

UNIVERSITY OF KENTUCKY MARTIN SCHOOL OF PUBLIC
ADMINISTRATION

Impact of levalbuterol versus Albuterol in Kentucky Medicaid Patients



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Velma Henry PharmD/MPA Candidate 2010
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I. Executive Summary

Problem:

Asthma is a chronic pulmonary disease that occurs in approximately 10 percent of the population worldwide and is associated with a significant increase in direct medical expenditures. Levalbuterol and racemic albuterol are two short-acting β 2-agonists (SABA) prescribed for the treatment of asthma. Racemic albuterol has been used for more than 40 years but is associated with several side effects including tremor. When levalbuterol was approved in 2005 its manufacturer and several studies suggested that using levalbuterol results in better respiratory parameters, fewer hospitalizations, less adverse effects and therefore, lower overall treatment costs and hence less need for β -adrenergic agonist treatment. However, this pattern of results is not universal and some studies suggest no significant difference in clinical endpoints. With these conflicting data it is difficult to agree over the choice of which SABA; levalbuterol or racemic albuterol that should be used. The purpose of this study therefore is to compare asthma-related health care expenditures and treatment outcomes after initiation of maintenance treatment with levalbuterol or albuterol

Research Strategy:

This was a retrospective cohort study of pharmacy and medical claims from the Kentucky Medicaid MMIS database consisting of patients with asthma who received treatment with a short acting beta agonist (SABA); albuterol or levalbuterol between January 1, 2000 and December 31, 2008. Descriptive statistics were used to characterize the study group. Difference over time analyses were used to generate an estimate of the impact of using levalbuterol on asthma-related and total healthcare expenditure. Multiple linear regression analyses were used to obtain a more precise measure of the financial impact of using levalbuterol.

Major Findings:

The baseline characteristics for the two patient populations were significantly different. The levalbuterol group was much younger with an average age of 11 years whereas the racemic albuterol group had an average age of 25 years. The levalbuterol group on average spent \$US281 less on asthma related healthcare costs than the racemic albuterol group ($p < 0.001$). The levalbuterol group had an adjusted savings of \$US1317 per patient for total healthcare expenditures ($p < 0.001$) compared with the racemic albuterol group. This was mainly due to a large and statistically significant reduction in hospital visits costs of \$US788 ($p < 0.001$). The number of emergency department visits, physician visits, and hospitalizations increased statistically for both groups and there was a general shift from less severe to more severe asthma for both groups over time.

Recommendations:

This study showed that the added cost of using levalbuterol was more than offset by reductions in other types of healthcare expenditures. Levalbuterol should therefore become the drug of choice for exacerbation of asthma in the Kentucky Medicaid population. Randomized double-blind studies need to be done to verify these results and to determine whether the difference in total costs is due to fewer adverse effects, better adherence or better long-term efficacy.

I. Problem Statement

Asthma is a chronic pulmonary disease characterized by reversible airway obstruction and inflammation that occurs in 8 to 10 percent of the population.(Busse et al, 2004) There are an estimated 300 million patients with asthma worldwide (Masoli et al., 2004) including 22 million in the U.S.(CDC, 2006) The prevalence of asthma is increasing in most countries, especially among children, and if the current trends continue, it is estimated that there may be an additional 100 million asthmatics by 2025.(Bateman et al, 2008) Each year in the U.S., about 11 million patients have an acute deterioration of respiratory symptoms following a respiratory viral infection or exposure to environmental allergens or irritants. (CDC, 2008)

While most asthma exacerbations are managed in the outpatient setting, more severe exacerbations may require hospitalization and are responsible for a substantial proportion of healthcare expenditures for asthma. In the U.S., severe asthma exacerbations lead to over 400,000 hospitalizations each year and these hospitalizations constitute about one-third of the total annual asthma-related healthcare expenditures. (American lung Association, 2005) Asthma in both subpopulations, children and adults, is associated with a significant increase in direct medical expenditures, with the overall annual direct medical expenditure associated with asthma estimated at approximately \$37.2 billion in 2007 U.S. dollars. (Kamble, 2009)

Mainstay therapy for asthma includes the use of β_2 -receptor agonists for reversal of acute airway obstruction and asthma exacerbations such as cough. Thus, up to two thirds of asthma patients in the United States have received β_2 -receptor agonist therapy during the past 20 years. (Reed et al, 1985) Levalbuterol and racemic albuterol are two commonly prescribed short-acting β_2 -agonists used for the treatment of asthma. Racemic albuterol is formulated as a racemic mixture of equal parts of two mirror-image enantiomers, the (R)-and (S)-enantiomers, with the

(R)-enantiomer (levalbuterol) being responsible for bronchodilation and the bronchoprotective properties of the drug. (Lotval et al, 2001)

The relative safety of levalbuterol and racemic albuterol is quite controversial. (Ozminkowski et al, 2007) The (S)-isomer was initially believed to be inert, and its presence in the racemic drug of no consequence, but it is now thought to compress the potency and foreshorten the duration of (R)-albuterol. (Handley et al, 2000) Despite these in vitro and animal studies, studies in humans have not always shown clinically meaningful effects. Other studies suggest that racemic albuterol was associated with bothersome adverse effects, whereas, with levalbuterol, the adverse effects were less frequent and symptom relief was perceived to be better; which may lead to higher overall satisfaction with levalbuterol treatment. This is believed to be due to the fact that inhalation of racemic albuterol, results in the persistence of circulating S-albuterol 12 times longer than levalbuterol, suggesting potential for the paradoxical effects observed clinically. (Ameredes, 2009) Results from an in vitro study also demonstrated that levalbuterol is 2-fold more potent than racemic albuterol and 90- to 100-fold more potent than S-albuterol. (Penn et al, 1996) Accordingly, pure (R)-albuterol provides bronchodilation at lower doses than racemic albuterol, allowing for fewer β -adrenergic-mediated side effects. (Handley et al, 2000)

Levalbuterol is being lauded as a safer form of albuterol, and as is the case with most new therapies, this claimed superiority comes at a price. Levalbuterol can cost as much as 5 times more than a comparable generic racemic albuterol nebulizer solution. (Asmus, 2000) With regard to efficacy, some authors have found or suggested that using levalbuterol results in better respiratory parameters, fewer hospitalizations, and therefore, lower overall treatment costs and

less need for β -adrenergic agonist treatment. However, this pattern of results is not universal and some studies suggest no significant difference in clinical endpoints. (Ozminkowski et al, 2007)

With the literature now rife with conflicting data regarding potential anti-therapeutic effects of (S)-albuterol and purported advantages of levalbuterol, both in efficacy and in safety, it is difficult for doctors, patients, health plans, and policy makers to agree over the choice of which SABA; levalbuterol or racemic albuterol that should be used. This study addresses the potential consequences of short-acting β 2-adrenoceptor agonist drug choice for Kentucky Medicaid patients from a financial perspective. The purpose of this study therefore is to compare asthma-related health care expenditures and treatment outcomes in the year after initiation of maintenance treatment with levalbuterol or albuterol in the Kentucky Medicaid population.

II. Literature Review

Clinical studies suggest no overwhelming superiority of levalbuterol over racemic albuterol; however, levalbuterol's effects may be greatest in moderate to severe asthma patients, especially with racemic albuterol overuse. (Ameredes et al, 2009) Several small (N<33) human studies have been conducted but the results have been somewhat heterogeneous. (Ameredes et al, 2009) In one initial study levalbuterol suppressed bronchospasm more effectively than racemic albuterol and (S)-albuterol. (PerrinFayolle et al, 1996) Subsequent studies reported equivalencies of levalbuterol to racemic albuterol, with some indicating that the bronchodilatory effect of levalbuterol, 1.25 mg, was equivalent to that of racemic albuterol, 2.5 mg, with (S)-albuterol having little measurable effect. (Cockcroft, 1997; Cockcroft et al, 1999; Ramsay et al, 1999) However, the above studies were short-term and because of the effects of levalbuterol within the racemate, such a short-term approach would be expected to show equivalently strong effects. This approach did not provide an assessment of differences between racemic albuterol and albuterol isomers with chronic use.

One of the landmark clinical trials comparing levalbuterol and racemic albuterol was that of Nelson et al. (Nelson et al, 1998), in which patients were randomly assigned to levalbuterol, 0.63 or 1.25 mg, or racemic albuterol 1.25 or 2.5 mg. The trial was designed to prove the equivalency of equal mass levels of levalbuterol, with and without (S)-albuterol present. The results indicated significantly greater improvements in forced expiratory volume in 1 second (FEV₁) in the levalbuterol groups compared with the dose-equivalent racemic groups. Interestingly, the dose that provided numerically equivalent bronchodilation as that seen with the 2.5 mg of racemic albuterol was 0.63 mg of levalbuterol, not 1.25 (the mass equivalent dose). Thus the data have been interpreted as showing a detrimental effect of (S)-albuterol.

Several clinical studies have been conducted in pediatric asthma patients. A randomized, placebo-controlled comparator trial reported no significant differences between the drugs with respect to FEV₁. (Gawchick, 1999) Another double-blind, placebo-controlled, randomized trial concluded that no difference was found in bronchodilation with levalbuterol compared to racemic albuterol. There was no dose-response relationship in children with mild to moderate asthma but a dose-response relationship was observed for levalbuterol in children with more severe asthma. (Milgrom, 2001) In a sample of acutely asthmatic children aged 6–18 years presenting to a tertiary hospital emergency department (ED), the authors concluded that the more expensive Levalbuterol did not shorten ED length of stay, reduce number of nebulized treatments, improve peak expiratory flow (PEF) measurements, reduce symptomatic complications, or reduce unplanned return visits for asthma management when compared to racemic albuterol plus ipratropium (RAC/IB). Use of LEV did provide some benefit as demonstrated by its association with less tachycardia compared to RAC/IB. (Ralston, 2005)

A randomized, double-blind, age-stratified trial of patients presenting to the ED with the primary outcome being hospital admission rate found that hospitalization rate was significantly lower in the levalbuterol group than in the racemic albuterol group (36%, 45 %, $P = 0.02$). The adjusted relative risk of admission in the racemic group compared with the levalbuterol group was 1.25. Hospital length of stay was not significantly shorter in the levalbuterol group and no significant adverse events occurred in either group. The authors concluded that substituting levalbuterol for racemic albuterol in the ED management of acute asthma significantly reduced the number of hospitalizations. (Carl et al, 2003) A study done by Nowak et al. supported the idea that levalbuterol could be preferable to racemic albuterol in the emergent treatment of acute asthma. FEV₁ improvement was greater following Levalbuterol compared with racemic

albuterol, both after dose 1 and cumulatively over the entire treatment period. Other aspects of the study suggest that patients with high (S)-albuterol plasma levels have slower improvement in FEV₁ and a greater likelihood of hospital admission. (Nowak et al, 2006)

In several studies levalbuterol resulted in FEV₁ values that were comparable with or better than those observed with racemic albuterol and β -mediated side effects were lower for an equipotent dose of levalbuterol when compared with racemic albuterol. Treatment costs were lower with levalbuterol mainly because of a decrease in hospital admissions. The authors concluded that levalbuterol treatment in the ED resulted in higher patient discharge rates and may be a cost-effective alternative to racemic albuterol. In one study the authors concluded that compared with patients treated with racemic albuterol, those treated with levalbuterol required less medication, had shorter lengths of hospital stay, had decreased costs for nebulizer therapy and hospitalization, and appeared to have a more prolonged therapeutic benefit. Regression analysis indicated that levalbuterol was associated with a length-of-stay savings of 0.91 days ($p = 0.015$), a total cost savings of \$556 ($p = 0.013$), and a decrease in the likelihood of hospital readmission of 67% ($p = 0.056$) (Truit et al, 2003)

Several studies however resulted in similar improvements in FEV₁, and tolerability, but plasma (R)-albuterol levels and mean heart rate were less with levalbuterol. (Tripp et al, 2008; Hamilos et al, 2007) No differences were detected between groups after the first, third, and fifth nebulizer treatments in the primary outcome of improvement in asthma score or percentage of predicted FEV₁, and no differences were found in the secondary outcomes of the number of nebulizer treatments given; length of care; rate of hospitalization; and changes in pulse rate, respiratory rate, and pulse oximetry readings. There were no differences between groups in adverse effects. (Qureshi et al, 2005)

III. Research Strategy and Methods

Study design:

This analysis was conducted as a retrospective cohort study of pharmacy and medical claims from the Kentucky Medicaid (MMIS) database of patients with asthma who received treatment with a short acting beta agonist (SABA), albuterol or levalbuterol between January 1, 2000 and December 31, 2008. Pharmacy data were identified by using the American Hospital Formulary Service code and the National Drug Code. Included in the pharmacy data were the drug dispensed, date the drug was dispensed, quantity and days supplied and amount paid. Medical claims were identified by using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Included in the medical claims data were the date of service, point of service, and amount paid. In addition, data were available for date of birth, gender, and plan enrollment time for each patient.

Study population:

To be eligible for inclusion in the study patients were required to have at least 1 pharmacy claim for either albuterol or levalbuterol between January 1, 2000 and December 31, 2008 with a primary ICD-9-CM code (493.xxx) for asthma at anytime in the database. The first pharmacy claim for albuterol or levalbuterol was designated as the index date. Enrollment in the plan had to be continuous for at least 24 months: 12 months before the first index prescription (baseline preindex period) and 12 months after (treatment postindex period). Identified patients could not have received albuterol and levalbuterol in the 12-month baseline preindex period to ensure that prior use of the drugs was not a confounding factor on asthma control and hence costs. In addition, several exclusion criteria were applied: any medical service claim coded

during the preindex period (or on the index date) with a primary or secondary diagnosis of chronic obstructive pulmonary disease [*ICD-9-CM*] codes 491.xx, 492.xx, 493.2x, 494.xx, 496.xx, 770.2), pulmonary hypertension (416.xx), pulmonary embolism (415.xx), or other pulmonary circulatory disorder (417.xx) These comorbid conditions were excluded because they may impede asthma management and will have an impact on treatment outcomes.

Outcome:

The primary outcome was trends over time in total medical expenditures and asthma-related expenditures for levalbuterol versus racemic albuterol patients. The secondary outcome was index of asthma control determined by the number of asthma controller medication needed and number of office visits, emergency department visits and hospitalizations. Total and asthma-related medical and pharmacy patient claims data were tabulated over the baseline and treatment periods (12 months each).

Analysis

This study examines treatment costs and asthma control of levalbuterol and albuterol over time. The number of prescribed controller medications (CM), emergency room visits, physician visits and hospitalizations were used as indices of asthma severity. Trends over time in total medical expenditures and asthma-related expenditures were compared for levalbuterol versus racemic albuterol patients. Trends over time were determined by post-index period minus pre-index period expenditures. This provided an initial unadjusted estimate of the relative cost impact of taking levalbuterol. Multiple linear regression analyses were used to account for the differences in the characteristics of the sample members and to compare the differences in pre- and post-index asthma control. All of the regression analyses were adjusted for differences due

to age, gender, race, and pre-index expenditures. Throughout the study continuous variables were analyzed using t-tests and characterized by mean and standard deviation. Categorical variables were analyzed using the chi-square test and characterized by frequency and percentage within each category. All statistical analyses were performed at a significance level of 0.05 in STATA version 9.1.

IV. Results

Sample characteristics for the pre-index period of the 21,511 levalbuterol patients and the 497,160 racemic albuterol patients are shown in Table I. The baseline characteristics for the two patient populations were significantly different.

Table I: Pre-index Characteristics of patients initiating albuterol or levalbuterol

	Levalbuterol (n=21,511)	Racemic Albuterol (n=497,160)	P-value
Mean \pm SD (yrs)	11.19 \pm 20.7	24.62 \pm 24.2	0.000
Gender no. (%)			
Females	9,801 (45.6)	273,167 (54.9)	} 0.000
Males	11,710 (54.4)	223,993 (45.1)	
Race no. (%)			
White	18,138 (84.3)	398,524 (80.2)	} 0.000
African American	1,362 (6.33)	54,667 (11.0)	
Hispanic/Latino	36 (0.17)	808 (0.16)	
Asian or Pacific Islander	35 (0.16)	990 (0.20)	
Other race or ethnicity	140 (0.65)	3,526 (0.71)	
Not Provided	1,800 (8.37)	38,645 (7.77)	
No (%) Controlling drugs (CD)			
LABA	21,454 (99.7)	457,310 (92.0)	0.000
LABA + ICS	1,194 (5.55)	45,600 (96.7)	0.000
ICS/OCS	11,590 (53.9)	192,035 (38.6)	0.000
LRA	21,501 (99.9)	497,038 (100)	0.052
MCS	68 (0.32)	3,170 (0.64)	0.000
Xanthenes	409 (1.90)	16,481 (3.32)	0.000
Omalizumab	4 (0.0002)	101 (0.0002)	0.862
Epinephrine	3,618 (16.8)	82,386 (16.6)	0.338
Severity of asthma (%)			
Intermittent	1(0.00005)	2 (0.000004)	} 0.0000
Mild	42 (0.20)	19,103 (3.84)	
Moderate	8,587 (39.9)	234,125 (47.1)	
Severe	13,081 (60.8)	243,930 (49.1)	

p-values for gender and race are based on independence chi-square tests. All others are t-tests. LABA, Long acting beta agonist; ICS, inhaled corticosteroid; OCS, oral corticosteroid; LRA, Leukotriene receptor antagonists; MCS, mast cell stabilizers

The levalbuterol group was much younger with an average age of 11 years whereas the racemic albuterol group had an average age of 25 years. There was not much difference in the age range between the two groups. The age ranged from 0 - 101 years in the levalbuterol group and 0 - 107 years in the racemic albuterol group. The levalbuterol group had more males (54.4%) whereas the racemic albuterol group had more females (54.9%). The racial distribution of the two groups was significantly different, but both groups had a racial population that reflected the Medicaid population with Caucasians accounting for 84.3% in the levalbuterol group and 80.2% in the racemic albuterol group. Race was not recorded for 8.37% of the levalbuterol group and 7.77% of the racemic albuterol group.

The class of drugs most utilized by both groups was the leukotriene receptor antagonists, 99.9% of the levalbuterol group and 100% of the racemic albuterol group. Ninety-nine percent of the levalbuterol population had a pharmacy claim for a long acting beta agonist. Ninety-two percent of the racemic group had a pharmacy claim for a long acting beta agonist and 96.7% had a claim for a long acting beta agonists/corticosteroids combination. The number of patients on a leukotriene receptor antagonist, omalizumab and epinephrine was not significantly different between the two groups ($p = 0.052, 0.862, 0.338$ respectively).

Severity of asthma was determined by the number of controller medications that the patient was taking. A patient was determined to have intermittent asthma if they were not taking any medication to control their asthma, mild if they were taking one controller medication, moderate if they were taking two, and severe if they were taking at least three medications to help control their asthma. Sixty-one percent of the levalbuterol population had severe asthma whereas the racemic group had a fairly even distribution between moderate asthma (47.1%) and severe asthma (49.1%).

Table II: Age Category Distribution of Patients Initiating Levalbuterol and Racemic Albuterol

Age Category yrs. (%)	Levalbuterol group (n=21,511)	Racemic Albuterol group (n=497,160)
0 – 4	13,027 (60.6)	128,508 (25.8)
5 – 11	4,418 (20.5)	101,519 (20.4)
12 – adults	4,066 (18.9)	267,133 (53.7)

The Guidelines for the Diagnosis and Management of Asthma has separate treatment guidelines for the three different age groups listed in table II. The type and number of drugs initiated at each step during asthma therapy differs depending on the age of the patient. Sixty percent of the levalbuterol group was between the ages of 0 – 4 years while 53.7% of the racemic group was \geq 12 years. Roughly 20% of the population of both groups was between the ages 5 – 11 years.

Table III: Patient Characteristics based on Age Groups

	Levalbuterol group (n=21,511) Age Groups (yrs)			Racemic Albuterol group (487,160) Age Groups (yrs)		
	0 – 4	5 – 11	\geq 12	0 – 4	5 – 11	\geq 12
Females no. (%)	5,267 (53.7)	1,807 (18.4)	2,727 (27.8)	51,255 (18.8)	41,859 (15.3)	180,053 (65.9)
No. (%) Controlling Drugs						
LABA	12,992 (60.6)	4,406 (20.5)	4,056 (18.9)	128,124 (28.0)	100,948 (22.1)	228,238 (49.9)
LABA + ICS	44 (3.69)	363 (30.4)	787 (65.9)	727 (1.59)	7,307 (16.0)	37,566 (82.4)
ICS/OCS	7,025 (60.6)	2,616 (22.6)	1,949 (16.8)	52,718 (27.5)	42,821 (22.3)	96,496 (50.2)
LRA	13,023 (60.6)	4,413 (20.5)	4,065 (18.9)	128,486 (25.9)	101,467 (20.4)	267,085 (53.7)
MCS	40 (58.8)	17 (25.0)	11 (16.2)	1,121 (35.4)	1,086 (34.3)	963 (30.4)
Xanthenes	83 (20.3)	28 (6.85)	298 (72.9)	405 (2.46)	383 (2.32)	15,691 (95.2)
Omalizumab	0 (0)	0 (0)	4 (100)	0 (0)	17 (16.8)	84 (83.2)
Epinephrine	1,485 (41.0)	1,256 (34.7)	877 (24.2)	14,114 (17.1)	28,147 (34.2)	40,125 (48.7)
Asthma Severity no. (%)						
Intermittent	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	2 (100)
Mild	26 (61.9)	9 (21.4)	7 (16.7)	249 (1.30)	303 (1.59)	18,551 (97.1)
Moderate	5,575 (64.9)	1,317 (15.3)	1,495 (17.4)	68,886 (29.4)	41,742 (17.8)	123,497 (52.7)
Severe	7,426 (56.8)	3,092 (23.6)	2,563 (16.6)	59,373 (24.3)	59,474 (24.4)	125,083 (51.3)

Table III presents the characteristic of the levalbuterol and racemic albuterol population based on the age group of the patients. Fifty-three percent of the female population of the levalbuterol group was between the ages of 0 – 4 years while 65.9% of the racemic albuterol's female population was \geq 12 years of age. In the levalbuterol group LABA, ICS/OCS combination, LRA, and epinephrine were mainly used by the 0 – 4 age group whereas in the racemic albuterol group they were mainly used by the \geq 12 age group. In both the levalbuterol and racemic groups the majority of LABA/ICS combination, xanthenes, and omalizumab were used by the \geq 12 age group and the majority of MCS was used by the 0 – 4 years age group. In the levalbuterol group the majority of patients for each of the severity categories (except intermittent) were 0 – 4 years of age whereas in the racemic group the same was true for the \geq 12 years age group.

Table IV presents the expenditure results obtained from the analyses of asthma related costs for the population and provides details for medications, emergency department, physician and hospitalization trends. Total expenditures are also recorded for both periods and both groups of patients. The top portion of the table focuses on our main analysis of asthma-related healthcare expenditures, while the bottom portion focused on all healthcare expenditures.

There was a significant difference in the price of asthma medication with levalbuterol patients spending an average of \$82 more than the racemic albuterol group ($p < 0.001$). They also spent more on average for hospitalizations but this was not statistically significant ($p = 0.227$). The levalbuterol group had a savings of only \$5 for physician visits and \$4 for emergency department visits. Levalbuterol patients had significantly higher total asthma related expenditures than racemic albuterol patients in the 12-month pre-index period (\$419 vs \$244; $p < 0.001$) and 12-month post-index period (\$833 vs \$569; $p = 0.001$). Expenditures increased over

time for both levalbuterol patients and racemic patients. On average the levalbuterol group had a total asthma related healthcare medication costs of \$89 more than the racemic albuterol group, which was statistically significant ($p < 0.001$).

In the bottom portion of table IV, where the focus was total healthcare expenditures for the entire sample, the levalbuterol group had an unadjusted savings of \$1056 per patient for their total healthcare expenditures ($p < 0.0001$). This was due to the large and statistically significant savings of \$788 per patient for total healthcare hospitalizations ($p < 0.0001$). The levalbuterol group on average spent \$37 more on medications than the racemic albuterol group but this was not statistically significant ($p = 0.067$). The levalbuterol group also had a statistically significant savings of \$25 over the racemic albuterol group for emergency department visits ($p = 0.0001$).

Table V presents the results obtained from the difference over time regression model that was used for the main analysis of asthma-related healthcare expenditures. The negative coefficient (-280.53; t-test $p < 0.0001$) suggests that trends over time in expenditures were statistically lower for levalbuterol users. Asthma related health care costs for patients ages 5 – 11 years (-79.605; t-test $p < 0.0001$) and ≥ 12 years (-21.308; t-test $p < 0.0001$) was statistically less compared with patients between the ages of 0 – 4 years. Asthma related healthcare costs for females was less compared with men (-7.0008; t-test $p = 0.211$) but this was not statistically significant. Asthma related healthcare cost for African-Americans was statistically more than Whites as suggested by the positive coefficient (62.290; t-test $p < 0.0001$), and cost for the “Other” classification was statistically less than Whites (-327.20; t-test $p < 0.0001$). All classes of drugs except omalizumab increased the asthma healthcare costs as suggested by the positive coefficients and P-values < 0.05 .

Table IV. Healthcare expenditures for Medicaid patients with asthma in 12-month pre-and post-index period

Type of Expenditure	Cost during 12-month pre-index period (\$US)			Cost during 12-month post-index period (\$US)			Difference in costs over time (post-pre) (\$US)		Difference (\$US)	
	Levalbuterol (n=16,608)	Racemic albuterol (n=205,470)	t-test p-value	Levalbuterol (n=16,608)	Racemic albuterol (n=205,470)	t-test p-value	Levalbuterol (n=16,608)	Racemic albuterol (n=205,470)	mean	t-test p-value
Asthma-related healthcare expenditures (average per patient)										
Medication	227.65	101.34	<0.0001	458.75	250.19	<0.0001	231.15	148.85	82.3	<0.0001
Physician visit	32.962	37.781	<0.0001	76.961	86.810	<0.0001	44.035	49.029	-4.994	0.0089
ED visits	7.8429	12.046	<0.0001	14.437	22.297	<0.0001	6.5943	10.251	-3.6567	<0.0001
Hospitalizations	150.37	92.977	<0.0001	282.69	209.59	<0.0001	132.32	116.62	15.7	0.2273
Total	418.79	244.14	<0.0001	832.84	568.89	<0.0001	414.05	324.75	89.3	<0.0001
All healthcare expenditures (average per patient)										
Medication	944.13	1260.8	<0.0001	1935.3	2215.3	<0.0001	991.19	954.51	36.68	0.0667
Physician visit	986.41	1783.6	<0.0001	1364.5	2440.4	<0.0001	378.07	656.76	-278.69	<0.0001
ED visits	190.80	324.13	<0.0001	269.77	428.51	<0.0001	78.965	104.39	-25.425	0.0001
Hospitalizations	3197.8	3717.1	<0.0001	2741.8	4049.3	<0.0001	-456.00	332.21	-788.21	<0.0001
Total	5319.1	7085.7	<0.0001	6311.3	9133.6	<0.0001	992.22	2047.9	-1055.7	<0.0001

Difference-in-difference corresponds to levalbuterol difference over time minus racemic albuterol difference over time. Negative values in column reflect savings associated with levalbuterol use. Positive values reflect losses associated with levalbuterol use

Table V: Asthma-Related health expenditures results obtained from the difference in time regression model for Medicaid patients with asthma (F=1442.89)

Independent variables	Parameter estimates	Standard error	t-Score	p-Value	95% CI
Intercept	3507.0	1113.9	3.15	0.002	1323.8, 5690.2
Levalbuterol user (n=16,608) [vs racemic Albuterol use (n=205,470)]	-280.53	14.101	-19.89	0.000	-308.17, -252.90
5 – 11 years (vs. 0 – 4 years)	-79.605	8.0791	-9.85	0.000	-95.440, -63.770
≥ 12 years (vs 0 – 4 years)	-21.308	7.1885	-2.96	0.003	-35.397, -7.2188
Female	-7.0008	5.5913	-1.25	0.211	-17.960, 3.9581
African-American (vs. White)	62.290	8.7406	7.13	0.000	45.159, 79.421
Hispanic/Latino (vs. White)	18.153	66.478	0.27	0.785	-112.14, 148.45
Asian or Pacific Islander (vs. White)	81.883	60.335	1.36	0.175	-36.372, 200.14
Other (vs. White)	-327.20	32.022	-10.22	0.000	-389.96, -264.44
Not Provided (vs. White)	49.134	10.072	4.88	0.000	29.392, 68.875
Mild asthma (vs. intermittent asthma)	-3203.6	1113.9	-2.88	0.004	-5387.0, -1020.3
Moderate asthma (vs. intermittent asthma)	-3406.8	1113.9	-3.06	0.002	-5590.0, -1223.6
Severe asthma (vs. intermittent asthma)	-3669.9	1113.9	-3.29	0.001	-5853.0, -1486.7
Long acting beta agonists use	1.9880	0.0233	85.42	0.000	1.9424, 2.0336
LABA/Corticosteroid combination use	0.8129	0.0205	39.62	0.000	0.7727, 0.8531
Corticosteroid use	1.3921	0.0179	77.81	0.000	1.3570, 1.4271
Leukotriene receptor antagonists use	2.0745	0.0446	46.49	0.000	1.9870, 2.1619
Mast cell stabilizers use	0.4488	0.0307	14.62	0.000	0.3886, 0.5089
Xanthene use	1.5278	0.2438	6.27	0.000	1.0498, 2.0054
Omalizumab use	-0.0234	0.0198	-1.18	0.237	-0.0623, 0.0154
Epinephrine use	2.1645	0.1180	18.34	0.000	1323.8, 5690.2

Table VI: Total health expenditures results obtained from the difference in time regression model for Medicaid patients with asthma (F=591.81)					
Independent variables	Parameter estimates	Standard error	t-Score	p-Value	95% CI
Intercept	20086	12948	1.55	0.121	-5291.9, 45465
Levalbuterol user (n=16,608) [vs racemic Albuterol use (n=205,470)]	-1317.2	163.92	-8.04	0.000	-1638.5, -995.98
5 – 11 years (vs. 0 – 4 years)	1800.1	93.914	19.17	0.000	1616.1, 1984.2
≥ 12 years (vs 0 – 4 years)	3812.8	83.562	45.63	0.000	3649.1, 3976.6
Female	205.04	64.995	3.15	0.002	77.650, 332.43
African-American (vs. White)	-57.366	101.60	-0.56	0.572	-256.50, 141.77
Hispanic/Latino (vs. White)	-950.34	772.76	-1.23	0.219	-2464.9, 564.25
Asian or Pacific Islander (vs. White)	-1092.5	701.36	-1.56	0.119	-2467.1, 282.14
Other (vs. White)	1195.0	372.24	3.21	0.001	465.39, 1924.5
Not Provided (vs. White)	-2736.6	117.08	-23.37	0.000	-2966.0, -2507.1
Mild asthma (vs. intermittent asthma)	-20154	12949	-1.56	0.120	-45534, 5225.5
Moderate asthma (vs. intermittent asthma)	-21294	12948	-1.64	0.100	-46672, 4084.3
Severe asthma (vs. intermittent asthma)	-22935	12948	-1.77	0.077	-48312, 2443.3
Long acting beta agonists use	13.033	0.2705	48.17	0.000	12.502, 13.563
LABA/Corticosteroid combination use	5.5391	0.2385	23.22	0.000	5.0716, 6.0065
Corticosteroid use	-0.3865	0.2080	-1.86	0.063	-0.7941, 0.0212
Leukotriene receptor antagonists use	19.504	0.5187	37.60	0.000	18.487, 20.521
Mast cell stabilizers use	4.9842	0.3569	13.97	0.000	4.2847, 5.6837
Xanthene use	13.647	2.8336	4.82	0.000	8.0930, 19.201
Omalizumab use	-0.5946	0.2303	-2.58	0.010	-1.0459, -0.1433
Epinephrine use	-13.447	1.3722	-9.80	0.000	-16.136, -10.757

Table VI presents the results obtained from the difference over time regression model that was used for the analysis of total healthcare expenditures. The negative coefficient (-1317.2; $p < 0.0001$) suggests that trends over time in expenditures were statistically lower for levalbuterol users. In this regression analysis the cost of total healthcare for females was statistically more compared to men (205.04; t-test $p = 0.002$). Statistically, more was paid in total health care for patients ages 5 – 11 years (1800.1; t-test $p < 0.0001$) and ≥ 12 years (3812.8; t-test $p < 0.0001$) compared to patients between the ages of 0 – 4 years. The total healthcare cost for African-Americans, Hispanics, and Asians were less compared with Whites but they were not statistically significant ($p = 0.572, 0.219, 0.119$ respectively). Total healthcare cost for the “Other” category was statistically more compared to Whites (1195.0; t-test $p = 0.001$). All of the classes of drugs except for corticosteroids had a statistical impact on the cost of healthcare as suggested by p values < 0.0001 .

The results from table VII was used to determine if the use of levalbuterol or racemic albuterol had a statistically significant impact in decreasing the number of controller medications used, emergency department visits, physician visits, and hospitalizations. This was used as an indicator of efficacy since a decrease in any of these could suggest better control of asthma as a result of initiating the drug. The results indicate that over the 12 month period medication use for both groups decreased in the mild and moderate asthma category but increased for the severe category. The change in use of controlling asthma drug over time was statistically significant for both groups ($p = < 0.0001$). Asthma related emergency department visits, physician visits and hospital visits increased statistically for both groups. All healthcare related emergency department visits, physician visits, and hospitalizations also increased significantly over the 12

month period. These results indicate that neither drug had a significant impact in improving the control of asthma.

Table VII: Total number Medications other than SABA needed to control asthma

	Levalbuterol (n=21,511)			Racemic Albuterol (n=497,160)		
	Pre-Index period	Post-Index Period	p-value	Pre-Index period	Post-Index Period	P-value
Asthma Related						
Controlling medications						
0 (Intermittent)	1	0		2	3	
1 (mild)	42	13	<0.0001	19,103	9,528	<0.0001
2 (moderate)	8,387	4,451		234,125	136,421	
≥3 (Severe)	13,081	17,047		243,930	351,208	
ED visits	1,324	2,561	<0.0001	47,542	86,105	<0.0001
Physician visits	9,712	24,694	<0.0001	229,278	552,736	<0.0001
Hospitalizations	2,099	3,849	<0.0001	32,028	64,656	<0.0001
All Healthcare Related						
ED Visits	39,861	55,525	<0.0001	1,147,940	1,503,224	<0.0001
Physician visits	213,275	295,634	<0.0001	5,553,357	7,460,980	<0.0001
Hospitalizations	34,367	38,727	<0.0001	720,215	887,907	<0.0001

V. Discussion

The results from this experiment suggest that over time the use of levalbuterol results in statistically significant savings both in asthma-related and total healthcare cost. The analyses that were conducted for this project were split into two major types. First, expenditures that were specific to asthma were considered then all healthcare expenditures. Several different approaches were used to analyze the data in order to address the perspective of the Medicaid policy maker, physician, and others. Medicaid policy makers are most concerned with trends in total healthcare expenditures, since Medicaid pays for all such expenditures, not just those for a particular disease. Physicians and other clinicians prefer analyses of expenditures that are tied more closely to the diseases of interest.

The two patient populations were very different with the racemic group accounting for approximately 23X the size of the levalbuterol group. This study suggests that levalbuterol is used more in younger children compared to older children and adults since 61% of the levalbuterol group were in the age group 0 – 4 years. The levalbuterol group appeared to have more severe asthma than the racemic albuterol group since 60.8% of the levalbuterol group compared to the 49.1% of the racemic group had severe asthma as determined by the number of controller medications used in the pre-index period.

The unadjusted difference over time analysis of asthma-related expenditures suggests that asthma related expenditures for levalbuterol patients over a year were at least \$US89.30 more than expenditures for racemic albuterol patients. However, the regression analysis controlling for patient characteristic suggests that in fact there is a savings of \$US280.53 for levalbuterol patients compared to racemic albuterol patients. The results of total healthcare expenditures suggests that levalbuterol was the more economical choice since on average patients saved

\$US1317.2 more than racemic albuterol patients. This was due to a large and statistically significant decrease in hospitalization expenditures. This may mean that patients achieved better control of their asthma while using levalbuterol versus albuterol which resulted in better control of other disease states that can be exacerbated by asthma. Alternatively, it could just be a coincidence since the study was not designed to detect correlation between asthma and other disease states. The financial results of this study was similar to that of Ozminkowski et al who found that levalbuterol use was associated with a savings in total healthcare costs of \$US1122. However they found that levalbuterol patients on average paid \$US853 more for asthma-related healthcare cost than racemic albuterol patients.

The results of table VII suggest that neither levalbuterol nor racemic albuterol was able to statistically decrease the number of emergency department visits, physician visits or hospitalizations over time. This was also shown in the increase in costs for all of the above from the pre-index period to the post-index period in table IV. Although this suggests that neither drug was more efficacious compared to the other, important factors such as change in lung function, improvement in activities of daily living, safety, patient satisfaction or other important issues were not taken into consideration.

If financial costs rather than efficacy, safety, patient satisfaction, or other issues is what drives the market for these drugs then from a purely financial perspective, this study suggests that levalbuterol was a more economical choice. Analyses of both asthma-related expenditures and total healthcare expenditures favored levalbuterol. This unfortunately does not solve the problem as to which drug should be used since the drugs were used in such different population and so a direct comparison is not very informative. It is also difficult to determine which drug is better from this study since a decrease in healthcare expenditure does not always equal an

improvement in healthcare status. Medicaid policy makers may want to use levalbuterol due to the overall decrease in costs, whereas physicians and other providers may want to continue to use racemic albuterol due to the fact that it has been used for years, it is cheaper for patients and may result in better medication adherence and hence better asthma control.

This study has several limitations. First, this is a retrospective, non-randomized study so data could be lost or miscoded. Although multiple regression models were used to control for confounding variables, some bias may remain as a result of omitted variables. Secondly, the number of levalbuterol users was low compared with the number of racemic Albuterol users. While this reflects the market of these two drugs in Kentucky Medicaid patients, greater statistical power may have been achieved with a larger patient sample of levalbuterol users. Thirdly, this study was limited to Kentucky Medicaid patients with asthma. It is therefore not clear whether results can be generalized to other states or to Chronic Obstructive Pulmonary Disease (COPD) patients.

In the analyses of disease-specific expenditures it is impossible to know for certain which expenditures were really related to asthma and which expenditures were not. Patients may have other chronic conditions and asthma may either complicate these in unknown ways or vice versa. Thus, relying on diagnosis codes found in medical claims data may not be ideal for inferring whether costs are related to asthma versus other conditions.

The study is limited because it does not analyze the five components of assessing and monitoring asthma control and severity; the intrinsic intensity of the asthma process, the degree to which the manifestation of asthma are minimized by therapeutic interventions and the goals of therapy are met, the ease with which asthma control is achieved by therapy, frequency and

intensity of symptoms and functional limitations the patient experienced, and the likelihood of either asthma exacerbation, or progressive decline in lung function (PEF or FEV₁)

VI. Recommendations

This study showed that the added cost of using levalbuterol was more than offset by reductions in other types of healthcare expenditures. Levalbuterol provides a financial benefit over racemic albuterol both in asthma-related and total healthcare costs. It is therefore recommended that levalbuterol become the drug of choice for exacerbation of asthma in the Kentucky Medicaid population unless adverse effects, patient satisfaction or lung function dictates otherwise. Randomized double-blind studies of the Kentucky Medicaid population still needs to be done to validate this change in medication preference. A better understanding of the impact of levalbuterol use would result from studies of long term use. If total costs are lower for levalbuterol patients, then it should be determined whether this is due to fewer adverse effects, better adherence or better long-term efficacy. The issue of efficacy would be better addressed by a long-term randomized trial that measures the five components of assessing and monitoring asthma control and severity and uses FEV₁ as a measure of efficacy. The issue of adverse-effect and adherence could be addressed in studies of patient satisfaction.

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