

Clinical Outcomes of Levalbuterol Versus Racemic Albuterol in Pediatric Patients With Asthma: Propensity Score Matching Approach in a Medicaid Population

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Summary. Objective: Racemic albuterol and levalbuterol are used to treat acute episodes of asthma. The main objective of this study was to compare levalbuterol therapy to albuterol therapy on incidence rates of subsequent emergency department (ED) visits and hospitalizations. Method: We conducted a retrospective cohort study of asthmatic children who had pharmacy refills for levalbuterol/albuterol in the South Carolina Medicaid database in 2002–2011. Children receiving levalbuterol were matched to those receiving albuterol using propensity score matching technique. For ED visits and separately for hospitalizations, multivariable negative binomial regression was used to estimate the two group-specific incidence rates and the incidence rate ratio (IRR). Results: A total of 8,172 asthmatic patients aged 2–18 years were identified in the South Carolina Medicaid database. During the 12-month follow-up period, the levalbuterol group had fewer asthma-related ED visits and hospitalizations: 939 (11.49%) children had asthma-related ED visits (levalbuterol: 8.76%; albuterol: 14.21%), and 89 (1.09%) children had asthma-related hospitalizations (levalbuterol: 1.07%; albuterol: 1.12%). Comparing the levalbuterol group to the albuterol group, the adjusted IRR estimate was 0.57 (95% confidence interval [CI], 0.49–0.65) for asthma-related ED visits, and 0.93 (95%CI, 0.99–1.63) for hospitalizations. Children filling levalbuterol also had a lower IRR of all-cause ED visit (0.88; 95%CI, 0.82–0.95), but similar IRR of all-cause hospitalizations (1.08; 95%CI, 0.82–1.42). Conclusion: This observational study of children aged 2–18 demonstrated levalbuterol prescription fills were associated with reduced ED visits, but not hospitalizations. Additional research may be necessary to assess this association. **Pediatr Pulmonol.** © 2016 Wiley Periodicals, Inc.

Key words: asthma; levalbuterol; albuterol; pediatric; Medicaid.

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BACKGROUND

Asthma affects more than 7 million children in the United States (U.S.) and is a leading cause of emergency and inpatient care with a substantial economic impact in the U.S.¹ In the National Surveillance for Asthma conducted by the Centers for Disease Control and Prevention (CDC), asthma was responsible for 439,000 hospitalizations and 1.8 million Emergency department (ED) visits, and cost approximately \$50.1 billion annually.²

Short-acting β_2 -agonists—racemic albuterol and levalbuterol—are commonly prescribed and considered as the most effective bronchodilators for treating acute episodes of asthma and preventing exercise-induced bronchoconstriction.³ Racemic albuterol is a mixture of equal parts of (R)- and (S)-albuterol stereoisomers. (R)-enantiomer, also known as levalbuterol, binds to beta2-adrenergic receptors and produces bronchoprotective and bronchodilatory effects. The effects of (S)-albuterol are still controversial.⁴ In *in vitro* studies, (S)-albuterol was reported to enhance airway hyper-responsiveness, leading to opposing the therapeutic effects of (R)-albuterol.^{5,6} However, some *in vivo* studies failed to support this antagonistic effect.^{7–9} Recently published studies suggest additional conflicting results when the effects of levalbuterol to racemic albuterol on lung functions among adults with asthma are assessed. Several studies demonstrated the superior efficacy or effectiveness of levalbuterol,^{10,11} while other studies suggested similar effects compared to racemic albuterol.^{12,13} Data for children ages 2–18-year-old are limited and inconsistent in the clinical effects of levalbuterol and racemic albuterol, due to the specialty of pediatric patients.^{12,14,15} Possible reasons for these inconsistent results include small sample size and different sample selection criteria.

Recently, American Thoracic Society/European Respiratory Society's taskforce recommended using unscheduled use of health care (i.e., ED visits, hospitalization admissions) as an indirect clinical outcome measure in clinical trials and practices.^{16,17} The loss of asthma control may result in unscheduled ED visits or hospitalizations, which have significant clinical and economic implications. Hence, ED visits or hospitalizations can serve as surrogate measures for asthma control in population-based studies, because direct clinical measures may not be available on a population level.¹⁷ However, few studies have evaluated the relative effect of levalbuterol and albuterol on ED visits and hospitalizations. Considering the high frequency of exacerbations among children, additional studies are necessary to better understand the clinical effectiveness of levalbuterol compared to albuterol at a population level. Our study compared the clinical effects of racemic albuterol and levalbuterol in terms of asthma-related hospitalizations and ED visits in pediatric patients with asthma.

METHODS

Study Design

We conducted a population-based retrospective cohort study using South Carolina (SC) Medicaid fee-for-service data between January 1, 2002 and December 31, 2012. The index date was defined as the first recorded date that a prescription was filled for levalbuterol or albuterol. A 12-month period before the index date was used to identify baseline characteristics, including demographic and clinical characteristics. The follow-up period for each patient was defined as the 12-month period after the index date. Pharmacy fills of prescription medication, albuterol, and levalbuterol, was identified in the pharmacy claims using National Drug Code (NDC), brand name and generic name. Health conditions, that is, asthma, were identified in the Medical claims using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes. Since this study is a retrospective study analyzing de-identified administrative claims, it is exempted from Institutional Review Board (IRB) review.

Cohort Selection

Patients were included in the cohort if they met all of the following criteria: (1) at least one pharmacy claim of levalbuterol or albuterol between January 1, 2003 and December 31, 2011; (2) with a diagnosis of asthma using ICD-9-CM code (493.xx) before or on the index date; (3) aged 2–18 years old on the index date; and (4) continuously enrolled in SC Medicaid Fee-For-Service during baseline and follow-up period.

Patients were excluded from the analysis due to one of the following reasons: prescription for ipratropium inhalation, which is used as a quick-relief medication for asthma; or having primary or secondary diagnosis of COPD (491, 492, 493.2, 494, 496, 770.2); or filling both levalbuterol and albuterol during follow-up period.

Clinical Outcomes

The outcomes of interest were the number and occurrences of asthma-related ED visits and hospitalizations from the index date to the end of follow-up period. Asthma-related medical claims were defined as those claims with asthma diagnosis listed as primary diagnosis (ICD-9-CM code 493.xx). The number of ED visits and hospitalizations were counted for each patient. Separate analyses were performed for ED visits and hospitalizations.

Potential Confounders

The possible confounding factors included age (2–4, 5–11, 12–17 years), gender (female, male), race (whites,

blacks, others), time since initial asthma diagnosis (0–1 and >1 year), year of index date (2002–2004, 2005–2007, 2008–2011), and proxies for asthma severity that was reflected by the use of systemic corticosteroid and prior asthma-related ED visits or hospitalizations.¹⁸ This measure of asthma severity has been adopted in observational studies.¹⁸ The occurrences of ED visits or hospitalizations during the baseline period were controlled in the analysis because it may be a confounder. Systemic corticosteroid includes methylprednisolone, prednisolone, prednisone, methylprednisolone, dexamethasone, and hydrocortisone. We also measured the use of other concomitant asthma medications, including inhaled corticosteroids (beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone, fometasone), long acting beta agonists (arformoterol, formoterol fumarate, salmeterol xinafoate), and combination products (e.g., fluticasone/salmeterol, budesonide/formoterol).

Statistical Analysis Strategy

Baseline covariates that may have influenced both the choice of treatment (levalbuterol versus albuterol) and the clinical outcomes were identified as potential confounding factors. To minimize bias due to confounding, propensity score matching was then performed.¹⁹ First, patient-specific propensity scores were estimated by fitting a logistic regression model which expressed the odds of being prescribed levalbuterol (instead of albuterol) in terms of a linear function of the selected baseline covariates: age, gender, race, time since initial asthma diagnosis, year of index date, proxies for asthma severity (e.g., the use of systemic corticosteroid, prior asthma-related ED visits, and hospitalizations). Levalbuterol-albuterol pairs of patients with matching propensity scores were formed via a greedy matching algorithm. Residual unmatched patients were excluded. This “design stage” of the analysis strategy was intended to produce comparable treatment groups balanced in terms of the distributions of the baseline covariates. Comparability was assessed via diagnostic methods that included side-by-side boxplots, distribution comparisons via density estimation. Balance was evaluated by comparing the standardized differences, which was calculated as the difference in proportion between two groups divided by the pooled standard deviation of the covariate’s distribution.²⁰ A standardized difference <10% was considered as a good balance in covariates between groups.¹⁹

The levalbuterol and albuterol groups were compared in terms of distributions of patient characteristics: age, sex, race, concomitant asthma medications, time since initial asthma diagnosis, year of the patient’s index date, and the number of prior ED visits and hospitalizations during the baseline period. Comparison of the two

treatment groups, levalbuterol versus albuterol, in terms of the ED visit incidence rate (visits/year) relied on a multivariable negative binomial regression model for the ED visit because of the over-dispersion of count data. The squares of the SD values in Table 2 are larger than the tabulated means, indicating that a negative binomial regression model may fit the data better than the Poisson regression model that was fitted initially. The regression equation included age, gender, race, time since initial asthma diagnosis, year of index date, and proxies for asthma severity as covariates. Since recent studies have shown the benefits of combining propensity score matching and outcome regression models, the outcome regression models used the covariates from the propensity score estimation models.²¹ A similar negative binomial regression model was fitted separately for hospitalizations. All statistical computations were performed using SAS software, version 9.3 (SAS Institute, Cary, NC).

To evaluate the robustness of the main results to reasonable perturbations of the statistical methods and assumptions, we conducted sensitivity analyses which included the following: 1) To investigate the impact of coding inaccuracies in claims, we performed comparable analyses in which the outcomes were all-cause ED visits and all-cause hospitalizations. 2) To investigate the impact of excluding patients who could not be matched on their propensity scores, we used inverse-probability-of-treatment weighting (instead of matching) to re-fit the Poisson regression and the negative binomial models with all eligible subjects included. 3) We also fit the Poisson regression models and the negative binomial models without the covariates included in the models.

RESULTS

We identified 4,086 children filling levalbuterol and 26,092 children filling albuterol in SC Medicaid database during 2002–2012 (Fig. 1). After propensity score matching, there were a total of 9,612 asthmatic children, with 4,806 in levalbuterol group and 4,806 in albuterol group. Side by side box-plots demonstrate well overlapped distribution of propensity score between two groups. In addition, the standardized differences of measured covariates were reduced below 5% in absolute value, suggesting substantial improvement in covariate balance across the treatment groups. The two groups were well-balanced on all the baseline covariates (Table 1).

ED Visits

During the 12-month follow-up period, a total of 939 (11.49%) children had asthma-related ED visits. There were 358 (8.76%) children who used ED services in levalbuterol group, and 581 (14.22%) children in the

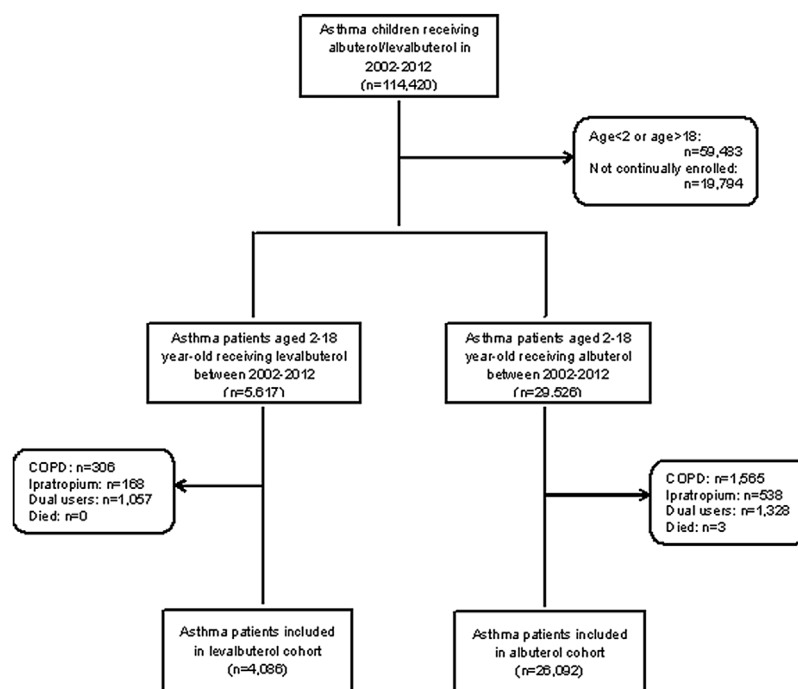


Fig. 1. Attrition flow chart of cohort selection.

albuterol group. During 1-year follow-up period, children filling levalbuterol had a lower mean number of ED visits than those receiving albuterol (Table 2, 0.11 vs. 0.19). After adjustment for potential confounders mentioned above, the adjusted incidence rate ratio (IRR) for asthma-related ED visits was 0.57 (95% confidence interval [CI], 0.49–0.65) for children filling levalbuterol compared with those filling albuterol (Table 3).

In the sensitivity analysis, the average number of all-cause ED visits was lower in children receiving levalbuterol than in the albuterol group (Table 2, 0.62 vs. 0.70). The IRR of all-cause ED visits was 0.88 (Table 4, 95%CI, 0.82–0.95) for children filling levalbuterol compared with those filling albuterol. The unadjusted IRR of asthma-related ED visit was 0.58 (Supplement Table S1; 95%CI, 0.51–0.67), which is similar to the adjusted IRR in the main analysis. The IRR obtained from inverse-probability-of-treatment weighting was 0.55 (95%CI, 0.47–0.63).

Children aged 5–11 years had lower IRR of asthma-related and all-cause ED visits than those aged 2–4 years. Patients filling systemic corticosteroids had similar IRR for both asthma-related and all-cause ED visits compared to those who did not fill these medications. Children who had asthma-related ED visits in the baseline were more likely to visit ED during follow-up.

Hospitalizations

There were a total of 89 (1.09%) children with asthma-related hospitalizations during the 12 month follow-up

period with 43 (1.05%) children in levalbuterol group and 46 (1.13%) in albuterol group. Children filling levalbuterol and albuterol had the same mean number of asthma-related hospitalizations during 12-month follow-up period (Table 2). For children filling levalbuterol, after controlling for potential confounders, the adjusted IRR of asthma-related hospitalizations was 0.93 (Table 3, 95%CI, 0.61–1.41), compared with those filling albuterol.

In the sensitivity analysis, children filling levalbuterol had slightly higher number of all-cause hospitalizations than those filling albuterol (Table 2, 0.044 vs. 0.042). The adjusted IRR of all-cause hospitalizations was 1.08 (Table 4, 95%CI, 0.82–1.42). The unadjusted IRR of asthma-related hospitalization was 0.92 (Supplement Table S1; 95%CI, 0.60–1.40), which is similar to the adjusted IRR in the main analysis. The IRR obtained from inverse-probability-of-treatment weighting was 0.85 (95%CI, 0.62–1.16).

Children aged 12–17 years had higher IRR of all-cause hospitalizations and asthma-related hospitalizations. Female patients had similar IRR of asthma-related and all-cause hospitalizations compared to their male counterparts. Patients filling systemic corticosteroids had similar IRR for both asthma-related and all-cause hospitalizations compared to those who did not receive these medications. Children who had asthma-related hospitalizations in the baseline had higher IRR for both asthma-related and all-cause hospitalizations compared to those without prior hospitalizations.

TABLE 1—Characteristics of Asthmatic Children Receiving Levalbuterol/Albuterol in SC Medicaid¹

Characteristics	Levalbuterol (n = 4,086)		Albuterol (n = 4,086)		Std.Diff. (%) ²
	n	%	n	%	
Age, %					
2–4 years	2,330	57.0	2,328	57.0	0.1
5–11 years	1,454	35.6	1,460	35.7	–0.3
12–17 years	302	7.4	298	7.3	0.4
Sex, %					
Male	2,217	54.3	2,224	54.4	–0.3
Female	1,869	45.7	1,862	45.6	0.3
Race					
Whites	1,418	34.7	1,482	36.3	–3.3
Blacks	2,116	51.8	2,068	50.6	2.4
Others	552	13.5	536	13.1	1.2
Concomitant asthma medications					
Systemic corticosteroid	536	13.1	534	13.1	0.1
Inhaled corticosteroid	339	8.3	330	8.1	0.8
Combination	76	1.9	88	2.2	–2.1
LABA	39	1.0	31	0.8	2.1
LTRA	376	9.2	368	9.0	0.7
Time since initial asthma diagnosis					
0–1 year	3,576	87.5	3,582	87.7	–0.4
>1 year	510	12.5	504	12.3	0.4
Prior asthma-related ED visits					
0	3,709	90.8	3,708	90.8	0.1
≥1 visit	377	9.2	378	9.3	–0.1
Prior asthma-related hospitalizations					
0	3,977	97.3	4,003	98.0	–4.2
≥1 visit	109	2.7	83	2.0	4.2
Year of index date					
2002–2004	660	16.2	661	16.2	–0.1
2005–2007	1,657	40.6	1,657	40.6	0
2008–2011	1,769	43.3	1,768	43.3	0.05

LTRA, leukotriene receptor antagonists; LABA, long acting beta agonist; ED, emergency department; Std. Diff., standardized difference.

¹Matched pairs were created via propensity score matching.

²Standardized difference is estimated to compare the difference in means expressed in percentage of the pooled standard deviation of the covariate's distribution. A standardized difference <10% was considered as a good balance in covariates between groups.

DISCUSSION

In this retrospective cohort study, the effectiveness of prescribing levalbuterol and racemic albuterol were compared in pediatric patients aged 2–18 years with asthma diagnosis. Compared to those receiving albuterol, asthmatic children receiving levalbuterol had lower number of asthma-related and all-cause ED visits. In addition, children in the levalbuterol group were less likely to have an ED visit than those in the albuterol group, but had similar likelihood of a hospitalization, after adjusting for potential confounders. These findings suggest that levalbuterol demonstrated better clinical effects than racemic albuterol in terms of health care utilization, in particular, ED visits.

TABLE 2—Mean Number of ED Visits/Hospitalizations Associated With Levalbuterol and Albuterol During 12-Month Follow-Up Period

Type of visits	Levalbuterol (n = 4,086)		Albuterol (n = 4,086)	
	Mean	SD	Mean	SD
Asthma-related medical care				
ED visits	0.11	0.39	0.19	0.53
Hospitalizations	0.012	0.11	0.012	0.12
Total medical care				
ED visits	0.62	1.05	0.70	1.15
Hospitalizations	0.044	0.28	0.042	0.38

ED, emergency department; SD, standard deviation.

There is an ongoing debate concerning the clinical benefit of levalbuterol versus albuterol, because the significant cost differences between these two drugs and insufficient evidence supporting superior clinical effects of levalbuterol over racemic albuterol. (R)-albuterol demonstrates 100-fold greater binding affinity to β_2 -receptor than (S)-albuterol,²² resulting in broncho-protective and bronchodilator effects of racemic albuterol. While (S)-albuterol fails to show the effect of bronchodilation in asthma.²³ A recent re-analysis of clinical trials reported that, levalbuterol has greater bronchodilation effect than equivalent doses of racemic mixture.²⁴ However, a double-blind, placebo-controlled clinical trial found similar dose-response characteristics between (R)-albuterol and racemic albuterol.²⁵ Moreover, current studies suggest conflicting benefits of using levalbuterol over racemic albuterol in treating asthmatic patients. Some studies proposed that no clinically significant differences in improved lung function exist between levalbuterol and albuterol.^{24,26–28} In the contrast, Wilkinson et al. demonstrated that albuterol was better than levalbuterol in improving lung functions measured with Forced Expiratory Volume (FEV) and asthma score.¹⁴ Lower hospital admission rate was also observed in children receiving levalbuterol in the ED.^{15,29} This study provides “real world” insights in comparing the clinical outcomes of levalbuterol and albuterol in pediatric patients with asthma.

The present study compares favorably with previously published studies examining the effectiveness of levalbuterol compared to racemic albuterol. First, this study used ED visits and hospitalizations, which were recently recommended by the American Thoracic Society/European Respiratory Society, rather than forced expiratory volume as outcome measures.¹⁷ In general, poor asthma control leads to exacerbations, resulting in ED visits and hospitalizations, as well as higher medical costs and³⁰ lower quality-of-life. Crimi et al.³¹ and Rosi et al.³² suggested that symptoms were poorly correlated with

TABLE 3—Adjusted Incidence Rate Ratio of Asthma-Related ED Visits/Hospitalizations for Asthmatic Children Receiving Levalbuterol Versus Albuterol during 12-Month follow-Up Period¹

Characteristics	Asthma-related ED visits		Asthma-related hospitalizations	
	Estimate	95%CI	Estimate	95%CI
Albuterol	Ref	—	Ref	—
Levalbuterol	0.57	(0.49–0.65)	0.93	(0.61–1.41)
Age, years				
2–4 years	Ref	—	Ref	—
5–11 years	0.76	(0.65–0.88)	0.55	(0.32–0.95)
12–17 years	1.06	(0.82–1.38)	2.57	(1.39–4.76)
Sex				
Male	Ref	—	Ref	—
Female	1.02	(0.89–1.17)	0.81	(0.53–1.23)
Race				
Whites	Ref	—	Ref	—
Blacks	1.15	(0.99–1.34)	1.12	(0.67–1.89)
Others	1.20	(0.97–1.49)	3.38	(1.93–5.93)
Concomitant asthma medications				
Systemic corticosteroid	1.07	(0.87–1.30)	0.83	(0.44–1.60)
Inhaled corticosteroid	1.19	(0.91–1.57)	1.18	(0.51–2.71)
Combination	0.97	(0.57–1.65)	1.03	(0.19–5.48)
LABA	1.15	(0.57–2.30)	n/a	—
LTRA	1.09	(0.85–1.40)	0.69	(0.28–1.70)
Time since initial asthma diagnosis				
0–1 year	Ref	—	Ref	—
>1 year	0.87	(0.70–1.08)	0.88	(0.43–1.80)
Asthma-related ED visits				
0	Ref	—	Ref	—
≥1 visit	2.81	(2.33–3.40)	2.05	(1.13–3.70)
Asthma-related hospitalizations				
0	Ref	—	Ref	—
≥1 visit	1.37	(0.91–2.05)	6.37	(3.38–12.0)
Year of index date				
2002–2004	Ref	—	Ref	—
2005–2007	0.92	(0.76–1.12)	1.01	(0.56–1.80)
2008–2011	0.83	(0.68–1.01)	0.57	(0.30–1.07)

LTRA, leukotriene receptor antagonists; LABA, long acting beta agonist; ED, emergency department.

¹Adjustment for age, sex, race, year of index date, length of having asthma, and proportions of days covered by concomitant asthma medications.

lung function measures, such as FEV₁, which was widely used as outcome measures in published clinical trials. Second, unlike the published clinical trials, this study had a larger sample size and hence sufficient power to detect small differences in the outcomes between levalbuterol and albuterol. Finally, we used propensity score matching methods to reduce the bias due to confounding factors, which was not considered in the previously published studies. Therefore, this study provides valuable information on clinical effectiveness of levalbuterol versus albuterol in low-income asthmatic children who have a high risk of asthma exacerbation.

TABLE 4—Adjusted Incidence Rate Ratio of All-Cause ED Visits/Hospitalizations for Asthmatic Children Receiving Levalbuterol Versus Albuterol during 12-Month Follow-Up Period¹

Characteristics	Total ED visits		Total hospitalizations	
	Estimate	95%CI	Estimate	95%CI
Albuterol	Ref	—	Ref	—
Levalbuterol	0.88	(0.82–0.95)	1.08	(0.82–1.42)
Age, years				
2–4 years	Ref	—	Ref	—
5–11 years	0.74	(0.68–0.80)	0.86	(0.63–1.18)
12–17 years	1.19	(1.04–1.36)	4.31	(2.84–6.53)
Sex				
Male	Ref	—	Ref	—
Female	0.96	(0.90–1.04)	0.83	(0.63–1.10)
Race				
Whites	Ref	—	Ref	—
Blacks	0.90	(0.84–0.98)	0.85	(0.62–1.17)
Others	1.13	(1.01–1.26)	2.87	(1.97–4.19)
Concomitant asthma medications				
Systemic corticosteroid	1.01	(0.90–1.12)	1.22	(0.81–1.83)
Inhaled corticosteroid	0.85	(0.73–1.00)	1.17	(0.66–2.08)
Combination	1.09	(0.81–1.46)	0.33	(0.08–1.36)
LABA	1.42	(0.98–2.06)	0.88	(0.20–3.87)
LTRA	0.97	(0.85–1.11)	0.66	(0.38–1.15)
Time since initial asthma diagnosis				
0–1 year	Ref	—	Ref	—
>1 year	1.00	(0.90–1.12)	1.15	(0.76–1.75)
Asthma-related ED visits				
None	Ref	—	Ref	—
Any visits	1.66	(1.48–1.86)	1.29	(0.83–2.02)
Asthma-related hospitalizations				
None	Ref	—	Ref	—
Any visits	1.19	(0.95–1.48)	3.27	(1.69–6.33)
Year of index date				
2002–2004	Ref	—	Ref	—
2005–2007	0.98	(0.88–1.08)	1.10	(0.74–1.64)
2008–2011	0.84	(0.76–0.93)	0.65	(0.42–0.98)

LTRA, leukotriene receptor antagonists; LABA, long acting beta agonist; ED, emergency department.

¹Adjustment for age, sex, race, year of index date, length of having asthma, and proportions of days covered by concomitant asthma medications.

When interpreting the results, it is important to bear in mind that this study is an observational study using administrative claims data to identify children filling albuterol or levalbuterol and quantify the number of ED visits and hospitalizations. Since randomization of treatments (levalbuterol vs. racemic albuterol) was not performed in this study, a selection bias may exist in the two groups. In fact, we observed inhaled and systematic corticosteroids were used more commonly in children receiving levalbuterol than albuterol, indicating levalbuterol group was more severe at baseline. To reduce or eliminate such bias, propensity score matching methods were used to account for selected known, measured confounders. Propensity score matching

produced two groups that appeared to be well balanced on the baseline covariates of interest. However, a limitation of this study is that propensity score technique cannot account for bias due to unknown or unmeasured confounders, such as, asthma education, access to specialists, and quality of asthma care. Another limitation of this study is that the matching methods excluded a large number of eligible patients who could not be matched. Consequently, the two groups established by matching may not be fully representative of the target population from which they were drawn. However, we used inverse probability of treatment weight to model all the sample subjects, and obtained similar results, indicating that the results are robust for the unmatched subjects. Third, it is possible that the diagnosis of asthma was not coded correctly in the claims database. However, all-cause ED visits and hospitalizations were included in the sensitivity analysis. Negligible differences in the primary outcome measures were observed when comparing asthma-related and all cause ED visits/hospitalizations in the sensitivity analyses. Fourth, since we analyzed only SC Medicaid data, the results may not be generalizable to patients who are not Medicaid beneficiaries or who do not reside in SC. Medicaid beneficiaries have lower family income and socio-economic status, and may not represent the general population. Finally, our findings are largely hypothesis generating, we cannot rule out the possibility that the clinical advantages we found could be explained by chance. However, there is evidence suggesting potential biological mechanisms to support these findings.^{5,6}

CONCLUSIONS

In conclusion, children aged 2–18 with asthma who received levalbuterol exhibited a clinically significant benefit as measured by reduced asthma-related ED visits when compared to similar children who received albuterol. Further studies are needed in a more diverse and representative sample of children to confirm these findings.

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