Drug Use Research & Management Program
DHS Division of Medical Assistance Programs, 500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Combination Long-Acting Beta-Agonist Inhaled Corticosteroid: Summary of Clinical Evidence and Drug Utilization Evaluation

Currently, there are two FDA approved combination long-acting beta agonist (LABA) inhaled corticosteroid (ICS) products on the market: salmeterol / fluticasone propionate (*Advair diskus*, *Advair HFA*), and formoterol fumarate dehydrate / budesonide (*Symbicort*). Both drugs are approved for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Specifically, Advair is indicated for treatment of asthma in patients 4 years and older and treatment of airflow obstruction and reducing exacerbations in patients with COPD. Symbicort is approved for maintenance treatment of asthma in patients 12 years of age and older and treatment of airflow obstruction in patients with COPD. Both agents carry an FDA black box warning related to the excess risk of asthma-related death conferred by the LABA component. The FDA issued a Public Health Advisory and revised the product labeling in November 2005 and March 2006 respectively. In February 2010, the FDA recommended additional labeling changes based on a joint meeting of the Pulmonary Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees in December 2008. Summaries of combined LABA-ICS evidence of effectiveness and safety are provided below. Evidence for these summaries was collected from expert guidelines for the treatment of asthma and COPD, recent systematic reviews, FDA advisory committee materials, and recent landmark clinical trials.

Summary of Evidence of Effectiveness for Asthma

Long-term control medications are recommended by the National Heart Lung and Blood Institute (NHLBI) Guidelines for the Diagnosis and Management of Asthma Expert Panel Report 3 (EPR3) for the control of persistent asthma.[1] Inhaled corticosteroids are considered the most potent and effective long-term control treatment and have been documented to reduce asthma severity symptoms and control, improve quality of life, improve lung function, prevent exacerbations, reduce emergent health services utilization, and reduce the risk of death due to asthma. They have been shown to more effectively improve asthma control compared to any other single controller agent. Long-acting beta agonists exert their therapeutic effect through sustained smooth muscle airway relaxation. A Cochrane Collaborative systematic review involving 42,333 subjects and 67 studies published in 2007 compared LABA to placebo in adults and children with asthma.[2] A median of 62% of subjects were concurrently using ICS. In this evidence synthesis, LABA use was associated with improvements in measures of airway flow (e.g. morning PEF, FEV1), improved symptoms, and less use of rescue medication. A second Cochrane review specifically evaluated the efficacy of adding LABA to ICS relative to using a higher dose of ICS in adults and children with asthma.[3] This systematic review included 9509

subjects from 30 clinical trials. While, the addition of LABA to ICS was not found to result in lower exacerbation rate requiring systematic corticosteroids compared to an increased ICS dose approach, combination therapy was associated with improved measures of airway function, symptom –free days, and use of rescue inhalers. Patients using LABA-ICS were less likely to withdraw because of poor asthma control.

Accordingly, NHLBI guidelines state that LABA are the preferred adjunctive therapy, when combined with an ICS, in adults and children ≥12 years old. When added to ICS, LABA are more effective at improving lung function, symptoms, and short-acting beta$_2$-agonist (SABA) use compared to increased ICS or leukotriene receptor antagonist addition. Specifically, the EPR3 Guidelines recommend that LABA should be considered in patients ≥5 years of age who require more than a low-dose ICS to control their asthma symptoms. However, new safety data for LABA suggests that the addition of a LABA or increasing the ICS dose from low to medium should be given *equal consideration* in patients ≥12 years old with moderate persistent asthma or those whom are not adequately controlled on a low–dose ICS. For patients ≥5 years old with severe persistent asthma (step 4 or higher) the combination of LABA and ICS is recommended as the most effective option. In patients whom require more than a low-dose ICS to control asthma, the risk or severe exacerbation, associated with daily LABA treatment, should be weighed against the potential benefit.

A review of the comparative effectiveness of long term controller medications for asthma was conducted by the Drug Effectiveness Review Project (DERP) and generally came to similar conclusions.[4] This systematic review compared a variety of controller medications both within and across classes. They concluded that the data do not consistently support (Strength of evidence = moderate) combined LABA-ICS therapy compared to ICS alone as first line therapy. Their review of trials comparing LABA-ICS compared to ICS dose escalation supports improvements in symptom-free days, asthma symptoms, rescue –free days, and rescue inhaler use (Strength of evidence=high). This is consistent with FDA labeling that states LABA-ICS combination products are indicated only for patients not adequately controlled on other asthma controller medications.

A meta-analyses of 31 randomized controlled trials done by the Canadian Agency for Drugs and Technologies in Health (CADTH) suggest that LABA-ICS combination therapy may have a clinically meaningful benefit over higher-dose ICS monotherapy in improving peak expiratory flow (PEF), reducing the risk of an exacerbation and increasing the number of symptom free days (SFD) and days with optimal control.[5] Combined LABA-ICS had no impact on more severe exacerbations requiring oral corticosteroids or hospitalization. Additionally the two approaches were considered clinically equivalent in terms of effect on evening PEF, absolute and percent predicted FEV1, reducing SABA use and improving quality of life. A review of LABA-ICS combination compared to similar dose ICS monotherapy found the LABA-ICS combination

to have a treatment benefit. The CADTH technology assessment concluded that for most patients with persistent asthma, the initial and only therapy that is typically required is ICS. Adding a LABA to whom patients are controlled on an ICS alone may help to reduce overall ICS requirements as well as decrease the number and severity of exacerbations. Data suggest that although there are often statistical differences found when switching to LABA-ICS combination therapy from ICS monotherapy, in patients with uncontrolled asthma, the benefits are often not clinically significant. The technology appraisal also concluded that clinically important differences between the two LABA-ICS treatments do not exist.

Overall, systematic reviews and guidelines consistently demonstrate that adding LABA to ICS in adults and children with persistent asthma will improve airway function, asthma symptoms, quality of life, reduce short-acting rescue inhaler use compared to ICS dose escalation. The benefit of adding LABA to ICS for preventing severe exacerbations and mortality is not supported or is unclear.

Summary of Evidence of Effectiveness for COPD

New evidence and recently approved drugs have expanded the treatment options for treating COPD. Unfortunately, among the therapeutic options for treating COPD, only smoking cessation, lung volume reduction surgery for patients with severe obstruction, and oxygen therapy for individuals who are hypoxemic have been demonstrated to improve mortality.[6-8] Similar to asthma, current guidelines developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend a stepped approach to treatment.[9] Bronchodilators are a therapeutic pillar in the treatment of COPD. Both short and long-acting beta-agonists and anticholinergics have demonstrated their effectiveness in improving symptoms and lung function. The GOLD guidelines recommends the addition of a long-acting bronchodilator for moderate to severe COPD (stage II or higher).[9] For individuals who remain symptomatic on a long-acting beta-agonist, GOLD guidelines suggest the addition of a long-acting anticholinergic (e.g. tiotropium) may be helpful. Data from the UPLIFT trial, which studied nearly 6000 patients with COPD for a median of 4 years found that while tiotropium had no effect on FEV1 decline or quality of life, the exacerbation rates were improved.[10] Because the pathophysiology of COPD in some includes an inflammatory component, the use of ICS is sometimes helpful. Inhaled corticosteroids have been documented to reduce exacerbations; however their role in slowing lung function decline and reducing mortality is unclear.[11, 12] ICS have well established side effects (e.g. dysphonia, candidiasis) and have been shown to increase the risk of pneumonia in this population.[11] The GOLD guidelines recommend the combination of a LABA and ICS in patients with either severe and very severe disease (stage III and IV). Several recent large randomized trials have provided some new evidence about the role and sequencing of long-acting bronchodilators and ICS.[13, 14] The TORCH trial, included over 6000 individuals with severe COPD and randomized them to salmeterol, fluticasone, combination therapy, or placebo and followed them for three years.[14] Results from this study suggest that combination treatment

resulted in reductions in exacerbation rate, improved health status, and lung function relative to placebo and the other agents. A trend towards improved survival in the combination arm relative to placebo was observed, however this was not statistically significant and of questionable clinical relevance (absolute risk reduction ~ 2.6% over 3 years). The INSPIRE trial involved randomizing over 1200 patients with COPD to either fluticasone/salmeterol or tiotropium and following them for two years. While the study failed to show significant differences in the rate of the primary outcome, COPD exacerbation, patients treated with LABA-ICS showed significant improvement in health status, time until discontinuation, and overall mortality. A Cochrane Collaborative review evaluating combined LABA-ICS compared to LABA monotherapy in patients with COPD reviewed data from 10 clinical trials in 7598 patients.[15] The results of this systematic review showed that the risk of exacerbation in subjects using LABA-ICS was 18% less (RR=0.82; 95% CI 0.78-0.88) compared to subjects using LABA alone. Combination LABA-ICS use was also associated with improved quality of life and airflow measures. While morality between the groups was not different, the risk of pneumonia was 58% higher in subjects using LABA-ICS compared to LABA alone. Taken together these data suggest that LABA-ICS have beneficial effects for a number of important outcomes (quality of life, exacerbations) in patients with COPD. However, the appropriate sequencing of add on therapies (e.g. long-acting anticholinergic versus ICS) remain unclear as conflicting data exist.[16] Despite emerging therapies and combinations, only smoking cessation has been proven to both slow the decline in lung function and reduce mortality in patients with COPD.[6, 17]

Combination LABA-ICS appear to reduce the risk of exacerbation, improve lung function, and health status in patients with COPD. The addition of ICS to LABA does not appear to have meaningful impact on mortality and increases the risk for pneumonia.

Summary of Safety

All products containing LABA carry a black box warning on their label about the increased risk of asthma-related death which was observed in the Salmeterol Multicenter Asthma Research Trial (SMART). Several systematic reviews have evaluated the association between LABA use and life threatening adverse events.

Salpeter et al, conducted a meta-analysis combining data from randomized controlled trials, including SMART, found that use of LABA was associated with an increased risk of exacerbations requiring hospitalizations and life-threatening exacerbations.[18] The risk of asthma-related death was also significantly elevated relative to placebo. This study showed that the increased risk of asthma-related adverse outcomes was not mitigated by concurrent use of ICS. The absolute increase in risk indicates that 1 death in 1000 person-years can be attributed to LABA use. One criticism of this systematic review was that it included many studies where ICS were not required. A second meta-analysis of data comparing LABA-ICS use to ICS monotherapy and included published and unpublished trials posted to the GlaxoSmithKline

Clinical Trials Registry.[19] This analysis failed to demonstrate a statistically significant increased risk of asthma related hospitalization, however the median trial length in this study was 12 weeks.[19] In April 2009, The Cochrane collaborative published several meta-analyses of the safety of formoterol and salmeterol when combined with ICS relative to monotherapy with ICS.[20, 21] In their studies, significant risks of fatal or non-fatal adverse events associated with LABA use were not observed. However, the number of subjects having an event was too small to rule out the possibility that ICS do not completely mitigate the increased risk conferred by LABA. In late 2008, a joint meeting of the FDA respiratory-allergy and drug safety advisory committee met to discuss accumulated safety data for LABAs. Based on FDA meta-analyses of over 60,000 patients the excess risk for asthma-related death, death or intubation, asthma hospitalization, or a composite safety measure were all significantly elevated for patients using LABA. When trials were stratified by ICS at randomization, the risk appeared to be less and became non-significant, however due to lower sample sizes in these sub-analyses, the same risk excess cannot be ruled out. Given the magnitude of prescriptions written for LABA, even small increases in risk of adverse events can represent a large public health problem.

Author/Year	**Total N**	**Comparison**	**duration (months)**	**Adverse event association OR (95% CI)**
Salpeter; 2006	33,826	Formoterol/salmeterol vs. placebo	6	2.6 (1.6-4.3)*
Bateman; 2008	20,966	Salmeterol + ICS vs. ICS	3	1.07 (0.66-1.73)+
Cates CJ; 2009 Cochrane	10,873 (adults)	Salmeterol + ICS vs. ICS same dose	8	1.17 (0.91 - 1.51)+
Cates CJ; 2009 Cochrane	8,028 (adults)	formoterol + ICS vs. ICS same dose	8	0.99 (0.74 – 1.33)**
FDA	60,954	LABA vs. placebo (70% of subjects using ICS at baseline)	6.5	*Risk difference* = 2.8 (1.11 – 4.49)++ w/o ICS 3.63 (1.51, 5.75) w/ICS 0.25 (-1.69, 2.18)

*Asthma hospitalization

+all cause fatal and non-fatal serious adverse events

**all cause non-fatal adverse events

++Asthma death, hospitalization, intubation per 1000 subjects

On February 18, 2010, FDA issued a safety announcement based on these data and the past advisory group deliberations.[22] To ensure the safe use of LABA the FDA recommends the following:

- **The use of LABAs is contraindicated without the use of an asthma controller medication such as an inhaled corticosteroid. Single-ingredient LABAs should only be used in combination with an asthma controller medication; they should not be used alone.**
- **LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications.**
- **LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patients should then be maintained on an asthma controller medication.**
- **Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure compliance with both medications.**

FDA will also require Risk Evaluation and Mitigation Strategy to include enhanced patient and healthcare provider education about the safe use of these products. FDA will be gathering public input in the near future related to the conduct of additional clinical trials to evaluate safety.

While some data exist suggesting that this risk is similar to patients with COPD, the long-term large TORCH trial failed to demonstrate any increased mortality or exacerbation risk in patients treated with salmeterol alone relative to placebo.[14, 23] Recent FDA safety notifications do not extend to the use of LABA for COPD.

Summary of Policy Considerations

Advair, which consistently falls in the top ten drug expenditures for the Oregon FFS Medicaid program, represents a major cost center for the state. Previous analyses by OSU College of Pharmacy have suggested that the use of this drug does not conform to many clinical guidelines.[24] Specifically, it was shown that less than 10% of patients newly starting on Advair had any evidence of prior use of an ICS. This pattern of utilization has been demonstrated in other populations as well. In a claims-based study of over 200,000 individuals from commercially insured US healthcare plan Ye et al found that 10% had a previous history of ICS use in the year prior to their initial fill.[25] Only 38% of new starts on Advair were judged to meet evidence-based criteria suggesting more severe asthma which was defined by previous ICS or leukotriene receptor antagonist controller use, previous asthma hospitalization or emergency department visit, oral corticosteroid prescription, or excessive fills of a SBA. These findings have been replicated in other commercial and Medicaid populations.[26, 27]

Methods

The goals of this utilization review were to describe characteristics of incident users of LABA-ICS combination products. Patient characteristics included basic demographic, indicators of comorbidity, pharmacotherapy history, prescriber characteristics, and measures of respiratory disease severity. New Oregon FFS Medicaid users of a LABA-ICS (i.e. Advair, Symbicort) were identified between 1/1/07 and 12/31/2009, however pharmacy and medical claims data from 1/1/2006 – 12/31/2009 were used to characterize patterns of care and disease severity indicators.

Inclusion and Exclusion

In order to accurately ascertain previous pharmacotherapy and patterns of healthcare services utilization, patients were required to have six months of FFS Medicaid enrollment in the year prior to the incident prescription (index fill) for a LABA-ICS and continuous enrollment in the 3 months immediately prior to their index fill. The six months of eligibility could have been defined by up to two discrete spans of enrollment with a gap of no greater than 31 days between spans. Only subjects with valid demographic data between the ages of 5 through 64 on their index fill date were included in the analysis. The age restriction was applied to limit the analysis to adolescents and adults, where the evidence and guidelines are more clearly defined.

Variable Definitions

Age, sex, and race were ascertained on the index date of every included subject. Diagnosis of asthma was determined in three ways. First, all medical encounter data were screened for an ICD9 code for asthma (table 1) during the previous year. We also used established NCQA/HEDIS measures of asthma to ascertain disease status as recommended by the Oregon Asthma Program Data Workgroup.[28] The HEDIS definition of asthma and persistent asthma are shown in table 1. Similarly, the presence of COPD was defined as any medical encounter with an ICD9 code for COPD in the year previous. Additionally, we created another definition of COPD which excluded individuals who also meet the HEDIS criteria for asthma.

Pharmacotherapy

The index fill dose for Advair (fluticasone/salmeterol) or Symbicort (budesonide/formoterol) was classified as high if it was for the 230/21 (HFA), 250/50 (diskus), 500/50 (diskus) or 160 / 4.5 dosage strengths respectively. We also determined if the index drug was prescribed by one of three clinician groups: pulmonary: physician with an allergy, immunology, pediatric allergy, or pulmonary disease specialty, general practice: clinician with family practice, internal medicine, general practice, or nurse practitioner designation Medication history was established using pharmacy claims which documented a fill or evidence of medication availability (fill date plus day supply) in the 3 months (93 days) prior to index fill. Medication history was subdivided into drug classes for analysis and included ICS, LABA, and anticholinergics. An asthma controller indicator was created that included use of ICS, LABA, leukotriene agent, omalizumab,

mast cell stabilizer, or theophylline in the 93 days prior to index fill. A COPD controller variable was created which included inhaled anticholinergic or LABA. Finally, a combined controller variable was developed and included agents contained in asthma and COPD controller variables.

Disease Severity Measures

Several variables were developed in attempts to assess severity of respiratory disease. First, we quantified the number of emergency department encounters and hospitalizations for both asthma and COPD. A count of the number of fills for oral corticosteroids was constructed as a possible metric of asthma/COPD exacerbation. Several investigators have explored other claims-based measures as a way to predict future asthma exacerbation. One of the more promising metrics which is associated with a reduced likelihood of using acute services for asthma is based on ratio of controller medication fills to total asthma medication fills >=50%.[29, 30] We modified this indicator to identify individuals with ratios <50% who had a minimum of 4 total asthma drug prescriptions in the previous year. Finally, we created a combined disease severity variable to provide the greatest sensitivity for any history of possible asthma exacerbation. The asthma severity variable was defined by any of the following: a controller to total asthma drug ratio <50%, or >1 oral steroid prescription in the previous year, or ED visit or hospitalization related for asthma or COPD in the previous year.

Analysis

This utilization review primarily presents descriptive statistics for patients meeting inclusion and exclusion. Categorical data are presented as counts and percentages. Continuous and discrete data are presented as means with standard deviations. Summary data are presented for all included subjects and according diagnostic criteria of HEDIS defined asthma and COPD (not asthma). We explored the relationship between use of controller agents prior to initiating ICS-LABA and study subject characteristics (e.g. disease severity) in a series of chi-squared tests of proportion.

Table 1: Diagnostic Criteria

Asthma	Any encounter with an ICD9 code for asthma in the year prior to index date
HEDIS Asthma	*one of the following* metrics using pharmacy, encounter, and hospitalization data from year prior to index date a. >=3 asthma med dispensing* **OR** b. >=1 hospital discharge with primary diagnosis of asthma **OR** c. >=1 ED visits with primary diagnosis of asthma **OR** d. >=2 outpatient visits for asthma (anywhere)
HEDIS Persistent Asthma	*one of the following* metrics using pharmacy, encounter, and hospitalization data from year prior to index date a.>=4 asthma med dispensing* **OR** b.>=1 hospital discharge with primary diagnosis of asthma **OR** c.>=1 ED visit with primary diagnosis of asthma **OR** d>=4 outpatient visits with asthma (anywhere) AND 2>= asthma dispensing*
COPD	Any ICD9 code for COPD in previous year
COPD (not asthma)	Any ICD9 code for COPD in previous year AND does meet HEDIS asthma criteria
Asthma ICD9 Codes	493 ASTHMA 4930 EXTRINSIC ASTHMA 49300 EXTRINSIC ASTHMA, UNSPECIFIED 49301 EXTRINSIC ASTHMA WITH STATUS ASTHMATICUS 49302 EXTRINSIC ASTHMA, WITH EXACERBATION 4931 INTRINSIC ASTHMA 49310 INTRINSIC ASTHMA, UNSPECIFIED 49311 INTRINSIC ASTHMA WITH STATUS ASTHMATICUS 49312 INTRINSIC ASTHMA, WITH EXACERBATION 4932 CHRONIC OBSTRUCTIVE ASTHMA 49320 CHRONIC OBSTRUCTIVE ASTHMA UNSPECIFIED 49321 CHRONIC OBSTRUCTIVE ASTHMA W/STATUS ASTHMATICUS 49322 CHRONIC OBSTRUCTIVE ASTHMA WITH EXACERBATION 4938 OTHER FORMS OF ASTHMA 49381 EXERCISE INDUCED BRONCHOSPASM 49382 COUGH VARIANT ASTHMA 4939 UNSPECIFIED ASTHMA 49390 ASTHMA, UNSPECIFIED, UNSPECIFIED STATUS 49391 ASTHMA UNSPECIFIED WITH STATUS ASTHMATICUS 49392 ASTHMA UNSPECIFIED WITH EXACERBATION
COPD ICD9 Codes	4912 OBSTRUCTIVE CHRONIC BRONCHITIS 49120 OBSTRUCTIVE CHRONIC BRONCHITIS WITHOUT EXACERBAT 49121 OBSTRUCTIVE CHRONIC BRONCHITIS WITH EXACERBATION 49122 OBST CHRONIC BRONCHITIS W/ACUTE BRONCHITIS 492 EMPHYSEMA 4920 EMPHYSEMATOUS BLEB 4928 OTHER EMPHYSEMA 496 CHRONIC AIRWAY OBSTRUCTION NEC 5064 CHRONIC RESPIRATORY CONDITIONS DUE FUMES&VAPORS 5181 INTERSTITIAL EMPHYSEMA 5182 COMPENSATORY EMPHYSEMA
*HEDIS asthma medication = ICS, theophylline, mast cell stabilizer, leukotriene active agent, LABA, anti-IgE	

Results

Between 2007 and 2009 we identified 3,071 unique individuals with a prescription for an ICS-LABA product. After applying inclusion and exclusion criteria, the number of individuals retained for the analysis was 583 (19%). Most individuals were excluded because of eligibility requirements (figure 1).

Figure 1: Subject Selection

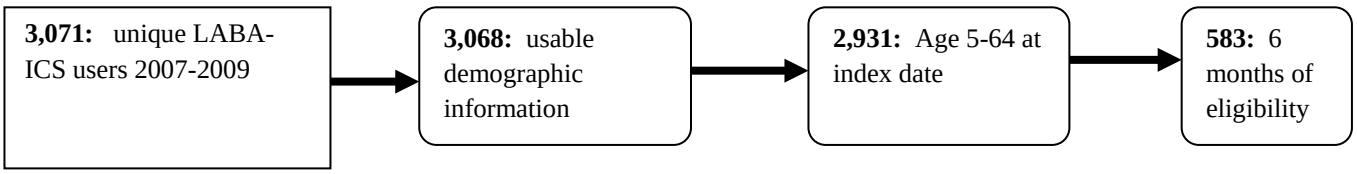

Table 2 reports characteristics of all 583 selected individuals, those who meet the HEDIS definition of asthma (n=170; 29%), and those with a diagnosis of COPD, but not asthma (n=76; 13%). The average age of all incident ICS-LABA users was 35 years. Age differed by diagnostic criteria as expected. The age of incident users with asthma was 29. The age of incident users with COPD was 53.

The predominate ICS-LABA product used was Advair. A majority of new users started on one of the available higher doses (250 or 500 mcg of fluticasone versus 100 mcg; 160 budesonide versus 80). Initial treatment was linked to a physician with a pulmonary, allergy, or immunology specialty in about 4-8% of patients. Nearly half of all new prescriptions were linked to prescribers with a family practice or internal medicine background. Overall, while 52% of individuals had a diagnosis for asthma in the previous year, only 30% of individuals using an ICS-LABA met the HEDIS criteria for asthma. Only 15% of new users met the HEDIS criteria for persistent asthma. We found that 17% of individuals had a diagnosis for COPD, however, only 13% had a COPD diagnoses without a HEDIS asthma diagnosis.

Measures of disease severity generally correlated with the presence of specific diagnoses. Only 4% of new users had more than 1 previous prescription for an oral steroid and 13% of individuals had a previous ED or hospitalization for asthma or COPD. Among those individuals with HEDIS defined asthma, 7% had more than 1 prescription for an oral steroid and nearly 40% had an ED or hospitalization for a respiratory diagnosis. This partly reflects the definition of the HEDIS criteria.

Table 2: Demographics and comorbidity information

	All users		**HEDIS Asthma**		**COPD (no asthma)**	
n	583		170		76	
	mean	**SD**	**mean**	**SD**	**mean**	**SD**
age	35.27	16.86	28.87	15.73	53.37	6.66
ED visits	0.28	1.11	0.85	1.87	0.28	0.72
Hospitalizations	0.06	0.45	0.18	0.81	0.08	0.27
Oral steroid Rx	0.22	0.71	0.34	0.97	0.21	0.6
	count	**%**	**count**	**%**	**count**	**%**
Sex (female)	396	67.9%	111	65.3%	47	61.8%
Race (non-white)	130	22.3%	53	31.2%	8	10.5%
Index Drug Characteristics						
Index Drug Advair	553	94.9%	162	95.3%	72	94.7%
Index Dose (high versus other)	408	70.0%	119	70.0%	58	76.3%
Index Prescriber Specialty						
Pulmonary	21	3.6%	9	5.3%	6	7.9%
Pediatrics	51	8.7%	17	10.0%	0	0.0%
General practice	270	46.3%	66	38.8%	32	42.1%
Other	241	41.3%	78	45.9%	38	50.0%
Diagnostic Characteristics						
Asthma (any dx)	303	52.0%	160	94.1%	18	23.7%
Asthma (HEDIS)	170	29.2%	170	100.0%	0	0.0%
Persistent Asthma (HEDIS)	89	15.3%	89	52.4%	0	0.0%
COPD (any dx)	97	16.6%	21	12.4%	76	100.0%
COPD (no HEDIS asthma)	76	13.0%	0	0.0%	76	100.0%
Disease Severity Indicators						
Controller Ratio <50%	38	6.5%	19	11.2%	7	9.2%
>1 oral steroid	21	3.6%	12	7.1%	2	2.6%
ED/Hosp for asthma/COPD	78	13.4%	63	37.1%	15	19.7%
Severity (controller ratio <50% or >1 oral steroid or ED/Hosp)	101	17.3%	65	38.2%	22	28.9%

Table 3 shows pharmacotherapy history in each of these diagnostic groups. Of the 583 index users, only 70 (12%) had pharmacy claim evidence of using an asthma controller agent in the 3 months prior to their initial ICS-LABA prescription. When the definition of controller was expanded to include anticholinergics, the percentage of individuals using a controller increases to 22%. This likely reflects individuals with COPD. Among individuals with asthma, the number of subjects using a controller agent prior to starting ICS-LABA increased to 28%. Similarly, among those with COPD, the proportion with a history of COPD controller use increased to 43%. The absolute use of ICS in the overall study population was low at 35 (6%).

Table 3: Pharmacotherapy history

	All Users	583	**HEDIS Asthma**	170	**COPD (no asthma)**	76
	count	%	count	%	count	%
ICS	35	6.0%	23	13.5%	5	6.6%
LABA	5	0.9%	5	2.9%	0	0.0%
Anticholinergic	71	12.2%	18	10.6%	33	43.4%
Asthma Controller	70	12.0%	47	27.6%	7	9.2%
COPD Controller	76	13.0%	23	13.5%	33	43.4%
Any Controller	129	22.1%	57	33.5%	38	50.0%

Table 4 shows the results of contingency analyses of categorical data. As expected, a diagnosis of asthma, using any criteria, was significantly associated with having prior use of an asthma controller agent. Similarly, having a diagnosis of COPD was associated with using a COPD controller agent prior to starting an ICS-LABA drug. Subjects meeting the asthma/COPD severity measure were significantly more likely to have used a controller agent compared to subjects without the severity of disease indicator (41.6% versus 18.1%). Individuals using higher doses were significantly more likely to have used a controller drug compared to those starting on a lower dose. Choice of initial ICS-LABA and prescription by a specialist was not associated with having a controller agent prescribed.

Table 4: Selected group comparisons

% Using a Controller			p-value
Asthma Controller			
Any Asthma Diagnosis / no diagnosis	15.5 %	8.2 %	0.0068
Asthma (HEDIS) / no diagnosis	27.7 %	5.6 %	<.0001
Persistent Asthma / no diagnosis	31.5 %	8.5 %	<.0001
COPD Controller			
Any COPD / no diagnosis	44.3 %	6.8 %	<.0001
COPD (not asthma)/ no diagnosis	43.4 %	8.5 %	<.0001
Any Controller			
Severity / No indicator	41.6 %	18.1 %	<.0001
Advair / Symbicort	22.2 %	20. %	0.7732
High dose / low dose	24.5 %	16.6 %	0.0343
Pulmonary or Pediatrics / other	22.2 %	22.1 %	0.9834

Discussion and Recommendation

Clinical evidence and professional guidelines for both asthma and COPD are consistent in their suggestion that combined LABA-ICS should be reserved for those individuals who remain symptomatic on controller monotherapy. The guidance is more defined for adolescents and adults with asthma. The most recent NHLBI asthma guideline revisions state that in patients inadequately controlled on low doses of ICS the addition of an LABA should be given equal consideration to increasing to a medium dose of ICS. While controversy exists about the presence and magnitude of risk associated with LABA use, professional guidance along with manufacturing labeling are clear in stating that LABA should not be used as monotherapy and combination therapy should be reserved for individuals who cannot be managed with ICS and occasional rescue beta-agonists. To help manage this risk FDA recommends that LABA should be used for the shortest duration of time required to achieve control of asthma and discontinued

Medicaid claims data analyses suggest that utilization patterns are not consistent with these practice recommendations. Depending on the denominator, between 6% and 14% of patients were using ICS prior to starting LABA-ICS. Using a less conservative definition of controller increased the proportion of users to between 22% to 50%. While asthma appears to represent the predominate condition treated, individuals with COPD may represent a significant proportion (13%) of individuals. This likely reflects the age demographic of Medicaid and epidemiology of asthma and COPD. Our analysis also clearly demonstrates that individuals with a history suggesting worse severity of disease are more likely to have previous controller use prior to starting LABA-ICS treatment. General practitioners represent the largest prescribers of this drug class.

Potential Policy Proposals.

1) Prior authorize new starts of Advair or Symbicort. Electronically exempt individuals with any evidence increased asthma severity of disease or evidence of COPD (i.e. HEDIS asthma definition, COPD, >1 oral steroid Rx, specialist prescriber, any previous controller prescription). Current users would be grandfathered in.

Pros: Prospectively identifies patients for reduced exposure to unnecessary LABA

Cons: Risks delay of care for moderate-severe asthma patients in crisis. Risks are mitigated by electronically excluding clients with descriptors of more severe disease.

2) Prior authorize LABA monotherapy. Electronically exempt individuals with evidence of COPD or evidence of concurrent asthma controller agent.

Pros: Prospectively identifies patients at highest risk for reduced exposure to unnecessary LABA.

Cons: Limited risk (currently very low utilization) of delay of care for moderate-severe COPD clients.

3) Reconstitute the retrospective education program to target prescribers using LABA-ICS in individuals without evidence of asthma or asthma-related severity.

Pros: No access risk. Education on risks is provided.

Cons: The restrospective intervention did not change prescribing behavior.

References

1. US Department of Health and Human Services NH, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. . National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. ; 2007.

2. Walters EH, Gibson PG, Lasserson TJ, Walters JA. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. *Cochrane Database Syst Rev.* 2007(1):CD001385.

3. Greenstone IR, Ni Chroinin MN, Masse V, et al. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. *Cochrane Database Syst Rev.* 2005(4):CD005533.

4. Jonas DE, Kiser K, Bryant B, Morgan LC, Thieda P, Reuland D. *Drug Class Review: Controller Medications for Asthma*: Cecil G. Sheps Center for Health Services Research; 2008.

5. Bond K, Coyle D, O'Gorman K, et al. *Long-Acting Beta2-Agonist and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation.* Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

6. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med.* Feb 15 2005;142(4):233-239.

7. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med.* May 22 2003;348(21):2059-2073.

8. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med.* Sep 1980;93(3):391-398.

9. Global Strategy for Diagnosis, Management and Prevention of COPD, 2009 (update).

10. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med.* Oct 9 2008;359(15):1543-1554.

11. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Jama.* Nov 26 2008;300(20):2407-2416.

12. Yang IA, Fong KM, Sim EH, Black PN, Lasserson TJ. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2007(2):CD002991.

13. Wedzicha JA, Calverley PMA, Seemungal TA, et al. The Prevention of Chronic Obstructive Pulmonary Disease Exacerbations by Salmeterol/Fluticasone Propionate or Tiotropium Bromide. *Am. J. Respir. Crit. Care Med.* January 1, 2008 2008;177(1):19-26.

14. Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease. *N Engl J Med.* February 22, 2007 2007;356(8):775-789.

15. Nannini LJ, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2007(4):CD006829.

16. Rabe KF, Timmer W, Sagkriotis A, Viel K. Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. *Chest.* Aug 2008;134(2):255-262.

17. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med.* Sep 1 2002;166(5):675-679.

18. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-Analysis: Effect of Long-Acting {beta}-Agonists on Severe Asthma Exacerbations and Asthma-Related Deaths. *Ann Intern Med.* June 20, 2006 2006;144(12):904-912.

19. Bateman E, Nelson H, Bousquet J, et al. Meta-analysis: Effects of Adding Salmeterol to Inhaled Corticosteroids on Serious Asthma-Related Events. *Annals of Internal Medicine.* July 1, 2008 2008;149(1):33-42.

20. Cates CJ, Lasserson TJ, Jaeschke R. Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events. *Cochrane Database Syst Rev.* 2009(2):CD006924.

21. Cates CJ, Lasserson TJ, Jaeschke R. Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events. *Cochrane Database Syst Rev.* 2009(3):CD006922.

22. FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm#_Ref252304498 (accessed 2/23/10).

23. Salpeter SR, Buckley NS, Salpeter EE. Meta-analysis: anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. *J Gen Intern Med.* Oct 2006;21(10):1011-1019.

24. *Oregon State University College of Pharmacy. Drug Use Evaluation: LongActing Beta Agonist (LABA)* 2006.

25. Ye X, Gutierrez B, Zarotsky V, Nelson M, Blanchette CM. Appropriate use of inhaled corticosteroid and long-acting beta(2)-adrenergic agonist combination therapy among asthma patients in a US commercially insured population. *Curr Med Res Opin.* Sep 2009;25(9):2251-2258.

26. Friedman HS, Eid NS, Crespi S, Wilcox TK, Reardon G. Retrospective claims study of fluticasone propionate/salmeterol fixed-dose combination use as initial asthma controller therapy in children despite guideline recommendations. *Clin Ther.* May 2009;31(5):1056-1063.

27. Helm ME, Vargas PA, Jones SM. Advair prescribing patterns in a state medicaid and child health insurance program. *American Academy of Allergy, Asthma, and Immunology Annual Meeting*. San Diego, California; 2007.

28. *Technical Specifications for Quantifying Measures in the Guide to Improving Asthma Care in Oregon*: Oregon Asthma Program Public Health Division; 2009.

29. Samnaliev M, Baxter JD, Clark RE. Comparative evaluation of two asthma care quality measures among Medicaid beneficiaries. *Chest.* May 2009;135(5):1193-1196.

30. Yong PL, Werner RM. Process quality measures and asthma exacerbations in the medicaid population. *J Allergy Clin Immunol.* Nov 2009;124(5):961-966.