

Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies

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Background: Improved adherence to inhaled corticosteroids (ICSs) has also been associated with decreased asthma-associated morbidity and mortality.

Objective: The purpose of this study was to assess patient medication refill persistence with fluticasone propionate (FP) and salmeterol combination in a single inhaler (FSC), FP and salmeterol in combination from 2 separate inhalers, FP and montelukast in combination, FP as monotherapy, and montelukast as monotherapy.

Methods: We performed a retrospective, observational, 24-month (12-month baseline and 12-month follow-up) database study using medical and pharmacy claims from a large managed care organization. We identified 2511 subjects 12 years of age or older with a claim for asthma (International Classification of Diseases, Ninth Revision: 493.XX): 563 patients receiving FSC, 224 receiving FP plus salmeterol, 75 receiving FP plus montelukast, 798 receiving FP only, and 776 receiving montelukast only. Refill rates of FP, as a measure of adherence, were compared for each FP-containing cohort during the 12-month follow-up period. In addition, refill rates were compared between FSC, an inhaler, and montelukast, an oral medication.

Results: Twelve-month baseline asthma medication use and patient demographics were comparable among cohorts. Patients in the FSC cohort obtained significantly more refills compared with the number of FP refills in the other FP-containing cohorts (4.06 for FSC vs 2.35 for FP plus salmeterol, 1.83 for FP plus montelukast, and 2.27 for FP alone) over the 12-month follow-up period. In addition, patients taking FSC had similar refill persistence compared with patients taking the oral leukotriene modifier montelukast (4.51).

Conclusion: FSC might increase ICS refill persistence compared with FP alone in a single inhaler, FP in combination with salmeterol from 2 separate inhalers, and FP in combination with montelukast. In addition, FSC in a dry powdered inhaler had similar refill rates compared with an oral asthma agent, montelukast. Use of a single inhaler containing both an ICS (FP) and a long-acting bronchodilator (salmeterol) might

increase the likelihood that patients are getting more optimal ICS therapy, as well as the benefits from the long-acting bronchodilator, with patient adherence comparable to an oral agent. (*J Allergy Clin Immunol* 2004;113:245-51.)

Key words: Asthma, fluticasone propionate, salmeterol, montelukast, refill persistence, long-acting bronchodilator, oral leukotriene modifier, inhaled corticosteroid, adherence

The lifetime prevalence of asthma in the United States is 26.7 million and in 1999 accounted for nearly 2 million emergency department visits, 478,000 hospitalizations, and 4657 deaths.¹ Hospital and emergency department use both represent evidence of treatment failure, and undertreatment of the disease might add significantly to the direct costs of asthma care. In 1998, the total annual cost of asthma-related hospitalizations has been estimated to be almost \$2.1 billion.² Most importantly, asthma-related hospitalizations are an important risk factor for asthma mortality and for subsequent asthma-related hospital readmission.³⁻⁸

Inhaled corticosteroids (ICSs) are recommended by both the National Asthma Education Prevention Program (NAEPP) and the Global Initiative for Asthma as the preferred controller therapy for patients of all ages with persistent asthma of all disease severities.^{9,10} In addition, the NAEPP and Global Initiative for Asthma recommend, as preferred therapy, the addition of a long-acting bronchodilator for asthmatic patients who require further therapy to achieve the goals of asthma therapy. Treatment with ICSs has been associated in observational studies with decreased exacerbations, including hospitalizations and emergency department visits.¹¹⁻¹⁴ In addition, clinical trials have demonstrated that the combination of ICSs and a long-acting β -agonist further reduces exacerbations.¹⁵⁻²¹ Furthermore, improved adherence to ICSs has also been associated with decreased asthma-associated morbidity and mortality,^{12,13,22,23} whereas underuse of prescribed therapy, which includes poor adherence, significantly contributes to poor control of asthma. The consequences of poor adherence in asthma include increased morbidity and sometimes mortality and increased health care expenditures.²⁴ Poor adherence with ICSs is recognized as a contributor to treatment failure, resulting in increased morbidity and mortality. Improved adherence with anti-inflammatory medications is dependent on good provider behavior associated with patient commu-

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Abbreviations used

FP:	Fluticasone propionate
FSC:	Fluticasone propionate and salmeterol combination
ICD-9:	International Classification of Diseases, Ninth Revision
ICS:	Inhaled corticosteroid
MPR:	Medication possession ratio
NAEPP:	National Asthma Education Prevention Program
SABA:	Short-acting β -agonist

nication and patient education. This includes focus on explaining the rationale for asthma management, written action plans, and scheduled routine follow-up.²⁵ Patient adherence to medication regimens is a universal and not disease-specific problem.

The coadministration of fluticasone propionate (FP) and salmeterol in a single inhaler (FSC) was developed to provide patients with a medication that treated both airway inflammation and smooth muscle dysfunction. The use of a single device allows a greater concentration of both medications to reach the target cells²⁶ and potentially might increase compliance over ICSs taken alone or in combination with other controller medications. This study was therefore designed to investigate whether the use of FSC in a single inhaler will increase the refill persistence compared with the use of an ICS alone or in combination with other controllers. A second research question was whether the refill persistence of FSC in a dry powder inhaler is similar to the refill persistence of an oral asthma agent, montelukast.

METHODS**Data source**

This is a retrospective observational cohort study using linked medical and pharmacy claims. The analysis was conducted by Ingenix, Inc, a UnitedHealth Group Company, which has access to a proprietary, Health Insurance Portability Accountability Act-compliant research database containing information from a noncapitated, managed, fee-for-service national health plan. This database is geographically diverse, containing more than 5 million annual covered lives, with integrated enrollment, laboratory, pharmacy, and medical claims data.

Study population

The study population consisted of subjects with both 1 or more medical claims for asthma (International Classification of Diseases, Ninth Revision [ICD-9]: 493.XX) and 1 or more pharmacy claims for FSC, FP, salmeterol, or montelukast anytime from April 1, 2001, to July 31, 2001. The first prescription was defined as the index prescription. Subjects were required to be 12 years and older at the time of the index event and continuously enrolled in the health plan for 12 months before and 12 months after the filing of index claims to be included in the study. Demographic data for this population were collected, including total health care costs, which consisted of all medical and pharmacy claims for asthma and all other indications.

Subjects were excluded if they had any chronic obstructive pulmonary disease (ICD-9: 491.XX, 492.XX, 494.XX, and 496.XX) or cystic fibrosis (ICD-9: 277.0X) claims. Fig 1 displays the study design.

Cohort definitions

Subjects were grouped into 5 study cohorts on the basis of their prescription claims within 60 days after their index date: (1) FSC, (2) FP plus salmeterol, (3) FP plus montelukast, (4) FP alone, and (5) montelukast alone. The FSC cohort was defined as an index FP-salmeterol single-inhaler preparation. The FP plus salmeterol and FP plus montelukast cohorts were defined as an index FP prescription claim and a subsequent salmeterol or montelukast prescription claim within 60 days of the FP index date. The FP-alone and montelukast-alone cohorts were defined as an index FP or montelukast prescription claim with no other controller claim within 60 days of the index date.

Outcomes

For the primary study cohort regimens (FSC, FP plus salmeterol, FP plus montelukast, FP alone, and montelukast alone), the following refill persistence measures were assessed and compared in the 12-month postindex period: (1) refill rates, (2) treatment days, and (3) medication possession ratio (MPR). Refill rates were defined as the number of monthly (30-day supply) prescription claims for the cohort regimens over the 12-month follow-up period, including the index claim. For dual controller use of 2 individual medications, the refill rate of each medication was assessed. Treatment days for the FSC, FP, and montelukast cohorts were defined as the total days' supply for each medication cohort in the 12-month postindex period, including the index prescription. For the FP plus salmeterol and FP plus montelukast cohorts, treatment days were defined as the number of days with both treatments supplied on that day; treatment days were also measured for each drug separately. The MPR was defined as the number or days supplied (from first to last prescription) divided by the treatment duration period (from index date to the exhaustion of the last prescription). In addition, mean short-acting β -agonist (SABA) use over the 12-month observation period was calculated and compared across cohorts.

Analysis

The primary analysis was the comparison of the adherence measures across study cohorts. The differences in possession ratios and refill rates are reported. ANOVAs adjusting for potential differences in demographic and baseline measures models were used to statistically test the differences in treatment days, MPRs, refill rates, and mean SABA use across cohorts. For the subjects with controller use that included FP, the refill rate of the ICSs was compared. The first model compared the refill rates of FSC with FP in each of the cohorts, and the second model focused on comparing FSC with montelukast in each of the cohorts. All analyses controlled for cohort demographics, physician specialty at index, preindex total health care costs, and preindex asthma medication use.

RESULTS**Subjects**

A total of 7899 subjects were identified with a medical claim for asthma and at least one of the specified pharmacy prescription claims in the capture period. A total of 2436 subjects satisfied the inclusion criteria and were classified in the 5 study cohorts on the basis of their index drug use and medication use within 60 days of the index date (FSC, $n = 563$; FP plus salmeterol, $n = 224$; FP plus montelukast, $n = 75$; FP alone, $n = 798$; and montelukast alone, $n = 776$). The groups had similar characteristics at baseline (Table I).

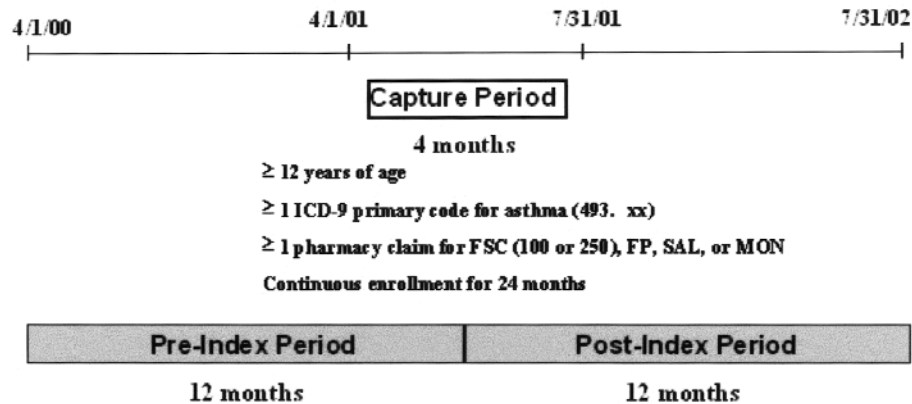


FIG 1. Study design.

Asthma, rhinitis, other
respiratory diseases

TABLE I. Demographics and subject characteristics

Characteristic	FSC	FP + SAL	FP + MON	FP	MON
N	563	224	75	798	776
Male sex, %	38.7	43.3	42.7	37.1	39.0
Age, y (mean)	38.9	38.2	32.6	37.2	33.4
Physician specialty					
General practice-internist, %	48.0	47.3	45.3	51.5	62.6
Allergist, %	29.1	18.8	13.3	17.5	27.3
Pediatrician, %	3.0	4.5	17.3	8.3	9.7
Pulmonary specialist, %	6.9	8.5	6.7	4.6	4.5
Other, %	13.0	21.0	17.3	18.0	15.5
Mean SABA use	1.87	2.11	1.77	1.54	1.64
Mean no. of asthma controller	1.01	2.46	1.20	1.14	1.04
Total health care costs	\$3233	\$3254	\$2591	\$2950	\$2544

SAL, Salmeterol; MON, montelukast.

Refill rates

The mean number of refills obtained by patients in the FSC cohort (4.06 claims; CI, 3.76-4.36) were significantly higher ($P < .001$) compared with the ICS component (FP) of the FP plus salmeterol cohort (2.35 FP claims [CI, 2.05-2.65] and 2.44 salmeterol claims), the FP plus montelukast cohort (1.83 FP claims [CI, 1.53-2.13] and 3.68 montelukast claims), and the FP-alone cohort (2.27 FP claims; CI, 1.97-2.57; Fig 2). In addition, the mean number of refills for the FSC cohort (4.06 claims; CI, 3.76-4.36) was not significantly different from the number of refills observed in the oral leukotriene-only (montelukast) cohort (4.51 claims; CI, 4.21-4.81; Fig 3). Furthermore, more than 99% of the FP claims and 90% of the salmeterol claims were metered-dose inhalers.

Treatment days

The mean treatment days for the FSC cohort (129.37 days; CI, 119.54-139.21) and montelukast-only cohort (150.98 days; CI, 141.15-160.82) were significantly higher ($P < .05$) than the mean treatment days of the FP plus salmeterol (54.63 days; CI, 44.80-64.47), FP plus montelukast (45.59 days; CI, 35.76-55.43), and FP-only

(64.19 days; CI, 54.36-74.03) cohorts over the 365-day postindex period (Fig 4). Furthermore, the FSC cohort had the highest number of treatment days for a regimen containing an ICS. Montelukast had the highest number of treatment days ($P < .05$) for a single controller. Treatment days were also significantly different for FSC compared with montelukast as monotherapy ($P < .05$).

MPR

The mean MPR for patients undergoing a therapy containing an ICS was significantly higher for the FSC cohort (68.9%; CI, 65.64%-72.17%; $P < .05$) compared with the FP plus salmeterol (57.7%; CI, 54.44%-60.97%) and FP plus montelukast (34.2%; CI, 34.20%-37.47%) cohorts (Fig 5). However, the FSC MPR was not significantly different compared with the single controller cohorts (68.1% [CI, 64.84%-71.37%] for FP and 75.2% [CI, 71.94%-78.47%] for montelukast).

Postindex SABA use

The FSC cohort had the lowest use of postindex SABAs compared with all cohorts, whereas the postindex SABA use was highest in the FP plus montelukast cohort. However, the mean postindex use of SABAs in

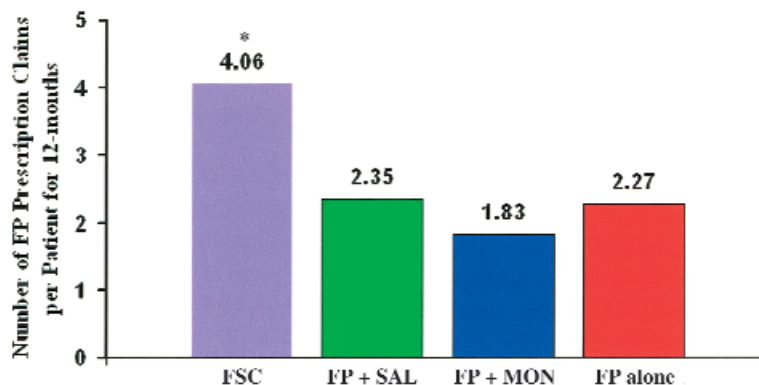


FIG 2. Mean number of ICS prescription claims dispensed within the 12-month postindex period. Number of ICS claims refers to the number of FP prescriptions dispensed as a separate inhaler or in combination with other drugs. SAL, Salmeterol; MON, montelukast. * $P < .05$ compared with the number of ICS prescription claims dispensed in the other cohorts.

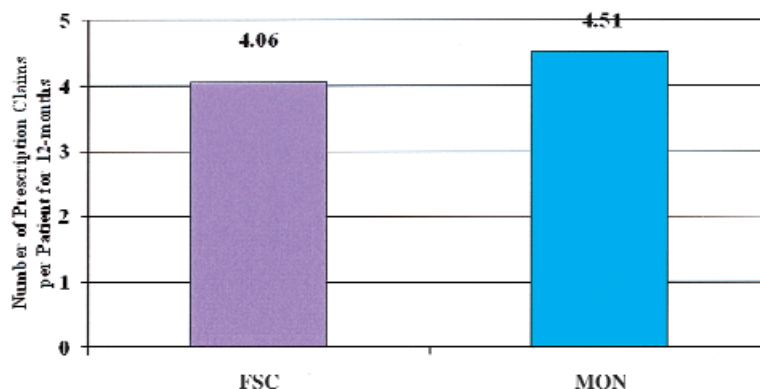


FIG 3. Mean number of FSC and montelukast claims 12 months postindex. MON, Montelukast. Patients in the FSC cohort had similar ($P =$ not significant) refill rates compared with patients using montelukast alone.

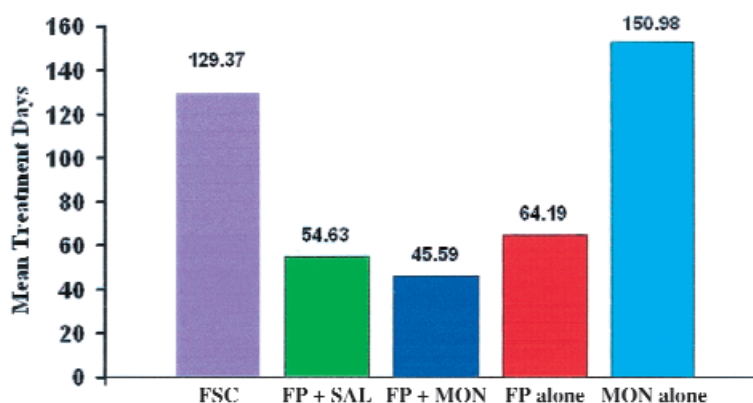


FIG 4. Mean number of treatment days. FSC had the highest number of treatment days for a regimen containing FP ($P < .05$). SAL, Salmeterol; MON, montelukast.

the FSC cohort (1.61; CI, 1.37-1.85) was significantly lower ($P < .05$) compared with that in the FP plus salmeterol (2.28; CI, 2.04-2.52) and FP plus montelukast (2.53; CI, 2.29-2.77) cohorts but not compared with that in the FP-alone (1.97; CI, 1.73-2.21) or montelukast-alone (mean, 1.97; CI, 1.73-2.21) cohorts. Fig 6 shows the mean number of albuterol prescriptions (postindex) over a 12-month period.

DISCUSSION

The results from this study demonstrate that the use of FSC increases the refill persistence of ICSs over 12 months compared with using FP and salmeterol in separate inhalers, using FP with a leukotriene modifier, or even using FP alone. The annual refill rate for FSC was significantly higher when compared with the number of FP

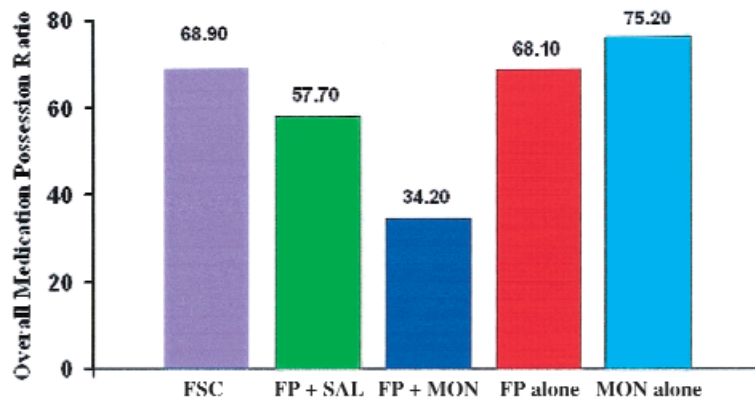


FIG 5. Mean MPR. MPR was the same for FSC, FP, and montelukast. SAL, Salmeterol; MON, montelukast.

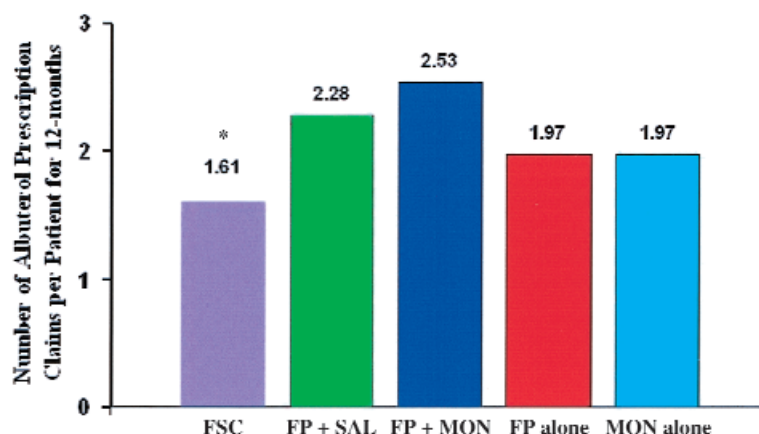


FIG 6. Mean number of SABA prescription claims dispensed within the 12-month postindex period. SAL, Salmeterol; MON, montelukast. * $P < .05$, FSC compared with combination cohorts. The FSC cohort had a significantly lower mean number of SABA claims dispensed in the 12-month postindex period compared with that in the FP plus salmeterol and FP plus montelukast cohorts.

claims in the FP plus salmeterol cohort, the number of FP claims in the FP plus montelukast cohort, and the number of FP claims by patients using FP as a single controller. Use of an ICS was at least 73% higher when a subject was prescribed FSC compared with other FP-containing medication regimens, including FP as a single controller.

Even though the mean treatment days were significantly higher for patients using the oral leukotriene modifier montelukast when compared with the FSC users, the refill persistence and the MPR were similar between the 2 cohorts. However, when montelukast was combined with an ICS, the mean treatment days for the ICS were 64% less ($P < .05$) compared with that in the FSC cohort.

ICSs are the most effective component of long-term controller medication currently available for all levels of treatment of persistent asthma.^{9,10} Clinical trials have consistently demonstrated in both children and adults that ICSs provide superior improvement in clinical outcomes when compared with cromolyn, leukotriene modifiers, long-acting bronchodilators, nedocromil, and sustained-release theophylline.^{9,10,27-31}

Results from large clinical trials have demonstrated that the use of ICSs reduces the morbidity and mortality associated with asthma.^{16,32,33} These findings are confirmed and expanded in observational studies that indicate that the use of ICSs improves symptoms of asthma while protecting against severe exacerbations requiring hospitalizations, emergency department visits, and readmissions.^{11,13,14,34,35} In addition, large observational studies have demonstrated that the use of ICSs is associated with a reduction in the risk of fatal or near-fatal asthma.^{12,36,37} According to the evidence-based NAEPP guidelines,⁹ the addition of a long-acting bronchodilator to an ICS is the preferred treatment in asthmatic patients who might need more than low-dose ICSs to gain control of asthma symptoms and exacerbations.

Implementation and adherence with guideline recommendation is an important aspect of successful attainment of the goals of asthma care. Greater reductions in exacerbations are noted in clinical trials when ICSs are combined with long-acting bronchodilators.¹⁵⁻¹⁹ Several studies have demonstrated that as refill persistence

increases, morbidity and mortality decreases.^{12,13,22,37} Greater refill persistence with specific medications that have been associated with reduced morbidity and mortality is clearly an important goal. In our analysis the use of FP and salmeterol in a single device provides the greatest refill persistence with ICSs and long-acting inhaled bronchodilators compared with FP alone and other combinations containing FP. Although this study was not designed to study the efficacy of therapy, patients using FSC had both the highest refill persistence with ICSs and the lowest use of SABAs when compared with the other treatment cohorts. However, the mean refill persistence with FSC was still less than 50%. The data of Suissa et al^{12,22} and Schatz et al¹³ demonstrate that dramatic reductions in morbidity and mortality can be achieved with only modest refill persistence, 4 to 6 canisters of ICSs per year. Achieving greater refill persistence still must remain a goal until the minimal dosage of FSC that affords control of symptoms, exacerbation, and disease progression is determined.

Improved adherence with medications might be due to several factors. The literature demonstrates that there is an inverse relationship between adherence and the number of medications prescribed, although it is unclear how many medications are needed before the negative effect of multiple medications significantly affects adherence.³⁸⁻⁴⁰ Patients with persistent asthma might be prescribed 1 to 3 asthma controllers, as well as having a SABA for rescue and prednisone for acute exacerbations. In addition, medication might be available to treat their comorbid conditions. Simplification of the medication regimen while achieving comparable or greater clinical improvement should increase patient adherence. The assurance of appropriate controller therapy with ICSs is important, as are the additional benefits achieved with long-acting bronchodilators. The use of the salmeterol component of FSC has been demonstrated to further reduce symptoms and exacerbations in patients whose symptoms are not controlled by ICSs alone.^{15,16,18,19}

There are several limitations to this analysis. First, claims data are collected for the purpose of payment and not for research, and the presence of a prescription claim does not necessarily imply the drug was taken. Second, it is possible that a longer postindex period might have revealed different refill persistence. Third, the use of the supply in days field in the claims might not accurately depict the length of the treatment period considering that how the physician prescribes the drug is not recorded in the data. In addition, the definition of refill persistence based on the supply in days might incorrectly classify subjects as having nonpersistent disease. Fourth, although we adjusted for differences in demographics, preindex asthma medication use, physician specialty, and index total health care costs, this might not accurately adjust for disease severity that could be correlated with differences in refill persistence. However, because of the large number of observations over time, this analysis presents a potentially valuable means of assessing medication use.

In conclusion, the use of FSC appears to maximize

adherence with ICSs and long-acting β -agonists when delivered from a single dry powder inhaler compared with the use of an ICS alone or in combination with either montelukast or salmeterol in separate inhalers. This study supports the belief that simplified medication regimens with effective therapies might promote better refill persistence with prescribed medications. The combined use of an ICS and a long-acting bronchodilator is the preferred therapy by the NAEPP for patients who require more than low-dose ICSs to achieve the goals of asthma therapy. In addition, the refill persistence with FSC is similar to that of subjects using an oral once-daily leukotriene modifier (montelukast). FP and salmeterol delivered from a single inhalation device has been demonstrated to be an effective medication regimen and might enhance refill persistence over that of other controllers alone or in combination, promote better asthma control, and achieve the goals of asthma guideline management.

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