The treatment of asthma has changed dramatically in the last 25 years. When I first started volunteering at a camp for children with asthma in the Los Angeles area in 1976, we used more than 100 injections of subcutaneous epinephrine to get 60 children through the 7 days. In the last 20 years, I cannot recall a single dose of epinephrine being used at camp because nebulized albuterol became the treatment of choice for acute exacerbations. Now since the early 1990s, the number of nebulizer treatments has decreased as the use of inhaled anti-inflammatory agents increased, even in the pediatric age group.

During this same time period, the number of patients taking oral theophylline has dwindled. Of the more than 7,000 patients with asthma in my medical group, only a handful take theophylline. Since the late 1980s, office practice changed from doing finger pricks for determining serum theophylline concentrations to teaching patients how to use spacer devices and peak-flow meters.

In this paper, I will review the basis for these shifts in the therapeutic approach to asthma and the rationale for using dual-controller therapy of an inhaled corticosteroid (ICS) and inhaled long-acting beta2-agonist (LABA) to treat asthma. Although there are 5 ICSs and 2 LABAs available on the market (i.e., formoterol and salmeterol), this review will focus mainly on fluticasone and salmeterol. In addition, the strengths and weaknesses of randomized clinical trials (RCTs) and retrospective cohort analyses using large data sets to compare the clinical and economic outcomes of various treatment approaches will be described. The consistency of the scientific evidence supporting dual-controller therapy with the clinical and economic evidence gleaned from several recent studies will be reviewed. This is especially timely in light of the 2002 update to the NIH guidelines for the diagnosis and treatment of asthma, which recommends dual-controller therapy as preferred treatment in children as well as adults with moderate or severe persistent asthma.1

Disease of Inflammation

The cause of asthma and treatment approaches generated a controversy among health care disciplines over the years. Clinicians traditionally focused on using bronchodilator therapy to relieve bronchoconstriction of asthma. This is understandable given that since the 1920s or 1930s bronchodilation was the only way to bring relief to patients with asthma.

Colleagues in respiratory physiology maintained that the primary problem in asthma was not bronchospasm but rather hyperreactive airway disease. According to them, the lungs of patients with asthma are too twitchy, too sensitive. Looking at autopsy specimens of patients with asthma, pathologists described asthma as a variant of eosinophilic bronchitis—a
**FIGURE 1** Mediators and Cells Associated with Asthma Pathology (Used with permission from GlaxoSmithKline.)

**FIGURE 2** Effect of Leukotriene Modifiers on Inflammatory Cells (Used with permission from GlaxoSmithKline.)
term used in the literature from the 1930s to 1960s. Considering our current understanding of asthma, it is apparent that our pathology colleagues were closer to the truth.

A series of experiments beginning in the 1970s changed our view of asthma. Researchers developed techniques for performing bronchoalveolar lavage and bronchial biopsies in patients with mild asthma. This work revealed that asthma is a disease of inflammation. Their findings resulted in renewed interest in the inflammatory process and new approaches to treat asthma.

### Pathophysiology of Asthma

One obvious feature associated with asthma is airflow obstruction. Airflow obstruction, however, is not caused solely by bronchospasm. Rather, cellular events that occur during airway inflammation contribute to the bronchoconstriction, such as edema of the wall that narrows the airway and hypersecretion of mucus into the lumen of the airway.

When this inflammatory process continues unabated, anatomical changes in the lung may occur, such as cellular metaplasia and hypertrophy of the submucosal region. The muscle itself becomes thickened, resulting in smooth muscle hypertrophy. Also seen are collagen deposition and subepithelial matrix protein deposition.

Figure 1 shows the key cells involved in the inflammatory response in the airway. Around each cell are listed cytokines and cellular mediators that are released during inflammation.

It is instructive to see how different classes of asthma medications influence the inflammatory process. As shown in Figure 2, leukotriene modifiers influence several mediators at the level of the basophil, mast cell, and eosinophil. Figure 3 shows the effects of beta-adrenergic receptor agonists—effects not appreciated 10 years ago that go beyond the smooth muscle cell. Corticosteroids (inhaled or systemic) have dramatic effects on multiple cells and multiple mediators in the inflammatory process (Figure 4).

The anti-inflammatory effect of ICSs is visible on biopsy. The left half of Figure 5 shows the intense inflammatory response of a pretreatment bronchial biopsy specimen from a patient with asthma. After 3 months of treatment with inhaled budesonide 600 mcg twice daily, the integrity of the epithelial barrier is restored (Figure 5, right). The basement membrane is far better organized, and the cellular element of inflammation is absent.

Eosinophils play a major proinflammatory role in the pathogenesis of asthma. Corticosteroids have been shown to influence eosinophil survival in an in vitro study. Of 5 different ICSs, beclomethasone dipropionate, which was the first ICS available, is the least effective in diminishing eosinophil survival, with a 50% inhibitory concentration (IC_{50}) of 290 nM. Flunisolide and triamcinolone acetonide are intermediate inhibitors with IC_{50} values of 32 and 25 nM, respectively. The 2 most potent inhibitors of eosinophils are budesonide and fluticasone propionate (IC_{50} of 8.5 and 2.3 nM, respectively). Since this was an in vitro study, the clinical relevance of these findings is unknown.

### Scientific Rationale for Dual-Controller Therapy

Airway inflammation and smooth muscle dysfunction are interrelated in asthma (Figure 6). In patients who warrant more aggressive treatment, the combination of an ICS and an inhaled LABA, termed dual-controller therapy, works at different levels to prevent asthma symptoms.

In vitro studies have shown that ICSs increase beta-receptor function and up-regulate the beta-receptor. This supports clinical experience that overuse of oral or systemic beta-agonists, which can diminish a patient’s reactivity to subsequent administration of the medication, is reversed by the use of corticosteroids. In addition, LABAs prime corticosteroid receptors to make the receptors more active. Both ICSs and LABAs also enhance eosinophil apoptosis or programmed cell death, which may be one of the important features in halting the inflammatory process in the lung.

Nasal mucosa resembles lower respiratory mucosa. Since nasal mucosa is easily accessible, it is frequently used as a surrogate for respiratory mucosal. Up-regulation of beta-receptors occurs in nasal mucosa with as little as 3 days of therapy with topical applied corticosteroid.

The changes in receptors attributed to dual-controller therapy can be seen graphically in Figure 7. In the control on the left, most of the glucocorticoid receptors exist in the cytosol, which is the liquid medium of the cytoplasm. Only a small amount exists in the nucleus. After pretreating these cells with salmeterol, some translocation of the receptors from the cytosol into the nucleus occurs. The effect is more substantial when a corticosteroid is used; in this case, fluticasone propionate. When a LABA is combined with fluticasone propionate, however, there is a dramatic increase in the translocation of the receptor from the cytosol to the nucleus.

Figure 8 illustrates the proposed complementary mechanism of action of salmeterol and fluticasone propionate. The fluticasone molecule is transported across the cell membrane, binds to a receptor that is inactive in the cytoplasm, and must be translocated to the nucleus where it increases messenger RNA, causing the anti-inflammatory response. By adding a long-acting bronchodilator like salmeterol, the beta receptor in the cell membrane moves into the cytoplasm, where it primes the corticosteroid receptor for its interaction with fluticasone, resulting in increased translocation into the nucleus.

Studies of eosinophil survival also support the complementary effect of a LABA with an ICS on eosinophil survival. Amenden et al. showed that the combination of salmeterol and fluticasone propionate had an EC_{50} (effective dose causing a 50% reduction in eosinophil survival) of 0.05 nM compared with 0.32 nM for fluticasone propionate alone or 4.5 nM for salmeterol alone.

### Asthma Management

Our understanding of the pathophysiology of asthma has enabled...
FIGURE 3  
Effect of Beta2-adrenergic Receptor Agonists on Inflammatory Cells  
(Used with permission from GlaxoSmithKline.)

FIGURE 4  
Effect of Corticosteroids on Inflammatory Cells  
(Used with permission from GlaxoSmithKline.)
us to move away from the symptomatic treatment of bronchospasm into a treatment arena that addresses inflammation as a causative event. The complementary mechanisms of action of LABAs and corticosteroids at the receptor level have been documented, and this forms the basis for the NIH treatment guidelines for moderate and severe persistent asthma. Since most patients with asthma are treated in the primary-care setting, it is not enough for just asthma specialists to understand and use this information. Rather, all primary-care providers, including family practitioners, pediatricians, internists, nurse practitioners, and physician assistants, should apply the NIH asthma treatment guidelines described by Turk across the entire spectrum of care. This is especially important from a population health-management perspective.

There is no way to identify patients, prospectively, who will be high resource users. In the early 1990s, we thought we had an answer when we discovered that 80% of the available resources were being consumed by 20% of the patients with asthma. Using the 80/20 rule, a fix seemed easy: identify the 20% of the patients with asthma using the emergency room and hospital and target interventions specifically for that population; the result would be diminished resource use. Studies showed that resource use for that 20% dramatically decreased during the following year, but the total resource use across the system did not change at all. That is because the 20% who are high-resource users one year will not be the same 20% who are high-resource users the next year. By using guideline therapy for all patients with asthma, physicians treat the entire spectrum of patients with asthma who potentially could increase resource use.

Overall, we are not taking good care of patients with asthma in the United States. Patient compliance may be an issue. Large surveys indicate that two thirds of patients with severe persistent asthma report having an inhaled steroid, but only half of them use it on a regular basis. A patient may use a peak-flow meter for a while, but then stop using it.

Diabetes mellitus and asthma are the most popular diseases from a disease-management perspective. The commonalities are substantial. First, there are nationally accepted guidelines for treatment of both diseases. Also, both asthma and diabetes mellitus have what is termed “low-hanging fruit.” In the case of asthma, the low-hanging fruit is prevention of emergency room visits and hospitalizations. Health care expenditures decrease and the quality of care delivered to patients improves. The same happens for patients with diabetes mellitus when complications involving the eye, heart, kidney, and peripheral vascular system are prevented. Little wonder why these 2 disorders are frequent targets for disease-management programs.

### Clinical Evidence Supporting Dual-Controller Therapy

The term “combination therapy” generally has a negative connotation in asthma circles, dating to the days when Marax and Tedral were the mainstay treatment for asthma. Marax (theophylline, ephedrine sulfate, and hydroxyzine hydrochloride; Roerig) is still available; Tedral (theophylline, ephedrine hydrochloride, and phenobarbital; Parke-Davis) was discontinued in 1997. Now we seem to be coming back to this concept of combination therapy, newly named dual-controller therapy.

If a patient takes an ICS and is still exhibiting symptoms, what is the preferred treatment? Options include increasing the dose of the ICS, adding an inhaled LABA, or adding a leukotriene modifier. These options will be examined from the perspectives of symp-
Clinical Effect of Increasing ICS Dose or Adding a LABA

Seven clinical studies in which salmeterol added to an existing dose of ICS was compared with at least doubling the ICS dose in patients with symptoms yielded consistent results.9-15 The studies involved a total of 3,326 patients; study size ranged from 274 to 738. Budesonide was used as the ICS in 3 studies,9-11 beclomethasone dipropionate in one,12 and fluticasone propionate in 3.13-15 The study duration varied from 12 to 24 weeks.

All studies demonstrated greater clinical efficacy as measured by peak expiratory flow (PEF) or forced expiratory volume in one second (FEV₁) and better overall asthma control (decreased symptoms and decreased use of rescue albuterol) when salmeterol was added compared with at least doubling the dose of ICS. In some cases, the ICS dose was 2.5 to 3 times the dose of the ICS taken at baseline.

Looking at one study in detail, all patients were using fluticasone propionate 88 mcg twice daily for a 2 to 4 week run-in period.13 Then all patients were randomly assigned to receive either the combination of salmeterol 42 mcg plus this existing dose of fluticasone twice daily or fluticasone propionate 220 mcg twice daily for a 6-month treatment period. As shown in Figure 9, the mean change in peak expiratory flow rate occurred within a month of onset of therapy and was significantly greater at every time point for the combination of salmeterol and low-dose ICS therapy compared with high-dose ICS therapy. Coincident with the improved lung function was the finding that the change in the percentage of symptom-free days was substantially better in favor of the low-dose ICS and salmeterol group (Figure 10). The percentage of days in which rescue albuterol use was not needed mirrored the other 2 parameters.

Matz et al.16 specifically looked at the effect on asthma exacerbations of adding an inhaled LABA to ICS therapy in patients who had symptoms versus simply using a higher dose of ICS. An exacerbation was defined as worsening of asthma requiring treatment with oral prednisone. One group of 467 patients took salmeterol 42 mcg and fluticasone propionate 88 mcg twice daily for 24 weeks; the other group of 458 patients took fluticasone propionate 220 mcg twice daily for the same time period. Nine percent of patients in the dual-controller therapy group had at least one exacerbation compared with 14% of patients receiving the increased ICS dose. The total number of exacerbations was 47 in the dual-controller therapy group, for an exacerbation rate of 0.29%. For those receiving the increased ICS dose, the total number of exacerbations was 75 for an exacerbation rate of 0.48%. The mean duration of exacerbation was 8.4±0.9 days and 10.5±1.2 days, respectively.

Since it is optimal to control asthma with a minimum dose of inhaled steroid, it is clear that there are substantial advantages in pulmonary function, diminished rescue medication use, better symptom control, and fewer exacerbations by using the dual-controller approach rather than increasing the dose of ICS.

Clinical Effect of Adding LABA or Leukotriene Modifier to ICS Therapy

Two studies have compared the clinical efficacy of adding either an inhaled LABA to ICS therapy in patients who had symptoms versus simply using a higher dose of ICS. An exacerbation was defined as worsening of asthma requiring treatment with oral prednisone. One group of 467 patients took salmeterol 42 mcg and fluticasone propionate 88 mcg twice daily for 24 weeks; the other group of 458 patients took fluticasone propionate 220 mcg twice daily for the same time period. Nine percent of patients in the dual-controller therapy group had at least one exacerbation compared with 14% of patients receiving the increased ICS dose. The total number of exacerbations was 47 in the dual-controller therapy group, for an exacerbation rate of 0.29%. For those receiving the increased ICS dose, the total number of exacerbations was 75 for an exacerbation rate of 0.48%. The mean duration of exacerbation was 8.4±0.9 days and 10.5±1.2 days, respectively.

Since it is optimal to control asthma with a minimum dose of inhaled steroid, it is clear that there are substantial advantages in pulmonary function, diminished rescue medication use, better symptom control, and fewer exacerbations by using the dual-controller approach rather than increasing the dose of ICS.
od was 4 and 12 weeks, respectively.

The results consistently showed that salmeterol plus an ICS was superior to a leukotriene modifier plus an ICS in symptomatic patients for lung function measured as FEV₁ or peak flow, symptoms, and rescue albuterol use. In the Nelson et al.¹⁸ study, 447 patients took fluticasone propionate 100 mcg twice daily for a 3-week run-in period. Then half of the patients were randomly assigned to take a combination product containing fluticasone propionate 100 mcg and salmeterol 50 mcg twice daily (Advair Diskus, GlaxoSmithKline). The other half received fluticasone propionate 100 mcg twice daily plus montelukast 10 mg daily by mouth.

Nelson et al.¹⁸ found that patients taking fluticasone propionate and salmeterol had better lung function, improvement in symptom-free days and rescue-free days, and a significant reduction in asthma exacerbations compared with montelukast plus an ICS. Both treatments were equally well tolerated. Within one week, there was a substantial difference in mean morning PEF for the group receiving the combination of fluticasone propionate and salmeterol, and this continued for the entire 12-week treatment period.

The results of this study abated the concern that chronic use of LABAs may mask symptoms of asthma, resulting in a worsening of asthma exacerbations. In the group receiving salmeterol, only 2% had an exacerbation, defined as having to intervene in some way (generally with a course of oral corticosteroids), compared with 6% in the leukotriene modifier group.

A meta-analysis of 10 studies corroborated the finding that patients treated chronically with LABAs do not experience an increase in severity or frequency of asthma exacerbations.¹⁹ In fact, asthma exacerbations decreased after adding salmeterol to ICS therapy compared with increasing the dose of the ICS.

### Decreasing ICS Dose

The addition of a LABA has allowed a reduction of the steroid dose in patients with stable asthma without a decline in short-term asthma control. Nielsen et al.²⁰ found that more than 75% of patients who had salmeterol 50 mcg twice daily added to their ICS regimen experienced at least a 50% reduction in ICS use. Fewer than 25% of patients receiving placebo were able to achieve that reduction. Whether the ICS dose reduction can be maintained long term without any deleterious effects remains unknown.

### Use of Retrospective Research Designs

Over the past 40 years, our ability to determine whether drugs are safe and effective has improved substantially. Study design has evolved from the concepts of placebo control and randomization to block enrollment with stratification and the use of single-dummies and double-dummies. Wash-ins, run-outs, and crossovers have become common.

Over the past 15 years, 2 parallel developments have added to the information obtained from RCTs. One is the development and validation of quality-of-life instruments used in conjunction with RCTs. The other is the development of pharmaco economics. Each of these has strengths and weaknesses, but the results can provide complementary information.

On the experimental side of the continuum of research designs is the RCT, the classic design to determine efficacy (Figure 11).²¹
Continuum of Research Designs from Basic Science to Observational Studies

**RCT (Randomized Clinical Trial):**
- Prospective
- Retrospective
- Claims

**CEA (Cost-Effectiveness Analysis):**

**Basic Science:**
- Cohort study
- Descriptive/Case study

**Experimental**

**Observational**

RCTs also provide information about safety. Some RCTs provide a hint of economic analysis. Typically, the results of cost-effectiveness studies are of limited value in a real-world setting, however, because the cost is reported in dollars per unit of improvement in FEV1 or peak flow rate. It is difficult to translate this to meaningful clinical information.

The far right side of the continuum represents strictly observational studies, the most common type being the case study. Intermediate between observational and experimental studies are cohort studies. In this section, I will discuss how cohort studies can be used to answer questions that cannot be answered through RCTs and to provide evidence to support or dispute the results of RCTs. Cohort studies relying on claims analysis can have both prospective and retrospective components.

Typically in an RCT, patient eligibility is very narrowly defined through inclusion and exclusion criteria. For instance, one can enroll only patients with a certain level of asthma, judged according to specific severity or symptom criteria. The obvious strength of an RCT is the randomization process, which fairly allocates potential confounding variables to all treatment groups. This results in high internal validity.

There are limitations to RCTs, though. Many have relatively small sample sizes. By using strict exclusion and inclusion criteria and short duration (usually 4 to 12 weeks), the results may have limited relevance to clinical practice in the office setting. Statisticians refer to this as low external validity.

Retrospective cohort analysis is just coming into its own in terms of study design. Using this approach, researchers use administrative data sets to identify cohorts of patients who are receiving alternative therapeutic regimens and then compare the associated pharmacy use, medical use, and costs for each cohort. In this observational study design, investigators do not determine enrollment criteria or assign patients randomly to treatment groups. Since variables are measured at least twice (both backward and forward in the claims record from an index event, such as having a prescription filled for a specific drug), these studies are longitudinal.

The strength of cohort analyses is relevance to real-world clinical practice (thus, good external validity). Plus, they are efficient. Once the method is learned, cohort analyses can be completed quickly, providing swift feedback for clinical decision making at a lower cost than RCTs.

The limitations of retrospective cohort analyses have to be addressed, however. In the retrospective cohort analysis, patient assignment to treatment groups is determined by an index event, such as a physician prescribing or the patient filling a prescription for a specific medication, not by randomization. Since physicians may use certain criteria for deciding to put patients on one therapeutic regimen versus another, it would not be fair to compare those 2 regimens because of confounding variables. A variety of regression analysis techniques, such as multiple linear regression, logistic regression, Poisson regression, or instrumental variables regression, can adjust for these confounding variables. This is probably the most important advance in the last 15 years in the use of pharmacoeconomic data.

Since retrospective analyses rely on existing databases at the administrative level, one must take steps to control for threats to internal validity. This is often done by comparing the accuracy of claims data with the corresponding medical records for a certain percentage of patients.

Just within the last few years, retrospective cohort analyses based on large administrative data sets have been recognized as a useful research tool for making informed decisions about treatment. Concato and colleagues recently wrote, “The popular belief that only RCTs produce trustworthy results and that observational studies are misleading does a disservice to patient care, clinical investigation, and the education of health care professionals.”

**Economic Evidence Supporting Dual-Controller Therapy**

Recently Stempel et al.23 completed a research project in which the health care use and costs associated with common dual-controller therapies in the treatment of asthma in patients enrolled in one health plan were evaluated. A summary of the study and results illustrates the consistency of results from basic scientific, clinical, and economic analyses as well as the usefulness of retrospective cohort analyses in clinical decision making. Four other studies of the pharmacoeconomics of dual-controller therapy have also been completed.24-28 Collectively, these 5 studies have involved 52 participating health plans and 16.8 million covered lives.

The analyses for all 5 studies were conducted by the individual health plans. The inclusion criterion was a medical claim for asthma with the appropriate ICD9 code of 493.2X. Treatment was specified as at least one prescription filled for the medication of interest during the treatment period.
Outcomes measured include 5 domains of cost: (1) pharmacy; (2) outpatient care, which might include ancillaries; (3) emergency department use; (4) hospitalization; and (5) the total asthma-care charges (the total of the other 4 domains).

Multivariate regression was used to control for potential preindex confounding variables. Variables typically adjusted for include age, gender, type of health plan, preindex asthma pharmacy costs, comorbid respiratory conditions, and preindex use of short-acting beta2-agonists and oral corticosteroids, as well as preindex hospitalization, emergency department visits, and physician office visits.

The Stempel et al. study conducted in September 2000 included patients age 4 years or older with asthma who were continuously enrolled for at least 24 months in one of 13 geographically diverse health plans with 2 million covered lives. In the preindex period, patients used an ICS as single-controller therapy. The index event was the patient's filling a prescription for either salmeterol or montelukast, which is a leukotriene modifier.

Patients were divided into 3 groups: fluticasone propionate and salmeterol (n=261), ICS (except fluticasone) plus salmeterol (n=361), and any ICS (including fluticasone) and montelukast (n=216).

The mean adjusted pharmacy cost per patient over a 12-month follow-up for the group using fluticasone propionate and salmeterol was very similar to that of the group using another ICS with salmeterol ($578 and $582, respectively). The average pharmacy cost per patient in the group using an ICS plus montelukast was significantly higher at $973/year.

Table 1 shows the percentage of patients in each group visiting emergency departments and requiring hospitalization over the 12-month follow-up. The results mirror the RCTs results regarding exacerbation rates.16-18 The hospitalization rate for all groups was relatively low: 1.1%, 1.9%, and 4.6% for fluticasone/salmeterol, other ICS/salmeterol, and any ICS/montelukast, respectively.

The mean total adjusted asthma-related cost per patient per year for the group of patients taking any ICS and montelukast was $1,539. This was significantly greater than the cost per patient in the fluticasone propionate and salmeterol group ($945) and in the ICS and salmeterol group ($887).

All studies except the first had controls for age, gender, preindex asthma costs, preindex asthma pharmacy use, comorbidity, preindex hospitalization, and emergency department visits. Stempel et al. also controlled for provider specialty. Wang et al. had controls for age, gender, and comorbidity only because it was a cross-sectional study with no preindex period. Used with permission from GlaxoSmithKline.

As shown in Figure 12, the risk-adjusted mean total asthma cost per patient per month favored the ICS and salmeterol groups over the ICS and leukotriene modifier group in all studies. This consistency is particularly impressive since the 5 studies were done by different plans, and the data were analyzed at the plan level. Legorreta describes 2 of these studies in more depth in this supplement.

All of these studies have been either published in a peer-reviewed journal or presented at a national meeting in the field of allergy and asthma. The consistency of the clinical benefits of the combination of an ICS and salmeterol compared with an ICS and leukotriene modifiers shown in RCTs and the economic benefits of an ICS and salmeterol shown in retrospective cohort analyses lends additional credibility to the results. This is a good example of the complementary nature of cohort analyses and
randomized clinical trials.

These results are also consistent with the 2002 update to the NIH guidelines for the diagnosis and treatment of asthma, which recommends dual-controller therapy as preferred treatment in children as well as adults with moderate or severe persistent asthma.3

**Conclusion**

Techniques have been developed for addressing economic questions posed by colleagues on pharmacy and therapeutic committees regarding comparable therapies. Information generated by retrospective cohort analyses using large administrative data sets can help us make important decisions about how to treat our patients. The combination of an inhaled corticosteroid and salmeterol possessed clinical and economic advantages over increased doses of inhaled corticosteroid alone or the combination of an inhaled corticosteroid and a leukotriene modifier.

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