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New products

Series editors: Donald Y. M. Leung, MD, PhD, Harold S. Nelson, MD, Stanley J. Szeftler, MD, Philip S. Norman, MD, and Andrea Apter, MD, MSc

Advair: Combination treatment with fluticasone propionate/salmeterol in the treatment of asthma

Harold S. Nelson, MD

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Advair: Combination treatment with fluticasone propionate/salmeterol in the treatment of asthma

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Several classes of medications are available for the treatment of asthma, and often they must be taken concurrently to achieve asthma control. Based on the understanding of asthma as an inflammatory disease, the National Heart Lung and Blood Institute guidelines provide a stepwise approach to pharmacologic therapy. Corticosteroid therapy, principally inhaled corticosteroid (ICS) therapy, is considered the most effective anti-inflammatory treatment. In cases of moderate-to-severe persistent asthma, the addition of a second long-term control medication to ICS therapy is one recommended treatment option. A combination-product inhaler (Advair, Seretide) was developed to treat both the inflammatory and bronchoconstrictive components of asthma by delivering a dose of the ICS, fluticasone propionate, and a dose of the long-acting β_2 -adrenergic (LABA) bronchodilator, salmeterol. The Advair Diskus is available in 3 strengths of fluticasone propionate (100, 250, and 500 μ g) and a fixed dose (50 μ g) of salmeterol. Combination treatment with both ICS and LABA provides greater asthma control than increasing the ICS dose alone, while at the same time reducing the frequency and perhaps the severity of exacerbations. Furthermore, salmeterol added to ICS therapy provides superior asthma control compared with the addition of leukotriene modifiers or theophylline. The superior control is likely a consequence of the complementary actions of the drugs when taken together, including the activation of the glucocorticoid receptor by salmeterol. By combining anti-inflammatory treatment with a long-acting β_2 -agonist in a single inhaler (1 inhalation twice daily), physicians can provide coverage for both the inflammatory and bronchoconstrictive aspects of asthma without introducing any new or unexpected adverse consequences. The most common drug-related adverse events were those known to be attributable to the constituent medications (ICS therapy and/or LABA therapy). Although the benefits of combined ICS plus LABA therapy can be achieved with separate inhalers, the convenience of the combination product may improve patient adherence and may therefore reduce the morbidity of asthma. (*J Allergy Clin Immunol* 2001;107:397-416.)

Key words: Asthma, Advair, salmeterol, fluticasone propionate, combination therapy, Seretide, leukotriene modifiers, exacerbations, Serevent, Flovent

OVERVIEW

Several classes of medications are used in the treatment of asthma, including glucocorticoids, short-acting and long-acting β -adrenergic (LABA) bronchodilators, leukotriene modifiers, mast cell stabilizers, methylxanthines, and anticholinergics. These medications are often used in combination to optimize asthma control by improving pulmonary function, preventing symptoms, reducing the need for rescue medication, normalizing activity levels, preventing exacerbations, and minimizing the impact of disease on patient quality of life. The necessity for multiple medications, however, can complicate treatment regimens and may contribute substantially to medication misuse. A new combination powder inhaler under the trade name of Advair or Seretide (Glaxo Wellcome) has been developed that combines a dose of inhaled corticosteroid (ICS) (fluticasone propionate [FP]) and a LABA bronchodilator (salmeterol xinafoate) in a single breath-activated device (Diskus). Each inhalation from the Advair Diskus inhaler provides 50 μ g of salmeterol and, depending on the selected Advair strength, 100, 250, or 500 μ g of FP. This article is a review of the scientific and clinical evidence for the combined use of ICSs with long-acting bronchodilators, specifically focusing on the new Advair product. The objectives of this manuscript are:

- To review the positioning in the guidelines for the combined use of ICS and LABA in the treatment of asthma.
- To review the scientific basis for ICS and LABA use in asthma.
- To review the clinical evidence of the complementary actions of ICS and LABA in asthma.
- To address the potential issues inherent in the combined use of ICS and LABA.
- To review the clinical evidence published to date describing the use of the combination Advair product at all 3 strengths.

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Abbreviations used

BDP:	Beclomethasone dipropionate
BHR:	Bronchial hyperresponsiveness
FP:	Fluticasone propionate
ICS:	Inhaled corticosteroid
LABA:	Long-acting β_2 -adrenergic
MDI:	Metered-dose inhaler
PEF:	Peak expiratory flow
RR:	Relative risk

NATIONAL HEART LUNG AND BLOOD INSTITUTE GUIDELINES FOR THE TREATMENT OF ASTHMA

The National Heart Lung and Blood Institute Expert Panel 2 Guidelines to the Diagnosis and Management of Asthma classify asthma into 4 levels of severity based on symptoms and lung function measures assessed before the initiation of treatment: (1) mild intermittent asthma, (2) mild persistent asthma, (3) moderate persistent asthma, and (4) severe persistent asthma.¹ Corresponding to the 4 levels of severity, a 4-step approach to asthma therapy has been defined. The medications used in this step therapy are classified as providing long-term control or quick relief. The long-term control medications include corticosteroids (oral and inhaled), cromolyn and nedocromil, sustained-release theophylline, long-acting β_2 -agonists, and leukotriene pathway modifiers. The medications providing quick relief are short-acting β_2 -agonists, anticholinergics, and systemic corticosteroids.

Patients with mild intermittent asthma, characterized by symptoms twice weekly or less and normal pulmonary function between episodes, require only a quick relief medication that can be used for episodes of asthma and also can be used prophylactically to prevent symptoms, particularly those associated with exercise (step 1). Patients with mild persistent asthma (symptoms more than twice weekly but less than daily with normal lung function but peak flow variability) are appropriately treated with a long-term control medication with anti-inflammatory properties (step 2). For these patients, low-dose ICSs are the preferred agents and the standard to which all others are compared. When low-dose ICSs do not provide the requisite asthma control, treatment options include increasing the dose of the ICS or adding another long-term control medication, including long-acting inhaled β_2 -agonists such as salmeterol, sustained-release theophylline, or leukotriene pathway modifiers to low-to-medium doses of ICSs (step 3). The current evidence reviewed in this article suggests that the preferred treatment option for these patients is combination therapy with low- to moderate-dose ICSs and long-acting β_2 -agonists. For severe persistent asthma, multiple medications may be necessary, including high-dose ICSs, additional long-term control medications, and occasionally oral prednisone (step 4).

EVIDENCE FOR THE EFFECTIVENESS OF ICS THERAPY

Importance of ICS therapy in the treatment of asthma

The importance of ICS therapy in the treatment of asthma cannot be overstated. Asthma is a chronic inflammatory disorder of the airways involving multiple cells and cellular elements including mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells.¹ The magnitude of the inflammation and the thickening of the subepithelial layer (airway remodeling) are generally correlated with the severity of asthma but have been observed to some degree even in mild intermittent asthma.^{2,3} In addition to the disruption in epithelial integrity, the inflammatory response leads to abnormalities in autonomic neural control of airway tone, mucus hypersecretion, change in mucociliary function, and increased airway smooth muscle responsiveness.¹ These inflammatory changes are believed to eventually result in the clinical manifestation of the disease, including symptoms, airflow obstruction, and bronchial hyperresponsiveness (BHR).¹ Because of this, the early introduction of ICS therapy into the treatment of asthma is recommended. Treatment with ICS therapy diminishes the overall inflammatory reaction in the airways, improves the structure of the bronchial epithelium, and reduces the number of eosinophils in the bronchial walls.⁴⁻⁶ These actions are believed to translate into the improvements in clinical outcomes of asthma that have been observed with ICS treatment.

Prevention of asthma complications

ICS therapy reduces the severity of symptoms and airway hyperresponsiveness, improves peak flow and spirometry, prevents exacerbations, and possibly even prevents and/or reverses airway wall remodeling.^{1,7} ICS therapy may also prevent the development of fixed airflow obstruction; however, a delay in the introduction of ICS therapy may blunt this beneficial effect. An inverse relationship between the duration of asthma before the introduction of ICS therapy and subsequent response to treatment has been observed (ie, patients in whom ICS therapy was introduced early demonstrated greater improvements in FEV₁ than patients in whom ICS therapy was delayed⁸). This work corroborates the earlier report of Haahtela et al, who observed that patients with newly diagnosed asthma who had a 2-year delay in the introduction of ICS therapy had a diminished improvement in peak expiratory flow (PEF) compared with patients with newly diagnosed asthma in whom ICS therapy was instituted immediately.⁹ Furthermore, patients with long-standing asthma in whom introduction of ICS therapy was delayed have been observed to have a smaller improvement in airway hyperresponsiveness to methacholine than those in whom ICS therapy was introduced earlier.¹⁰

ICS therapy has been demonstrated to reduce the morbidity and mortality of asthma by decreasing exacerbations requiring additional corticosteroids,¹¹ reducing the risk of hospitalizations due to asthma,¹²⁻¹⁴ decreasing the rate of decline in pulmonary function,¹⁵ and reducing the risk of death.^{16,17}

Asthma control: Evidence with FP

FP is one of the available ICSs that has been widely observed to have a favorable risk-to-benefit ratio when used in a variety of doses and in patients with varying severities of asthma. One of FP's unique features is that it is available in a variety of strengths such that twice-daily administration of 1 to 4 puffs can deliver between 88 and 1760 $\mu\text{g}/\text{d}$. In multiple clinical trials in adult patients previously treated only with as-needed short-acting bronchodilators, FP has been observed to improve lung function, reduce the occurrence of asthma exacerbations, and reduce symptoms and bronchodilator usage in comparison to placebo,^{18,19} theophylline,²⁰ and zafirlukast.²¹ Similar findings were observed with FP in comparison to cromolyn in children.²²

FP at dosages of 88 to 440 μg bid has been observed to improve asthma control in patients who are switched from other ICSs, specifically 8 to 16 puffs/day of beclomethasone dipropionate^{23,24} or 8 to 12 puffs/day of triamcinolone acetonide or beclomethasone dipropionate (BDP).^{25,26} In patients with severe oral prednisone-dependent asthma, FP at dosages of 500 to 1000 μg bid (440-880 μg bid for metered-dose inhalers [MDIs]) has been observed to eliminate or reduce the need for prednisone while maintaining and improving lung function and other measures of asthma control.^{27,28} In head-to-head comparisons of efficacy, FP at a lower dose has been observed to be more effective than triamcinolone acetonide,^{25,26} BDP,^{29,30} and budesonide.²⁹ The onset of these benefits of FP, particularly on the improvements in PEF, symptoms, and rescue albuterol use, can be observed within the first week of treatment and often within the first day.³¹ From the perspective of safety, FP at dosages of 50 to 100 μg bid has been observed to have negligible adverse effects on linear growth in children during a period of 12 to 20 months^{22,32,33} or on bone mineral density in adults after 6 months (FP dosages of 500-1000 μg bid)³⁴ and 2 years (FP dosage of 500 μg bid) of treatment.³⁵

EVIDENCE FOR THE EFFECTIVENESS OF LABA THERAPY

Efficacy of salmeterol

Salmeterol, a potent β_2 -adrenergic agonist, is the only long-acting bronchodilator currently available in the United States. Salmeterol provides superior bronchodilation in 12-hour serial pulmonary function studies in comparison to placebo³³⁻³⁸ and albuterol administered every 6 hours.³⁶⁻³⁹ Additionally, salmeterol provides significantly greater improvement than albuterol in predose FEV₁ and morning PEF while reducing the requirement for rescue albuterol.³⁶⁻³⁹ As one would predict on the basis of its prolonged bronchodilation, salmeterol provides excellent relief of nocturnal symptoms and reduces daytime symptoms of chest tightness, shortness of breath, wheeze, and cough.^{36,37,40} Salmeterol is given at a dosage of 50 μg bid (powder delivery systems) or 42 μg bid for MDIs. Higher dosages of salmeterol (100 μg bid)

have been evaluated, but because they provide little or no additional benefit⁴⁰⁻⁴² and can be associated with a higher incidence of side effects,⁴²⁻⁴⁴ they are rarely used.

Salmeterol studies of up to 1 year's duration have demonstrated undiminished bronchodilator effect and no increase in asthma exacerbations compared with placebo (as-needed albuterol) even when used without attendant anti-inflammatory drugs.^{39,45-47} Moreover, the responsiveness to albuterol was preserved during treatment with salmeterol, irrespective of ICS therapy.^{47,48} Although a partial loss of the initial bronchoprotective effect against methacholine or histamine challenge by salmeterol has been observed, particularly in those studies in which salmeterol treatment followed a β -agonist washout period,⁴⁹⁻⁵² no loss of long-term protection or rebound hyperresponsiveness has been observed.⁵³ Salmeterol has been observed to provide protection from exercise-induced bronchoconstriction, but again, some decrease from the initial degree of protection has been reported with twice-daily dosing in adults⁵⁴ and children when taking salmeterol once daily.⁵⁵ Despite this decrease from the initial level, the continuing bronchoprotective effect of salmeterol exceeded that of the control group, suggesting that the partial tolerance is of limited clinical significance.

Despite the clinical benefit observed with salmeterol, it is particularly important to stress that salmeterol, like other medications that do not have direct anti-inflammatory activity, is not recommended as monotherapy.¹ Salmeterol monotherapy has been shown to provide poorer asthma control than ICS therapy in children^{56,57} and adults, as will be discussed later in combination FP/salmeterol studies.^{58,59} The same has been shown for the leukotriene pathway modifiers^{21,60,61} and theophylline^{20,62} when used as monotherapy compared with ICS therapy.

Effects on asthma morbidity and mortality

Several studies have been conducted that provide reassurance that salmeterol does not increase asthma morbidity or mortality.⁶³⁻⁶⁶ Salmeterol, like theophylline and ipratropium before it, was preferentially prescribed in patients with more severe asthma in the years immediately after its introduction. As a result of this and in response to the increase in asthma mortality reported with another long-acting β -agonist, fenoterol,⁶⁷ salmeterol was closely evaluated with respect to asthma mortality with reassuring results.^{63,64} No evidence was produced that salmeterol contributed to death in any patients in a large prescription-event monitoring study involving 15,407 patients.⁶⁴ Additionally, salmeterol use was not associated with any increase in mortality compared with theophylline or ipratropium in a study of the first 16 weeks of prescription, according to a database representing 4 million patients in the United Kingdom.⁶³ Moreover, salmeterol recipients did not have a greater risk than theophylline recipients for emergency care (relative risk [RR] = 1.09), hospitalization (RR = 1.09), or intensive care unit stays (RR = 0.81), based on the automated records of a large New England insurer.⁶⁵

Clinical outcomes: ICS plus LABA therapy

The efficacy of adding an LABA to ICS therapy versus increasing the dose of ICS therapy in patients in whom low- to moderate-dose ICS therapy alone provided insufficient asthma control has been evaluated in a number of studies^{41,68-74} and a recent meta-analysis.⁷⁵ All are in agreement that improvement in pulmonary function and asthma symptoms is greater with low-dose ICS plus an LABA than with higher dose ICS therapy. Addition of salmeterol to low-dose⁶⁸⁻⁷⁰ or high-dose⁴¹ beclomethasone or to low-dose^{71,72} or high-dose^{73,74} FP resulted invariably in greater improvement in pulmonary function when compared with at least a doubling of the dose of the same ICS. In most instances symptoms were improved and rescue medication use was reduced compared with the treatment with larger doses of ICS alone. Because of the well-recognized relatively flat dose-response curve to ICSs, especially at higher doses, those studies at the low-dose range of 400 µg/d of beclomethasone⁶⁸⁻⁷⁰ and 176 µg/d of FP^{71,72} are perhaps the most clinically relevant.

The use of LABA added to ICS has not been implicated, despite concerns to the contrary, in contributing to worsening asthma or in magnifying the problems associated with asthma exacerbations. In studies evaluating the addition of an LABA to ICS versus higher doses of ICS, combination ICS plus LABA therapy has been observed to neither mask the detection of declining asthma control^{76,77} nor increase the frequency or severity of exacerbations, regardless of whether the patients were receiving low- or high-dose ICS therapy.^{77,78} Specifically, Matz et al⁷⁷ evaluated the frequency and severity of asthma exacerbations in a large number (*n* = 925) of patients taking FP 88 µg bid plus salmeterol versus higher dose FP (220 µg bid) for 6 months. Significantly fewer patients in the FP plus salmeterol group (41 [8.8%]) than in the higher dose FP group (63 [13.8%]) had exacerbations (*P* = .017). Lower exacerbation rates were observed with combination treatment in patients with both mild-to-moderate airway obstruction (60%-85% predicted) and severe obstruction (40%-60% predicted) at baseline. Furthermore, an analysis of the time to first exacerbation revealed that FP plus salmeterol therapy was significantly (*P* = .049) more protective than higher dose FP therapy. When exacerbations occurred leading to treatment with prednisone, there was evidence that patients receiving combination FP plus salmeterol treatment did not have any delay in recognition of the exacerbation and recovered significantly faster in terms of return to pre-exacerbation levels of PEF, symptoms, and rescue albuterol use.

Comparisons of LABA versus other long-term control medications

The addition of an LABA to ICS therapy is one of several available step 3 options recommended by the guidelines, but how does this option compare with others, specifically, adding either a leukotriene pathway modifi-

er or a sustained-release theophylline to ICS therapy? Whereas all options provide benefit,⁷⁹⁻⁸³ recent evidence suggests that the addition of an LABA to ICS therapy is a superior choice. The addition of salmeterol versus zafirlukast was compared in patients whose asthma was not adequately controlled (>80% of whom were taking ICSs).⁷⁹ In this study, designed to compare zafirlukast 20 mg bid to salmeterol 42 µg bid for a period of 4 weeks, salmeterol compared with zafirlukast resulted in an improvement in morning PEF of 30 L/min versus 13 L/min, an improvement in symptom-free days of 22% versus 9%, and an improvement in nights with no rescue medication required of 31% versus 11%. In a more recent direct comparison, the benefits of combination therapy with FP and salmeterol were observed to be superior to those achieved with FP and montelukast, as will be discussed in detail later.⁸⁰ By way of contrast, the benefits of the addition of both leukotriene pathway modifiers⁸¹ and sustained release theophylline^{82,83} to ICS therapy have been found to be generally comparable to those achieved with doubling the dose of ICS. In an abstract report by Nayak et al,⁸¹ the addition of zafirlukast 40 mg bid or 80 mg bid to BDP 336 µg bid was found to be as effective as but not superior to doubling the dose of BDP (672 µg bid). The mean percentage of improvement in asthma symptom scores was comparable between groups: 16% in both the low-dose zafirlukast and the higher dose BDP group, and 23% in the higher dose zafirlukast group. Mean improvements in PEF were higher in all groups but were also comparable between treatments. In other studies, when theophylline was added to ICS therapy versus doubling the dose of ICS, similar results were observed.^{82,83}

In studies directly comparing salmeterol with theophylline, usually in combination with ICS therapy, salmeterol was found to be superior. A meta-analysis of 9 studies involving 1330 patients comparing salmeterol to theophylline found that all outcomes significantly favored salmeterol.⁸⁴ Salmeterol compared with theophylline increased morning PEF by 20 L/min versus 10 L/min, produced 51% versus 39% symptom-free days, and produced 63% versus 52% symptom-free nights, and more patients withdrew due to side effects with theophylline.

CONCERNS ABOUT COMBINATION ICS PLUS LABA THERAPY

Evidence that LABAs may mask inflammation

Although long-acting inhaled β_2 -agonists clearly are the most effective bronchodilators to add to ICS therapy, concerns persist that by allowing the use of a lower dose of ICS, the underlying inflammation of asthma will be masked. This has been fueled by a crossover study where 13 patients taking at least 1500 µg/d of ICS for control of asthma were subjected to a steroid taper while receiving either salmeterol or placebo.⁸⁵ As predicted, while receiving salmeterol, the patients were able to taper their

ICS to a lower dose before having an exacerbation. At this lower dose of ICS, there was a significantly higher percentage of eosinophils in induced sputum compared with the percentage in patients who had exacerbations at a higher dose of ICS plus placebo, suggesting that the ongoing inflammation was greater in the salmeterol-treated group. Ten of 13 subjects in the salmeterol arm had tapered completely off of ICS therapy by the time of their exacerbations. Therefore this study addresses the potential consequences of salmeterol monotherapy more than it addresses the masking of inflammation with LABA plus ICS therapy.

However, in this study, there were also increasing eosinophil levels in the placebo group because their dose of ICSs was reduced. Importantly, this raises the possibility that "smoldering" airway inflammation is not limited to patients receiving long-acting β -agonists. One could also argue that, just as long-acting β -agonists may control clinical manifestations of asthma but leave persisting bronchial inflammation, ICSs can do the same. This was demonstrated by Sont et al,⁸⁶ who treated subjects with ICS for 2 years, basing dosing in half of the subjects on clinical parameters and in the other half also on the degree of BHR. Those patients treated to reduce BHR received 4 times the dose of ICS and had fewer exacerbations and greater increases in FEV₁ than those treated in response to clinical symptoms. Reduction in bronchial eosinophils correlated with reduction in BHR.

Clearly, the dose of ICS must be carefully selected and individualized to provide the requisite anti-inflammatory coverage, a prospect made difficult by the fact that there is no noninvasive and readily available inflammation marker for this purpose. Guideline recommendations to use the lowest effective dose of ICS (and thereby avoid unwanted adverse systemic effects of ICS therapy) should be interpreted conservatively so that inflammation and the corresponding detrimental effects of it are avoided whenever possible. It remains critical that physicians continue to have the flexibility to adjust the ICS dose.

Evidence that LABAs do not mask inflammation

Despite the above concerns to the contrary, there is ample evidence that the use of an LABA in combination with ICS therapy does not mask inflammation. From a clinical perspective, if use of long-acting β -agonists permitted greater airway inflammation, it is reasonable to expect that there would be a higher incidence of asthma exacerbations in long-term studies. Reassurance in this regard comes from several studies.^{75,77,78} In a 1-year study conducted in 852 patients with asthma, patients' conditions were first stabilized for 1 month with 1600 μ g/d of budesonide.⁷⁸ Patients were then randomly assigned to receive budesonide 200 or 800 μ g/d; half in each group also received the long-acting inhaled β -agonist formoterol. Asthma control in terms of pulmonary function and symptoms was improved by the addition of formoterol, but more importantly, the frequency of both moderate and severe exacerbations was reduced with the

addition of formoterol treatment compared with both high- and low-dose ICS therapy alone. This study indicates that rather than increasing exacerbations, the long-acting β -agonist formoterol decreased the incidence of both moderate and severe exacerbations. Among the severe exacerbations that occurred in the same series, 153 occurred with low-dose budesonide, 125 occurred with low-dose budesonide plus formoterol, 90 occurred with high-dose budesonide, and 57 occurred with high-dose budesonide plus formoterol.⁷⁶

Similar data are available for salmeterol during a 6-month period, as described earlier by Matz et al.⁷⁷ Furthermore, a meta-analysis of studies comparing the addition of salmeterol to ICS therapy versus at least a doubling of the ICS dose demonstrated that, rather than increasing asthma exacerbations, the addition of salmeterol to ICS therapy had a positive effect (ie, that of reducing the number of exacerbations) (Fig 1).⁷⁵ Accompanying this reduction in exacerbations was an increase in pulmonary function (Fig 2) and an increase in symptom-free days (Fig 3).

Further direct evidence that LABAs do not mask inflammation comes from biopsy studies^{87,88} or studies of bronchial alveolar lavage^{89,90} and induced sputum.⁹¹ Sue-Chu et al⁸⁷ studied the effects on inflammation of 3 twice-daily treatments, FP 200 μ g, FP 500 μ g, or FP 200 μ g plus salmeterol, and found that the addition of salmeterol to low-dose FP treatment, rather than masking inflammation, had a beneficial effect. Patients receiving FP 200 μ g treatment alone were observed to have significantly increased CD3 and CD4 lymphocyte levels compared with those receiving other treatments, whereas the FP plus salmeterol treatment group had significantly decreased submucosal mast cell and CD25⁺ lymphocyte levels. In a study with formoterol, the number of submucosal mast cells and to a lesser extent the number of eosinophils were found by biopsy to be significantly reduced.⁸⁸ In bronchial alveolar lavage studies, there was no evidence of a deterioration in the underlying inflammatory disease process as assessed by cell profiles for macrophages, eosinophils, lymphocytes, epithelial cells, neutrophils, or mast cells after treatment with salmeterol for 8 weeks.⁸⁹ In a study of 60 patients who were initially treated with salmeterol 1600 μ g/d and then randomly assigned to receive either budesonide 200 μ g/d plus formoterol or budesonide 800 μ g/d for 1 year, no significant differences were observed between groups in terms of clinical asthma control or the proportion of eosinophils or EG2⁺ cells.⁹¹ Moreover, there was no increase in the level of sputum eosinophils during the year of treatment.

SCIENTIFIC RATIONALE: COMPLEMENTARY ACTION OF ICS PLUS LABA

Considerable research effort has been aimed at characterizing the precise mechanisms of asthma and the contributions of various asthma treatments, fueled in part by the observed and otherwise unexplained clinical benefits of combination therapy with ICS and LABAs. The interac-

Image available in print only

FIG 1. Difference in proportion of patients with 1 or more exacerbations (with 95% CIs). Meta-analysis of studies comparing the treatment options of adding salmeterol to ICS therapy or increasing (at least doubling) the dose of ICS in patients symptomatic while receiving ICS therapy. Positive differences indicate treatment benefit with addition of salmeterol. (Reprinted with permission from Shrewsbury et al. *BMJ* 2000;320:1368-73.)

Image available in print only

FIG 2. Difference in mean clinic FEV₁ after 6 months of treatment (with 95% CIs). Meta-analysis of 7 studies of 6 months' duration comparing the treatment options of adding salmeterol to ICS therapy or increasing (at least doubling) the dose of ICS in patients symptomatic while receiving ICS therapy. Positive differences indicate treatment benefit with addition of salmeterol. (Adapted with permission from Shrewsbury et al. *BMJ* 2000;320:1368-73.)

Image available in print only

FIG 3. Difference in mean percentage of symptom-free days after 6 months of treatment (with 95% CIs). Meta-analysis of 7 studies of 6 months' duration comparing the treatment options of adding salmeterol to ICS therapy or increasing (at least doubling) the dose of ICS in patients symptomatic while receiving ICS therapy. Positive differences indicate treatment benefit with addition of salmeterol. (Adapted with permission from Shrewsbury et al. *BMJ* 2000;320:1368-73.)

tions between corticosteroids and β_2 -agonists in asthma have been excellently reviewed.⁹² Perhaps the most important finding in this regard has been the demonstration of the positive complementary actions of ICS and LABA therapy on receptors for the other agent. In a study by Eickelberg et al,⁹³ it was demonstrated that the β_2 -adrenergic agonists salmeterol and albuterol promoted the ligand-independent activation of the glucocorticoid receptors in vitro in human lung fibroblasts and vascular smooth muscle cells. The complementary actions, howev-

er, are not limited to β -agonists. Using a human nasal mucosa model, Baraniuk et al⁹⁴ demonstrated that clinical doses of glucocorticoids increase the number of β_2 -adrenergic receptors as well. Other studies have demonstrated the complementary or synergistic actions of ICS plus LABA and characterized the nonbronchodilator properties of salmeterol (Table I). Taken together, these data provide a foundation not only for the better understanding of asthma but also for a solid scientific basis for the use of combined ICS and LABA therapy.

TABLE I. Findings from other studies regarding the complementary actions of ICS and LABA and the nonbronchodilatory properties of LABA

Study	Finding
Complementary actions of ICS and LABA	
Eickelberg et al ⁹³	β_2 -Agonists activate the glucocorticoid receptor (in vitro)
Baraniuk et al ⁹⁴	Glucocorticoids increase β_2 -receptor number (in vivo/in vitro)
Pang ¹⁰⁸	Synergistic inhibition by β_2 -agonists and corticosteroids of TNF- α -induced IL-8 release (in vitro)
Pang and Knox ^{109*}	Synergistic inhibition by β_2 -agonists and glucocorticoids of TNF- α -induced eotaxin release (in vitro)
Oddera et al ¹¹⁰	Salmeterol enhances inhibitory activity of corticosteroids on allergen-induced blood mononuclear cell activation (in vitro)
Anenden et al ^{111*}	Salmeterol facilitates FP-induced eosinophil apoptosis (in vivo)
Mak et al ¹¹²	Glucocorticoids have protective effects on downregulation of β_2 -adrenergic receptors (in vivo)
Mak et al ¹¹³	Glucocorticoids increase β_2 -adrenergic receptor transcription (in vitro)
Nonbronchodilatory properties of LABA	
Proud et al ¹¹⁴	Salmeterol inhibits allergen-induced vascular permeability (in vivo)
Bissonnette and Befus ¹¹⁵	Salmeterol and albuterol inhibit the IgE-dependent release of TNF- α (in vitro)
Butchers et al ¹¹⁶	Salmeterol inhibits release of histamine, leukotriene C ₄ , and prostaglandin D (in vitro)
Nials et al ¹¹⁷	β_2 -Agonists (salmeterol, formoterol, albuterol) inhibit release of histamine from human lung fragments (in vitro)
Chong et al ¹¹⁸	Salmeterol inhibits IgE-mediated release of histamine from human lung mast cells by β -adrenoceptor-dependent and β -adrenoceptor-independent mechanisms (in vitro)
Dowling et al ¹¹⁹	Salmeterol reduces <i>Pseudomonas aeruginosa</i> -induced damage to organ culture and nasal epithelium (in vitro)
Dowling et al ¹²⁰	Salmeterol protects respiratory epithelium against <i>Haemophilus influenzae</i> -induced damage (in vitro)

*Abstracts.

STUDIES OF ADVAIR THERAPY

The clinical and scientific rationale for the combined use of ICS and LABA is well founded and compelling. No other single therapy or combination of other therapies has been shown to provide equal asthma control or to equally prevent the sequelae of uncontrolled asthma, including exacerbations and hospitalizations. Provided there is flexibility to vary the ICS dose, a combination ICS plus LABA product represents an important treatment advance. Furthermore, there is a compelling need for asthma therapies that reduce the complexity of treatment, particularly in patients who require multiple therapies, and improve the likelihood of patient adherence.

The combination product has been evaluated in several multicenter trials of 4 to 28 weeks' duration to compare the efficacy and safety of the combination product to the efficacy and safety of the constituent medications taken individually.^{58,59} the constituent medications taken concurrently in separate inhalers,^{95,96} and other alternative treatments⁸⁰ (Table II). Although these trials differ in the severity of asthma and the dose of FP being evaluated, the results are remarkably similar. These studies will be reviewed below.

Each of these studies included a run-in period of 1 to 3 weeks to collect information on lung function, symptom scores, and albuterol use before randomization to study treatments. This design enabled an evaluation of patient compliance with study medication (in those with a single-blind placebo run-in period) and study proce-

dures and provided baseline data for later comparative purposes. Lung function was generally assessed by pre-dose morning spirometry, 12-hour serial pulmonary function testing, and twice-daily PEF measurements. Additionally, symptom scores, nighttime awakenings due to asthma, rescue use of albuterol, and asthma exacerbations (generally defined as a clinical deterioration requiring the use of oral prednisone) were recorded. In 2 studies,^{58,59} a uniform definition of worsening asthma based on a composite of lung function, clinical symptoms, nighttime awakenings, and use of rescue albuterol was used to assess asthma stability (Table III). If patients met these criteria, they were withdrawn early, and alternative therapy was instituted. In addition to ensuring safety in these placebo-controlled trials, the comparative asthma stability of the varying treatments could be compared. The arms using placebo and salmeterol alone afforded the opportunity for the researchers to observe the effects of discontinuation of ICS therapy on the control of asthma in those patients previously treated with ICS therapy.

Pilot study: Concurrent FP and salmeterol via MDI

The first study, by Pearlman et al,⁹⁵ was not an Advair study per se but was an important pilot study because it compared the benefits of several doses of concurrent therapy (in separate MDIs) with those obtained by the constituent medications taken alone. Despite the concurrent use of these medications for several years, this had not

TABLE II. Study designs

Study	Design	Treatments (BID via Diskus)	N	Duration (wk)	Patients
Pearlman et al ⁹⁵	R	Placebo (MDI)	136	4	Age: ≥12 y; FEV ₁ : 50%-80%; no CSs within 1 mo
	DB	FP 88 µg (MDI)			
	PC	FP 220 µg (MDI)			
	PG	Salm 42 µg (MDI), FP 88 µg + Salm 42 µg (separate MDIs), FP 220 µg + Salm 42 µg (separate MDIs)			
Kavuru et al ⁵⁸	R	Placebo	356	12	Age: ≥12 y; FEV ₁ : 40%-85%; stratified: ± previous ICS use
	DB	FP 100 µg			
	PC	Salm 50 µg			
	PG	Advair 100/50 µg (FP 100/Salm 50)			
Shapiro et al ⁵⁹	R	Placebo	349	12	Age: ≥12 y; FEV ₁ : 40%-85%; previous ICS: medium-dose for ≥12 wk
	DB	FP 250 µg			
	PC	Salm 50 µg			
	PG	Advair 250/50 µg (FP 250/Salm 50)			
Aubier et al ⁹⁶	R	Advair 500/50 µg (FP 500/Salm 50)	503	28	Age: ≥12 y; FEV ₁ : 50%-100%; previous ICS: high-dose for ≥12 wk
	DB	FP 500 µg + Salm 50 µg (separate inhalers)			
	PG	FP 500 µg			
Nelson et al ⁸⁰	R, DB	Advair 100/50 µg (FP 100/Salm 50)	447	12	Age: ≥15 y; FEV ₁ : 50%-80%; previous ICS: low-medium dose
	AC, PG	FP 100 µg + montelukast 10 mg QD orally			

R, Randomized; DB, double-blind; PC, placebo-controlled; PG, parallel-group; AC, active controlled; Salm, salmeterol; QD, once daily.

been fully evaluated. A total of 136 adolescent and adult patients with asthma controlled previously with only daily or as-needed short-acting bronchodilators were enrolled. Patients with life-threatening asthma, those who had received any corticosteroid therapy within 1 month, and those who had unstable asthma during the 2-week single-blind placebo screening period were excluded. In a double-blind, double-dummy design, eligible patients were randomly assigned to receive 1 of the following 6 treatments via MDI without a spacer twice daily for 4 weeks: (1) placebo, (2) salmeterol 42 µg, (3) FP 88 µg, (4) FP 220 µg, (5) FP 88 µg plus salmeterol 42 µg, and (6) FP 220 µg plus salmeterol 42 µg. Patients treated with concurrent doses of FP and salmeterol had significantly greater improvements in FEV₁ over baseline at the end-point (0.6-0.7 L) compared with patients receiving salmeterol alone (0.3 L), FP alone, (0.3 L), or placebo (no change). Improvements in the mean maximum percent change from baseline in FEV₁ were observed after the first dose (~40% improvement in both combination groups), and these were maintained after 4 weeks of treatment. The magnitude of the mean improvement in FEV₁ associated with combination FP plus salmeterol treatment (0.6-0.7 L) is virtually unprecedented in clinical trials.

TABLE III. Predefined criteria indicating worsening asthma for studies by Kavuru et al⁵⁸ and Shapiro et al⁵⁹

Category	Criteria
Clinical	Clinical exacerbation requiring emergency department or hospital drugs or additional asthma medications
FEV ₁	≥20% decrease from predose baseline
PEF	≥20% decrease from mean baseline morning PEF on >3 of 7 d before visit
Rescue medication	≥12 puffs of albuterol on >2 of 7 d before visit
Nighttime awakenings	≥2 nighttime awakenings/week because of asthma symptoms that required albuterol

Low-strength Advair

The efficacy and safety of the low-strength combination product (FP 100 µg + salmeterol 50 µg bid via Diskus) was compared with the efficacy and safety of FP 100 µg bid, salmeterol 50 µg bid, and placebo in a 12-week study.⁵⁸ In total, 356 patients were stratified into 2 groups: those who had previously taken low-dose ICS for at least 3 months before screening (n = 250), and those

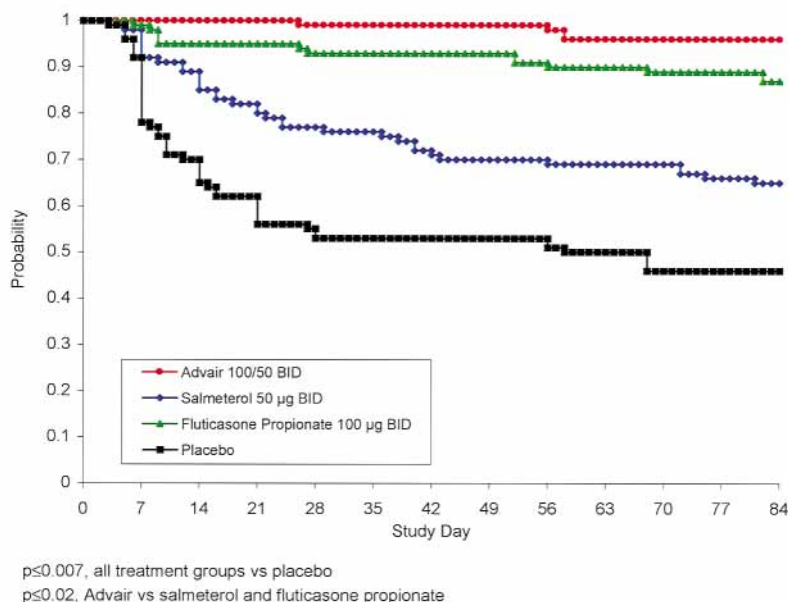


FIG 4. Probability of remaining in the study (Kaplan-Meier survival curve) without exhibiting signs of worsening asthma. Low-dose Advair study. (Reprinted with permission from Kavuru et al. *J Allergy Clin Immunol* 2000;105:1108-16.)

who had taken salmeterol for at least 1 week and no ICS therapy for at least 1 month ($n = 106$). This design enabled an evaluation of the effects of both switching to combination therapy from other ICS therapies and initiating combination therapy in patients previously not taking ICSs. After the 2-week baseline period, during which patients continued their usual asthma medication, patients were randomly assigned to study treatments, and prior therapies (other than the as-needed use of albuterol) were discontinued. Twelve-hour serial pulmonary function tests were performed after the first dose (day 1) and after 1 and 12 weeks of treatment. Morning and evening PEF, asthma symptom scores, nighttime awakenings due to asthma, and rescue albuterol use were recorded on diary cards. At each clinic visit, lung function and diary data were reviewed to determine whether the patient was eligible to continue. Patients who met predefined criteria for worsening asthma were withdrawn from the study.

The treatment groups were balanced at baseline: mean age 35 to 39 years, 51% to 59% male, 83% to 87% white, 64% with FEV₁ predicted normal (all groups), and 29% to 32% reversibility in response to albuterol. The mean albuterol use during baseline was 3 puffs/day, asthma symptoms were present on 75% to 87% of days, and patients were relatively undisturbed by asthma during the night (90%-92% of nights without awakenings).

Patients in the combination group were significantly less likely to be withdrawn because of worsening asthma (Fig 4). Only 3% of patients treated in the combination group were withdrawn due to worsening asthma in comparison with FP alone (11%), salmeterol alone (35%), or placebo (49%, $P \leq .020$). It is worth noting that asthma stability was particularly compromised in patients who

were not receiving ICS therapy. This was exaggerated by the fact that most patients treated with salmeterol alone or placebo (as-needed albuterol only) had their previous baseline ICS therapy discontinued, and thus this finding illustrates the importance of anti-inflammatory therapy in preventing asthma exacerbations and the potential consequences of salmeterol and as-needed albuterol monotherapy.

Combination therapy provided significantly greater improvement in lung function (FEV₁ [Fig 5], PEF [Fig 6]). Mean changes from baseline during 12-hour serial pulmonary function tests were significantly greater in the combination group on day 1, week 1, and week 12 compared with placebo (all time points, $P < .001$), FP (all time points, $P \leq .002$), or salmeterol (all time points weeks 1 and 12, $P \leq .047$). The percent change from baseline in FEV₁ on day 1, although superior to that with placebo and FP, as might be expected, was not different from that with salmeterol; however, with continued treatment (12 weeks), the improvements in the combination group surpassed improvements seen with salmeterol alone (Fig 5). Similarly, with morning PEF, patients in the combination group had improvement on the first day of treatment, and this increased over time (Fig 6).

Combination therapy provided significantly greater improvement than all other treatments in PEF, asthma symptom scores, nighttime awakenings, and rescue albuterol use (Table IV). Most notably, albuterol use was decreased by 1.9 puffs/day to approximately 1 puff/day in the combination group, and it was reduced slightly in the salmeterol and FP groups (0.3-0.4 puffs/day) and increased by 1.7 puffs/day in the placebo group. The deterioration in asthma control observed in the placebo

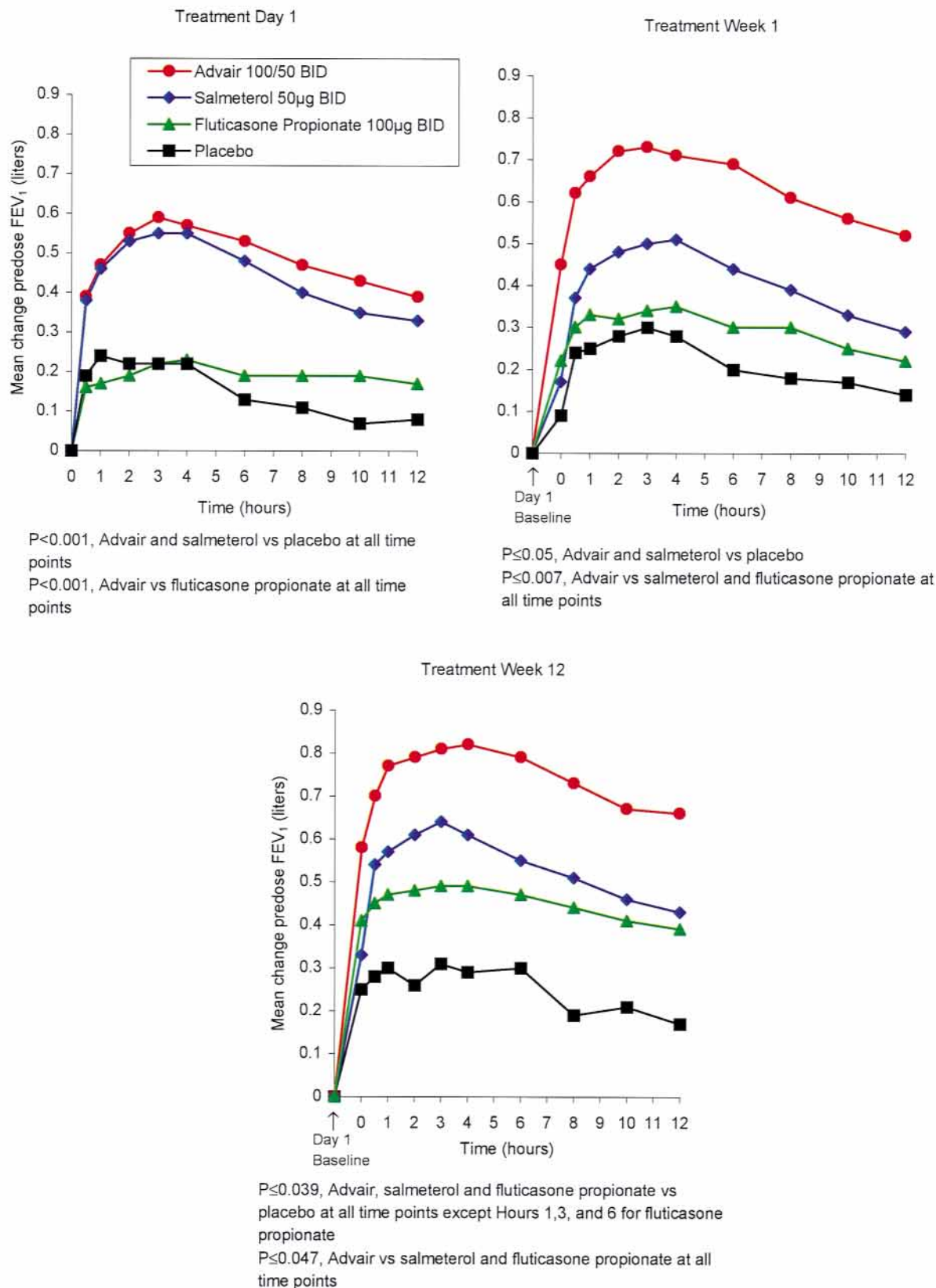


FIG 5. Mean change from baseline (before randomization of study drug) in serial FEV₁ for 12 hours at day 1, week 1, and week 12. Low-dose Advair study. (Reprinted with permission from Kavuru et al. J Allergy Clin Immunol 2000;105:1108-16.)

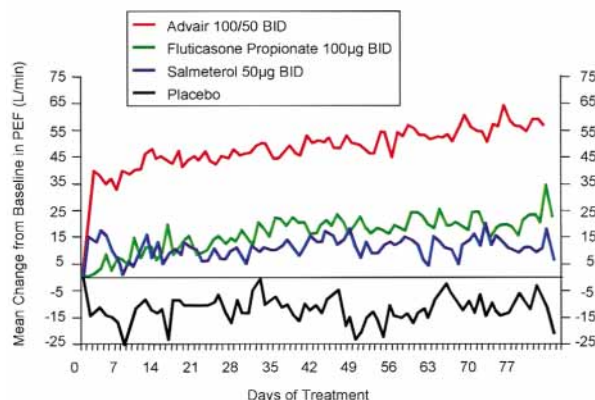


FIG 6. Mean change from baseline in daily mean morning PEF. Low-dose Advair study. (Reprinted with permission from Kavuru et al. *J Allergy Clin Immunol* 2000;105:1108-16.)

group and to a lesser extent in the salmeterol group again highlights the importance of continued anti-inflammatory treatment for optimal asthma control.

Medium-strength Advair

The medium-strength combination product was evaluated in a double-blind, parallel-group, placebo-controlled trial that required all patients to be receiving moderate doses of ICS therapy at baseline before being randomly assigned to combination therapy twice daily (250 µg FP, 50 µg salmeterol), FP 250 µg bid, salmeterol 50 µg bid, or placebo.⁵⁹ Baseline lung function and symptoms were collected during a 2-week single-blind run-in period before the randomization to treatment (and discontinuation of previous ICS therapy). Patients were evaluated at 1- to 2-week intervals during the study and were permitted to continue in the study only if their asthma was stable.

In total, 349 patients were enrolled in the study: 93 in the placebo group, 84 in the combination group, 88 in the salmeterol 50 µg group, and 84 in the FP 250 µg group. The groups were similar at baseline: mean age 38 to 40 years, 41% to 54% male, 73% to 89% white, FEV₁ 68% to 69% predicted normal, and 28% to 29% reversibility to albuterol. Additionally, the mean albuterol use was 3 to 4 puffs/day, asthma symptoms were present on 63% to 81% of days, and patients were undisturbed by asthma during the night on 90% to 91% of the nights.

As was observed with low-strength combination therapy, the combination group had significantly greater asthma stability than all other treatment groups (Fig 7). During 12 weeks of treatment, 4% of the combination group was withdrawn due to worsening asthma as compared with 22%, 38%, and 62% of the patients in the FP, salmeterol, and placebo groups, respectively. Like the study by Kavuru et al,⁵⁸ asthma stability was considerably compromised in those patients in whom ICS therapy was discontinued at randomization (ie, the placebo- and salmeterol-alone groups). Most of the deterioration in asthma occurred within 1 month of the discontinuation of ICS therapy.

Greater improvement in predose FEV₁ was observed with combination therapy than with salmeterol alone, FP alone, and placebo at each study visit, and at endpoint, an analysis that included the last available measurement for all patients revealed differences that were statistically significant (Fig 8). The improvement in lung function in the combination group was observed initially after the first dose but became more pronounced after continued treatment. The magnitude of the improvement and the onset of effect (significantly improved compared with salmeterol alone within hours of the first dose) provide support that there are complementary actions of ICS and LABA taken in combination. After 12 weeks of treatment, FEV₁ values, including those obtained before the morning dose of medication, had increased 26% to 33% over the pretreatment baseline values in the combination group.

Combination therapy also provided superior control of asthma compared with all other treatments with respect to symptoms, nocturnal awakenings, and albuterol use (Table V). With combination therapy, mean morning PEF increased to 90% of predicted at endpoint, an increase of 53.5 L/min, or approximately 15% from baseline. The improvements with FP 250 µg were more modest (86% of predicted, +15.2 L/min), whereas PEF declined with salmeterol and placebo treatment, a likely consequence of the discontinuation of ICS therapy. Combination therapy resulted in an increase in the percentage of days with no asthma symptoms from 27% at baseline to 51% at endpoint, and albuterol use was reduced from 3.5 puffs/day to just more than 2 puffs/day. The need for rescue albuterol was unchanged for the salmeterol group and actually increased nearly 1 puff/day in the placebo group.

High-strength Advair

Twice-daily administration of the high-strength combination product (FP 500 µg + salmeterol 50 µg) was compared with twice-daily concurrent use of FP 500 µg plus salmeterol 50 µg in separate Diskus inhalers and FP 500 µg bid via Diskus taken alone in a randomized, double-blind, parallel-group study.⁹⁶ Because of the severity of asthma and the duration of this study (28 weeks), no placebo arm was included. All patients were required to have an FEV₁ between 50% and 100% of predicted normal while taking high-dose ICS therapy (BDP or budesonide 1500-2000 µg/d or FP 750-1000 µg/d). After the 2-week run-in period, only those patients who were symptomatic and had a PEF between 50% and 85% of maximum after albuterol were enrolled. Patients were evaluated after 2, 4, 12, 20, and 28 weeks of treatment and kept diary records of PEF, daytime and nighttime asthma symptom scores, and albuterol use during the first 12 weeks of treatment. Adverse events and changes in concurrent medications were monitored throughout the 28-week treatment period.

A total of 503 patients were randomly assigned to treatment: 167 in the combination group, 171 in the concurrent FP plus salmeterol group, and 165 in the FP 500 µg group. Most patients had long-standing asthma (>15 years); the mean age ranged from 46 to 50 years, slightly more men than women participated, and the mean percentage of predicted FEV₁ was 73%.

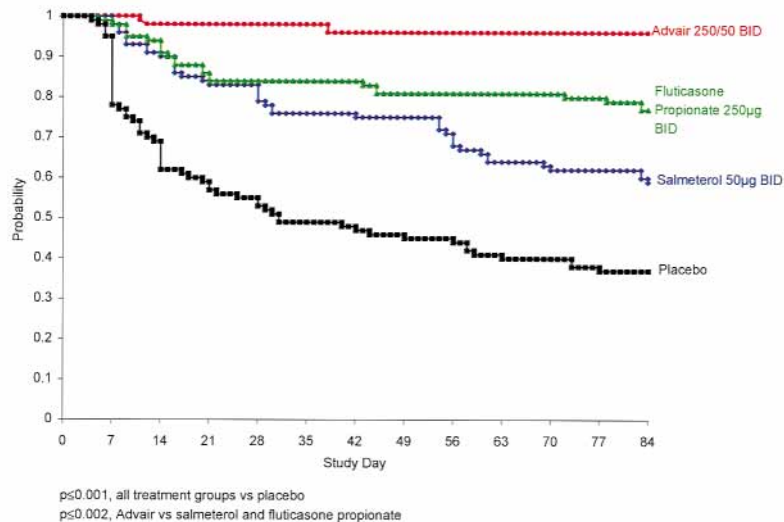


FIG 7. Probability of remaining in the study (Kaplan-Meier survival curve) without exhibiting signs of worsening asthma. Medium-dose Advair study. (Reprinted with permission from Shapiro et al. *Am J Respir Crit Care Med* 2000;161:527-34.)

TABLE IV. Low-strength Advair: Mean (SE) change from baseline at endpoint

	Placebo (n = 77)	Advair 100/50 µg (n = 87)	Salmeterol 50 µg (n = 86)	FP 100 µg (n = 85)
Morning PEF (L/min)				
Baseline	382 (11.7)	393 (10.6)	369 (9.5)	374 (11.3)
Mean change	-23.7 (4.8)	52.5 (5.3)*†‡	-1.7 (4.6)*	17.3 (4.4)*
Evening PEF (L/min)				
Baseline	398 (11.5)	418 (10.7)	396 (9.6)	390 (11.0)
Mean change	-13.3 (4.4)	35.0 (4.7)*†‡	-7.4 (4.9)	18.0 (4.6)*
Asthma symptom score (0-5 scale)				
Baseline	1.8 (0.11)	1.5 (0.11)	1.8 (0.10)	1.6 (0.11)
Mean change	0.4 (0.10)	-0.7 (0.11)*†‡	-0.1 (0.1)*	-0.2 (0.09)*
Days with no asthma symptoms (%)				
Baseline	15.8 (3.33)	25.2 (4.00)	12.6 (2.78)	19.4 (3.74)
Mean change	-3.8 (3.01)	22.6 (4.59)*†‡	8.0 (3.29)*	7.2 (4.09)
Nights with no awakenings (%)				
Baseline	89.9 (1.44)	91.7 (1.58)	91.6 (1.45)	91.3 (1.79)
Mean change	-16.5 (3.42)	4.6 (1.73)*†	-5.3 (2.57)*	2.4 (2.34)*
Albuterol use (puffs/d)				
Baseline	3.2 (0.24)	3.1 (0.28)	3.3 (0.28)	3.1 (0.27)
Mean change	1.7 (0.26)	-1.9 (0.26)*†‡	-0.3 (0.26)*	-0.4 (0.21)*

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All doses were administered twice daily. Endpoint analyses included data from the final visit during treatment for patients completing the study and the last available data for patients who were withdrawn early. Days with no symptoms and nights with no awakenings were recorded as 0.

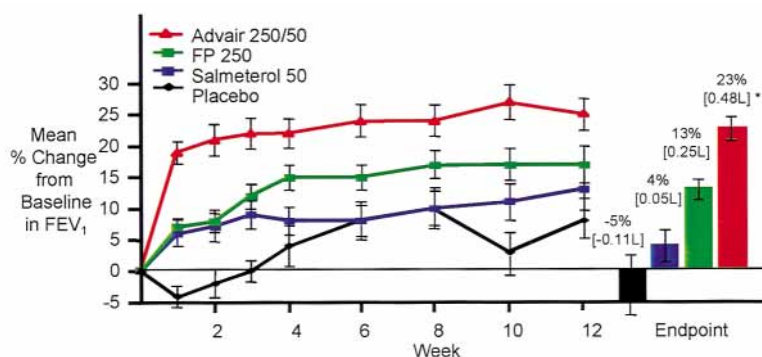
* $P \leq .013$ vs placebo.

† $P \leq .023$ vs salmeterol 50 µg.

‡ $P \leq .025$ vs FP 100 µg.

As expected, both groups that received FP and salmeterol together, either via the combination device or concurrently in separate inhalers, fared better than those who received only FP for morning PEF (Fig 9). Morning PEF in the combination group and the concurrent therapy group was improved 12% and 10%, respectively, over baseline levels with high-dose ICS therapy. No differences were observed between combination use and concurrent use of FP and salmeterol for PEF at any time point. Other measures of asthma control, including FEV₁ and symptom scores, nighttime awakenings, and

albuterol use, were improved to a greater degree in the combination group than in the concurrent treatment group or the FP group; however, these differences were not generally statistically significant. The incidence of asthma exacerbations was not reported in this 28-week study, but a similar number of patients (19% in the combination group, 16% in the concurrent therapy group, and 25% in the FP 500 µg group) were withdrawn for a variety of reasons. This further supports that idea that the addition of LABA to ICS therapy does not increase the incidence of asthma exacerbations. These results corrob-



*Differs from FP 250, salmeterol, placebo at endpoint $P \leq 0.003$

FIG 8. Mean percent change from baseline in clinic FEV_1 at each clinic visit and at endpoint. Endpoint includes the last available FEV_1 value for all patients, regardless of whether the patient was withdrawn early. Medium-dose Advair study. (Adapted with permission from Shapiro et al. *Am J Respir Crit Care Med* 2000;161:527-34.)

TABLE V. Medium-strength Advair: Mean (SE) change from baseline at endpoint

	Placebo (n = 90)	Advair 250/50 (n = 81)	Salmeterol 50 μ g (n = 84)	FP 250 μ g (n = 81)
Morning PEF (L/min)				
Baseline	373 (10.5)	367 (11.0)	372 (10.1)	374 (8.4)
Mean change	-14.1 (3.9)	53.5 (5.6)*†‡	-11.6 (5.2)	15.2 (4.6)*
Morning PEF (% predicted)				
Baseline	82 (1.9)	79 (1.8)	79 (1.7)	83 (1.7)
Mean change	-3.1 (0.9)	11.8 (1.2)*†	-2.2 (1.1)	3.3 (1.0)*
Evening PEF (L/min)				
Baseline	396 (10.0)	388 (11.7)	393 (10.2)	388 (8.5)
Mean change	-15.8 (4.4)	45.4 (5.2)*†‡	-13.7 (4.8)	7.9 (4.5)*
Asthma symptom score (0-5 scale)				
Baseline	1.6 (0.12)	1.4 (0.11)	1.6 (0.10)	1.6 (0.12)
Mean change	0.4 (0.1)	-0.8 (0.12)*†‡	0.1 (0.1)*	-0.4 (0.09)*
Days with no asthma symptoms (%)				
Baseline	24.1 (3.6)	26.5 (4.1)	19.2 (3.7)	23.5 (4.0)
Mean change	-7.9 (3.4)	33.8 (4.6)*†‡	2.1 (3.6)	15.4 (4.2)*
Nights with no awakenings (%)				
Baseline	89.1 (1.9)	90.7 (1.8)	89.7 (2.0)	90.5 (2.1)
Mean change	-12.0 (3.4)	7.2 (1.9)*†‡	-8.0 (3.6)	2.8 (2.4)*
Albuterol use (puffs/d)				
Baseline	3.8 (0.3)	3.5 (0.4)	3.8 (0.3)	3.2 (0.3)
Mean change	0.9 (0.3)	-2.3 (0.4)*†‡	0 (0.3)*	-0.9 (0.2)*

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All doses were administered twice daily. Endpoint analyses included data from the final visit during treatment for patients completing the study and the last available data for patients who were withdrawn early. Days with no symptoms and nights with no awakenings were recorded as 0.

* $P \leq .036$ vs placebo.

† $P \leq .003$ vs salmeterol 50 μ g.

‡ $P \leq .015$ vs FP 250 μ g.

orated the findings of other researchers who had investigated the effects of the lower strength combination product versus those of concurrent therapy via separate inhalers.^{97,98}

Advair versus other treatment options

How does Advair compare with other treatments that could be added to ICS therapy? The answer to this question is a subject of considerable interest and research effort today that, given time, will yield important information for clinicians.⁹⁹ The available evidence suggests

that the combination product provides better asthma control than adding the leukotriene pathway modifier, montelukast, to ICS therapy, as described below.⁸⁰

A randomized, double-blind trial was conducted in patients aged 15 years and older who demonstrated inadequate asthma control (as defined by lung function, the presence of symptoms, and frequent albuterol use) despite treatment with low-dose ICS therapy. Clinically, these patients were classic candidates for step 3 therapy. All patients were switched from their previous ICS to FP 100 μ g bid for a 3-week run-in period. This was done to

permit stabilization with a uniform ICS before randomization as well as to exclude those patients whose symptoms improved (and were therefore no longer symptomatic) as a result of switching to FP. As predicted, a number of patients were excluded after switching to FP, and among those that continued in the study, mean lung function improved from 67% to 70% of predicted during run-in. At the end of the run-in period, patients who were still in need of an additional asthma medication (defined as an FEV₁ between 50% and 80% of predicted normal and at least 1 additional sign of inadequate asthma control based on albuterol use, symptoms, or nighttime awakenings) were assigned to Advair 100/50 µg bid or FP 100 µg bid plus montelukast 10 mg orally once daily in the evening.

A total of 447 patients were randomly assigned to the study treatment: 222 in the combination group and 225 in the FP plus montelukast group. At baseline, the groups were balanced with respect to age (mean 40-43 years), sex (60%-61% female), ethnic origin (84%-91% white), lung function (70%-71% predicted FEV₁), and rescue albuterol use (3.7-3.8 puffs/day).

Both treatment groups' symptoms improved relative to baseline; however, when the improvements were compared between treatments, the combination group fared better in terms of lung function (both PEF and FEV₁, Figs 10 and 11, respectively), albuterol use, and shortness of breath scores (Table VI). Moreover, although the study lasted only 12 weeks, the combination group had significantly ($P = .031$) fewer asthma exacerbations (4 patients, 2%) compared with the FP plus montelukast group (13 patients, 6%).

Adverse events and safety

The safety of ICSs has been extensively reviewed for the local effects of the drug as well as the potential, unintended systemic effects on growth, bone mineral density, hypothalamic-pituitary-adrenal axis function, and cataract formation.¹⁰⁰⁻¹⁰³ Without exception, the consensus remains that, while there are risks inherent in particularly high-dose administration, ICSs remain the best anti-inflammatory treatment option for patients with persistent asthma. Potential systemic effects can be minimized or altogether avoided by obtaining control quickly with higher doses and then reducing the ICS dose to the minimum dose required to control asthma.

Likewise, multiple studies and years of clinical use have found the risk-benefit ratio of the long-acting β_2 -adrenergic bronchodilator salmeterol to be favorable, even desirable.^{104,105} Not only has salmeterol been demonstrated to provide sustained bronchodilation but its use neither masks underlying inflammation nor contributes to increases in asthma exacerbations.

The relevant issue with the use of Advair is whether there are any new and unexpected adverse consequences of taking the drugs in combination that have not been previously observed, and the simple answer is that there are not. In the reviewed studies, adverse events were reported at similar frequencies across treatment groups.

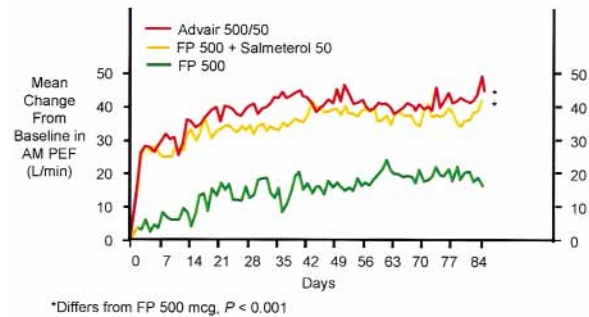


FIG 9. Mean change from baseline in daily morning PEF. High-dose Advair study. (Adapted with permission from Aubier et al. *Respir Med* 1999;93:876-84.)

TABLE VI. Advair versus FP plus montelukast

	Advair 100/50	FP + montelukast	P value
Morning PEF (L/min)			
Baseline	398.3 (5.9)	392.1 (6.3)	
Change weeks 1-12	+24.9 (2.1)	+13.0 (2.1)	<.001
Evening PEF (L/min)			
Baseline	419.4 (6.1)	410.9 (6.4)	
Change weeks 1-12	+18.9 (1.9)	+9.6 (1.9)	<.001
FEV ₁ (L)			
Baseline	2.38 (0.04)	2.39 (0.04)	
Change at endpoint	+0.34 (0.03)	+0.20 (0.02)	<.001
Days with no albuterol use (%)			
Baseline	14.0 (1.7)	15.8 (1.9)	
Change weeks 1-12	+26.3 (2.3)	+19.1 (2.1)	.032
Total albuterol use (puffs/d)			
Baseline	3.77 (0.16)	3.73 (0.16)	
Change weeks 1-12	-1.55 (0.14)	-1.14 (0.12)	.014
Shortness of breath score (scale 0-5)			
Baseline	1.52 (0.07)	1.54 (0.07)	
Change weeks 1-12	-0.56 (0.05)	-0.40 (0.04)	.017
Chest tightness score (scale 0-5)			
Baseline	1.39 (0.06)	1.32 (0.07)	
Change weeks 1-12	-0.49 (0.05)	-0.43 (0.04)	.521
Wheeze score (scale 0-5)			
Baseline	1.18 (0.07)	1.13 (0.07)	
Change weeks 1-12	-0.41 (0.05)	-0.38 (0.05)	.279
Overall daytime symptom scores (0-5 scale)			
Baseline	1.36 (0.06)	1.33 (0.06)	
Change weeks 1-12	-0.49 (0.04)	-0.41 (0.03)	.199

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No significant differences were found between treatment groups at baseline. All treatment groups experienced significant within-treatment group improvements over baseline for all efficacy measures ($P < .001$). Overall daytime score is mean of individual symptom scores (shortness of breath, chest tightness, and wheeze).

The most common drug-related adverse events were those attributable to ICS therapy (oral candidiasis, sore/irritated throat, hoarseness/dysphonia) or LABA treatment (tremor, nervousness, muscle cramping) or

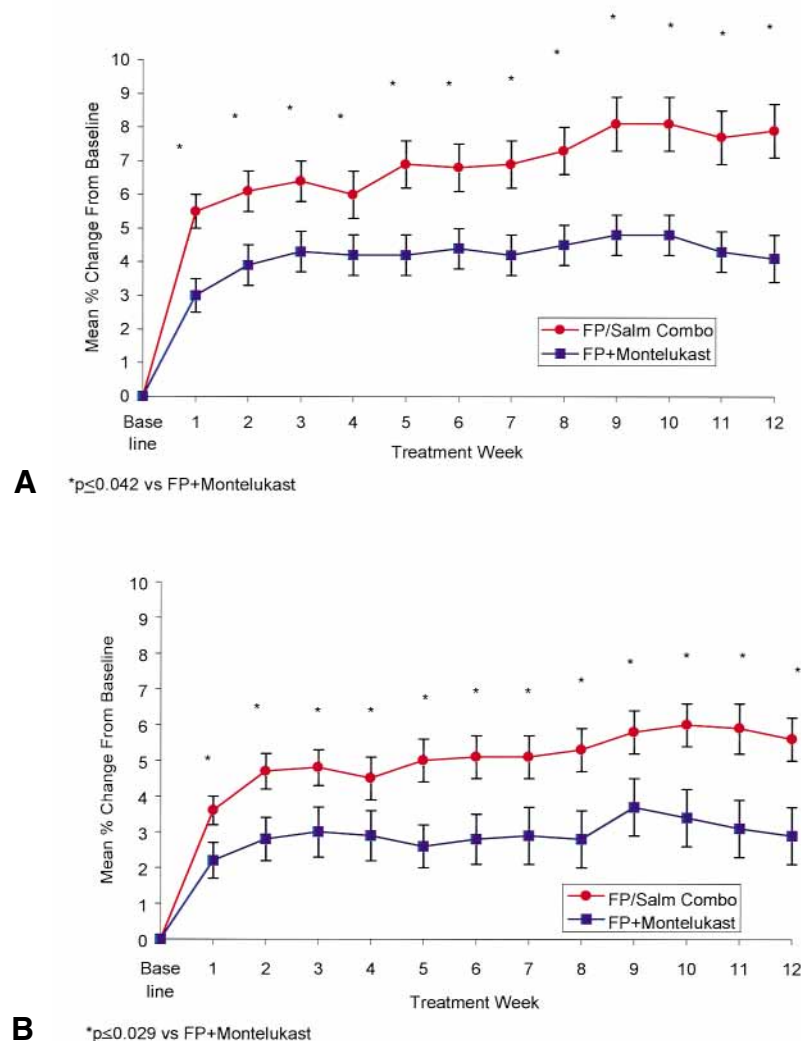


FIG 10. Mean percent change from baseline in morning (**A**) and evening (**B**) PEF. Advair therapy versus FP plus montelukast study. Baseline values obtained during treatment with FP 100 μ g bid. Comparable baseline morning PEF (398 L/min, 392 L/min) and evening PEF (419 L/min, 411 L/min) for FP/salmeterol combination and FP plus montelukast groups, respectively. (Reprinted with permission from Nelson et al. *J Allergy Clin Immunol* 2000;106:1088-95.)

both (headache, cough), and even the most common of these events occurred infrequently ($\leq 3\%$) and rarely led to discontinuation of treatment. Holter monitoring for potential cardiovascular effects and assessments of hypothalamic-pituitary-adrenal axis function for potential systemic corticosteroid effects were consistently found in multiple studies to be similar to those of the constituent medications.

Other considerations: Convenience and compliance

Combination therapy with FP and salmeterol undoubtedly represents an advance in terms of the convenience of asthma treatment. With 1 inhalation twice daily, patients can receive potent anti-inflammatory treatment along with a superior bronchodilator and, because there are 3

strengths, the FP dose can be modified commensurate with asthma control. The Advair Diskus is a breath-actuated powder device that obviates the need to coordinate actuation and inhalation. Furthermore, the Advair Diskus has a dose counter (60 doses, a 1-month supply) so that patients can keep track of their usage and anticipate the need for refills.

Whether the introduction of Advair will ultimately increase patient adherence to this important therapy is not known. A number of factors contribute to medication adherence rates, including the patient's perception of the benefits and risks.^{106,107} Steroid phobia regrettably still exists and limits the widespread and aggressive use of ICS. A concern with salmeterol has been that patients will perceive the improvement in symptoms associated with salmeterol treatment and choose, without counsel-

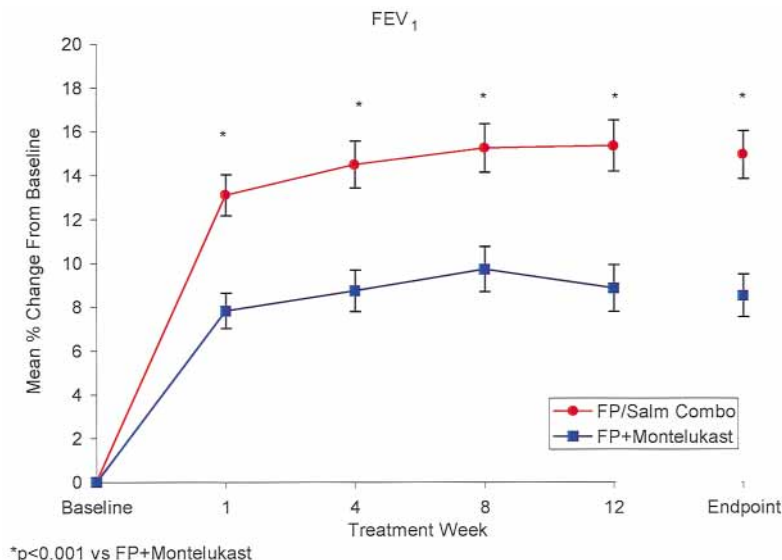


FIG 11. Mean percent change from baseline in clinic FEV₁. Clinic FEV₁ conducted in the morning, 2 to 4 hours after the morning dose of study medication. Advair therapy versus FP plus montelukast study. Baseline FEV₁ values were 2.38 L (70% predicted normal) in the FP/salmeterol combination group and 2.39 L (71% predicted normal) in the FP plus montelukast group after 3 weeks of run-in treatment with FP. (Reprinted with permission from Nelson et al. *J Allergy Clin Immunol* 2000;106:1088-95.)

ing to the contrary, to stop taking their anti-inflammatory therapy. Because the two medications are combined in a single inhaler, Advair therapy may improve adherence and prevent patients from making preferential and potentially ill-advised medication choices to stop one medication or another.

CONCLUSION

This article has reviewed the scientific and clinical rationale for and the efficacy and safety of Advair, a new combination inhaler for the treatment of asthma composed of the ICS fluticasone propionate and the long-acting β_2 -agonist salmeterol. For patients whose symptoms are inadequately controlled on low-dose ICS therapy, combination therapy provides better asthma control than increasing the dose of ICS. Combination treatment also provides superior asthma control than adding a leukotriene modifier or theophylline to ICS therapy. Despite concerns to the contrary, combination therapy has not been shown to be associated with evidence of masking the inflammation of asthma, but instead it has been observed to reduce surrogate markers of inflammation. The superior clinical efficacy of combination treatment is likely a consequence of the complementary actions of these two classes of drugs when taken together. Advair is a unique combination therapy that permits treatment of both the inflammatory and bronchoconstrictive components of asthma in a single inhalation device.

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