2,153 (4.7)	1,524 (4.8)	0.57
COPD as principal diagnosis for index admission	66,562 (86.0)	39,061 (85.6)	27,501 (86.7)	<0.001
Comorbidities				
Hypertension	51,600 (66.7)	30,737 (67.3)	20,863 (65.8)	<0.001
Diabetes without chronic complications	21,648 (28.0)	13,000 (28.5)	8,648 (27.3)	<0.001
Fluid and electrolyte disorders	21,432 (27.7)	12,992 (28.5)	8,440 (26.6)	<0.001
Congestive heart failure	20,818 (26.9)	12,702 (27.8)	8,116 (25.6)	<0.001
Deficiency anemias	13,653 (17.6)	8,119 (17.8)	5,534 (17.4)	0.22
Depression	13,362 (17.3)	7,576 (16.6)	5,786 (18.2)	<0.001
Obesity	11,789 (15.2)	7,060 (15.5)	4,729 (14.9)	0.03
Hypothyroidism	11,119 (14.4)	6,778 (14.8)	4,341 (13.7)	<0.001
Renal failure	10,321 (13.3)	6,454 (14.1)	3,867 (12.2)	<0.001
Peripheral vascular disease	7,001 (9.0)	4,099 (9.0)	2,902 (9.1)	0.42
Other neurological disorders	6,234 (8.1)	3,955 (8.7)	2,279 (7.2)	<0.001
Valvular disease	5,676 (7.3)	3,421 (7.5)	2,255 (7.1)	0.04
Psychoses	4,464 (5.8)	2,720 (6.0)	1,744 (5.5)	0.01
Comorbidity score, median (Q1–Q3)	2 (1–4)	2 (1–4)	2 (1–4)	<0.001
Hospital characteristics				
Bed size				
Small, <200	17,166 (22.2)	10,374 (22.7)	6,792 (21.4)	<0.001
Medium, 200–400	32,525 (42.0)	19,303 (42.3)	13,222 (41.7)	
Large, >400	27,687 (35.8)	15,976 (35.0)	11,711 (36.9)	
Region				
Northeast	13,655 (17.6)	7,614 (16.7)	6,041 (19.0)	<0.001
Midwest	14,706 (19.0)	8,842 (19.4)	5,864 (18.5)	
South	37,653 (48.7)	22,831 (50.0)	14,822 (46.7)	
West	11,364 (14.7)	6,366 (13.9)	4,998 (15.8)	
Teaching status				
Teaching	23,727 (30.7)	13,624 (29.8)	10,103 (31.8)	<0.001
Nonteaching	53,651 (69.3)	32,029 (70.2)	21,622 (68.2)	
Rural/urban status				
Rural	13,721 (17.7)	8,320 (18.2)	5,401 (17.0)	<0.001
Urban	63,657 (82.3)	37,333 (81.8)	26,324 (83.0)	
Admitting physician specialty				
Pulmonary/intensivist	6,101 (7.9)	3,955 (8.7)	2,146 (6.8)	<0.001
Family practice	12,595 (16.3)	7,502 (16.4)	5,093 (16.1)	
Internal medicine	35,105 (45.4)	20,294 (44.5)	14,811 (46.7)	
Hospital medicine	16,230 (21.0)	9,420 (20.6)	6,810 (21.5)	

(Continued)

Table 1. (Continued)

	Overall, n (%)	No Long-Acting Bronchodilator, n (%)	Treated with Long-Acting Bronchodilator, n (%)	P Value
Other specialty	7,347 (9.5)	4,482 (9.8)	2,865 (9.0)	
Treatments and diagnostic tests				
Short-acting anticholinergic	61,184 (79.1)	35,248 (77.2)	25,936 (81.8)	<0.001
Short-acting β_2 -adrenergic agonist	66,880 (86.4)	37,718 (82.6)	29,162 (91.9)	<0.001
Inhaled steroid	31,437 (40.6)	5,558 (12.2)	25,879 (81.6)	<0.001
Methylxanthine bronchodilator	5,202 (6.7)	2,637 (5.8)	2,565 (8.1)	<0.001
Opiates	14,918 (19.3)	8,680 (19.0)	6,238 (19.7)	0.02
Nicotine replacement	10,396 (13.4)	5,964 (13.1)	4,432 (14.0)	<0.001
Loop diuretics	27,513 (35.6)	16,355 (35.8)	11,158 (35.2)	0.06
Noninvasive ventilation	11,413 (14.8)	6,763 (14.8)	4,650 (14.7)	0.55
Antibiotics				
Cephalosporin	26,413 (34.1)	15,999 (35.0)	10,414 (32.8)	<0.001
Macrolides	27,909 (36.1)	16,706 (36.6)	11,203 (35.3)	<0.001
Antipseudomonal penicillins	4,890 (6.3)	2,905 (6.4)	1,985 (6.3)	0.55
Quinolones	40,086 (51.8)	23,702 (51.9)	16,384 (51.6)	0.45
Tetracyclines	3,724 (4.8)	1,957 (4.3)	1,767 (5.6)	<0.001
Sputum culture	8,107 (10.5)	4,680 (10.3)	3,427 (10.8)	0.01
Arterial blood gas	33,280 (43.0)	19,854 (43.5)	13,426 (42.3)	<0.001
B-type natriuretic peptide	48,598 (62.8)	29,163 (63.9)	19,435 (61.3)	<0.001
Outcomes				
Duration of intravenous steroids, median (Q1–Q3), d	3 (2–5)	3 (2–5)	3 (2–5)	<0.001
Hospital-acquired pneumonia	1,041 (1.3)	625 (1.4)	416 (1.3)	0.49
Late invasive mechanical ventilation	1,682 (2.2)	1,058 (2.3)	624 (2.0)	<0.001
Late noninvasive ventilation	2,253 (3.4)	1,291 (3.3)	962 (3.6)	0.10
In-hospital death	1,415 (1.8)	881 (1.9)	534 (1.7)	0.01
30-d All-cause readmission	6,544 (8.6)	3,895 (8.7)	2,649 (8.5)	0.32
30-d COPD readmission	2,142 (2.8)	1,176 (2.6)	966 (3.1)	<0.001
Treatment failure	10,356 (13.4)	6,198 (13.6)	4,158 (13.1)	0.06
Arrhythmia	2,253 (2.9)	1,335 (2.9)	918 (2.9)	0.80
Hypokalemia	1,524 (2.0)	932 (2.0)	592 (1.9)	0.08
Urinary retention	248 (0.3)	134 (0.3)	114 (0.4)	0.11
Length of stay, median (Q1–Q3), d	4 (3–6)	4 (3–6)	4 (3–6)	0.78
Cost, median (Q1–Q3), US dollars	6,167 (4,247–9,391)	6,100 (4,186–9,359)	6,258 (4,345–9,437)	<0.001

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; Q1–Q3 = interquartile range.

days, they were cared for by an attending physician from a specialty that would not be expected to treat COPD (e.g., psychiatry), they had a Medicare Severity Diagnosis-Related Group inconsistent with COPD or its sequelae, or they were treated initially with invasive mechanical ventilation (because long-acting agents cannot be delivered in this context). For patients with multiple admissions during the study period, we randomly selected one admission to reduce the possibility of survival bias associated with admission frequency.

Patient and Hospital Information

In addition to age, sex, race, ethnicity, marital status, and primary insurance coverage, we recorded the presence of up to 29 unique comorbidities using software provided by the Healthcare Costs and

Utilization Project of the Agency for Healthcare Research and Quality (20). Comorbidities were summarized into a score using methods described by Gagne and colleagues that combines Charlson comorbidities with those defined by the Agency for Healthcare Research and Quality (21). To help assess the severity of the patient's lung disease, we noted whether there were any hospitalizations for COPD in the year before the index admission and whether the patient had been treated with invasive and noninvasive mechanical ventilation.

In addition to these patient factors, we recorded the specialty of the admitting and attending physician and, for each hospital, the number of beds, teaching status, geographic region, and whether it served an urban or rural population. Using data

from the American Hospital Association Annual Survey we computed the staff-to-bed ratios of full-time equivalent hospitalists, intensivists, nurses, and respiratory therapists (22).

Use of Long-Acting Bronchodilators and Other Treatments

Using pharmacy billing records, we assessed whether patients were administered a long-acting β_2 -receptor agonist or tiotropium on the first or second hospital day. The first 2 days were chosen to assess exposure to treatment because, in administrative datasets, the duration of the first hospital day includes partial days. To control for other potential confounders, we also recorded exposure to short-acting β -agonists and anticholinergic agents, antibiotics, methylxanthines, inhaled

corticosteroids, loop diuretics, opiates, and nicotine replacement. We also assessed whether sputum, arterial blood gas, or B-type natriuretic peptide testing was performed on the first or second hospital day.

Outcomes

The primary study outcome was a composite measure of treatment failure, defined as the receipt of invasive or noninvasive mechanical ventilation, in-hospital death, or readmission within 30 days of discharge. Outcomes related to mechanical ventilation and death were assessed after Hospital Day 2 to avoid immortal time bias (23). Secondary outcomes included the number of days of treatment with intravenous steroids, length of stay, and hospital costs. We also estimated the risk of a composite measure of complications related to bronchodilator use, including arrhythmia, hypokalemia, and urinary retention, which were assessed using ICD-9-CM secondary diagnosis codes.

Analyses

We calculated summary statistics using frequencies and proportions for categorical data and means, medians, and interquartile ranges for continuous variables. We compared the characteristics of patients who received LABDs during the first 2 hospital days with those who did not using chi-square or z-tests.

We developed a series of multivariable regression models to assess the independent effect of LABD administration on the composite measure of treatment failure, length of stay, and costs, while adjusting for principal diagnosis, all patient and hospital characteristics, and other early diagnostic tests and treatments. Hierarchical generalized linear models (SAS PROC GLIMMIX) were used to account for the clustering of patients within hospitals. Poisson models with a log link were used for treatment failure and identity link models, for the log-transformed length of stay and cost, after trimming extreme values.

Additionally, we used propensity score methods to mitigate confounding related to differences in LABD-treated and -nontreated patients. We developed a nonparsimonious logistic regression model to estimate a patient's propensity

for treatment that included all patient and hospital characteristics and all other early treatments and diagnostic tests in which receipt of an LABD by Day 2 was considered the outcome (24). We then applied a series of analyses to evaluate for heterogeneity of treatment effect. We used the propensity score as an additional covariate in multivariable modeling. Each treated patient was then matched with a nontreated patient with a similar propensity using a Greedy Match algorithm (25). The matched cohort was evaluated for differences for each potential confounding factor; conditional logistic regression was used to assess the association between exposure and treatment failure while adjusting for any remaining differences between groups ($P < 0.05$), estimating treatment effect in a population with risk factors like the matched subset of treated patients. In addition to matching, we applied two propensity weighting methods: stabilized inverse-probability-of-treatment weighting, which produces an estimate of the treatment effect in a population with a risk factor distribution similar to that of the full study population, and standardized mortality ratio weighting, which yields an effect estimate in a population with a risk factor distribution similar to those actually treated with LABDs (26, 27).

We performed several secondary analyses. First, rather than categorizing patients according to whether they received any long-acting agent, we

examined long-acting β -agonists separately from tiotropium. Second, we compared the outcomes of patients who received the combination of long-acting β -agonists and tiotropium to those who received no long-acting treatment. Third, we restricted the analysis to patients who were simultaneously treated with inhaled corticosteroids. Last, we compared the risk of cardiovascular complications among patients who received both SABDs and LABDs to those who received only short-acting agents.

All significance tests were two-sided, with a 0.05 significance level. All analyses were performed using the Statistical Analysis System (version 9.3; SAS Institute, Inc., Cary, NC). The Institutional Review Board at Baystate Medical Center approved the study.

Results

Among the 77,378 patients who met our enrollment criteria (Figure 1), the mean age was 69 years, 58% were women, 77% were white, and 1,415 patients (1.8%) died during the hospitalization (Table 1). The median (interquartile range) length of stay was 4 (3–6) days. A total of 31,725 patients (41%) received treatment with LABDs within the first 2 hospital days. Of these, 15,356 (48.4%) were treated with long-acting β_2 -agonists alone, 6,665 (21.0%) received tiotropium alone, and 9,704 (30.6%) received both classes of

Figure 2. Association between treatment with long-acting bronchodilators (LABDs) and outcomes; results of multivariable analyses. SIPTW = stabilized inverse-probability-of-treatment weighting; SMRW = standardized mortality ratio weighting.

Table 2. Characteristics and outcomes of patients in the propensity-matched analysis

	Overall, n (%)	No Long-Acting Bronchodilator, n (%)	Treated with Long-Acting Bronchodilator, n (%)	P Value
Age, median (Q1–Q3), yr	70 (61–78)	70 (61–78)	70 (61–78)	0.41
Sex				
Female	29,633 (58.0)	14,797 (57.9)	14,836 (58.1)	0.73
Race/ethnicity				
White	39,374 (77.0)	19,699 (77.1)	19,675 (77.0)	0.80
Black	4,448 (8.7)	2,197 (8.6)	2,251 (8.8)	
Hispanic	1,173 (2.3)	582 (2.3)	591 (2.3)	
Other	6,115 (12.0)	3,077 (12.0)	3,038 (11.9)	
Marital status				
Married	18,814 (36.8)	9,367 (36.7)	9,447 (37.0)	0.67
Single	28,260 (55.3)	14,180 (55.5)	14,080 (55.1)	
Other/missing	4,036 (7.9)	2,008 (7.9)	2,028 (7.9)	
Insurance payor				
Medicare	37,212 (72.8)	18,610 (72.8)	18,602 (72.8)	0.99
Medicaid	4,522 (8.8)	2,256 (8.8)	2,266 (8.9)	
Private	6,630 (13.0)	3,307 (12.9)	3,323 (13.0)	
Uninsured	1,773 (3.5)	889 (3.5)	884 (3.5)	
Other	973 (1.9)	493 (1.9)	480 (1.9)	
Indicator of COPD severity				
Admission for COPD in past year	9,494 (18.6)	4,741 (18.6)	4,753 (18.6)	0.89
Noninvasive ventilation in past year	4,919 (9.6)	2,449 (9.6)	2,470 (9.7)	0.75
Invasive mechanical ventilation in past year	2,324 (4.5)	1,152 (4.5)	1,172 (4.6)	0.67
COPD as principal diagnosis for index admission	44,169 (86.4)	22,087 (86.4)	22,082 (86.4)	0.95
Comorbidities				
Hypertension	34,026 (66.6)	17,042 (66.7)	16,984 (66.5)	0.59
Diabetes without chronic complications	14,308 (28.0)	7,127 (27.9)	7,181 (28.1)	0.59
Fluid and electrolyte disorders	14,132 (27.7)	7,148 (28.0)	6,984 (27.3)	0.10
Congestive heart failure	13,609 (26.6)	6,759 (26.4)	6,850 (26.8)	0.36
Deficiency anemias	9,030 (17.7)	4,441 (17.4)	4,589 (18.0)	0.09
Depression	8,996 (17.6)	4,509 (17.6)	4,487 (17.6)	0.80
Obesity	7,657 (15.0)	3,821 (15.0)	3,836 (15.0)	0.85
Hypothyroidism	7,203 (14.1)	3,577 (14.0)	3,626 (14.2)	0.53
Renal failure	6,557 (12.8)	3,253 (12.7)	3,304 (12.9)	0.50
Peripheral vascular disease	4,643 (9.1)	2,275 (8.9)	2,368 (9.3)	0.15
Other neurological disorders	3,935 (7.7)	1,192 (7.7)	1,963 (7.7)	0.88
Valvular disease	3,731 (7.3)	1,866 (6.3)	1,865 (7.3)	0.99
Psychoses	2,887 (5.6)	1,440 (5.6)	1,447 (5.7)	0.89
Comorbidity score, median (Q1–Q3)	2 (1–4)	2 (1–4)	2 (1–4)	0.48
Hospital characteristics				
Bed size				
Small, <200	10,863 (21.3)	5,426 (21.2)	5,437 (21.3)	0.98
Medium, 200–400	22,029 (43.1)	11,024 (43.1)	11,005 (43.1)	
Large, >400	18,218 (35.6)	9,105 (35.6)	9,113 (35.7)	
Region				
Northeast	8,942 (17.5)	4,496 (17.6)	4,446 (17.4)	0.77
Midwest	9,427 (18.4)	4,695 (18.4)	4,732 (18.5)	
South	24,742 (48.4)	12,334 (48.3)	12,408 (48.6)	
West	7,999 (15.7)	4,030 (15.8)	3,969 (15.5)	
Teaching status				
Teaching	15,767 (30.8)	7,869 (30.8)	7,898 (30.9)	0.78
Nonteaching	35,343 (69.2)	17,686 (69.2)	17,657 (69.1)	
Rural/urban status				
Rural	8,959 (17.5)	4,489 (17.6)	4,770 (17.5)	0.83
Urban	42,151 (82.5)	21,066 (82.4)	21,085 (82.5)	
Admitting physician specialty				
Pulmonary/intensivist	3,447 (6.7)	1,723 (6.7)	1,724 (6.7)	0.76
Family practice	8,332 (16.3)	4,171 (16.3)	4,161 (16.3)	
Internal medicine	23,468 (45.9)	11,738 (45.9)	11,730 (45.9)	
Hospital medicine	11,036 (21.6)	5,473 (21.4)	5,563 (21.8)	

(Continued)

Table 2. (Continued)

	Overall, n (%)	No Long-Acting Bronchodilator, n (%)	Treated with Long-Acting Bronchodilator, n (%)	P Value
Other specialty	4,827 (9.4)	2,450 (9.6)	2,377 (9.3)	
Treatments and diagnostic tests				
Short-acting anticholinergic agent	42,818 (83.8)	21,427 (83.8)	21,391 (83.7)	0.67
Short-acting β_2 -adrenergic agonist	46,642 (91.3)	23,360 (91.4)	23,282 (91.1)	0.22
Inhaled steroid	23,881 (46.7)	3,334 (13.0)	20,547 (80.4)	<0.001
Methylxanthine bronchodilator	3,307 (6.5)	1,648 (6.4)	1,659 (6.5)	0.84
Opiates	10,222 (20.0)	5,218 (20.4)	5,004 (19.6)	0.02
Nicotine replacement	7,060 (13.8)	3,584 (14.0)	3,476 (13.6)	0.17
Loop diuretics	18,140 (35.5)	9,033 (35.3)	9,107 (35.6)	0.49
Noninvasive ventilation	7,695 (15.1)	3,818 (14.9)	3,877 (15.2)	0.47
Antibiotics				
Cephalosporin	16,951 (33.2)	8,464 (33.1)	8,487 (33.2)	0.83
Macrolides	18,187 (35.6)	9,109 (35.6)	9,078 (35.5)	0.77
Antipseudomonal penicillins	3,283 (6.4)	1,685 (6.6)	1,598 (6.3)	0.12
Quinolones	26,739 (52.3)	13,350 (52.2)	13,389 (52.4)	0.73
Tetracyclines	2,607 (5.1)	1,307 (5.1)	1,300 (5.1)	0.89
Sputum culture	5,414 (10.6)	2,703 (10.6)	2,711 (10.6)	0.91
Arterial blood gas	21,979 (43.0)	10,962 (42.9)	11,017 (43.1)	0.62
B-type natriuretic peptide	31,863 (62.3)	15,902 (62.2)	15,961 (62.5)	0.59
Outcomes				
Duration of intravenous steroids, median (Q1–Q3), d	3 (2–5)	3 (2–5)	3 (2–5)	0.04
Hospital-acquired pneumonia	697 (1.4)	341 (1.3)	356 (1.4)	0.57
Late invasive mechanical ventilation	1,038 (2.0)	526 (2.1)	512 (2.0)	0.66
Late noninvasive ventilation	1,500 (3.5)	705 (3.2)	795 (3.7)	0.02
In-hospital death	923 (1.8)	468 (1.8)	455 (1.8)	0.67
30-d All-cause readmission	4,258 (8.5)	2,144 (8.5)	2,114 (8.4)	0.62
30-d COPD readmission	1,408 (2.8)	661 (2.6)	747 (3.0)	0.02
Treatment failure	6,738 (13.2)	3,374 (13.2)	3,364 (13.2)	0.90
Arrhythmia	1,505 (2.9)	745 (2.9)	760 (3.0)	0.69
Hypokalemia	1,003 (2.0)	504 (2.0)	499 (2.0)	0.87
Urinary retention	166 (0.3)	75 (0.3)	91 (0.4)	0.21
Length of stay, median (Q1–Q3), d	4 (3–6)	4 (3–6)	4 (3–6)	0.18
Cost, median (Q1–Q3), US dollars	6,128 (4,230–9,331)	6,024 (4,152–9,252)	6,226 (4,313–9,411)	<0.001

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; Q1–Q3 = interquartile range.

medication. The composite measure of treatment failure was experienced by 10,356 (13.4%) patients, including 1,682 (2.2%) who were treated with mechanical ventilation after the second hospital day, 2,253 (3.4%) who received noninvasive ventilation, 1,415 (1.8%) who did not survive to discharge, and 6,544 (8.6%) who were readmitted. A total of 4.9% of patients developed a complication, including 2,253 (2.9%) cases of arrhythmia, 1,524 (2.0%) of hypokalemia, and 248 (0.3%) of urinary retention.

When compared with those who were not treated with LABDs, treated patients were younger and had a modestly lower combined comorbidity score (mean, 2.5 vs. 2.7; $P < 0.0001$) but were more likely to have had a prior admission for COPD (21.6% vs. 16.3%, $P < 0.0001$). Patients

treated with LABDs were far more likely to receive concomitant treatment with inhaled corticosteroids (82 vs. 12%, $P < 0.0001$).

Results of Multivariable Analyses

In models that adjusted for clustering within hospital as well as patient, hospital, and physician characteristics, including the propensity for treatment with LABDs and the early use of other treatments and diagnostic tests, we found no differences in the risk of treatment failure, duration of treatment with intravenous steroids, or length of stay; however, treated patients had marginally higher costs (Figure 2). Analyses using stabilized inverse-probability-of-treatment weighting and standardized mortality ratio weighting methods yielded similar results.

Overall, 81% of patients treated with an LABD by Hospital Day 2 were successfully matched to a nontreated patient with a similar propensity (Table 2). Within this propensity-matched sample, the incidence of treatment failure was 13.2% in both treated patients and matched control subjects ($P = 0.90$); there were no differences in the incidence of the composite complication measure ($P = 0.79$). Conditional logistic regression on the matched sample yielded similar results (Figure 2).

In secondary analyses we examined the association between exposure to a long-acting β -agonist and treatment failure separately from tiotropium; in neither case did we find a significant association (β -agonist: relative risk [RR], 0.99; 95% confidence interval [CI], 0.94–1.04; anticholinergic: RR, 0.97; 95% CI, 0.90–

1.04). Similarly, we found no association between receipt of the combination of a long-acting β -agonist and tiotropium compared with no long-acting agents and outcome (RR, 1.04; 95% CI, 0.97–1.10). When restricted to patients who were also treated with inhaled corticosteroids, the results were similar to models including all patients (RR, 0.98; 95% CI, 0.91–1.06). Finally, there was no difference in the risk of cardiovascular complications among patients who received long-acting agents combined with short-acting agents compared with those receiving short-acting agents alone (RR, 1.04; 95% CI, 0.89–1.21).

Discussion

In this study of more than 77,000 patients at 421 U.S. hospitals with exacerbations of COPD, we found that, in the absence of supportive evidence or recommendations from clinical guidelines, some 40% of patients were treated with LABDs—almost always in conjunction with short-acting agents and generally combined with inhaled corticosteroids. Although receipt of long-acting agents was associated with marginally higher hospital costs, we observed no benefit regarding length of stay, duration of therapy with intravenous steroids, the risk of treatment failure (including late ventilation, inpatient mortality, readmission), or complications related to therapy.

Little is known about the effects of LABDs in the inpatient setting or how often these agents are used in routine clinical care. In theory, the addition of an LABD could extend the period of bronchodilation and reduce the need for acute symptom control using short-acting agents. To test these hypotheses, Di Marco and colleagues randomized 21 patients with AECOPD to receive formoterol, tiotropium, or both at one hospital. They reported that patients treated with combination therapy experienced greater improvement in lung function than those treated with single agents (11). Drescher and colleagues compared the outcomes of patients with acute exacerbations before and after implementation of a respiratory therapist-driven bronchodilator protocol that included tiotropium compared with

a historical control group receiving only SABDs. The authors reported that treated patients had a reduced need for short-acting agents and a 1-day shorter length of stay than patients who did not receive tiotropium (12). Although our study cannot answer questions about the effects of LABDs on lung function, we did not observe a clinically meaningful association between treatment and a broad set of patient outcomes, including length of stay. Finally, Bollu and colleagues conducted a retrospective study of patients hospitalized with COPD and compared the risk of readmission of those treated with a long-acting β -agonist to those treated with nebulized short-acting β -agonists. They reported a significantly lower adjusted risk of readmission among patients treated with arformoterol, a finding that we were not able to replicate in our own analysis (28).

Current guidelines recommend the use of SABDs in patients with AECOPD but point out the lack of evidence regarding the concurrent use of long-acting agents. In the absence of clear recommendations we observed a high rate of cotreatment. Virtually all patients who received LABDs were simultaneously undergoing treatment with short-acting β_2 -agonists or inhaled anticholinergic medications, and many received treatment with both classes of short-acting agents. Moreover, although all of the patients in the study were treated with systemic corticosteroids, approximately 80% of the patients treated with LABDs were simultaneously treated with inhaled corticosteroids in addition to systemic steroids. These findings raise a question of whether the prescribing patterns we observed may be influenced by efforts to improve medication reconciliation at study sites. To comply with standards established by the Joint Commission on the Accreditation of Health Care Organizations, since 2005, hospitals have increasingly focused on preventing inadvertent discontinuation of home medications. Hospital-based physicians are typically presented with the choice, either on paper or through electronic medical record, to either hold or continue use of each home medication. Although there is nothing inherent in the process of medication reconciliation that encourages the continuation of

a home medication when a similar agent is being used acutely, we suspect that some of the duplicative prescribing we observed may be driven by the concern that by temporarily withholding a medication, there is a risk that the medications might not be restarted at the time of discharge. Beyond medication reconciliation, physicians may also have concerns about the potential for clinical deterioration associated with acutely stopping these medications. An additional possibility is that physicians are continuing long-acting agents in the hospital despite prescribing short-acting agents out of the belief that the LABDs may be a useful adjunct when the patient presents with a severe exacerbation of COPD.

Our findings should be interpreted in light of several limitations. First, because our analysis included a very large cohort of patients, we used ICD-9-CM codes rather than chart review to select cases. Although the sensitivity and specificity of this approach is imperfect, we enhanced the likelihood that patients had COPD exacerbation by requiring receipt of systemic corticosteroids (19). Second, although our study was performed within a diverse sample of hospitals, our findings may not be fully generalizable to all U.S. facilities. In this regard, it was notable that hospital treatment rates varied from 19 to 64% across institutions at the 10th and 90th percentiles of use, suggesting that inpatient receipt of LABDs is influenced more by local hospital preferences than by patient factors. Third, although our analyses controlled for a large number of clinically important variables, including demographic characteristics of the patients, comorbidities, the number of admissions for COPD in the prior year (including prior receipt of noninvasive and invasive forms of ventilation), a comprehensive set of diagnostic tests and other treatments, and the effects of clustering, we did not have information about the patient's lung function or functional status. Receipt of LABDs in the ambulatory setting may be a marker of more advanced disease, and our propensity-matched analyses may reflect residual confounding, potentially obscuring a benefit of treatment. Fourth, because we only had information about medications prescribed in the hospital we

were not able to identify when patients had their medications stopped. Last, we were unable to assess the administration adequacy of the inhaled medications that we studied.

In conclusion, although LABDs are widely used in the management of

patients hospitalized with AECOPD, we found no evidence that treatment was associated with meaningful clinical benefits. Given the vast number of patients who are hospitalized each year, randomized trials are needed to

determine the optimal clinical strategy regarding the use of these medications in the acute care setting. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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