Long-Acting Beta-Agonists
Role in Asthma Management

Key Points and Recommendations

- The inhaled long-acting β2-adrenergic agonists are associated with an increase in asthma-related deaths and life-threatening experiences. (SOR: B)

- The results of the Salmeterol Multicenter Asthma Research Trial (SMART) suggest that patients receiving salmeterol were at increased risk for fatal asthma events. In the total population, a higher rate of asthma-related death occurred in patients treated with salmeterol than those treated with placebo. (SOR: B)

- The results of SMART are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, or other asthma-controller therapy modified the risk of asthma-related death with salmeterol. (SOR: B)

- Long-acting β2-agonists (LABAs) and combination products containing a LABA such as Advair Diskus® are not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled short-acting β2-agonists. (SOR: B)

- The goal of asthma treatment is to titrate to the lowest effective dose after achieving stable asthma. (SOR: B)
Putting inhaled $\beta_2$-agonists in perspective

Evidence for the role of long-acting $\beta_2$-agonists

The inhaled LABA class was introduced in the United States in 1994. Both salmeterol and formoterol were shown to produce greater improvement in pulmonary function and a greater decrease in symptoms and use of rescue bronchodilators compared with regularly administered short-acting inhaled $\beta_2$-agonists or placebo. The beneficial effects of LABAs have been found to be additive when combined with an inhaled corticosteroid. The combination has been shown to improve lung function and increase the number of days and nights without symptoms or the need for rescue medication, with no increase in exacerbations of any severity, compared with administering twice as much of the inhaled corticosteroid as monotherapy. The LABAs, however, have been shown to have no clinically significant effect on airway inflammation, which is the key cause of asthma, either as monotherapy or as add-on therapy to an inhaled corticosteroid. Nonetheless, the benefits of LABAs as bronchodilators have been demonstrated clearly. For this reason, the LABAs were included in the revised guidelines issued by the NAEPP in 1997.

Concerns about the LABAs began shortly after the commercial availability of salmeterol. Most of these concerns stemmed from experience with the short-acting $\beta_2$-agonists, particularly their association with an increase in deaths due to asthma. A case-controlled study showed that for each additional canister administered each month, the odds ratio of death from asthma increased by 2.6. Given these concerns regarding the regular use of a $\beta_2$-agonist, the Salmeterol Nationwide Surveillance (SNS) study was initiated in 1990 to compare the safety of the regular use of salmeterol and albuterol.

Salmeterol Nationwide Surveillance study

The SNS study, conducted in the United Kingdom in 1990-1991, randomized 25,180 patients with asthma considered to require regular treatment with bronchodilators. Patients received salmeterol, 50 mcg twice daily (N=16,787), or albuterol, 200 mcg 4 times daily (N=8,393), in combination with previously prescribed asthma drugs for 16 weeks. Approximately three quarters of patients were taking an oral or inhaled corticosteroid. The incidence of drug-related serious events was similar in both groups (1.19% vs 1.15%, respectively), although a significantly lower rate of severe, nonfatal asthma-related events was observed in the salmeterol group compared with the albuterol group (9.9% vs 11.6%, respectively). The incidence of the combined endpoint of respiratory and asthma-related deaths was higher but not statistically significantly so in the salmeterol group compared with the albuterol group (0.07% vs 0.02%, respectively).

Salmeterol Multicenter Asthma Research Trial

A multicenter, randomized, placebo-controlled study was launched in 1996 to compare the safety of usual asthma therapy with and without salmeterol. The Salmeterol Multicenter Asthma Research Trial (SMART) enrolled subjects 12 years or older with asthma. Subjects received either salmeterol, 42 mcg twice daily, via metered-dose inhaler (MDI) or placebo twice daily via MDI for 28 weeks. A planned interim analysis was conducted after 26,355 subjects had been randomized. At that time, the study was terminated because the overall rate of death was higher in patients treated with salmeterol than placebo.

The interim analysis showed that the occurrence of the primary outcome, combined respiratory-related deaths or life-threatening experiences, was low and not statistically different between groups. Similarly, asthma overall did not appear to worsen in those receiving salmeterol. There was, however, a small but statistically significant increase in respiratory-related deaths (24 vs 11) and asthma-related deaths (13 vs 3) in subjects receiving salmeterol vs placebo, respectively. Post hoc analysis showed that...
compared with placebo, a higher rate of asthma-related deaths occurred in the salmeterol group in both whites (0.01% vs 0.07%) and African Americans (0.04% vs 0.31%), respectively. While the relative risks of asthma-related deaths were similar in both groups, estimates of excess deaths attributable to salmeterol were greater in African Americans, primarily because they demonstrated a higher rate of these events. Also observed was that the occurrence of asthma-related deaths and life-threatening experiences occurred nearly equally in the salmeterol and placebo cohorts in those using inhaled corticosteroids at baseline (16 vs 13, respectively). However, the study design does not allow for conclusions about whether inhaled corticosteroids significantly change the asthma death risk profile of salmeterol or any LABA.

**Combined formoterol trials**
The FDA staff analyzed data from 3 clinical trials submitted by Novartis Pharmaceuticals Corporation in support of the approval of Foradil Aerolizer for marketing in the United States. The prospective, randomized, placebo-controlled, and double-blind trials compared formoterol, 12 mcg twice daily or 24 mcg twice daily, with albuterol, 180 mcg 4 times daily, or placebo. [The 24 mcg twice daily dose of formoterol is not within the currently approved product labeling for Foradil Aerolizer.] Both formoterol doses were statistically significantly superior to placebo for the primary endpoint of improvement in FEV\(_1\) at 12 weeks. The studies did not show a statistically significant benefit for formoterol, 24 mcg twice daily, compared with formoterol, 12 mcg twice daily. Serious asthma exacerbations occurred more frequently in the formoterol, 24 mcg twice daily, group compared with placebo, albuterol, or formoterol, 12 mcg twice daily, groups (TABLE 1).

In the 2 12-week studies in adults/adolescents, 9 patients in the formoterol, 24 mcg twice daily, groups experienced a serious asthma exacerbation; all required hospitalization. One patient died because of a cardiorespiratory arrest. Two placebo-group patients experienced a serious but nonfatal asthma exacerbation; both were hospitalized. In the 1-year pediatric study, 11 patients had serious nonfatal asthma exacerbations in the formoterol, 24 mcg twice daily, group.

**16-week phase IV formoterol trial**
In a 16-week, randomized, double-blind, placebo-controlled phase 4 study, the occurrence of asthma exacerbation was evaluated in 2085 adolescent and adult subjects with a mean FEV\(_1\) of 69% of predicted. Subjects received formoterol, 12 mcg twice daily or 24 mcg twice daily; formoterol 12, mcg twice daily combined with up to 2 additional as-needed doses; or placebo. A serious respiratory-related adverse event requiring hospitalization occurred in 0.9%, 0.4%, 0.2%, and 0.2% of the subjects, respectively (TABLE 2).

**Summary of prospective study results**
Investigations have identified an increased risk of asthma-related death or life-threatening experience but not an overall worsening of asthma control in those treated with salmeterol. This risk appears to be especially high in African Americans. Formoterol use is associated with more frequent serious asthma exacerbations compared with placebo.
The revised labeling pertains to salmeterol xinafoate (Serevent Diskus) and fluticasone propionate and salmeterol xinafoate (Advair Diskus); the labeling for formoterol fumarate (Foradil Aerolizer) remains unchanged.

- No studies with objectives similar to SMART have been conducted for formoterol fumarate. However, the FDA believes there is a potential for a class effect.

- LABAs and LABA combination products are not indicated for first-line treatment in asthma. They should be used according to the NAEPP guidelines revised in 2002\textsuperscript{26} (TABLE 4) and should not be used for patients with mild intermittent or mild persistent symptoms; they should be used only for patients with moderate or severe persistent asthma in combination with an inhaled corticosteroid. Salmeterol, formoterol, and salmeterol and fluticasone should be administered twice daily in doses listed in the approved product labeling.

- LABAs and LABA combination products should not be used to treat worsening wheezing, which indicates an increase in airway inflammation requiring the initiation of or increased dosage of an anti-inflammatory medication, generally an inhaled corticosteroid.

- An inhaled short-acting $\beta_2$-agonist not a LABA should be used to manage acute asthma symptoms.

**FDA actions**

On March 2, 2006, the FDA approved new safety labeling for fluticasone propionate/salmeterol xinafoate (Advair Diskus) and salmeterol xinafoate (Serevent Diskus). For Advair Diskus, this labeling contains a black box warning stating that: Long acting $\beta_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in Advair Diskus, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe Advair Diskus for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies.

A similar warning has been included in the prescribing information for salmeterol xinafoate. The labeling for formoterol fumarate (Foradil Aerolizer\textsuperscript{®}) remains unchanged.

**Implications for primary care**

Given the evidence now available, the following should be considered\textsuperscript{1,2,5} (TABLE 3).

- The recent evidence and the FDA actions pertain to asthma only.
- It is unknown whether or not similar concerns exist with LABA use for exercise-induced bronchospasm or chronic obstructive pulmonary disease.
- The revised labeling pertains to salmeterol xinafoate (Serevent Diskus) and fluticasone propionate and salmeterol xinafoate (Advair Diskus); the labeling for formoterol fumarate (Foradil Aerolizer\textsuperscript{®}) remains unchanged.
- No studies with objectives similar to SMART have been conducted for formoterol fumarate. However, the FDA believes there is a potential for a class effect.
- LABAs and LABA combination products are not indicated for first-line treatment in asthma. They should be used according to the NAEPP guidelines revised in 2002\textsuperscript{24} (TABLE 4) and should not be used for patients with mild intermittent or mild persistent symptoms; they should be used only for patients with moderate or severe persistent asthma in combination with an inhaled corticosteroid. Salmeterol, formoterol, and salmeterol and fluticasone should be administered twice daily in doses listed in the approved product labeling.
- LABAs and LABA combination products should not be used to treat worsening wheezing, which indicates an increase in airway inflammation requiring the initiation of or increased dosage of an anti-inflammatory medication, generally an inhaled corticosteroid.
- An inhaled short-acting $\beta_2$-agonist not a LABA should be used to manage acute asthma symptoms.

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**TABLE 1**

Occurrence of serious asthma exacerbations in 3 asthma studies with formoterol

<table>
<thead>
<tr>
<th></th>
<th>Formoterol 12 mcg BID</th>
<th>Formoterol 24 mcg BID*</th>
<th>Albuterol 180 mcg QID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-wk trial in adults/adolescents</td>
<td>0/136 (0)</td>
<td>4/135 (3)</td>
<td>2/134 (1.5)</td>
<td>0/136 (0)</td>
</tr>
<tr>
<td>12-wk trial in adults/adolescents</td>
<td>1/139 (0.7)</td>
<td>5/136 (3.7)</td>
<td>0/138 (0)</td>
<td>2/141 (1.4)</td>
</tr>
<tr>
<td>1-y trial in pediatric patients</td>
<td>8/171 (4.7)</td>
<td>11/171 (6.4)</td>
<td>0/176 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Data reported as n (%)

*Not within currently approved product labeling for Foradil Aerolizer\textsuperscript{®}

**TABLE 2**

Formoterol-associated respiratory-related serious adverse events requiring hospitalization

<table>
<thead>
<tr>
<th>Formoterol 12 mcg BID (n=527)</th>
<th>Formoterol 24 mcg BID* (n=527)</th>
<th>Formoterol 12 mcg BID+ on demand\textsuperscript{†} (n=517)</th>
<th>Placebo (n=514)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (0.9%) \textsuperscript{‡}</td>
<td>2 (0.4%)</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

*Not within currently approved product labeling for Foradil Aerolizer\textsuperscript{®}; \textsuperscript{†}Up to 2 doses/day; \textsuperscript{‡}2 were not asthma-related

Implications of clinical trials and FDA actions for primary care

- Clinical trial results and FDA advisory pertain to asthma only
- Revised labeling pertains to salmeterol xinafoate (Serevent Diskus) and fluticasone propionate and salmeterol xinafoate (Advair Diskus)
- LABAs are not first-line for asthma
- Add LABA only if other medicines, including low- to medium-dose corticosteroids, do not control asthma
- Do not use LABA to treat wheezing that is getting worse
- A short-acting bronchodilator— not a LABA— should be used to relieve sudden wheezing
- Ensure that airway inflammation is adequately controlled with anti-inflammatory therapy
- Communicate with the patient

FDA, US Food and Drug Administration; LABA, long-acting β-agonists

Role of inhaled long-acting β₂-agonists as a controller in asthma*

<table>
<thead>
<tr>
<th>Asthma severity</th>
<th>Infants and young children (age &lt; 5 y)</th>
<th>Adults and older Children (age &gt; 5 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild intermittent</td>
<td>No role for inhaled LABA</td>
<td>No role for inhaled LABA</td>
</tr>
<tr>
<td>Mild persistent</td>
<td>No role for inhaled LABA</td>
<td>No role for inhaled LABA</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>Preferred treatments:</td>
<td>Preferred treatment:</td>
</tr>
<tr>
<td></td>
<td>• Low-dose ICS + inhaled LABA or</td>
<td>• Low- to medium-dose ICS + inhaled LABA</td>
</tr>
<tr>
<td></td>
<td>• Medium-dose ICS</td>
<td>Alternative treatments:</td>
</tr>
<tr>
<td></td>
<td>Alternative treatments:</td>
<td>• Medium-dose ICS or</td>
</tr>
<tr>
<td></td>
<td>• Low-dose ICS + LRA or</td>
<td>• Low- to medium-dose ICS + LRA or</td>
</tr>
<tr>
<td></td>
<td>• Low-dose ICS + theophylline</td>
<td>• Low- to medium-dose ICS + theophylline</td>
</tr>
<tr>
<td></td>
<td>If needed (recurring severe exacerbations)</td>
<td>Preferred treatment:</td>
</tr>
<tr>
<td></td>
<td>Preferred treatment:</td>
<td>• Medium-dose ICS + inhaled LABA</td>
</tr>
<tr>
<td></td>
<td>• Medium-dose ICS + LRA or</td>
<td>Alternative treatments:</td>
</tr>
<tr>
<td></td>
<td>• Medium-dose ICS + theophylline</td>
<td>• Medium-dose ICS + LRA or</td>
</tr>
<tr>
<td>Severe persistent</td>
<td>Preferred treatment:</td>
<td>Preferred treatment:</td>
</tr>
<tr>
<td></td>
<td>• High-dose ICS + inhaled LABA AND, if needed:</td>
<td>• High-dose ICS + inhaled LABA</td>
</tr>
<tr>
<td></td>
<td>• Oral corticosteroid 2 mg/kg/d (NMT 60 mg/d)</td>
<td>AND, if needed:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Oral corticosteroid 2 mg/kg/d (NMT 60 mg/d)</td>
</tr>
</tbody>
</table>

*In addition to an inhaled short-acting β₂-agonist
ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; LRA, leukotriene receptor antagonist; NMT, not more than
Physician/patient communication and asthma management

The importance of patient communication remains a critical aspect of asthma management. Patients should be made aware of the benefits and risks of treatment, and steps to take in the event of destabilizing symptoms. Symptom and lung-function monitoring ensure that appropriate therapy, particularly anti-inflammatory therapy, is being provided. Bronchodilators, including short-acting and long-acting β₂-agonists, must not be overused as this may temporarily mask an increase in airway inflammation.

Summary

The LABAs have played an important role in the management of asthma over the past decade. They are of clear benefit in reducing asthma-related symptoms and improving lung function when used in combination with an anti-inflammatory agent. Studies have shown, however, that their use has been associated with various negative outcomes, which has led to a restricted indication for salmeterol xinafoate (Serevent Diskus) and fluticasone propionate and salmeterol xinafoate (Advair Diskus), along with medication guides that will be given to patients with every new and refill prescription. Convincing data now exist that show an association of salmeterol with an increase in asthma-related deaths and life-threatening exacerbations, while formoterol is associated with more frequent serious asthma exacerbations. Nonetheless, LABAs remain an important component of asthma therapy. Further clarification about their role may occur with the release of additional analyses from SMART, as well as updated guidelines from the NAEPP Expert Panel, both expected later in 2006. In the meantime, LABAs and LABA-containing products are to be used only for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. The NHLBI/NAEPP guidelines recommend inhaled corticosteroids as the first step in controller therapy, with LABAs as an option if low- to medium-dose inhaled corticosteroids do not adequately control the patient’s asthma."

REFERENCES