Long-Acting β-Agonist Monotherapy Among Children and Adults With Asthma

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Objectives: To determine the prevalence of long-acting β-agonist (LABA) monotherapy among a Medicaid-enrolled population with asthma and to describe continued LABA monotherapy use.

Study Design: Retrospective cohort.

Methods: Administrative Medicaid claims data for Michigan were used to identify children and adults with asthma, defined as having 4 or more asthma medication–dispensing events during a calendar year between 2006 and 2008. We determined the annual prevalence of LABA monotherapy, defined as having at least 1 dispensing event for a LABA medication in the absence of any other maintenance therapy. The cohort using LABA monotherapy was followed up for 12 months after the identification year to assess continued LABA monotherapy and the frequency of missed opportunities for changes in therapy. Analyses included prevalence proportions, median numbers of office visits, and χ^2 tests to test for significant differences between subgroups.

Results: LABA monotherapy among persons with asthma was uncommon (<1%) and decreased over time. LABA monotherapy was more prevalent among female subjects, persons of white race, and older age groups. The prevalence of continued LABA monotherapy during the follow-up year was 41.2% among the cohort of LABA monotherapy users. Most users of continued LABA monotherapy (92.9%) had at least 1 missed opportunity for therapy change or patient education during the follow-up period.

Conclusion: Although our results indicate that LABA monotherapy was rare, this study provides further evidence supporting enhanced information sharing between points of service about medication utilization that is inconsistent with accepted guidelines.

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The National Asthma Education and Prevention Program's Expert Panel Report 3 guidelines[1] indicate that long-acting β-agonist (LABA) monotherapy is considered unsafe and should not be used for long-term control of asthma. Investigators have reported an association between LABA monotherapy and severe outcomes, such as hospitalizations and death.[2-6] These studies prompted the US Food and Drug Administration (FDA) in August 2003 to require LABA medication package inserts and "black box" labels that warn of these risks, with July 2005 and June 2010 revisions.[7,8] Despite existing evidence, the FDA[9] highlights the need for conclusive studies that evaluate the safety of LABAs when used in combination with inhaled corticosteroids (ICS). The most recent alert by the FDA[8] to healthcare professionals (June 2010) stated that LABA monotherapy is "absolutely advised against" for the treatment of asthma and that LABA monotherapy should only be considered for patients who are not adequately controlled on a long-term asthma control medication. The guidance underscores that LABA monotherapy should be discontinued when asthma control can be maintained without it and that pediatric patients requiring adjunct LABA therapy should be prescribed a combination product to enhance adherence.

Despite the national guideline recommendations and these safety concerns, little is known about the frequency of LABA monotherapy among persons with asthma. The objectives of this study were to determine the annual prevalence of LABA monotherapy among a Medicaid-enrolled population with asthma during the period immediately preceding the 2010 FDA recommendation against this approach to asthma treatment and to describe continued LABA monotherapy use.

METHODS

This study was a retrospective analysis of administrative data maintained by the Michigan Medicaid program, including beneficiary enrollment, utilization, and filled prescriptions for medications. Our study population included children and adults 64 years or younger with asthma who were enrolled in Medicaid between 2006 and 2008. We restricted our study cohort to Medicaid enrollees with full-benefit coverage and no other source of health insurance so that a complete claims history was available for analysis.

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Long-acting β-agonist (LABA) monotherapy among children and adults enrolled in Michigan Medicaid is uncommon. Continued LABA monotherapy is characterized by the following:

- More than 40% of LABA monotherapy users demonstrate continued use of this therapy over a second year.
- There is a high frequency of missed opportunities for patient education or changes in therapy among those with evidence of continued LABA monotherapy.
- Opportunities may exist to emphasize the risks associated with LABA monotherapy among patients with asthma. Enhanced mechanisms are needed to enable information sharing between points of service to alert primary care providers of such opportunities.

To determine the annual prevalence of LABA use and LABA monotherapy, we used the following 2-step process: (1) The denominator was patients with asthma who were continuously enrolled for at least 11 months within each sequential calendar year between 2006 and 2008. The case definition for asthma was having 4 or more asthma medication–dispensing events (ie, filled prescriptions) during a calendar year, with an event defined by 1 prescription of a 30-day supply or less for oral medications or 1 prescription of any days' supply for inhaled medications; asthma medications were determined using Healthcare Effectiveness Data and Information Set criteria.[10] We excluded persons having evidence of chronic obstructive pulmonary disease (COPD), defined by having at least 1 claim for an office visit, emergency department visit, or inpatient stay with a diagnosis of COPD (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 491, 492, or 496). (2) The numerator was LABA monotherapy users among identified patients with asthma within each sequential calendar year. We identified the subset with at least 1 dispensing event for a LABA medication (formoterol fumarate or salmeterol) during a calendar year with no dispensing event for any other type of maintenance therapy during the same calendar year (eg, ICS, leukotriene modifiers, mast cell stabilizers, methylxanthines, and antibody inhibitors). The use of short-acting β-agonists (SABAs) was excluded from our classification of LABA monotherapy. To determine the prevalence of LABA use, we identified the subset receiving at least 1 dispensing event for a LABA medication, irrespective of any other filled prescriptions for asthma medications.

To explore continued LABA monotherapy, we used the following 3-step process: (1) We selected the subset of persons identified as LABA monotherapy users during 2006 or 2007; the initial year of LABA monotherapy was considered the identification year. (2) We assessed medication use in the 12-month period following the identification year (the follow-up year) to determine whether LABA monotherapy was continued or discontinued, as evidenced by initiation of other long-term control medications. (3) We quantified missed opportunities for medication changes or patient education, defined as office visits during the follow-up year with no evidence that LABA monotherapy had been discontinued. These analyses were restricted to patients with asthma who were continuously enrolled in Medicaid for at least 22 months during their respective identification and follow-up years.

Annual prevalence estimates of LABA monotherapy were calculated as proportions per 1000 population; χ^2 tests were used to test for significant differences between demographic subgroups. The frequency of continued LABA monotherapy and missed opportunities were determined using prevalence estimates and median numbers of office visits.

RESULTS

During the study period, there were 39,809 asthma cases in 2006, 40,855 asthma cases in 2007, and 42,727 asthma cases in 2008 (**Table**). The distribution of asthma cases across age, race, and sex variables did not significantly differ across the 3 years; in 2006, most patients with asthma were female (54.8%), of white race (54.9%), and 11 years or younger (45.9%). Among persons with asthma, LABA use was documented in about 1.5%, which decreased over time. LABA monotherapy was recorded in less than 1% of persons with asthma but in about 11% of LABA users. For each year, the prevalences of LABA use and LABA monotherapy were higher among female vs male subjects and higher among persons of white vs black race; the prevalences increased with older age groups. There were statistically significant differences in LABA monotherapy prevalences between demographic subgroups within each year (P <.05 for all years). In 2006, most LABA monotherapy users were female (67.1%), of white race (80.8%), and aged 35 to 64 years (65.8%); the distribution of these characteristics for LABA monotherapy users did not differ significantly over the 3 study years.

A total of 68 children and adults used LABA monotherapy in 2006 or 2007. Of these, most were female (66.2%), of white race (77.9%), and aged 35 to 64 years (45.6%); the mean age of the cohort was 33.7 years. Among these 68 LABA monotherapy users, 58 (85.3%) had at least 1 asthma medication claim in the follow-up year (**Figure**). Continued LABA monotherapy during the follow-up year was evident among 41.2% of LABA monotherapy users and did not differ significantly by age group (P >.05). Among LABA monotherapy users during the follow-up year, most (92.9%) had at least 1 missed opportunity for patient education or a change in their maintenance therapy, with a median of 4 missed opportunities per person. Almost one-fifth (19.1%) of the

Table. LABA Use Among Persons 64 Years or Younger With Asthma Between 2006 and 2008

Variable	Prevalence per 1000 Population (No.)					
	2006 (n = 39,809)		2007 (n = 40,855)		2008 (n = 42,727)	
	LABA Use (n = 741)	LABA Monotherapy (n = 73)	LABA Use (n = 586)	LABA Monotherapy (n = 64)	LABA Use (n = 516)	LABA Monotherapy (n = 58)
Sex						
Male	13.3 (240)	1.3 (24)	10.3 (192)	0.9 (17)	7.2 (139)	0.6 (11)
Female	23.0 (501)	2.2 (49)	17.7 (394)	2.1 (47)	16.1 (377)	2.0 (47)
Race						
Black	12.3 (190)	0.6 (10)	9.2 (145)	0.8 (13)	7.9 (131)	0.5 (8)
White	23.6 (515)	2.7 (59)	18.3 (412)	2.1 (48)	15.1 (354)	1.8 (43)
Other or unknown	14.1 (36)	1.6 (4)	11.0 (29)	1.1 (3)	11.4 (31)	2.6 (7)
Age, y						
≤11	8.1 (148)	0.3 (6)	5.8 (109)	0.1 (2)	4.2 (81)	0.2 (4)
12-34	21.9 (266)	1.6 (19)	17.7 (219)	1.7 (21)	14.9 (194)	1.2 (15)
35-64	34.9 (327)	5.1 (48)	26.9 (258)	4.3 (41)	23.4 (241)	3.8 (39)

LABA indicates long-acting βagonist.
LABA monotherapy defined as >1 dispensing event for a LABA medication and 0 dispensing events for other types of long-term therapy (inhaled corticosteroids, leukotriene modifiers, mast cell stabilizers, methylxanthines, and antibody inhibitors).

cohort had evidence of only SABA medication during the follow-up year, 84.6% of whom had a missed opportunity for therapy changes, with a median of 4 missed opportunities per person. One-quarter of the cohort (25.0%) had long-term controller use during the follow-up year, providing evidence that LABA monotherapy had been discontinued.

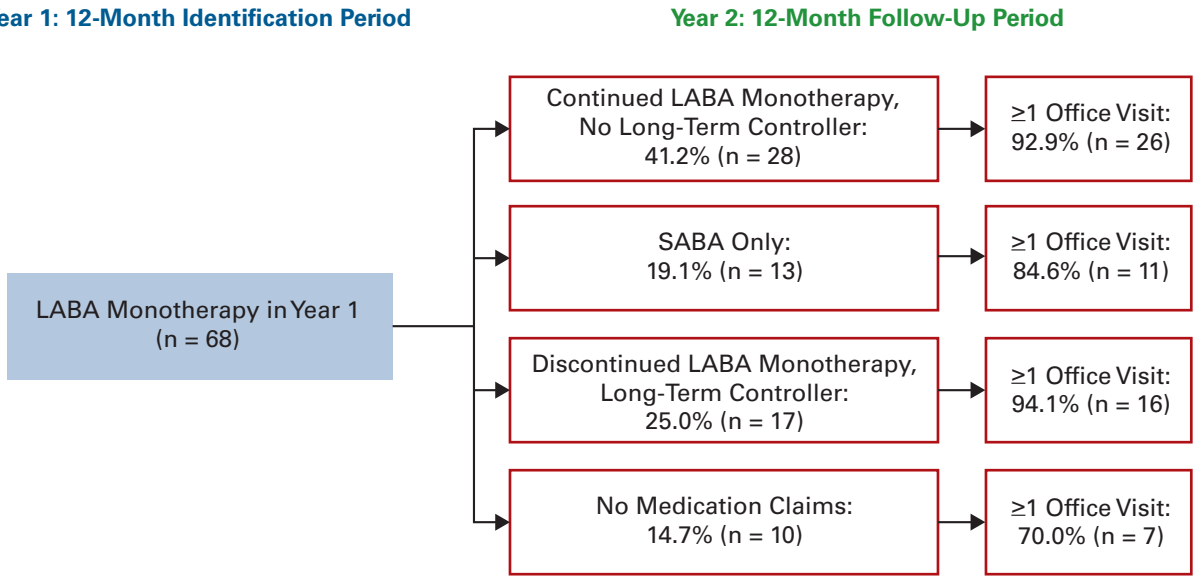
DISCUSSION

To our knowledge, this is the first population-based study of the prevalence of LABA monotherapy and the degree to which it may continue among persons with asthma. We found that LABA monotherapy was uncommon among Michigan Medicaid enrollees with asthma, becoming increasingly rare over time. LABA monotherapy was more common among female subjects, persons of white race, and older age groups. Although the overall use of LABA monotherapy among the population with asthma was small, the prevalence of LABA monotherapy among LABA users was about 11%. In addition, 41.2% of LABA monotherapy users continued that treatment for a second year, and most had office visits where there was an opportunity to change their therapy or to obtain education about appropriate adherence to prescribed medications.

The National Asthma Education and Prevention Program and the FDA have underscored safety concerns about LABA monotherapy, including the increased risk of exacerbation of asthma symptoms and severe adverse events. The use of LABAs is contraindicated in the absence of asthma controller medication use and should be discontinued when symptom control is achieved, if possible.[1,8] Long-term use of LABAs as an adjunct therapy is recommended only for those who cannot achieve asthma control with another controller therapy.[1,8] Little is known about adherence to these guidelines; authors of a 2008 study[11] reported that 2 per 1000 commercially insured members had evidence of LABA monotherapy in the year preceding an initial claim for an ICS-LABA combination product. However, given that the study selected a population using an ICS-LABA, the authors' estimates of LABA monotherapy prevalence are not directly comparable to our study findings.

The rarity of LABA monotherapy among Michigan Medicaid enrollees is an encouraging finding and suggests some degree of success in provoking an appropriate response by providers and patients to LABA safety concerns. However, we found that opportunities may still exist to emphasize the risks associated with LABA monotherapy among LABA users to improve self-management of their asthma. Importantly, policies supporting enhanced mechanisms to enable information sharing among pharmacies, providers, and health plans to alert primary care providers of such opportunities may be warranted. Integrated

Figure. Changes in Therapy and Missed Opportunities for LABA Monotherapy Users 64 Years or Younger With Asthma



LABA indicates long-acting β-agonist; SABA, short-acting β-agonist.
LABA monotherapy defined as ≥1 dispensing event for a LABA medication and 0 dispensing events for other types of long-term therapy (inhaled corticosteroids, leukotriene modifiers, mast cell stabilizers, methylxanthines, and antibody inhibitors).

profiles of patients' asthma prescription fills would enable providers to more clearly recognize patterns of medication use that are inconsistent with accepted guidelines. Such alerts could encourage timely patient-specific feedback to providers, which has been reported to prompt changes in therapy to more appropriate regimens.[12] Prior investigations have illustrated the potential need for such mechanisms to alert primary care physicians of patients having asthma with evidence of SABA overuse prescribed by multiple physicians.[13] Notifying providers of potentially dangerous medication use patterns may be an important initial step toward achieving improvements in long-term asthma control.

This study was limited in that the data source includes only prescriptions that were filled. Providers may have prescribed the appropriate combination of LABA and ICS medications, but the patient may have filled only the LABA portion or an incomplete portion of the ICS prescription. Consequently, our findings may overstate opportunities to influence therapy change and instead may represent opportunities for improved patient education. Also, although we excluded patients with evidence of COPD, the study population may have included patients who had this diagnosis but who did not receive health services for COPD during the study period. Finally, although our study population was drawn from a large pool of Medicaid beneficiaries younger than 65 years, the results may not be generalizable to the wider US population with asthma.

In conclusion, LABA monotherapy was uncommon among Medicaid-enrolled persons with asthma. However, most LABA monotherapy users had multiple office visits at which their healthcare provider could make changes to their therapeutic regimen or emphasize appropriate adherence to prescribed medications. Additional analysis is needed to more fully understand the health services utilization and cost implications of LABA monotherapy and the mechanisms to effectively target interventions aimed at prescribers and patients with asthma. Future work should explore the extent to which enhanced information sharing among pharmacies, providers, and health plans could serve to reduce the number of persons with continued LABA monotherapy.

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