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A simple rule to identify patients with chronic obstructive pulmonary disease who may need treatment reevaluation

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Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICS, inhaled corticosteroid; IMPACT™, Impact National Benchmark Database; IV, intravenous; LABA, long-acting inhaled β_2-agonist; LAMA, long-acting inhaled muscarinic antagonist; MDI, metered-dose inhaler; MPR, medication possession ratio; ORD, Optum Research Database; PPY, per patient year; SABA, short-acting inhaled β_2-agonist; SAMA, short-acting inhaled muscarinic antagonist; SD, standard deviation.

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KEYWORDS
COPD;
Exacerbation;
SABA;
Maintenance therapy

Summary
Background: A simple rule based on short-acting inhaled β_2-agonist (SABA) use could identify patients with chronic obstructive pulmonary disease (COPD) at increased risk of exacerbations and signal the need for maintenance therapy change, similar to asthma "Rules of Two®".
Methods: Associations between SABA use, COPD exacerbations, and health care costs over 1 year were examined retrospectively using de-identified patient data from the Optum Research Database (ORD; $N = 56,581$) and the Impact National Benchmark Database (IMPACT™; $N = 9423$). Nebulized and metered-dose inhaler (MDI) SABA doses were normalized to 2.5 mg and 90 mcg albuterol equivalents, respectively.
Results: The GOLD initiative establishes ≥2 exacerbations/year as indicative of increased risk in COPD. We identified a correlation ($p < 0.0001$) between 1.5 SABA doses/day and this frequency of exacerbations. In ORD, patients using ≥1.5 versus <1.5 SABA doses/day experienced significantly more exacerbations: 1.92 (95% confidence interval [CI], 1.89—1.96) versus 1.36 (95% CI, 1.34—1.38) per patient year (PPY). Above-threshold use was associated with higher average annual COPD-related costs (2010 $US): $21,868 (standard deviation [SD], $53,910) versus $11,686 (SD, $32,707) for nebulized SABA only, $9216 (SD, $30,710) versus $7334 (SD, $24,853) for MDI SABA only, and $15,806 (SD, $35,260) versus $11,233 (SD, $27,006) for both nebulized and MDI SABA. IMPACT™ validated these findings.
Conclusion: Patients with COPD using ≥1.5 SABA doses/day were at increased risk of exacerbations. Our results suggest a "Rule of 3—2": SABA use ≥3 times in 2 days should be considered a clinical marker for needing treatment reevaluation.

Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide [1] and the third leading cause of death in the United States [2]. Its prevalence is expected to increase dramatically in many countries with the aging of individuals born between 1946 and 1964 (colloquially, the "baby boomer" generation). The risk of developing COPD by age 80 is estimated to be about 28% [3].

Most cases of COPD are diagnosed clinically; a recent study in developed countries found that only 32% of patients undergo an objective evaluation that includes spirometry [4]. In the absence of spirometry, the American College of Physicians recommends using age, smoking history, and presence of wheezing to diagnose COPD [5]. After diagnosis, follow-up usually relies on clinical signs and symptoms without spirometry or validated questionnaires to inform treatment decisions [6].

COPD exacerbations can reduce quality of life, accelerate loss of lung function, and lead to hospitalization or death if not promptly managed [7—10]. Furthermore, treatment of exacerbations contributes significantly to the overall health care cost associated with COPD [11]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) advises using history of exacerbations as an indicator of future risk of exacerbations [9]. A reduced forced expiratory volume in 1 s (FEV_1) has been associated with an increased risk of exacerbations [12], but few patients undergo spirometry [4].

We sought to develop a much-needed, easy-to-use clinical marker to identify patients with COPD at increased risk of exacerbations (similar to the "Rules of Two®" [13] in asthma). We hypothesized that increased frequency of short-acting inhaled β_2-agonist (SABA) use could be associated with increased risk of exacerbations and, therefore, serve as a signal for reevaluation of maintenance therapy.

Methods

Study design

We performed a retrospective, administrative claims—based analysis based on two US databases: the Optum Research Database (ORD) and the Impact National Benchmark Database (IMPACT™), which contain data from commercial and Medicare Advantage enrollees [14,15]. All records were de-identified, and no identifiable protected health information was extracted or accessed during the study, pursuant to the United States Health Insurance Portability and Accountability Act [16]. ORD was used to develop a rule based on SABA use to identify patients with COPD at increased risk of exacerbations, and IMPACT™ was used to validate findings.

Study patients

Patients with the following criteria were included in the analysis: at least one medical claim with COPD diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 491.xx, 492.x, 496) from January 1, 2008 through March 31, 2010; a second claim with COPD diagnosis at least 1 day following the first COPD diagnosis and within a 1-year period (date of second COPD diagnosis = Index Date); age ≥ 40 years at Index Date;

continuous enrollment for 6 months (182 days) before Index Date (baseline period); continuous enrollment for at least 1 year (365 days) after and including Index Date (follow-up period) unless there was earlier evidence of death; and at least one pharmacy or medical claim indicating use of SABA during the 1-year follow-up period.

Patients were excluded if they died before the Index Date or had evidence of inpatient hospitalization within the 90 days before the Index Date or a prescription fill for nebulized long-acting inhaled β_2-agonist (LABA) during the baseline or follow-up periods.

Use of metered-dose inhaler (MDI) and nebulized SABA

Daily use of SABA (isoetharine, levalbuterol, albuterol [including albuterol/ipratropium], bitolterol, isoproterenol, pirbuterol, terbutaline, and metaproterenol) was measured over 1 year, starting with the Index Date. One dose of MDI SABA was defined as 2 puffs (1 puff = 90 mcg albuterol equivalent); 1 dose of nebulized SABA was defined as 1 nebulization using 1 vial (2.5 mg albuterol equivalent). SABA quantities prescribed over the period of analysis were converted to puffs or vials, based on packaging information. For MDI SABA, number of puffs was divided by number of days to obtain *puffs per day*, which was divided by 2 to determine *doses per day*. For nebulized SABA, number of vials was divided by number of days to obtain *vials per day*, same as *doses per day*.

Outcomes

The primary outcome for the 1-year follow-up period was COPD exacerbations. These were identified by an ICD-9-CM code for an exacerbation (ICD-9-CM 491.21 and 492.22); a COPD-related hospitalization, emergency department visit, or urgent care visit; a new prescription for an oral corticosteroid or administration of an injectable/intravenous (IV) corticosteroid within 7 days following a COPD-related ambulatory visit; or a new prescription for an oral antibiotic or administration of an injectable/IV antibiotic within 7 days following a COPD-related ambulatory visit. Each "episode" may have consisted of multiple health care encounters (exacerbation events) and was considered complete after 7 days without any exacerbation events.

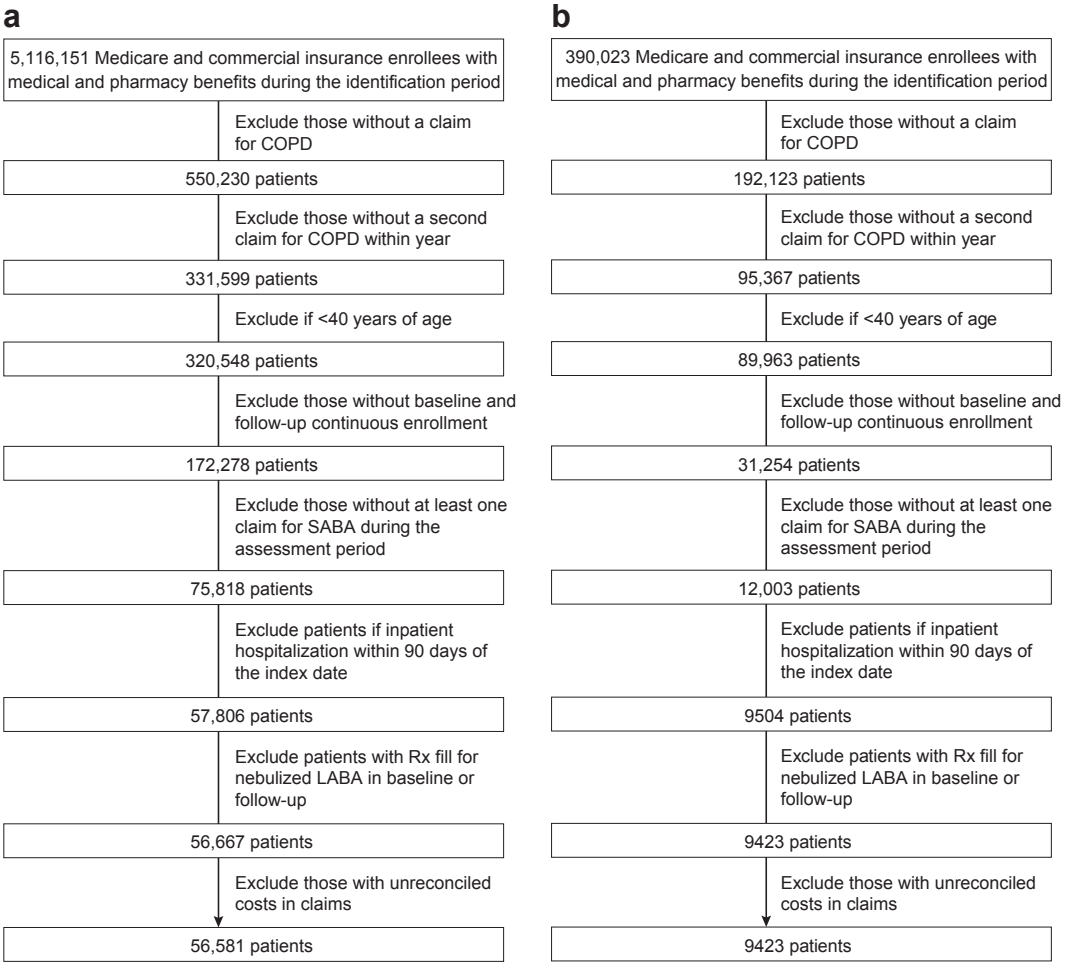

Figure 1 a: Sample attrition for the Optum Research Database (ORD). b: Sample attrition for the Impact National Benchmark Database (IMPACT™). COPD = chronic obstructive pulmonary disease; LABA = long-acting inhaled β_2-agonist; Rx = prescription; SABA = short-acting inhaled β_2-agonist.

The secondary outcome was COPD-specific health care costs, computed as combined health plan and patient paid amounts in the 1-year follow-up period. Costs were adjusted using the annual medical care component of the Consumer Price Index to reflect inflation between 2007 and 2010 [17]. Outcomes (exacerbations per patient year [PPY], rounded to an integer, and COPD-related costs per year) accounted for variable follow-up times caused by death.

Covariates

Comorbidity burden was determined using the Quan-Charlson comorbidity score, based on diagnosis codes in the baseline period [18]. COPD medications used during baseline and follow-up periods were captured at the class level (eg, nonnebulized LABA, short-acting inhaled muscarinic antagonists [SAMA], SAMA/SABA, long-acting inhaled muscarinic antagonists [LAMA], inhaled corticosteroids [ICS], and fixed combination inhaler therapies of LABA/ICS) and included administrations and pharmacy fills.

Descriptive analysis

To develop a claims-based marker for overuse of SABA, the relationship between SABA measures and outcomes during the analysis period was examined using descriptive statistics and plots of SABA use by exacerbations PPY. After a level of SABA use signaling high risk had been selected, exacerbations ($\geq$2 versus $<$2 based on GOLD initiative classification of high risk) and COPD-related costs per year for those above and below the marker level were examined.

Sensitivity analysis

Four sensitivity analyses were conducted. First, specificity and sensitivity were examined among subgroups of patients within age category, sex, insurance type (commercial or Medicare), and levels of compliance with various classes of concomitant COPD medications (measured by medication possession ratio [MPR]). The purpose of this analysis was to determine if the marker performed similarly among different types of patients (and could therefore be applied generally across the study population). Second, SABA use was investigated across 90- and 180-day periods to determine if the length of time over which SABA use was assessed altered findings. Third, multivariate analysis accounting for patient factors was performed to assess potential confounding. A negative binomial model including quartile of SABA use (vials or inhalations per day) as the primary predictor and COPD exacerbations per year as the outcome, adjusted for baseline covariates and patient characteristics, was created. Generalized linear modeling (GLM) with a gamma distribution and a log link modeled COPD-related costs. Finally, findings were validated with IMPACT™, a second and separate data set.

Table 1 Patient demographics and clinical characteristics by data source.

	Data source	
	ORD (N = 56,581)	IMPACT™ (N = 9423)
Mean (SD) age, years	67.8 (11.3)	62.2 (9.9)
Gender		
Male, *n* (%)	25,050 (44.3)	4271 (45.3)
Insurance type		
Commercial, *n* (%)	29,487 (52.1)	7301 (77.5)
Medicare Advantage, *n* (%)	27,094 (47.9)	2122 (22.5)
Quan-Charlson comorbidity index, mean (SD)	2.02 (1.60)	1.58 (1.39)
Select AHRQ comorbid conditions		
Asthma, *n* (%)	12,103 (21.4)	2144 (22.8)
Other lower respiratory disease, *n* (%)	27,660 (48.9)	4415 (46.8)
Respiratory infections, *n* (%)	20,237 (35.8)	3192 (33.9)

AHRQ = Agency for Healthcare Research and Quality; IMPACT™ = Impact National Benchmark Database; ORD = Optum Research Database; SD, standard deviation.

Results

Population characteristics

The total number of available commercial and Medicare Advantage enrollee records containing medical and pharmacy benefit claim data was >5.5 million across the two database populations. Development and validation populations consisted of 56,581 and 9423 patients with COPD in ORD and IMPACT™, respectively (Fig. 1a and b).

Although there were significant ($p < 0.05$) differences between the ORD and IMPACT™ patients in age, insurance coverage, and overall and respiratory comorbidities, these differences were based on the large sample sizes and not felt to be clinically meaningful (Table 1). Approximately one-fifth of patients in each group had diagnosed asthma. During the 6-month baseline period, most patients (60.3% ORD, 55.6% IMPACT™) used SABA rescue therapy (Supplemental Table 1). Fewer received SAMA monotherapy (24.3% ORD, 20.1% IMPACT™). About a third of patients in each database received systemic corticosteroids (35.9% ORD, 32.0% IMPACT™). In the baseline period, the two most commonly used maintenance therapies were LAMA (18.4% ORD, 17.5% IMPACT™) and ICS/LABA (24.8% ORD, 27.3% IMPACT™). ICS monotherapy, nonnebulized LABA, and methylxanthine were used less often.

During the 1-year follow-up, over one-half of patients from ORD (54.4%) and IMPACT™ (69.8%) used rescue SABA only with an MDI; 22.0% from ORD and 11.5% from IMPACT™ used SABA only by nebulization (Fig. 2a and b). The remaining patients used both. Systemic corticosteroid use was common (Table 2). The MPR for the two most commonly used maintenance medications, ICS/LABA and LAMA, ranged from 0.39 to 0.64 for the various subgroups examined. However, in general, less than one-third of patients using ICS/LABA and LAMA had an MPR $\geq$0.80.

Determination of the clinical marker

A positive linear relationship ($p < 0.0001$) was observed between the number of SABA doses/day and the incidence

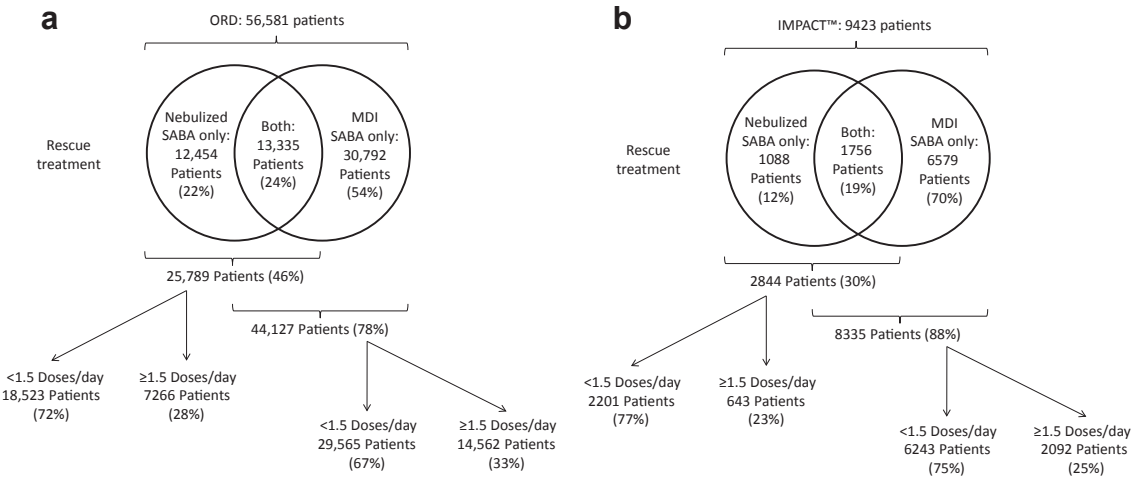

Figure 2 a: SABA use in ORD. b: SABA use in IMPACT™. IMPACT™ = Impact National Benchmark Database; MDI = metered-dose inhaler; ORD = Optum Research Database; SABA = short-acting inhaled β_2-agonist.

of exacerbations (Fig. 3) in ORD. A similar relationship was observed with IMPACT™. The GOLD initiative establishes ≥2 exacerbations per year (ie, frequent exacerbations) as indicative of increased risk in COPD [19]. In ORD, this frequency of exacerbations was correlated with ≥1.5 SABA doses/day. Data from IMPACT™ supported this threshold. This level of SABA use (≥1.5 SABA doses/day) was considered the clinical marker of high risk (Fig. 4). Patients using ≥1.5 SABA doses/day were significantly more likely to have ≥2 exacerbations during the year analyzed and to have significantly more days with exacerbation and exacerbations PPY in ORD (Supplemental Table 2). Similar trends were observed in IMPACT™.

In ORD, patients using more than the threshold of 1.5 SABA doses/day were significantly more likely to be receiving maintenance medications (Table 2). They had significantly higher annual COPD-related health care costs (2010 $US): $21,868 (standard deviation [SD], $53,910) versus $11,686 (SD, $32,707) for nebulized SABA only, $9216 (SD, $30,710) versus $7334 (SD, $24,853) for MDI SABA only, and $15,806 (SD, $35,260) versus $11,233 (SD, $27,006) for both nebulized and MDI SABA (Table 3). Results from IMPACT™ confirmed these findings. When costs were analyzed by site of care (inpatient, emergency department, outpatient, office visit, other medical, and pharmaceutical), ORD data indicated that ≥1.5 nebulized SABA doses/day significantly increased costs at all sites except the "other medical" category, with inpatient care having the highest cost. The increased costs with ≥1.5 MDI SABA doses/day were significant for all sites except inpatient or outpatient care. For patients using nebulized and MDI SABA, the difference in cost between patients using <1.5 SABA doses/day and patients using ≥1.5 SABA doses/day was significant in all categories except outpatient care. IMPACT™ showed significantly higher costs for pharmaceuticals with ≥1.5 nebulized SABA doses/day and for office visits and pharmaceuticals with ≥1.5 MDI SABA doses/day. For patients using both nebulized and MDI SABA, significantly higher cost was associated with ≥1.5 SABA doses/day in the categories of inpatient care, outpatient care, office visits, and pharmaceuticals.

Sensitivity and specificity

The overall sensitivity and specificity for identifying patients with ≥2 exacerbations PPY (using the marker of ≥1.5 SABA doses/day) were 44.3% and 68.0%, respectively, in ORD and 35.7% and 73.6%, respectively, in IMPACT™ (Table 4). This suggests that the marker is successful at identifying patients at low risk for future exacerbations and costs (specificity), but less so at accurately predicting risk of exacerbations. Sensitivity and specificity for the 1.5 doses/day cutoff were examined within various patient subgroups to determine if the marker would be applicable across multiple patient types. Marker performance was similar across various insurance and age groups, although sensitivity was slightly worse and specificity slightly improved in the youngest age group (40–54 years). Among patients using ICS/LABA or LAMA, sensitivity was higher (and specificity lower) for patients highly compliant with SABA (MPR ≥0.8 versus <0.8); however, the type of concomitant medication (ie, ICS/LABA or LAMA) did not seem to affect this relationship. Reducing the analysis period from a year to 90 or 180 days did not substantially alter sensitivity and specificity, suggesting that assessing SABA use over a shorter time period does not impact the performance of the marker. Findings were similar between databases.

Discussion

In this analysis, use of ≥1.5 SABA doses/day (nebulized or MDI) by patients with COPD was associated with significantly greater risk of exacerbation and significantly higher health care costs. The robustness of this finding, and its potential usefulness as a clinical marker, is supported by the consistency of results between two databases and by various sensitivity analyses.

Table 2 Medication use during the year post–index date with corresponding MPR in ORD and IMPACT™ combined, $N = 66{,}004$.

		SABA delivery						Nebulized SABA only *p* value	MDI SABA only *p* value	Nebulized + MDI SABA *p* value
		Nebulized SABA only		MDI SABA only		Nebulized + MDI SABA				
		<1.5 Doses/day ($n = 10{,}195$)	≥1.5 Doses/day ($n = 3347$)	<1.5 Doses/day ($n = 26{,}924$)	≥1.5 Doses/day ($n = 10{,}447$)	<1.5 Doses/day ($n = 5269$)	≥1.5 Doses/day ($n = 9822$)			
Rescue medications										
SAMA (monotherapy) use										
Patients with	n	2087	924	669	451	887	2154			
any fill	%	20.47	27.61	2.48	4.32	16.83	21.93	<0.001	<0.001	<0.001
SAMA/SABA combination use										
Patients with	n	4080	1702	5845	4052	2360	5675			
any fill	%	40.02	50.85	21.71	38.79	44.79	57.78	<0.001	<0.001	<0.001
Systemic corticosteroid use										
Patients with	n	5427	2024	13,400	5050	3918	7589			
any fill	%	53.23	60.47	49.77	48.34	74.36	77.27	<0.001	0.013	<0.001
Maintenance medications										
ICS (monotherapy) use										
Patients with	n	1301	674	2904	1825	890	2222			
any fill	%	12.76	20.14	10.79	17.47	16.89	22.62	<0.001	<0.001	<0.001
Patients with	n	51	126	191	371	40	329			
MPR ≥ 0.8	%	6.00	18.83	6.61	20.43	5.39	15.71	<0.001	<0.001	<0.001
MPR (continuous)	Mean	0.27	0.45	0.28	0.49	0.24	0.40	<0.001	<0.001	<0.001
	SD	0.26	0.31	0.25	0.30	0.23	0.31			
ICS/LABA combination use										
Patients with	n	2392	1046	9979	4796	2373	5383			
any fill	%	23.46	31.25	37.06	45.91	45.04	54.81	<0.001	<0.001	<0.001
Patients with	n	379	239	1614	1555	319	1284			
MPR ≥ 0.8	%	15.84	22.87	16.17	32.42	13.44	23.85	<0.001	<0.001	<0.001
MPR (continuous)	Mean	0.40	0.50	0.41	0.59	0.39	0.51	<0.001	<0.001	<0.001
	SD	0.30	0.30	0.30	0.31	0.29	0.31			
Methylxanthine use										
Patients with	n	425	201	722	590	301	1017			
any fill	%	4.17	6.01	2.68	5.65	5.71	10.35	<0.001	<0.001	<0.001
Patients with	n	150	86	191	281	86	407			
MPR ≥ 0.8	%	41.21	46.24	33.63	53.73	33.59	42.62	0.260	<0.001	0.009
MPR (continuous)	Mean	0.59	0.65	0.53	0.71	0.53	0.62	0.082	<0.001	<0.001
	SD	0.35	0.34	0.36	0.32	0.36	0.34			
Nonnebulized LABA use										
Patients with	n	203	115	725	522	156	488			
any fill	%	1.99	3.44	2.69	5.00	2.96	4.97	<0.001	<0.001	<0.001
Patients with	n	46	37	174	183	27	152			
MPR ≥ 0.8	%	22.66	32.17	24.00	35.06	17.31	31.15	0.063	<0.001	<0.001
MPR (continuous)	Mean	0.47	0.57	0.48	0.60	0.42	0.54	0.009	<0.001	<0.001
	SD	0.32	0.33	0.32	0.31	0.31	0.33			

(*continued on next page*)

Table 2 (*continued*)

		SABA delivery						Nebulized SABA only *p* value	MDI SABA only *p* value	Nebulized + MDI SABA *p* value
		Nebulized SABA only		MDI SABA only		Nebulized + MDI SABA				
		<1.5 Doses/day (n = 10,195)	≥1.5 Doses/day (n = 3347)	<1.5 Doses/day (n = 26,924)	≥1.5 Doses/day (n = 10,447)	<1.5 Doses/day (n = 5269)	≥1.5 Doses/day (n = 9822)			
LAMA (tiotropium) use										
Patients with any fill	n	1755	835	7324	3617	1693	3992			
	%	17.21	24.95	27.20	34.62	32.13	40.64	<0.001	<0.001	<0.001
Patients with MPR ≥ 0.8	n	372	239	1933	1522	383	1251			
	%	21.20	28.66	26.39	42.08	22.62	31.34	<0.001	<0.001	<0.001
MPR (continuous)	Mean	0.46	0.53	0.49	0.64	0.45	0.54	<0.001	<0.001	<0.001
	SD	0.32	0.32	0.33	0.32	0.32	0.33			
Oxygen use										
Patients with any oxygen use	n	3745	1565	4002	2324	1735	4448			
	%	36.73	46.76	14.86	22.25	32.93	45.29	<0.001	<0.001	<0.001

ICS = inhaled corticosteroid; IMPACT™ = Impact National Benchmark Database; LABA = long-acting inhaled β_2-agonist; LAMA = long-acting inhaled muscarinic antagonist; MDI = metered-dose inhaler; MPR = medication possession ratio; ORD = Optum Research Database; SABA = short-acting inhaled β_2-agonist; SAMA = short-acting inhaled muscarinic antagonist; SD = standard deviation.

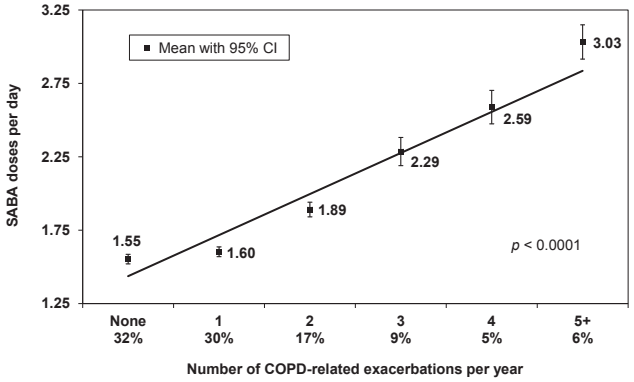

Figure 3 Distribution of SABA use by number of exacerbations, N = 56,581 (ORD). One dose of nebulized SABA was defined as 1 nebulization using 1 vial (2.5 mg albuterol equivalent). One dose of MDI SABA was defined as 2 puffs (1 puff = 90 mcg albuterol equivalent). CI = confidence interval; COPD = chronic obstructive pulmonary disease; ORD = Optum Research Database; SABA = short-acting inhaled β_2-agonist.

The ORD and IMPACT™ databases contained >56,000 and >9000 patients, respectively, who met inclusion criteria. Mean patient age (68 years, ORD; 62 years, IMPACT™) and male/female composition (44%/56%, ORD; 45%/55%, IMPACT™) were consistent with epidemiologic studies describing COPD profiles in Canada and the United States [2,20]. The statistically significant positive correlation between frequency of SABA use and exacerbations PPY in ORD allowed us to determine a clinically meaningful threshold (ie, marker) of SABA use. Relying on recommendations from the GOLD Initiative, [19] we identified a level of SABA use associated with ≥2 exacerbations per year, an indicator of increased risk and need for treatment reevaluation.

Determining which patients need reevaluation of maintenance therapy is important to clinicians, patients, payers, and public health officials. Less than half of the patients evaluated were receiving maintenance therapy. This important finding is consistent with results from a recent study showing that 66% and 71% of patients with

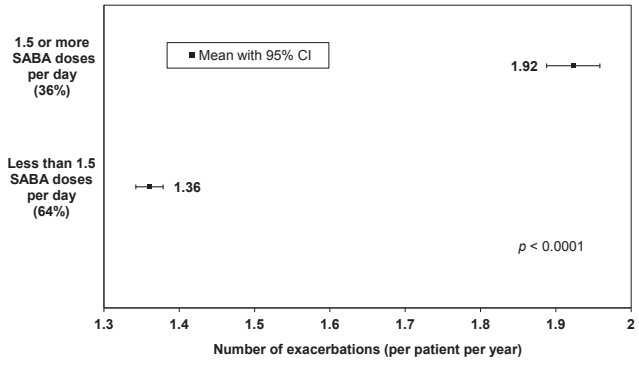

Figure 4 Mean exacerbations per patient per year using a cutoff of 1.5 doses of SABA (1 dose = 1 vial nebulized SABA or 2 puffs MDI SABA) in ORD and IMPACT™ combined, N = 66,004. CI = confidence interval; IMPACT™ = Impact National Benchmark Database; MDI = metered-dose inhaler; ORD = Optum Research Database; SABA = short-acting inhaled β_2-agonist.

Table 3 Costs per year (2010 $US) in the year post—index date for the ORD and IMPACT™ patient populations by SABA type and site of care.

	ORD			IMPACT™		
	<1.5 Doses/day	≥1.5 Doses/day	*p* Value	<1.5 Doses/day	≥1.5 Doses/day	*p* Value
Nebulized SABA only	*n* = 9306	*n* = 3148		*n* = 889	*n* = 199	
COPD-related total costs (PPY), mean (SD)	11,686.44 (32,707.21)	21,867.86 (53,910.13)	<0.001	10,577.25 (59,959.88)	16,566.24 (52,766.70)	0.159
Inpatient	9098.25 (31,796.54)	17,525.06 (52,651.21)	<0.001	8641.02 (59,336.42)	13,375.12 (52,238.79)	0.261
Emergency department	164.42 (773.45)	275.51 (1357.97)	<0.001	103.45 (429.68)	119.68 (380.58)	0.596
Outpatient	617.31 (2901.18)	898.03 (3968.39)	<0.001	398.72 (2281.05)	408.91 (2740.96)	0.961
Office visit	287.78 (1147.92)	350.69 (1238.97)	0.012	316.41 (383.44)	303.10 (396.55)	0.660
Other medical	957.68 (2110.92)	976.25 (1744.48)	0.625	386.20 (3144.25)	454.43 (1031.83)	0.595
Pharmaceutical	529.06 (935.51)	1782.58 (1832.27)	<0.001	702.55 (1090.45)	1859.73 (1787.89)	<0.001
MDI SABA only	*n* = 21,887	*n* = 8905		*n* = 5037	*n* = 1542	
COPD-related total costs (PPY), mean (SD)	7333.93 (24,853.49)	9216.39 (30,710.31)	<0.001	5094.99 (14,532.00)	5770.90 (12,399.49)	0.073
Inpatient	5230.52 (24,062.74)	5669.04 (29,960.33)	0.219	3303.97 (14,014.26)	2682.79 (11,851.05)	0.085
Emergency department	88.89 (479.17)	123.79 (657.60)	<0.001	77.09 (551.55)	94.59 (561.96)	0.278
Outpatient	633.16 (3074.86)	654.10 (2847.26)	0.568	417.08 (1925.19)	441.93 (1433.95)	0.585
Office visit	302.76 (659.36)	337.36 (729.35)	<0.001	278.73 (333.63)	325.31 (354.15)	<0.001
Other medical	238.89 (1162.34)	368.11 (1187.97)	<0.001	102.98 (636.45)	136.00 (837.16)	0.154
Pharmaceutical	819.66 (1041.91)	2038.81 (1475.96)	<0.001	901.21 (1115.54)	2074.52 (1479.51)	<0.001
Nebulized + MDI SABA	*n* = 4505	*n* = 8830		*n* = 764	*n* = 992	
COPD-related total costs (PPY), mean (SD)	11,232.65 (27,005.86)	15,805.73 (35,260.01)	<0.001	7952.04 (18,996.95)	12,534.35 (29,452.12)	<0.001
Inpatient	8166.61 (25,710.64)	10,689.88 (33,188.68)	<0.001	5503.74 (18,246.81)	8258.06 (28,518.52)	0.014
Emergency department	177.51 (657.46)	265.56 (1084.17)	<0.001	198.29 (839.23)	267.28 (1348.75)	0.189
Outpatient	816.41 (4547.45)	899.56 (3408.82)	0.279	401.87 (1292.00)	570.25 (1608.50)	0.015
Office visit	376.22 (490.62)	482.47 (755.71)	<0.001	349.78 (549.49)	477.91 (1376.11)	0.008
Other medical	693.04 (1425.61)	1065.84 (6605.16)	<0.001	386.67 (1844.45)	466.44 (1663.59)	0.349
Pharmaceutical	972.16 (1121.91)	2359.24 (1826.77)	<0.001	1089.97 (1191.29)	2460.16 (1851.53)	<0.001

COPD = chronic obstructive pulmonary disease; IMPACT™ = Impact National Benchmark Database; MDI = metered-dose inhaler; ORD = Optum Research Database; PPY = per patient year; SABA = short-acting inhaled β_2-agonist; SD = standard deviation.

COPD enrolled in several US commercial health plans and Medicare, respectively, did not receive any maintenance therapy [21]. Additionally, in our analysis, adherence to maintenance therapy (assessed by MPR) was generally poor. Relatively few patients had an MPR ≥ 0.80, which has been suggested as a reasonable long-term adherence threshold providing greater efficacy for inhaled drugs [22]. Patients using more doses of SABA (ie, those at greater risk of exacerbations) were more often receiving combination therapy and adhering to its use. However, sensitivity analyses indicated that performance characteristics for the 1.5 SABA doses/day threshold, which identified an increased risk of exacerbations, was not affected by concomitant medication use.

A major challenge for clinicians is deciding when to escalate therapy. Spirometry, while helpful in diagnosis and staging, continues to be underutilized, and even when it is performed, it does not help to determine disease stability. Questionnaires such as the COPD Assessment Test may be helpful but are underutilized [23]. Hence, there is a clear need for a simple, easy-to-use clinical marker to better guide patient care. For chronic asthma,

Table 4 SABA marker sensitivity and specificity.

	ORD (N = 56,581)				IMPACT™ (N = 9423)			
	Positive test count[a] (n)	Positive test probability[b] (%)	Sensitivity[c] (%)	Specificity[d] (%)	Positive test count[a] (n)	Positive test probability[b] (%)	Sensitivity[c] (%)	Specificity[d] (%)
Overall	20,883	36.91	44.31	67.97	2733	29.00	35.74	73.62
Commercially insured	10,277	34.85	43.52	70.08	2040	27.94	34.75	74.68
Medicare Advantage	10,606	39.15	45.04	65.38	693	32.66	39.05	69.93
Reference window of SABA use								
First 90 d post-index	21,075	37.25	42.68	66.33	2912	30.90	36.16	71.14
First 180 d post-index	22,192	39.22	45.50	64.91	2985	31.68	36.92	70.36
Concomitant medications								
ICS/LABA								
MPR $<$ 0.8	7131	40.89	47.97	65.21	1015	32.32	39.48	71.39
MPR $\geq$ 0.8	2657	59.75	66.72	45.21	421	44.64	54.91	59.58
LAMA (tiotropium)								
MPR $<$ 0.8	4800	41.31	48.01	65.76	631	33.30	39.55	70.52
MPR $\geq$ 0.8	2615	54.60	61.27	50.58	397	43.58	53.56	61.20
Age category (y)								
40–54	2414	30.18	39.49	74.35	552	24.75	31.27	77.30
55–64	5155	36.68	45.35	68.66	1025	28.50	36.81	74.82
65–74	6720	39.22	46.22	65.80	642	32.10	36.38	69.69
75+	6594	37.91	43.42	66.11	514	32.19	37.63	70.22

ICS = inhaled corticosteroid; IMPACT™ = Impact National Benchmark Database; LABA = long-acting inhaled β_2-agonist; LAMA = long-acting inhaled muscarinic antagonist; MPR = medication possession ratio; ORD = Optum Research Database; SABA = short-acting inhaled β_2-agonist.

[a] Number of patients with daily use above marker level.

[b] Percentage of patients with daily use above marker level.

[c] Percentage of patients with $\geq$2 exacerbations that have daily use above marker level.

[d] Percentage of patients with $<$2 exacerbations that have daily use below marker level.

the Rules of Two® were developed to assist patients and physicians with recognizing when to reevaluate maintenance therapy [24]. Similarly, the marker in our study serves as a proactive indicator for treatment reevaluation.

The large health care burden imposed by COPD is amplified by costs associated with poor disease control and exacerbations [25–27]. Our analysis revealed significantly higher health care costs in patients using $\geq$1.5 SABA doses/day. Overall, patients using nebulized (versus MDI) SABA had significantly higher health care costs, which may reflect higher disease severity in these patients. In ORD, health care costs were 87% higher for patients using $\geq$1.5 (versus $<$1.5) nebulized (only) SABA doses/day; health care costs were 26% higher for patients using $\geq$1.5 (versus $<$1.5) MDI (only) SABA doses/day.

There are limitations to this study. Information available in the databases was not sufficient to enable COPD severity categorization using GOLD-recommended approaches. However, the percentage of patients with $\geq$2 exacerbations in the assessment year, which varied from about 21% to 60% in the various subgroups included in the analysis, suggests that higher severity of COPD was common [28]. The nature of using pharmacy refills as an index of medication use limits time period analysis. However, sensitivity analyses showed that the 1.5 SABA doses/day threshold for identifying an increased risk of exacerbations worked well using follow-up periods shorter than 1 year, including periods as short as 90 days. In clinical practice, a 3-month period can be used easily during regular outpatient evaluations. This should reassure clinicians that using this threshold will be of clinical value, similar to the Rules of Two®, which are based on intensity of rescue inhaler use [13,24]. The marker has low sensitivity (but high specificity) in predicting future exacerbations. The sensitivity of the SABA marker could potentially be improved by taking into account other factors (eg, smoking and comorbidities), which also predict uncontrolled asthma [29]. Despite the lower than optimal sensitivity, the marker did predict future exacerbations among approximately 35% of those with SABA use above the 1.5 doses/day level. These represent potentially avoidable exacerbations if the patient therapy plan were reevaluated. The proposed use of the marker is to signal to physicians that reevaluation of current therapy may be

warranted; the consequence of the "intervention" for patients who were ultimately not at high risk for exacerbations (the "false positives") is minimal and may still lead to improved COPD management. Regarding potential limitations associated with the methodology, previously validated ICD-9-CM codes were used to identify exacerbations [30], although occasional coding errors are possible. Also, it is unknown whether our results would be similar in an uninsured population. To test any impact of the observational nature of the data on study results, ORD results were validated with IMPACT™.

Conclusion

Using a representative sample of the insured population of the United States, we developed a new tool that identifies a high-risk COPD population based on rescue medication use. We hope such a tool may be used to more effectively manage COPD and close the gap between clinical guidelines and clinical practice. Patients with COPD regularly using $\geq$1.5 SABA doses/day were at increased risk of exacerbations in our analysis and could benefit from treatment reevaluation. We recommend the "Rule of 3—2" (SABA use $\geq$3 times in 2 days) to be considered as an easily remembered and easily implemented tool to quickly evaluate the need for treatment reevaluation.

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Author contributions

AEA, JLK, and PRA contributed to conception and design. AEA and JLK contributed to the acquisition of data. AS, NAH, GLC, JFD, RR-R, and PRA provided feedback on the data. All authors contributed to the analysis and/or interpretation of data, revised the article critically for important intellectual content, and provided final approval.

Conflict of interest

AS has no conflicts of interest to disclose. NAH has received honoraria for serving on advisory boards or acting as a consultant for Sunovion, GlaxoSmithKline, Boehringer Ingelheim, Novartis, Pfizer, Mylan Specialty, L.P., and Pearl Therapeutics. His institution received research grant support from GlaxoSmithKline, Boehringer Ingelheim, Mylan Specialty, L.P., Sunovion, Novartis, and Pfizer. GLC has been a consultant, speaker, and advisory board member for Teva Pharmaceutical Industries LTD, Mylan Specialty, L.P., and Pearl Therapeutics. JFD serves as a consultant for Almirall, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Forest, Merck, Pfizer, Sunovion, Mylan Specialty, L.P., and Gilead and participates in Data Safety Monitoring Board activities for Novartis, Pneumrx, Otsuka, and Teva. AEA and JLK have no conflicts of interest to disclose. RR-R has lectured for Almirall, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Kyorin, Novartis, Pfizer, and UBC; consulted with Almirall, AstraZeneca, Boehringer Ingelheim, Foster, Merck, Sharp & Dome, Mylan Specialty, L.P., Novartis, Nycomed, Pearl Therapeutics, Procter & Gamble, Pfizer, and Teva Pharmaceutical Industries LTD; and received grant support from Almirall and Esteve always in relation to the general topic of COPD. He is a member of the GOLD Board of Directors and Science Committee. PRA was a full-time employee of Mylan Specialty, L.P., at the time that this analysis was performed.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2014.07.002.

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