

Adjunctive Therapy for Asthma: Treatment Options

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Abstract

The National Heart, Lung, and Blood Institute guidelines on the diagnosis and management of asthma recommend using inhaled corticosteroids (ICSs) at the lowest dose possible to maintain control of disease as the backbone of asthma therapy for persistent asthma at mild, moderate, and severe levels. In patients with persistent asthma, this can be accomplished with adjunctive, or add-on, therapy to low-dose ICS. Add-on therapeutic agents include long-acting β_2 -agonists (LABAs), theophylline, and leukotriene modifiers. The addition of LABAs to existing ICS therapy improves all aspects of asthma control, including exacerbations. Both LABAs and ICSs have complementary modes of action in treating asthma by affecting both airway inflammation and smooth muscle dysfunction. Theophylline and leukotriene modifiers as add-on therapy to ICSs are considered to be clinically equivalent to higher-dose ICS therapy. Like LABAs, theophylline and leukotriene modifiers offer a steroid-sparing effect. All 3 add-on therapies offer a more rapid onset of action than corticosteroid therapy alone, thus potentially increasing compliance. Current evidence suggests that LABAs are the most effective add-on therapy and are even more effective than higher doses of ICSs alone.

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The recent guidelines from the National Heart, Lung, and Blood Institute (NHLBI) recommend inhaled corticosteroids (ICSs) as first-line treatment for patients who have persistent asthma, whether it is mild, moderate, or severe. Inhaled corticosteroids are the most potent and effective anti-inflammatory treatment available. The guidelines also suggest cromolyns, leukotriene modifiers, and methylxanthines (eg, theophylline) as alternative therapy for mild persistent asthma, depending on the patient.¹

Inhaled corticosteroids are well tolerated at recommended doses. Studies suggest a shallow dose response, or an optimal dose, above which the improvement per dose increase of ICS plateaus and unwanted side effects begin to outweigh the benefits.^{2,3} Although the potential for airway remodeling exists for all patients with persistent asthma, the specific dose of ICS required to affect this process is unclear. Therefore, to give the safest perceived doses, the current recommendation is for treatment to be initially aggressive to bring the asthma under control, followed by an incremental decrease to the lowest possible ICS dose to maintain control.¹

Patients with moderate persistent asthma can present the greatest treatment challenge because of the number of therapeutic options available. Physicians must decide on a course of action if ICSs are not totally effective. Getting the most effective therapy may require adjunctive, or add-on, therapy rather than increasing the

dose of ICS. Adjunctive therapy can serve several purposes, including decreasing patients' perceived risk from corticosteroid therapy, which may result in better compliance.

A recent study showed clearly that despite the NHLBI guidelines, an inadequate number of patients are using ICSs for long-term control of their asthma.⁴ Consequently, patients have the associated morbidity and social impact with inadequately realized treatment goals, including sleep disruption, missed school and work, limitations in sports and recreation, and emergency department (ED) visits. Research shows that 36% of asthma patients experience limitations in physical exertion, 31% have limitations on their lifestyles, and 23% report an effect on social activities (Figure 1). This may be related to an overall lack of ICS use, but it may also be explained, at least in part, by patients' lack of perceived improvement in a short period of time, which results in them not staying on long-term therapy. Thus, another reason adjunctive therapy is useful is that patients will be more likely to remain on therapy if they feel they are improving early in the course of therapy.

Adjunctive therapy for asthma consists of ICSs combined with long-acting β_2 -agonists (LABAs), theophylline, or leukotriene modifiers. The role each type of adjunctive therapy plays in asthma management is discussed below.

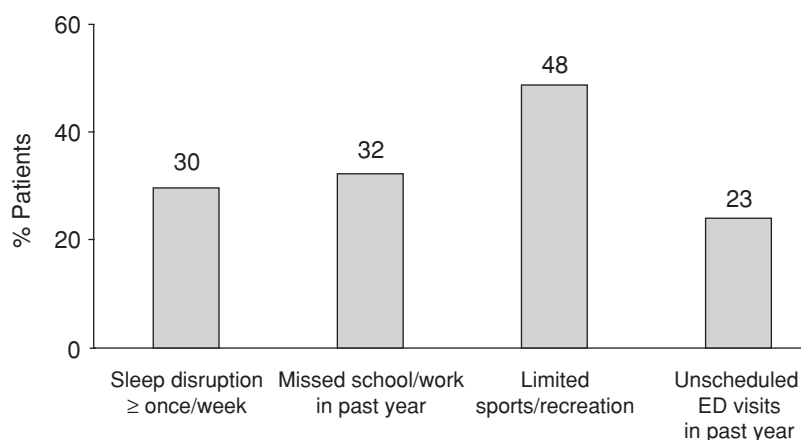
Long-Acting β_2 -Agonists

LABAs are complementary to corticosteroids in their actions on asthma pathophysiology—smooth muscle function and airway inflammation (Figure 2). Smooth-muscle dysfunction leads to bronchoconstriction, bronchial hyperreactivity, hyperplasia, and inflammatory mediator release. Airway inflammation leads to inflammatory-cell infiltration and activation, mucosal edema, cellular proliferation, epithelial damage, and

basement membrane thickening. Long-acting bronchodilators affect all of the processes that occur with smooth-muscle dysfunction as well as the mucosal edema with airway inflammation. Corticosteroids affect all of the processes associated with airway inflammation in addition to bronchial hyperreactivity from smooth muscle dysfunction. Their complementary modes of action are the rationale for using them to treat persistent asthma, while ICSs remain the backbone of asthma treatment.

A 1994 study compared the effect of a higher dose of beclomethasone dipropionate (BDP) with low-dose BDP combined with salmeterol (an LABA).⁵ This landmark study revolutionized asthma management, which, until that time, had emphasized high-dose ICS. At one time, doses of ICS as high as 2000 μg were being recommended for newly diagnosed asthma patients. In this study, patients with uncontrolled asthma were given BDP 200 μg twice daily plus salmeterol or BDP 500 μg twice daily. The combina-

Figure 1. The Goals of Asthma Therapy Are Inadequately Realized



Source: Reference 4. Although the recent guidelines recommend ICS for long-term control of persistent asthma, many patients are not using ICS and therefore are adversely affected by the morbidity and social impact. ED = emergency department.

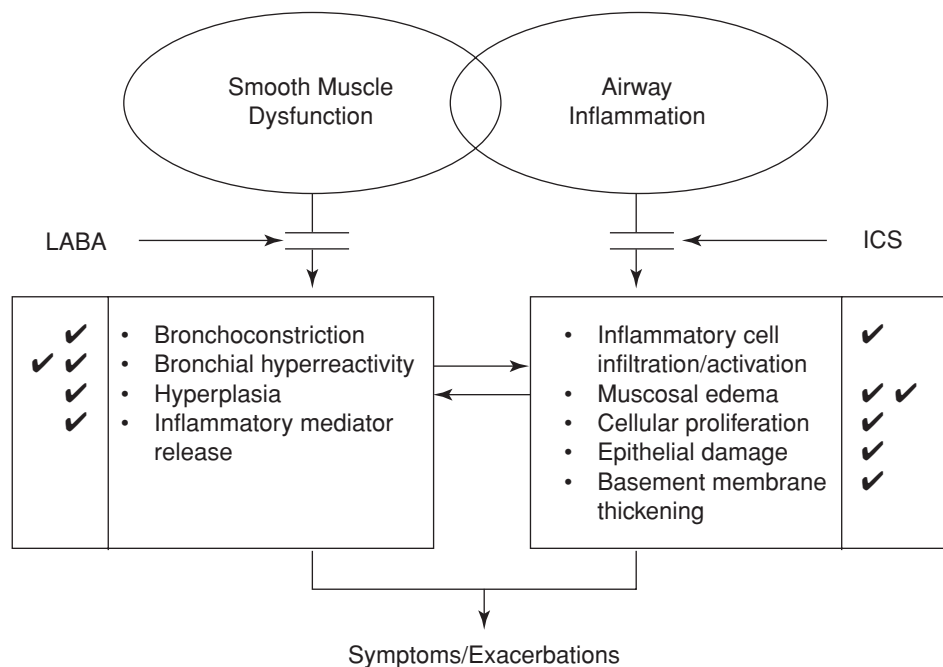
tion therapy was significantly more effective at all time points up to 21 weeks, for all efficacy measures: morning or evening peak expiratory flow rate (PEFR) measurements, nighttime symptoms, and daytime symptoms.⁵

A similar study looked at even higher doses of BDP (1000 µg twice daily) versus 500 µg twice daily combined with 2 doses of salmeterol (50 µg and 100 µg twice daily). The combination therapies were again consistently more effective than high-dose BDP in terms of symptom-free days, morning and evening PEFR rates, and rescue-free days and nights. Although no difference in exacerbation rate and bronchial hyperresponsiveness (BHR) was seen in any of the 3 treatment

groups, these data prompted clinicians to ask why higher doses of ICS were recommended if a greater response was not seen and combination therapy consistently produced better outcomes.⁶

When considering other ICS, fluticasone shows the same effect when combined with salmeterol in studies designed similarly to the Greening study.^{7,8} Combination therapy (fluticasone 88 µg twice daily plus salmeterol) compared with high-dose fluticasone (220 µg fluticasone twice daily) showed statistically significant greater efficacy in lung function and symptom control including symptom-free days at all time points throughout the 6-month study.

Figure 2. Asthma Pathophysiology



Long-acting β_2 -agonists (LABAs) are complementary to corticosteroids (CS) in their effect on asthma pathophysiology.

ICS = inhaled corticosteroids; LABA = long-acting β_2 -agonist.

The published study also showed a benefit in exacerbation rate, although it was not powered to determine whether a statistical difference would be seen.⁷ When this data was combined with data from a replicate study, the overall data clearly showed statistically significant improvement in exacerbation rate.⁸ Exacerbations are a key outcome measure in many trials for 2 reasons. First, reducing exacerbations is the main improvement clinicians would like to see for their patients. Second, exacerbations may be a marker for ongoing or active inflammation, although no data is available to verify this hypothesis.

In all studies comparing salmeterol plus low-dose ICS with at least 2 times or greater doses of the ICS, greater improvement was observed with combination therapy in terms of lung function, symptom control, and rescue albuterol use (Table 1). The treatments were roughly equivalent in terms of exacerbations, but the stud-

ies were not powered to show differences in this outcome measure.⁵⁻¹²

Adding formoterol, another LABA, to budesonide (BUD), another ICS, appears to have additional benefit. In the Formoterol and Corticosteroids Establishing Therapy (FACET) study, patients received either low-dose BUD (200 µg/day) or a higher dose of BUD (800 µg/day) with or without formoterol as add-on therapy. The addition of formoterol to either dose of BUD resulted in greater improvement in symptom control and lung function than with the corresponding dose of BUD alone. In addition, low-dose BUD plus formoterol was better than high-dose BUD alone, with the greatest improvement seen in high-dose BUD plus formoterol. Similarly, those who received high-dose BUD and formoterol showed the best outcome in terms of mild and severe exacerbations (the primary efficacy measure).¹³ Quality-of-life data also showed maximal benefit with the

Table 1. Effect of Salmeterol Plus Inhaled Corticosteroids Versus 2 Times or Greater Doses of ICS

Reference	Comparator	Patients (N)	Study Duration (weeks)	Lung Function (PEFR or FEV ₁)	Symptoms	Rescue Albuterol Use
Greening et al, 1994 ⁵		426	24	↑	↓	↓
Woolcock et al, 1996 ⁶	BDP	738	24	↑	↓	↓
Murray et al, 1999 ⁹		514	24	↑	↓	↓
Pearlman et al, 1999 ¹⁰		136	4	↑	↓	↓
Condemi et al, 1999 ⁷		437	24	↑	↓	↓
Glaxo Wellcome Study RM, 1998 /001/31/00 ⁸	FP	478	24	↑	↓	↓
Baraniuk et al, 1999 ¹¹		680	12	↑	↓	↓
van Noord et al, 1999 ¹²		274	12	↑	↓	↓

All studies to date show a greater benefit with combined inhaled corticosteroid (ICS) and β₂-agonist (salmeterol) therapy compared with higher-dose ICS.

BDP = beclomethasone dipropionate; FP = fluticasone propionate; PEFR = peak expiratory flow rate; FEV₁ = forced expiratory volume in 1 second.

combination of high-dose BUD and formoterol.¹⁴ While these results may not warrant a high-dose approach for combination therapy, the data suggest an additive effect without lessening asthma control.

Long-Acting β_2 -Agonists: Potential for Masking Inflammation? Taken together, 10 clinical studies of 4650 symptomatic patients comparing the combination of an LABA and ICS with higher doses of ICS showed that better efficacy is seen with combination therapy, and both the physician and the patient feel better control is achieved. One of the concerns with LABAs was that they may contribute to overall disease worsening by masking inflammation, with the risk that declining asthma control would go unnoticed. The FACET study also examined the ability to detect exacerbation patterns in the 4 treatment groups. No difference was observed between the 4 treatment groups in the ability to measure the characteristic fall in PEFR or increase in asthma symptom scores before the exacerbation.¹⁵

A biopsy study showed that salmeterol combined with fluticasone appears to decrease the number of eosinophils in the lamina propria, while those taking only fluticasone or placebo (in addition to their normal corticosteroid therapy) showed no significant change.¹⁶ Another biopsy study measured mast cell numbers in patients taking only fluticasone (low and high dose) versus those taking combined therapy (low-dose fluticasone plus salmeterol). Again, the combination of the LABA plus the ICS decreased the number of mast cells.¹⁷ Based on these 3 studies, combination therapy does not appear to disguise deteriorating asthma and does not increase or mask airway inflammation.

The Future of Long-Acting β_2 -Agonists. Collectively, these data have led to the next generation of asthma therapy—2 drugs in 1 delivery device. Advair™ is a combination of salmeterol and varying doses of fluti-

casone. A study comparing Advair 100 (50 μg salmeterol, 100 μg fluticasone) with salmeterol alone, fluticasone alone, or placebo confirm the original data: combination therapy provides superior outcomes in every measure: PEFR, days without albuterol use, nighttime awakenings, or daytime symptoms.¹⁸

Fluticasone alone has been shown to have an onset of effect within 24 hours.¹⁹ Advair 100 had a median onset of effect of 25 minutes for patients previously on salmeterol only compared with 28 minutes for those previously on ICS.²⁰ This rapid mode of action is critical for compliance, and studies show that its effect continues to increase after 12 weeks. Exacerbation data also support the combination product. Two 12-week studies, 1 with Advair 100 and 1 with Advair 250 (50 μg salmeterol and 250 μg fluticasone), compared the combination product to its individual components and placebo. Both Advair 100 and Advair 250 had significantly fewer withdrawals (3% and 4%, respectively) associated with worsening asthma compared with fluticasone alone (11% and 22%), salmeterol alone (35% and 38%), and placebo (49% and 62%).^{21,22}

The studies using LABA and ICS support the model that asthma is a complex airway disease involving both smooth-muscle dysfunction and chronic inflammation. LABA and ICS have complementary mechanisms of action leading to broader and greater control of asthma pathophysiology. Combination therapy leads to greater clinical efficacy and better overall asthma control including fewer exacerbations than either agent alone.

Theophyllines

Theophylline is generally considered to be a mild-to-moderate bronchodilator drug, but its mechanism of action has yet to be completely established.¹ In a study modeled after the 1994 study discussed earlier, theophylline was added to BDP (400

µg/day) and compared with higher-dose BDP (800 µg/day) alone. No difference between the treatment groups in day or nighttime symptom scores, lung function, and home PEFr recordings was noted; the 2 treatments were clinically equivalent.²³ When BUD (800 µg/day) and theophylline were compared to BUD 1600 µg/day, a statistically significant difference was seen between the 2 treatment groups in favor of combination therapy regarding forced expiratory volume in 1 second (FEV₁) and forced vital capacity measurements. All other outcomes were equivalent.²⁴ These 2 studies, which produced similar results for ICS-plus-theophylline as twice the dose of ICS, support the use of theophylline because of its corticosteroid-sparing effect.

A meta-analysis of all studies comparing salmeterol to theophylline shows that salmeterol is the favored treatment for mean change in morning PEFr and withdrawals associated with adverse events by week 2, despite the marked patient variability between the studies. Also, patients taking salmeterol had a greater number of symptom-free nights by week 2 and a greater number of rescue-free days by week 2.²⁵ The second week marks the point at which compliance declines if patients do not perceive an improvement by that time.

Leukotriene Modifiers

Leukotrienes are involved in the pathogenesis of asthma by causing vascular leakage and tissue edema; they also promote mucus secretion and potent bronchoconstriction in patients with asthma. Studies have shown that leukotriene modifiers are effective in allergy- and exercise-induced asthma.²⁶⁻²⁹ Recently, leukotriene modifiers have gained recognition as a potential alternative add-on therapy for persistent asthma.¹

Several studies of leukotriene modifiers were designed to show a steroid-sparing effect in which patients who

were clinically stable on high levels of ICS could gradually lower their doses with the addition of leukotriene modifiers. This differs from the design of the 1994 study mentioned earlier,

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which used patients who were not stable on their current ICS dose. For these patients, the first response by clinicians is often to prescribe higher doses of ICS. As discussed previously, adding an LABA not only prevents increases in the ICS dose but also provides superior outcomes.

A study of patients on high doses of ICS (approximately 1600 µg) revealed 2 interesting patterns of outcomes. Patients were followed for 1 month before the study treatment began as they continued taking their ICSs at the regular dose. After 1 month of observation, patients were able to decrease their corticosteroid use by more than one third. This may be explained by the placebo effect. After randomization to placebo or montelukast, the placebo group showed a further 30% decline in corticosteroid use, but the montelukast group showed a statistically significant 47% decrease. This study reinforces the concept of step-down therapy—that many patients are being overtreated with corticosteroids—and it illustrates the steroid-sparing benefit of montelukast.³⁰ Studies with zafirlukast and other leukotriene modifiers not available in the United States versus placebo have shown similar steroid-sparing effects.^{31,32}

Zafirlukast as add-on therapy has also been shown to further improve

lung function in patients taking high-dose corticosteroids (1500-1600 µg daily) compared with those taking placebo as add-on therapy. Zafirlukast produced a 50% reduction in exacerbations and further improvement in PEFR compared with placebo.³³ When zafirlukast is used in patients taking lower doses of corticosteroids (200 to 400 µg per day), statistically significant improvements in morning PEFR and exacerbations are seen at each time point through 6 weeks.³⁴ These data suggest that leukotriene modifiers, like LABAs, are targeting mechanisms that corticosteroids cannot.

In another study, zafirlukast (40 mg twice daily) was added to low-dose BDP (200 µg twice daily) and compared with twice the dose of BDP (400 µg twice daily) alone. Small numeric changes favoring combination therapy were seen in 3 of the outcomes, but none was statistically significant. Similarly, small, non-significant changes in the remaining 3 outcomes favored high-dose BDP.³⁵ Therefore, leukotriene modifiers, like theophyllines, are clinically equivalent as add-on therapy with the ability to have a steroid-sparing effect.

In a direct comparison between zafirlukast and salmeterol in patients with persistent asthma, of which more than 80% were taking an ICS, both agents showed improvements in pulmonary function, asthma symptoms, and supplemental albuterol use compared to baseline. However, salmeterol was significantly more effective than zafirlukast for most efficacy measures, including morning PEFR, percentage of symptom-free days, and percentage of days and nights with no supplemental albuterol use.³⁶

... CONCLUSION ...

The body of literature on asthma therapy clearly shows that combination therapy (ICS plus add-on therapy) is more effective than high-dose monotherapy for controlling asthma.

The combination of an ICS and an LABA improved all aspects of asthma control, including severe exacerbations—one of the most important outcome measures for preserving quality of life and healthcare cost containment. While theophylline and leukotriene modifiers offer improvement and a steroid-sparing effect, they appear to be clinically equivalent only to higher doses of ICS. Their advantage lies in being an alternative to higher doses of corticosteroids, ie, steroid sparing, thus eliminating the fear factor among patients who are not comfortable with corticosteroid use. Additionally, all 3 therapies offer more rapid clinical response than corticosteroid therapy alone, which may translate into improved compliance. LABAs are the most effective among add-on therapy options.

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