The Safe and Effective Use of Long-Acting Beta-Agonists
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Long-acting beta-agonists (LABAs) are a class of medications currently approved for treatment of asthma and chronic obstructive pulmonary disease (COPD). Like the short-acting beta-agonists, they are potent bronchodilators. They differ, however, in their onset of action and duration of activity. Despite their benefits, unanswered questions surrounding their safety, specifically for use in asthma, still persist. This newsletter will briefly review the safety and efficacy of LABAs for asthma and COPD, as well as describe the recent labeling changes surrounding their use in the treatment of asthma.

Background
LABAs are beta₂-adrenergic agonists which produce bronchodilation resulting from relaxation of smooth muscles in the bronchial tree. They were developed in effort to find a longer-acting bronchodilator that could provide a more convenient dosing schedule, decreased incidence in adverse effects often associated with theophylline and frequent short-acting beta-agonist use, and fewer drug-drug interactions than theophylline. Compared to the short-acting beta₂-agonists (e.g., albuterol), they produce similar bronchodilatory effects but have a duration of action that is up to 12 hours, with the exception of indacaterol which is active for up to 24 hours. Another difference is their slower onset of action. Salmeterol can take up to 15-20 minutes, whereas formoterol, arformoterol, and indacaterol are closer to 5-7 minutes. Even though formoterol, arformoterol, and indacaterol have a more rapid onset of action, the clinical significance as it relates to the relief of acute symptoms has not been adequately evaluated.

Role in Asthma
In asthma, LABAs are classified as long-term controller medications and their place in therapy is influenced by the available safety and efficacy data. Since LABAs do not possess anti-inflammatory activity, they should always be used in conjunction with an anti-inflammatory medication, such as an inhaled corticosteroid (ICS), to prevent exacerbations. When used in addition to ICS therapy, LABAs are effective in reducing both daytime and night-time asthma symptoms, lowering rates of asthma exacerbations, improving quality of life, decreasing rescue inhaler use, minimizing the required dose of ICS, and improving lung function. Current asthma treatment guidelines recommend the following with regards to the use of LABAs in the treatment of asthma:

- LABAs should not be used to treat acute symptoms or exacerbations of asthma.
- LABAs are the preferred adjunctive therapy to be used in combination with ICS in patients ≥ 12 years of age.
- For patients with asthma not sufficiently controlled on low-dose ICS, the option to increase the ICS dose should be given equal weight to the addition of a LABA.
- LABAs in combination with a low-dose ICS are the preferred therapy in patients with moderate persistent asthma.
- LABA/ICS is the preferred therapy in patients with severe persistent asthma.
LABA Safety Concerns
Despite benefits that have been seen with LABA therapy in the treatment of asthma, there are still some unanswered questions as to their safety and if regular use would mask underlying asthma symptoms. These concerns were further brought to light with the Salmeterol Nationwide Surveillance (SNS) Study and the Salmeterol Multicenter Asthma Research Trial (SMART).6,7 The SNS study was a 16-week double-blind, randomized, parallel-group trial that was conducted in the United Kingdom to compare the safety of salmeterol (50 mcg b.i.d.) and albuterol (200 mcg q.i.d) in treating asthma.6 In this trial, there were an increased number of asthma-related deaths in patients receiving salmeterol (12 out of 16,787 patients) compared to patients receiving albuterol (2 out of 8,393 patients), however this difference was not statistically significant.6 Based on these findings and to further investigate the potential adverse effects of LABA therapy in asthma, SMART was conducted.

SMART was a 28-week double-blind, randomized, placebo-controlled, observational surveillance trial that compared the safety of salmeterol via metered-dose inhaler or placebo added to usual asthma care in patients ≥12 years of age.7 The primary objective of this trial was to further evaluate the effects of salmeterol (42 mcg b.i.d.) on respiratory- and asthma-related deaths or life-threatening episodes. Following an interim analysis in 26,355 subjects, the trial was terminated by the sponsor due to the preliminary findings in African Americans and recruitment difficulties.7

When the data was analyzed, there were no significant differences found between treatment groups in the number of study subjects with respiratory-related death or life-threatening experiences.7 There were however, small but statistically significant differences in the secondary endpoints. In the group receiving salmeterol, there were 13 asthma-related deaths and 37 combined asthma-related deaths or life-threatening experiences, while only 3 asthma-related deaths and 22 combined asthma-related deaths or life-threatening experiences in the patients receiving placebo.7 When the data was further analyzed by racial subgroup, there were significantly more treatment group differences in the African American population. Respiratory-related death or life-threatening experience occurred in more subjects receiving salmeterol than placebo (n= 20 vs. n= 5).7 This was also seen with combined asthma-related death or life-threatening experience in the salmeterol group (n= 19 vs. n= 4).7 It continues to be unknown whether this increased risk seen in the African American study population was due to a physiologic treatment effect, low baseline utilization of ICS therapy, genetic influences, or patient-related behaviors.4,5,7 As with all trials, both the SMART and SNS have study limitations and unfortunately still leave many unanswered questions.4,5

Labeling Changes
In February of 2010, the U.S. Food and Drug Administration (FDA) required changes be made to the prescribing information on how LABAs should be used in the treatment of asthma.8 These new recommendations include the following:

- The use of LABAs is contraindicated without the use of an asthma controller medication such as an inhaled corticosteroid.
- LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications.
- LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patients should then be maintained on an asthma controller medication.
- Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure compliance with both medications.

These new recommendations led to class-labeling revisions to all LABA-containing products and were based on the FDA’s analyses of the SNS and SMART data showing an increased risk of severe exacerbation of asthma symptoms in pediatric and adult patients using LABAs in the treatment of asthma.6,7,9 In addition to these changes, the FDA also required a Risk Evaluation and Mitigation Strategy
(REMS), including a revised Medication Guide and plans to educate healthcare professionals about the appropriate use of LABAs, and additional clinical trials to further evaluate the safety of LABAs used in conjunction with inhaled corticosteroids.

Role in COPD
The mainstay of treatment for COPD are the bronchodilators, which include short-acting bronchodilators (SABAs), LABAs, and short and long-acting bronchodilators. Similar to their use in asthma, LABAs are used as maintenance therapy to prevent or reduce symptoms while the SABAs are used for acute relief of symptoms and exacerbations. Clinical trials have shown that LABAs are superior to placebo or SABAs in reducing COPD exacerbations. In August 2011, the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society updated their guidelines for the diagnosis and management of COPD. They continue to recognize patients with respiratory symptoms and a forced expiratory volume in one second (FEV₁) <60% predicted as the COPD population that benefits most from inhaled therapies (i.e., LABA, long-acting anticholinergic, or ICS). In these patients, they recommend monotherapy with either a LABA, long-acting anticholinergic or ICS, in addition to a SABA, since clinical trials have shown these therapies are beneficial in reducing COPD exacerbations and improving health-related quality of life. COPD patients with respiratory symptoms and FEV₁ between 60% and 80% predicted may also benefit from inhaled bronchodilators (i.e., LABA, anticholinergics), however, more data is needed to assess their benefits on health-related outcomes. Another area of uncertainty pertains to the use of combination therapy. The guidelines currently acknowledge and support the use of combination therapy (LABA with other bronchodilators or ICS) in patients with stable COPD and an FEV₁ of <60%. However, it has yet to be determined when combination therapy should be used over monotherapy and if a preferential combination exists. These recommendations are similar to the Global Initiative for Chronic Obstructive Lung Disease guidelines which recommend therapy with a long-acting bronchodilator in patients with Stage II (moderate to severe) to Stage IV (very severe) COPD who continue to have symptoms with the use of a SABA.

Even though the recent LABA labeling revisions by the FDA do not apply to COPD, healthcare providers should make sure their patients have a good understanding of their role in therapy. Patients need to have a clear understanding of the difference between their SABA and LABA medications and when each should be used. Many times LABA therapy is prescribed when patients are using their SABA frequently throughout the day. Therefore, it is important to instruct patients that when LABA therapy is initiated, they should discontinue regular use of their SABA and use them only on an as needed basis for relief of acute symptoms of COPD not controlled by the LABA. Regular assessment can help ensure that patients are using these therapies appropriately and as prescribed.

Conclusion
Although improvements in asthma and COPD can be seen with the addition of a LABA to existing therapy, healthcare providers must closely monitor their patients while on these medications, and in the setting of asthma, balance the potential for increased morbidity and mortality. Patient education with regards to the role of LABA therapy, especially how it differs from SABA therapy, is essential to ensure that patients get the most benefit from these medications.

Additional Resources
American Lung Association: www.lungusa.org
Food and Drug Administration: www.fda.gov
Global Initiative for Chronic Obstructive Lung Disease: www.gold.copd.com
National Heart, Lung, and Blood Institute: www.nhlbi.nih
Table 1: FDA-Approved Long-Acting Beta-Agonist Products

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<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Dosage forms</th>
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<tbody>
<tr>
<td>Arzacta® Neohaler™ (indacaterol maleate)</td>
<td>COPD (adults): 1 capsule inhaled once daily</td>
<td>Capsule: 75 mcg</td>
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<tr>
<td>Brovana® (arformoterol tartrate)</td>
<td>COPD: 1 vial every 12 hours</td>
<td>Inhalation solution: 15 mcg/2ml</td>
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<tr>
<td>Foradil Aerolizer® (formoterol fumarate)</td>
<td><strong>Asthma (≥ 5 years): 1 capsule inhaled daily</strong></td>
<td>Capsule: 12 mcg</td>
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<tr>
<td></td>
<td>EIB (≥ 5 years): 1 capsule inhaled at least 15 minutes before exercise</td>
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<tr>
<td></td>
<td>COPD (adults): 1 capsule inhaled daily</td>
<td></td>
</tr>
<tr>
<td>Perforomist® (formoterol fumarate)</td>
<td>COPD (adults): 1 vial every 12 hours</td>
<td>Inhalation solution: 20 mcg/2ml</td>
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<tr>
<td>Serevent Diskus® (salmeterol xinafoate)</td>
<td><strong>Asthma (≥ 4 years): 1 inhalation twice daily with ICS therapy</strong></td>
<td>Inhalation powder†: 50 mcg</td>
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<tr>
<td></td>
<td>EIB (≥ 4 years): 1 inhalation at least 30 minutes before exercise</td>
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<tr>
<td></td>
<td>COPD: 1 inhalation twice daily</td>
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**LABA products**

- **Advair HFA®** (fluticasone propionate; salmeterol xinafoate)
  - **Asthma (≥ 12 years): 2 inhalations twice daily**
  - Inhalation aerosol†: FLU 45mcg/SAL 21 mcg
  - FLU 115mcg/SAL 21 mcg
  - FLU 230mcg/SAL 21 mcg

- **Advair Diskus®** (fluticasone propionate; salmeterol xinafoate)
  - **Asthma:**
  - ≥12 yrs: 1 inhalation twice daily*
  - 4 to 11 yrs: 1 inhalation of Advair 100/50 twice daily
  - COPD: 1 inhalation of Advair 250/50 twice daily
  - Inhalation aerosol†: MOM 100 mcg/FOR 5 mcg
  - MOM 200 mcg/FOR 5 mcg

- **Dulera®** (mometasone; formoterol fumarate dihydroate)
  - **Asthma (≥ 12 years): 2 inhalations twice daily**
  - Inhalation aerosol†: BUD 80 mcg/4.5 mcg
  - BUD 160 mcg/4.5 mcg

- **Symbicort®** (budesonide; formoterol fumarate dihydroate)
  - **Asthma (≥ 12 years): 2 inhalations twice daily**
  - Inhalation aerosol†: BUD 80 mcg/4.5 mcg
  - BUD 160 mcg/4.5 mcg

**Abbreviations**
- EIB: exercise induced bronchospasm
- COPD: chronic obstructive pulmonary disease
- ICS: inhaled corticosteroid
- FLU: fluticasone, SAL: salmeterol, MOM: mometasone, FOR: formoterol, BUD: budesonide
- * starting dose based on asthma severity
- ** starting dose based on patient’s asthma therapy
- † per inhalation
- ‡ per actuation

**Price (AWP) $$$$-most expensive to $-least expensive**

**References**


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