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Short-acting β -agonist use and its ability to predict future asthma-related outcomes

Richard H. Stanford, PharmD, MS^{*}; Manan B. Shah, PharmD, PhD[†]; Anna O. D'Souza, BPharm, PhD[‡]; Amol D. Dhamane, BPharm, MS[†]; and Michael Schatz, MD, MS[‡]

^{*} GlaxoSmithKline, Research Triangle Park, North Carolina

[†] Xcenda, Palm Harbor, Florida

[‡] Kaiser Permanente Medical Center, San Diego, California

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ABSTRACT

Background: Short-acting β -agonist (SABA) use is well established in predicting asthma events in adults. However, this predictive ability has yet to be established in a pediatric population together with an assessment of amount of use.

Objective: To identify the number of SABA canisters that best predicts future asthma-related exacerbations and the optimal length of time for measurement of SABA use in pediatric and adult asthma patients.

Methods: Asthma patients were identified from a Medicaid and a commercially insured database (January 1, 2004, through December 31, 2005, and January 1, 2004, through June 30, 2006, respectively). Following the date of first asthma medication, an assessment period (3, 6, or 12 months) was used to measure SABA use. Asthma-related exacerbations were identified in the subsequent 12-month period. Receiver operating characteristic curve analyses and logistic regression were used to select the critical values of SABA use and optimal assessment periods and to conduct incremental analysis, respectively.

Results: A total of 33,793 Medicaid and 101,437 commercial patients met the study criteria. Use of 3 or more SABA canisters during 12 months was identified in both pediatric Medicaid and commercial populations to best predict an increased risk of an asthma-related exacerbation. For adults, use of 2 or more SABA canisters was found as the critical value with shorter optimal assessment periods of 3 and 6 months. Each additional SABA canister resulted in an 8% to 14% and 14% to 18% increase in risk of an asthma-related exacerbation in children and adults, respectively.

Conclusion: The study identified critical values of SABA use that predict future asthma events. Each additional SABA canister predicted increases in exacerbation risk in children and adults.

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Introduction

Asthma is a common, chronic disease in the United States, with more than 22 million people diagnosed as having the condition in 2009.^{1,2} Sudden increases in severity of its symptoms may require emergency care or a hospitalization.¹ Asthma symptoms are often managed using long-term controller medications and quick-relief medications.³ Short-acting β -agonists (SABAs) are used to provide prompt symptomatic relief.^{4–6}

Asthma management techniques often use quality-of-care measures, developed using administrative claims data, which are helpful in predicting subsequent asthma-related outcomes.^{7–10} One

such measure is SABA dispensing to identify high-risk patients. The SABA measure is ideal for risk stratification because SABAs are used as rescue medications and elevated SABA use is considered a sign of uncontrolled asthma.³ Long-term (controller) asthma medications may prevent future asthma-related adverse outcomes.

SABA use, as a predictor of future asthma-related outcomes, usually has been measured during assessment periods of 3 or 12 months.^{8,9,11,12} The length of assessment periods affects the SABA threshold as a risk marker.

The predictive ability of SABAs has been assessed to a limited extent in pediatric and Medicaid populations.^{9,11,13–15} The need for additional investigation is justified because of a high prevalence of asthma in children. More than 25% of Americans with asthma are children.² Further, Medicaid patients—who tend to be of lower socioeconomic status, younger age, and female sex—have increased likelihood of experiencing asthma-related adverse events.^{16–20} In addition, Medicaid patients are reported to have poorer asthma control compared with those with private insurance or those who are uninsured.²⁰

Reprints: Anna O. D'Souza, BPharm, PhD, 8310 Tidewater Ct, Cincinnati, OH 45255; E-mail: anna.d'souza@xcenda.com.

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The study objective was to assess whether SABA dispensing can be used to predict future asthma outcomes in children and adults in Medicaid and commercial populations. This study explored the critical number of SABA canisters and the optimal time during which SABA use should be measured in relation to asthma exacerbation risk. In addition, it evaluated the incremental effect on the risk of asthma outcomes with each additional SABA canister.

Methods

Study design and population

This study had a retrospective cohort design and used two claims databases: the Ingenix Impact National Managed Care Database (commercial) and the MarketScan Medicaid Database (Medicaid). January 1, 2003, through June 30, 2008, data were used from the commercial database, and January 1, 2003, through December 31, 2007, data were used from the Medicaid database. The commercial database used the integrated medical and pharmacy administrative claims of more than 98 million lives from more than 46 different health care plans that spanned 9 US Census regions. The Medicaid database used nearly 7 million Medicaid enrollees across 8 states.

Patients with at least one pharmacy claim for asthma medication, excluding oral corticosteroids (OCSs), were identified. The index date was defined as the first chronologically occurring pharmacy claim for any asthma medication (inhaled corticosteroids [ICSs], long-acting β -agonists [LABAs], ICSs and LABA combination product, leukotriene modifiers, cromolyn sodium, nedocromil, methylxanthines, omalizumab, and SABAs) from January 1, 2004, through June 30, 2007, for commercial patients and January 1, 2004, through December 31, 2005, for Medicaid patients.

Following the index date, an assessment period was used to measure SABA use. The assessment period was varied for all patients (3, 6, or 12 months) to allow for evaluation of the optimal assessment period. Outcomes were computed in the subsequent 12-month period after the end of the assessment period.

The 1-year period before the index date (preindex period) was used for baseline assessments. Eligible patients met the following criteria: (1) age of 4 years or older on index date; (2) asthma diagnosis (at least one claim with an International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnosis code for asthma [493.xx] in any diagnosis field during

the preindex period or 30 days after the index date); (3) continuously enrolled to receive medical and pharmacy benefits in the preindex and 24-month postindex periods; and (4) absence of diagnosis of chronic obstructive pulmonary disease (COPD) (491.xx, 492.xx, 496.xx) anytime during the preindex and post-index periods.

SABA use

SABA use was quantified as the number of SABA canisters dispensed in the assessment period assuming that dispensed canisters were used. The number of canisters for inhaled formulations was calculated using the ratio of quantity to package size, whereas canister equivalents were computed for nebulized formulations. The canister-equivalent calculation was based on a comparison of the number of SABA doses in nebulized form to the number of SABA doses in inhaled form.

Study outcomes

The primary outcome was an asthma exacerbation, defined as an emergency department (ED) visit with a primary diagnosis of asthma (ICD-9-CM 493.xx) or a hospitalization with a primary discharge diagnosis of asthma. Asthma exacerbations were also alternately defined as follows: (1) an ED visit alone with a primary diagnosis of asthma, (2) a hospitalization alone with a primary discharge diagnosis of asthma, and (3) an OCS-dispensing event defined as a claim for an OCS prescription. All outcomes were measured during the 12-month follow-up period.

Statistical analysis

The final study sample for both commercial and Medicaid populations was split into pediatric (age range, 4–17 years) and adult (age range, ≥ 18 years) cohorts. A receiver operating characteristic (ROC) curve analysis was performed to select the critical number of SABA canisters and an optimal assessment period (3, 6, or 12 months) that could distinguish between patients with and without the primary outcome. This analysis was chosen because it provides indices of the area under the curve (AUC), sensitivity, and specificity for every possible threshold that can be used to assess optimal models. This analysis entailed comparing the AUCs obtained from the c-statistic of the logistic regression model for each level of SABA use within each assessment period.

Table 1
Baseline characteristics of study sample

Characteristics	Medicaid		Commercial	
	Children (4–17 years) n = 25,048	Adults (≥ 18 years) n = 8,745	Children (4–17 years) n = 41,753	Adults (≥ 18 years) n = 59,684
Demographics				
Age (mean, SD)	9.3 (3.9)	39.7 (16.2)	10.1 (4.0)	43.6 (13.3)
Male (n, %)	13,703 (54.7%)	1,654 (18.9%)	23,414 (56.1%)	21,473 (36.0%)
Clinical characteristics in pre-index period				
Charlson index in pre-index period (mean, SD)	0.1 (0.4)	0.9 (1.5)	0.1 (0.3)	0.4 (1.0)
Number of unique diagnoses (mean, SD)	6.9 (4.5)	13.2 (8.4)	5.8 (4.1)	8.5 (6.8)
Number of prescription drug categories (mean, SD)	5.4 (3.2)	11.3 (6.7)	3.4 (2.0)	5.5 (3.8)
Number of prescriptions filled (mean, SD)	5.9 (3.8)	12.8 (8.2)	3.6 (2.2)	5.9 (4.2)
Asthma severity in the assessment period				
Presence of asthma-related hospitalization (n, %)				
3 month	131 (0.5%)	67 (0.8%)	168 (0.4%)	324 (0.5%)
6 month	183 (0.7%)	85 (1.0%)	212 (0.5%)	396 (0.7%)
12 month	271 (1.1%)	115 (1.3%)	286 (0.7%)	548 (0.9%)
Presence of asthma-related ED visit (n, %)				
3 month	1,964 (7.8%)	1,177 (13.5%)	1,916 (4.6%)	3,284 (5.5%)
6 month	2,255 (9.0%)	1,287 (14.7%)	2,159 (5.2%)	3,531 (5.9%)
12 month	2,788 (11.1%)	1,483 (17.0%)	2,626 (6.3%)	4,081 (6.8%)

Abbreviations: ED, emergency department; SD, standard deviation.

Table 2
SABA use

Number of SABA canisters	Children (4–17 years)						Adults (≥18 years)					
	MARKER PERIOD						MARKER PERIOD					
	3 months		6 months		12 months		3 months		6 months		12 months	
Medicaid	n = 25,048						n = 8,745					
Mean (SD)	1.03	(0.90)	1.24	(1.18)	1.72	(1.86)	1.04	(1.06)	1.28	(1.57)	1.82	(2.71)
Number of patients (%)												
≥1 canister	27,540	66.0%	28,968	69.4%	31,352	75.1%	43,814	73.4%	45,071	75.5%	47,060	78.8%
≥2 canister	7,411	17.7%	10,382	24.9%	15,796	37.8%	9,277	15.5%	13,097	21.9%	19,460	32.6%
≥3 canister	1,518	3.6%	3,233	7.7%	7,306	17.5%	3,444	5.8%	5,855	9.8%	10,121	17.0%
Commercial	n = 41,753						n = 59,684					
Mean (SD)	1.20	(1.09)	1.48	(1.49)	2.05	(2.29)	1.18	(1.01)	1.50	(1.55)	2.12	(2.66)
Number of patients (%)												
≥1 canister	17,447	69.7%	18,048	72.1%	19,067	76.1%	6,962	79.6%	7,071	80.9%	7,275	83.2%
≥2 canister	6,190	24.7%	8,186	32.7%	10,915	43.6%	1,921	22.0%	2,643	30.2%	3,628	41.5%
≥3 canister	1,682	6.7%	3,296	13.2%	6,130	24.5%	671	7.7%	1,236	14.1%	2,068	23.7%

Abbreviation: SABA, short-acting β -agonist; SD, standard deviation.

The logistic regression models predicted the likelihood of the primary outcome and controlled for baseline characteristics computed in the preindex period (age, sex, Charlson comorbidity index, number of unique diagnoses codes, number of unique prescription drug categories, number of unique prescriptions filled, and asthma severity (presence of asthma-related hospitalizations or ED visits or number of OCS-dispensing events) during the assessment period. Higher AUCs for ROC curves have been found to reflect better discrimination between persons with and without the outcome.²¹ Accordingly, for the current study, the model with the highest AUC and having a statistically significant effect of the cutoff value of the SABA marker was considered in selecting the critical cutoff within an assessment period. After selecting the critical cutoff within each assessment period, the choice of an assessment period was based on a statistical comparison of the AUCs of the models selected for each of the 3 assessment periods. The following steps were used for this comparison. The highest AUC was compared with the lowest. If the difference was not statistically significant, then the shorter assessment period was chosen with its respective cutoff. If, however, the difference was statistically significant, then the comparison was repeated with the next-lowest AUC.

Multivariable logistic regression models that controlled for baseline characteristics were used to predict the odds of reported asthma exacerbations during the follow-up period. Adjusted odds

ratios (ORs) with corresponding 95% confidence intervals (CIs) are presented.

The effect of the incremental change in SABA use on the odds of the primary outcome—asthma exacerbations—was evaluated using a linear trend test and a graphic analysis showing increasing or decreasing OR value with increase in SABA use. If a linear relationship was found, SABA use was entered into a logistic regression model as a continuous variable adjusting for baseline covariates. The OR was then interpreted as the percentage change in risk of the primary outcome with each additional SABA canister dispensed.

Results

The sample that met study criteria consisted of 33,793 Medicaid patients (25,048 children and 8,745 adults) and 101,437 commercial patients (41,753 children and 59,684 adults). A demographic description of the study sample is provided in Table 1. Approximately two-thirds of the pediatric and three-fourths of the adult sample were using 1 or more SABA canister in all assessment periods in both the Medicaid and commercial populations (Table 2), respectively.

ROC analysis

Table 3 lists the AUCs obtained from the logistic regression models for each cutoff (≥1 to ≥6 canisters) in both the Medicaid

Table 3
Area under the ROC curve for the SABA use predicting the risk of asthma-related hospitalization or ED visit in the 12-month follow-up period

Number of SABA canisters	Children (4–17 years)			Adults (≥18 years)		
	Assessment periods			Assessment periods		
	3-month	6-month	12-month	3-month	6-month	12-month
Medicaid						
≥1	0.680	0.697	0.719	0.684	0.690	0.695
≥2	0.677	0.699	0.718	0.693	0.699	0.708
≥3	0.677	0.695	0.721	0.689	0.699	0.707
≥4	0.674	0.693	0.721	0.684	0.698	0.701
≥5	0.674	0.693	0.719	0.683	0.693	0.700
≥6	0.674	0.693	0.715	0.684	0.692	0.696
Commercial						
≥1	0.663	0.673	0.704	0.687	0.703	0.715
≥2	0.673	0.683	0.720	0.703	0.724	0.739
≥3	0.674	0.687	0.722	0.698	0.722	0.734
≥4	0.665	0.683	0.717	0.694	0.715	0.729
≥5	0.664	0.678	0.711	0.692	0.711	0.729
≥6	0.663	0.678	0.709	0.690	0.707	0.726

Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic; SABA, short-acting β -agonist.

Values in bold are highest AUCs for each marker period; and values in italics indicate AUC of critical level of SABA use and corresponding assessment period.

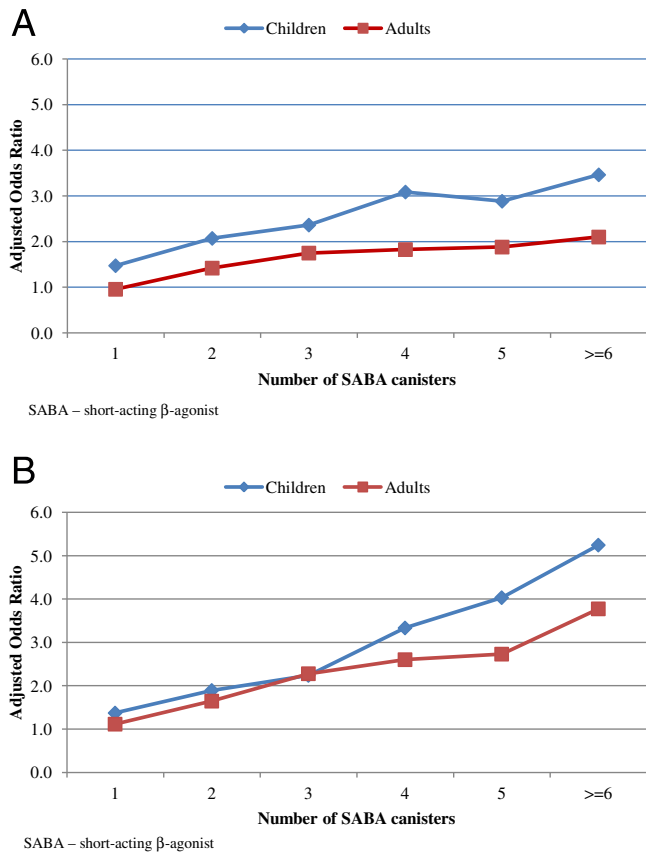


Fig. 1. (A) Odds of Asthma-related Hospitalization or emergency department visit by number of SABA canisters - Medicaid. (B) Odds of asthma-related hospitalization or emergency department visit by number of SABA canisters - Commercial.

and commercial population for children and adults. The AUCs ranged from 0.66 to 0.72 for children and 0.68 to 0.74 for adults. Within each assessment period, the highest AUC value is set in bold, indicating that the corresponding cutoff best discriminates between patients with and without an asthma-related hospitalization or ED visit during follow-up compared with the other cutoff values. The next step was the selection of the optimal of the 3 assessment periods (3 vs 6 vs 12 months). The optimal assessment period was chosen by statistical comparisons of the highest AUCs of each assessment period as described in the “Methods” section. For instance, in Medicaid children, comparisons of AUCs between 3- and 12-month assessment periods revealed a statistically significant difference ($P < .001$). Subsequent comparisons between 6- and 12-month assessment periods also revealed a statistically significant difference ($P = .04$). The 12-month assessment period

was therefore chosen as the optimal assessment period corresponding to 3 or more SABA canisters as the critical threshold in the pediatric Medicaid population. Within each population in Table 3, AUCs highlighted in gray indicate the optimal assessment period and corresponding critical number of SABA canisters.

Incremental risk analysis

An incremental effect was observed in the risk of hospitalization or ED visit during follow-up with each additional SABA canister in Medicaid children and adults. The incremental risk was more pronounced in children and leveled off for adults after the critical value of SABA canisters (Figure 1a). Overall, each additional SABA canister used in Medicaid patients resulted in 8% (OR, 1.08; 95% CI, 1.06–1.10) and 14% increased risk (OR, 1.14; 95% CI, 1.08–1.21) in children and adults, respectively. Similarly, in the commercial population, each additional SABA canister dispensed saw an increase in risk for both children and adults (Figure 1b), with a 14% (OR, 1.14; 95% CI, 1.11–1.16) and 18% (OR, 1.18; 95% CI, 1.16–1.21) increased risk in children and adults, respectively.

Predictive ability of SABA use on outcomes

The critical number of SABA canisters measured during the optimal assessment periods (listed in Table 4 for each population) conferred an approximately 2-fold increase in the risk of an asthma exacerbation defined as an asthma-related hospitalization or ED visit in children and adults in both the Medicaid and commercial populations. The magnitude of effect was slightly higher in the commercial than the Medicaid population (2.2 vs 1.8). Similar results were found when the components of the primary outcome were individually analyzed (ie, hospitalization alone or ED visit alone).

The number of SABA canisters was also found to significantly predict the probability of receiving OCSs in the subsequent year (Table 4). A greater effect was seen in children than adults in both the Medicaid and commercial populations. Medicaid children receiving 3 or more canisters per year had a 38% (OR, 1.38; 95% CI, 1.28–1.50) increased risk of being dispensed OCSs compared with those using fewer than 3 canisters. Medicaid adults had critical thresholds of 2 or more canisters per quarter, which was associated with a 15% (OR, 1.15; 95% CI, 1.03–1.28) higher risk compared with those using 1 or fewer canisters per quarter.

Discussion

The current study assessed the role of SABA use to predict subsequent asthma-related outcomes. Approximately a 2-fold increase in the risk of an asthma-related hospitalizations or an ED visit in the subsequent year for both the Medicaid and commercial populations was noted for patients using 3 or more SABA canisters per year (children) and 2 or more SABA canisters (adults) per

Table 4
Relationships of critical SABA use values to asthma-related outcomes in the 12-month follow-up period

Cohort	Critical SABA use and optimal assessment period	Asthma-related Exacerbations ^a			
		Hospitalization/ED visit	Hospitalization	ED visit	OCS-dispensing event
Medicaid					
Children (n = 25,048)	≥3 in 12 months	1.80 (1.60, 2.02) ^b	1.84 (1.36, 2.51) ^b	1.78 (1.57, 2.01) ^b	1.38 (1.28, 1.50) ^b
Adults (n = 8,745)	≥2 in 3 months	1.84 (1.57, 2.15) ^b	1.84 (1.18, 2.85) ^b	1.81 (1.53, 2.13) ^b	1.15 (1.03, 1.28) ^b
Commercial					
Children (n = 41,753)	≥3 in 12 months	2.23 (1.94, 2.56) ^b	2.63 (1.85, 3.74) ^b	2.16 (1.87, 2.49) ^b	1.60 (1.49, 1.71) ^b
Adults (n = 59,684)	≥2 in 6 months	2.21 (1.98, 2.47) ^b	2.08 (1.64, 2.65) ^b	2.23 (1.98, 2.50) ^b	1.45 (1.38, 1.53) ^b

Abbreviations: ED, emergency department; OCS, oral corticosteroid; SABA, short-acting β-agonist.

^aValues are odds ratio (95% confidence interval). Reference group is category below the cutoff.

^b $P < 0.05$.

quarter when compared with patients using fewer than 3 and fewer than 2 SABA canisters, respectively.

Our findings are consistent with previously published data.^{8,9,11,12} Silver et al⁹ found that patients with excessive SABA use (>3 SABA canisters per year) had at least a 3-fold increase in the likelihood of hospitalization or ED visit compared with patients using 3 or fewer SABA canisters. Paris et al⁸ reported a high likelihood of asthma-related hospitalization (20-fold increase) per unit increase in SABA use per day.

In other studies, significant associations were found at higher levels of SABA use (≥ 11 and > 14 SABA canisters).^{12,22} Differences in definitions, methods for selecting the thresholds, and populations may explain these ranges.⁹ The current study sample included patients with 1 or more asthma diagnosis and asthma medication, thus possibly including patients with intermittent asthma, whereas some of the prior studies have selected patients with persistent asthma based on Healthcare Effectiveness Data and Information Set criteria.²³ Critical thresholds in the present study were selected from a range of 1 or more to 6 or more SABA canisters because only a small proportion of patients used 7 or more SABA canisters. In a prior study, the critical value (cutoff) was chosen if the largest risk reduction was found at a particular level of SABA use. The rationale for this method was finding significant risk reduction at each critical level of SABA use analyzed (4–12 canisters).¹²

This study is unique in that we first identified optimal assessment periods (3, 6, and 12 months) in which SABA dispensing was measured, as opposed to the fixed assessment periods used in previous research. In the current study, the pediatric cohort had a longer optimal assessment period (12 months) compared with the adult cohort (3 or 6 months). The shorter optimal assessment periods for adults suggests that a shorter recall period can be used for adults compared with children at the time of assessment to permit timely intervention in patients with excess SABA use.

This study provides key information on SABA use as a risk predictor in pediatric and Medicaid populations. Validation in the Medicaid population extends the potential utility of the SABA marker to a population with lower socioeconomic status, who experience poorer asthma outcomes. Identification of patients needing intervention based on exceeding the critical SABA canister thresholds during optimal assessment periods defined in the current study could also help improve outcomes.^{7,13,15,22,24}

This study has potential limitations. First, an effect of unmeasured confounders on likelihood of future asthma-related outcomes cannot be excluded. Second, SABA use may be overestimated because pharmacy claims for filled prescriptions do not indicate that the medication was taken as prescribed. Third, presence of miscoding or undercoding of diagnoses in administrative claims data may occur. However, these coding errors would be consistent across comparison groups and therefore should not produce substantial misclassification bias.

In summary, the current study provides important data revealing associations between SABA canister dispensing and subsequent asthma exacerbations associated with asthma-related hospitalizations and ED visits. This study further emphasizes the need for careful monitoring of patients with asthma and identifying patients receiving SABAs at levels greater than the study-derived critical thresholds. Further investigation is needed to better understand whether clinical use of these thresholds will improve outcomes.

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