Bronchodilators, Long-Acting Beta-Agonists
Therapeutic Class Review (TCR)

November 29, 2016

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FDA-APPROVED INDICATIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Reversible Bronchospasm</th>
<th>Prevention of Exercise-Induced Bronchoconstriction</th>
<th>Chronic Obstructive Pulmonary Disease (COPD)</th>
<th>Age of Use (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>arformoterol inhalation solution (Brovana®)</td>
<td>Sunovion</td>
<td>--</td>
<td>--</td>
<td>X</td>
<td>≥ 18</td>
</tr>
<tr>
<td>formoterol inhalation powder in capsules (Foradil® Aerolizer®)</td>
<td>Merck Sharp &amp; Dohme</td>
<td>X</td>
<td>--</td>
<td>--</td>
<td>≥ 5</td>
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<tr>
<td>formoterol inhalation solution (Perforomist®)</td>
<td>Mylan</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>≥ 18</td>
</tr>
<tr>
<td>indacaterol inhalation powder (Arcapta™ Neohaler™)</td>
<td>Novartis</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>≥ 18</td>
</tr>
<tr>
<td>ololedaterol inhalation spray (Striverdi® Respimat®)</td>
<td>Boehringer Ingelheim</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>&gt; 18</td>
</tr>
<tr>
<td>salmeterol DPI (Serevent® Diskus)</td>
<td>GlaxoSmithKline</td>
<td>X</td>
<td>--</td>
<td>X</td>
<td>≥ 4</td>
</tr>
</tbody>
</table>

DPI=dry powder inhaler (breath activated device); COPD=Chronic Obstructive Pulmonary Disease

*Novartis and Merck have announced that they will voluntarily discontinue the manufacture of formoterol fumarate inhalation powder (Foradil Aerolizer). While inventory was estimated to be depleted by January 2016, some product may remain.

Arformoterol (Brovana), formoterol (Perforomist), indacaterol (Arcapta), and ololedaterol (Striverdi) are not indicated for the treatment of acute deteriorations of chronic obstructive pulmonary disease (COPD) or the management of asthma. Indacaterol (Arcapta Neohaler) is not indicated for the treatment of asthma.

OVERVIEW

Beta₂-agonist bronchodilators are used for the treatment and prevention of bronchospasm associated with asthma, prophylaxis of exercise-induced bronchospasm (EIB), and in the treatment of Chronic Obstructive Lung Disease (COPD).

Asthma

The mainstay of asthma therapy is the use of inhaled corticosteroids (ICS) alone or in combination with long-acting beta₂-agonists (LABAs) as controller medications. These agents lead to improvements in lung function and symptoms and reduce the need for short-acting beta₂-agonists (SABAs) for quick relief. LABAs are not to be used as monotherapy for controlling asthma. While the corticosteroid reduces inflammation, the long-acting beta₂-agonist acts principally to dilate the airways by relaxing airway smooth muscle.

The 2016 GINA guidelines offer a control-based management plan to adjust treatment in a continuous cycle of assessment, treatment, and review of the patient’s response as it relates to symptom control, future risk of exacerbations, and side effects. If the patient is not controlled on the current regimen,
treatment should be stepped up until control is achieved. If control is maintained for at least 3 months on the current regimen, treatment can be stepped down to the lowest step and dosage that maintains control. A combination ICS/LABA product is the preferred step-up treatment for adults and adolescents ≥ 12 years of age currently on a low dose ICS who continue to have persistent symptoms/exacerbations. For children (6 to 11 years of age) with persistent symptoms, an increased ICS dose is preferred over use of an ICS/LABA agent. The effect of a LABA or combination LABA/ICS has not been adequately studied in this patient population. Therefore, LABAs cannot be recommended in children 5 years and younger. The stepwise approach for asthma control in the GINA guidelines is described below.

**Stepwise Approach to Asthma Control from 2016 GINA Guidelines**

<table>
<thead>
<tr>
<th>Adults and Children 6 Years of Age And Older</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
</tr>
<tr>
<td>• Recommended: SABA</td>
</tr>
<tr>
<td>• Alternative Controller: consider low dose ICS</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
</tr>
<tr>
<td>• Preferred controller: low-dose ICS + SABA</td>
</tr>
<tr>
<td>• Alternative controllers: leukotriene modifier or low dose theophylline*</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
</tr>
<tr>
<td>• Preferred for adolescents and adults: low-dose ICS AND a LABA as maintenance plus as-needed SABA</td>
</tr>
<tr>
<td>• Preferred for children 6 to 11 years of age: medium dose ICS + as-needed SABA</td>
</tr>
<tr>
<td>• Alternative controllers: medium- or high-dose ICS, OR low-dose ICS + leukotriene modifier, OR</td>
</tr>
<tr>
<td>• Low-dose ICS + sustained-release theophylline*</td>
</tr>
<tr>
<td><strong>Step 4</strong></td>
</tr>
<tr>
<td>• Preferred for adolescents and adults: low dose ICS/formoterol as maintenance + reliever treatment; OR medium-dose ICS + LABA plus as-needed SABA</td>
</tr>
<tr>
<td>• Preferred for children 6 to 11 years of age: referral to expert for assessment and advice</td>
</tr>
<tr>
<td>• Alternative controllers:</td>
</tr>
<tr>
<td>o For adults and adolescents: medium- or high-dose ICS, OR low-dose ICS + leukotriene modifier, OR low-dose ICS + sustained release theophylline*, OR tiotropium</td>
</tr>
<tr>
<td><strong>Step 5</strong></td>
</tr>
<tr>
<td>• In addition to Step 4 treatment, refer for add-on treatment:</td>
</tr>
<tr>
<td>o Tiotropium, monoclonal antibody treatment (omalizumab [anti-IgE therapy], mepolizumab [anti-IL-5 therapy]), low dose oral corticosteroids, bronchial thermoplasty, or sputum guided therapy</td>
</tr>
</tbody>
</table>

* For children 6 to 11 years of age, theophylline is not recommended.

ICS = inhaled corticosteroid; LABA = long acting beta₂-agonist; SABA = short acting beta₂-agonist

In November 2007, the National Asthma Education and Prevention Panel (NAEPP) released a summary of the third report of the Expert Panel (EPR-3) emphasizing the importance of asthma control and identifying asthma severity as the intrinsic intensity of the disease process. They recommend that, for patients over age 5 years with moderate persistent asthma or asthma not controlled by low-dose corticosteroids, consideration be given for use of a combination of ICS and LABA or for increasing the dose of ICS. For patients with severe persistent asthma, a combination of a LABA and an ICS is recommended. For EIB, LABAs may be used for prevention; however, it is noted that frequent or chronic use may disguise poorly controlled persistent asthma.
**COPD**

The 2017 edition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define chronic obstructive pulmonary disease (COPD) as a common, preventable, and treatable disease in which its pulmonary component is characterized by persistent respiratory symptoms and airflow limitation that is usually progressive and is associated with airway and/or alveolar abnormalities caused by exposure to noxious particles or gases. It is estimated that the number of Americans with a COPD diagnosis exceeds 15 million. However, the U.S. Preventive Services Task Force (USPSTF) recommends against routine screening for COPD in asymptomatic adults.

Pharmacotherapy for COPD is used to decrease symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Bronchodilator medications are central to the symptomatic management of COPD. They improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance. They are given either on an as-needed basis for the relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms. Regular bronchodilation with these drugs does not modify the decline of lung function in mild COPD or the prognosis of the disease. The principal bronchodilator treatments are beta₂-agonists, anticholinergics, and theophylline. These may be given either as monotherapy or in combination. While short-acting beta agonists (SABAs) can be used on an as-needed basis in mild COPD, regular treatment with a long-acting agent is required as the disease progresses.

In their 2017 updated (GOLD) Global Strategy for the Diagnosis, Management, and Prevention of COPD, GOLD stresses a diagnosis of COPD should be considered in any individual who has dyspnea, chronic cough/sputum production, and a history of exposure to risk factors specific to the disease. Spirometry is required to effectively establish a clinical diagnosis of COPD. A postbronchodilator forced expiratory volume in 1 second to forced vital capacity ratio (FEV₁/FVC) < 0.7 confirms presence of airflow limitation and a diagnosis of COPD. The assessment of FEV₁ alone is a poor descriptor of disease status. Therefore, assessment of the patient’s symptoms, future risks of exacerbations, severity of airflow limitation, and comorbidities is essential in guiding therapy. The GOLD Classification of Airflow Limitation, which is divided into 4 grades (GOLD 1 [mild] to GOLD 4 [very severe]), utilizes these airflow limitation grades in addition to the number of exacerbations/hospitalizations to describe a patient’s disease severity. A COPD exacerbation is defined as an acute event characterized by worsening of the patient’s respiratory symptoms that varies from the normal daily variations and requires a change in medication. Hospitalization for a COPD exacerbation signifies a poor prognosis and increased risk of death. The COPD Assessment Test (CAT, 0-40) or the Clinical COPD Questionnaire (CCQ) is recommended for a comprehensive assessment of symptoms. The Modified British Medical Research Council (mMRC) questionnaire may be used but only assesses breathlessness. The St. George’s Respiratory Questionnaire (SGRQ) is a comprehensive measure of health status but is considered too complex for routine practice.

Previously, patient groups were classified into an alphabetic (ABCD) classification system based on exacerbation risk and symptoms in combination with airway limitation. However, patients are now classified separately by both their GOLD severity (airflow limitation) and exacerbation/symptom assessment (e.g., GOLD grade 4, group D). Therefore, exacerbation risk and symptoms alone are used to
define the ABCD classification. The patient groups, for which the definitions of airflow limitation and numerical values for exacerbations/symptoms have *not* changed, are summarized as follows:

- **Assessment of Airflow Limitation:**
  - GOLD 1: mild, FEV₁ ≥ 80% predicted
  - GOLD 2: moderate, FEV₁ 50% to 79% predicted
  - GOLD 3: severe, FEV₁ 30% to 49% predicted
  - GOLD 4: very severe, FEV₁ < 30% predicted

- **Assessment of Exacerbation Risk and Symptoms:**
  - Patient Group A – Low Risk, Less Symptoms: 0 to 1 exacerbations per year (not leading to hospitalization); and CAT score < 10 or mMRC grade 0 to 1
  - Patient Group B – Low Risk, More Symptoms: 0 to 1 exacerbations per year (not leading to hospitalization); and CAT score ≥ 10 or mMRC grade ≥ 2
  - Patient Group C – High Risk, Less Symptoms: ≥ 2 exacerbations per year or ≥ 1 exacerbation leading to hospitalization; and CAT score < 10 or mMRC grade 0 to 1
  - Patient Group D – High Risk, More Symptoms: ≥ 2 exacerbations per year or ≥ 1 exacerbation leading to hospitalization; and CAT score ≥ 10 or mMRC grade ≥ 2

The 2011 American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (ACP/ACCP/ATS/ERS) guidelines include a fifth category. This “At Risk” group is defined as the presence (FEV₁/FVC ratio < 0.7 and FEV₁ ≥ 50% predicted) or absence (FEV₁/FVC ratio ≥ 0.7) of mild to moderate airflow obstruction in asymptomatic individuals who also have other risk factors, including smoking or exposure to pollutants with cough, sputum, or dyspnea, or a family history of respiratory disease. These guidelines support the idea that history or physical examinations alone are poor predictors of airflow obstruction. Airway obstruction, as indicated by a post-bronchodilator ratio of FEV₁/FVC < 0.7, can be predicted by the presence of wheezing on auscultation, smoking history greater than 55 pack years, and patient self report of wheezing. Spirometry is a key diagnostic tool to determine respiratory disease and the severity of airflow obstruction.

The 2017 GOLD guidelines recommend treatment plans for COPD based on the aforementioned patient group categories, identified by symptoms/exacerbation risk and focus on individualized therapy. Bronchodilator medications continue to be central to symptom management in COPD across all groups. While the guidelines review multiple medications and state that bronchodilators are generally effective in their medication overview, GOLD notes that long-acting muscarinic antagonists (LAMAs) have a greater effect on exacerbation reduction and hospitalizations compared to long-acting beta₂-agonists (LABAs) in more severe patients (Evidence A and B, respectively). Likewise, they generally state that combination treatment with bronchodilators (e.g., beta₂-agonist and anticholinergic) is more effective than bronchodilator monotherapy. In regards to antiinflammatory therapy, the addition of an inhaled corticosteroid (ICS) to a LABA is more effective than a LABA alone (Evidence A) and triple therapy (ICS/LAMA/LABA) is more effective compared to an ICS/LABA or LAMA monotherapy (Evidence, A-B); however, data on triple therapy are limited. For the treatment of stable COPD with bronchodilators, LABAs and LAMAs are preferred over short-acting agents except in the case of patients with occasional dyspnea (Evidence A). Inhaled therapy is also preferred over oral therapy (Evidence A). Patients may be initiated on either bronchodilator monotherapy or dual...
bronchodilator therapy (LAMA/LABA); those initiated on monotherapy with persistent symptoms should be escalated to dual bronchodilator therapy (Evidence A). For the treatment of stable COPD with ICS, monotherapy with an ICS is not recommended (Evidence A), but long-term treatment with an ICS may be considered in addition to a LABA in patients with a history of exacerbations despite bronchodilator therapy (Evidence A). For the treatment of acute exacerbations, GOLD recommends the use of a SABA with or without a short-acting anticholinergic agent (Evidence C).

Following these general medication recommendations, GOLD provides a treatment algorithm based on the patient’s ABCD exacerbation/symptom assessment.26 Previously, GOLD had focused on recommendations for preferred and alternative initial therapy. In the revised guidelines, Group A patients should be initiated on a bronchodilator (short- or long-acting). Following an efficacy assessment, the patient may be continued on that bronchodilator or could be switched to an alternative bronchodilator class (e.g., LAMA to LABA). Patients in Group B should be initiated on a LABA or LAMA and, if symptoms persist, therapy may be escalated to LABA + LAMA combination therapy. If combination therapy does not provide an additional benefit, monotherapy should be resumed. No specific long-acting bronchodilator class is preferred in this population. Patients in Group C should be initiated on a LAMA, and if they have further exacerbations, treatment can be escalated to LAMA + LABA combination therapy (preferred) or a LABA + ICS combination therapy. Finally, Group D patients should be initiated on a LAMA + LABA (preferred), LAMA monotherapy, or a LABA + ICS (may be preferred in patients with asthma comorbidity). Patients with persistent symptoms and/or further exacerbations can have treatment escalated to triple therapy (LAMA + LABA + ICS; preferred) or switched to a LABA + ICS if they were not initially receiving this therapy. If further exacerbations occur following triple therapy, additional treatments may be considered (e.g., roflumilast or macrolide in select patients).

In 2015, ACCP published a joint guideline with the Canadian Thoracic Society (CTS) regarding the prevention of acute exacerbations of COPD.27 To prevent moderate to severe exacerbations in patients with moderate to severe COPD, they recommend use of a LABA or a LAMA over no therapy (placebo) (Grade 1B and 1A, respectively). In this same group, they recommend the use of a LAMA over a LABA (Grade 1C) and a LAMA over a short-acting muscarinic antagonist (SAMA) (Grade 1A). To prevent mild to moderate exacerbations in patients with moderate to severe COPD, they recommend use of a SAMA over a SABA (Grade 2C) and a SAMA + LABA over a LABA alone (Grade 2C). In patients with moderate to severe COPD, they recommend use of a SAMA + SABA over SABA monotherapy (Grade 2B) to prevent acute moderate exacerbations and use of a LABA over a SAMA to prevent acute exacerbations (Grade 2C). In patients with stable moderate to very severe COPD, ACCP recommends maintenance therapy with an ICS + LABA over placebo, ICS monotherapy, and LABA monotherapy (Grade 1B, 1B, and 1C, respectively) to prevent acute exacerbations. For patients with stable COPD, they recommend either LAMA/LABA or LAMA monotherapy as both are effective for exacerbations (Grade 1C). Likewise, in stable patients, either ICS/LABA or LAMA monotherapy is recommended (Grade 1C) and either a LAMA + ICS + LABA or LAMA monotherapy is recommended to prevent exacerbations (Grade 2C).

The 2011 ACP/ACCP/ATS/ERS guidelines recommend inhaled bronchodilators for symptomatic COPD patients with a FEV₁ between 60% and 80% of the predicted value (weak recommendation, low-quality evidence).28 For those with a FEV₁ < 60%, they also recommend inhaled bronchodilators (strong recommendation, moderate-quality evidence) as well as monotherapy with either a LAMA or LABA (strong recommendation, moderate-quality evidence). Treatment selection should be based on patient-specific factors (e.g., adverse effects, preference, cost). Combination therapy may also be
considered in this population (e.g., LAMA, LABA, or ICS) (weak recommendation, moderate-quality evidence).

**Devices**

In 2005, the American College of Chest Physicians (ACCP) and the American College of Allergy, Asthma, and Immunology (ACAAI) issued joint evidence-based guidelines for selecting aerosol delivery devices for use in asthma or COPD. The authors performed a systematic review of randomized controlled trials comparing the efficacy and adverse effects of treatment using nebulizers versus pressurized metered-dose inhalers (MDIs), with or without a spacer/holding chamber, versus dry powder inhalers (DPIs) as delivery systems for beta2-agonists, anticholinergic agents, and corticosteroids in several commonly encountered clinical settings and patient populations. DPIs are breath-actuated devices that release the medicine in the form of a dry powder when the user inhales. The authors conclude that devices used for the delivery of bronchodilators and steroids can be equally efficacious.

In children 5 years of age and younger, the 2016 GINA update maintains that inhaled therapy constitutes the cornerstone of asthma treatment. The preferred delivery system is a pressurized MDI with a valved spacer (with face mask for < 4 years old and mouthpiece for most 4 to 5 year olds). Since the dose may vary considerably from one spacer device to another, a spacer that has documented efficacy in young children is recommended. Nebulizers, the only viable alternative delivery system in children, should be reserved for the minority of children who cannot be taught effective use of a spacer device. Arformoterol (Brovana) and formoterol (Perforomist) inhalation solutions are delivered via a nebulizer. The breath-activated DPIs include the Aerosolizer (formoterol [Foradil]; discontinued), Diskus (salmeterol [Serevent]), and Neohaler (indacaterol [Arcapta]). DPIs require high inspiratory flow rates and may not work effectively in a patient with severe COPD. DPIs are also associated with high oropharyngeal deposition. Respimat, is not a breath-activated device; it is designed to release a soft mist of fine particles that leads to a lower amount of drug depositing in the mouth and throat and improved delivery of drug to the lungs compared to the pressurized MDI and DPI devices. Although, the Respimat is not a breath-activated device, it does require coordination of actuation and inhalation. Comparative studies of LABA agents delivered via Respimat and DPI devices are lacking.

The 2017 GOLD guidelines place a greater focus on the assessment of inhaler technique to improve therapeutic outcomes.

**PHARMACOLOGY**

Beta-agonists stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3'5' adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity, especially from mast cells. Beta2-agonists relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma, COPD, or bronchiectasis. Bronchodilation may additionally facilitate expectoration.

Although there are both beta1 and beta2 receptors in the heart, the latter are more predominant in the lungs, where they serve as the primary adrenergic receptors in bronchial smooth muscle. In order to reduce cardiac toxicities (e.g., tachyarrhythmias), the use of beta2 specific agonists is preferred in the treatment of bronchospasm. To further reduce cardiac toxicities, non-systemic dosage forms given by inhalation are preferred to oral dosage forms.
PHARMACOKINETICS\textsuperscript{42,43,44,45,46,47}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative $\beta_2$ Specificity</th>
<th>Onset of Action (minutes)</th>
<th>Duration of Action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long Acting Inhalation Agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>arformoterol inhalation solution (Brovana)</td>
<td>$\beta_2 &gt;&gt;&gt; \beta_1$</td>
<td>7-20</td>
<td>12</td>
</tr>
<tr>
<td>formoterol inhalation powder in capsules (Foradil Aerolizer)</td>
<td>$\beta_2 &gt;&gt;&gt; \beta_1$</td>
<td>5-15</td>
<td>12</td>
</tr>
<tr>
<td>formoterol inhalation solution (Perforomist)</td>
<td>$\beta_2 &gt;&gt;&gt; \beta_1$</td>
<td>11-13</td>
<td>12</td>
</tr>
<tr>
<td>indacaterol inhalation powder (Arcapta Neohaler)</td>
<td>$\beta_2 &gt;&gt;&gt; \beta_1$</td>
<td>15</td>
<td>40 - 56</td>
</tr>
<tr>
<td>olodaterol inhalation spray (Striverdi Respimat)</td>
<td>$\beta_2 &gt;&gt;&gt; \beta_1$</td>
<td>5-20</td>
<td>24</td>
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<tr>
<td>salmeterol DPI (Serevent Diskus)</td>
<td>$\beta_2 &gt;&gt;&gt; \beta_1$</td>
<td>30-48</td>
<td>12</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS/WARNINGS\textsuperscript{48,49,50,51,52,53}

Labeling for all LABAs contains a boxed warning about a small, but significant, increased risk of life-threatening asthma episodes or asthma-related deaths. This warning is based on results from the large, placebo-controlled Salmeterol Multicenter Asthma Research Trial (SMART) in which only the single component agent, salmeterol, was administered to patients. Post-hoc analysis indicates that the risk of these serious reactions was significantly higher in African Americans. However, the FDA did indicate that the benefits of salmeterol in patients with COPD or asthma outweigh the risks.\textsuperscript{54} Likewise, these products may increase the chance of severe asthma episodes, and death when those episodes occur.

In 2010, the FDA issued new recommendations on the safe use of LABAs in the treatment of asthma.\textsuperscript{55} These recommendations include the contraindication for use of LABAs without the use of an asthma controller medication, such as an inhaled corticosteroid (ICS). Single ingredient LABAs should only be used in combination with an asthma controller medication; they should not be used alone. LABAs should only be used long-term in patients whose asthma is not adequately controlled on asthma controller medications. LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and, if possible, discontinued once asthma control is achieved. Patients should then be maintained on an asthma controller medication. Labeling reflects this information. Pediatric patients who require the addition of LABAs to an ICS should use a combination product containing both an ICS and a LABA to ensure compliance with both medications.

LABAs should not be initiated in patients who are acutely deteriorating with COPD or for acute symptoms; a short-acting beta-agonist bronchodilator (SABA) should be used for acute symptoms.

Beta-adrenergic agonists can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, or symptoms. They should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

LABAs should also be used with caution in patients with convulsive disorders, thyrotoxicosis, or with sensitivity to sympathomimetic drugs.

Salmeterol (Serevent) is contraindicated in patients with severe hypersensitivity to milk proteins.
Arformoterol (Brovana) is contraindicated in patients with a known hypersensitivity to arformoterol, racemic formoterol (Foradil), or any of its components.

**DRUG INTERACTIONS**

**Monoamine Oxidase (MAO) Inhibitors and Tricyclic Antidepressants (TCAs)**

All LABAs should be administered with extreme caution to patients being treated with MAO inhibitors, tricyclic antidepressants (TCAs), or drugs known to prolong the QTc interval because these agents may potentiate the action of adrenergic agonists on the cardiovascular system. Allow 2 weeks after discontinuation of MAO inhibitors before initiating therapy with agents in this category.

**Beta-Adrenergic Receptor Blocking Agents**

Beta-blockers not only block the pulmonary effect of LABAs but also may produce severe bronchospasm in patients with asthma or COPD. In general, patients with asthma or COPD should not be treated with beta-blockers. However, under certain circumstances, such as prevention of myocardial re-infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma or COPD. In this setting, cautious use of cardioselective beta-blockers could be considered.

**Diuretics**

The electrocardiogram (ECG) changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium-sparing diuretics. Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

**CYP3A4 Inhibitors**

Co-administration of salmeterol and strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir,itraconazole, nefazodone, nelfinavir, saquinavir, and telithromycin) may result in a significant increase in plasma salmeterol exposure. Due to the potential increased risk of cardiovascular adverse event, the concomitant use of salmeterol with these agents is not recommended.
ADVERSE EFFECTS \(^{62,63,64,65,66,67}\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Headache</th>
<th>Nausea/ Vomiting</th>
<th>Nervousness</th>
<th>Palpitations</th>
<th>Tachycardia</th>
<th>Tremor</th>
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<td>&lt; 2</td>
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<td>4.9/2.4</td>
<td>nr</td>
<td>nr</td>
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<td>nr</td>
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<tr>
<td>(2.6/1.8)</td>
<td></td>
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<tr>
<td>formoterol inhalation powder in capsules (Foradil Aerolizer)</td>
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<td>reported</td>
<td>reported</td>
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<td>reported</td>
<td>1.9 (0.4)</td>
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<td>5.1</td>
<td>2.4</td>
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<td>nr</td>
<td>reported</td>
<td>nr</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>salmeterol DPI (Serevent Diskus)</td>
<td>13 (9)</td>
<td>3 (3)</td>
<td>reported</td>
<td>reported</td>
<td>reported</td>
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</tr>
</tbody>
</table>

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

SPECIAL POPULATIONS \(^{68,69,70,71,72,73}\)

Pediatrics

Formoterol inhalation powder (Foradil Aerolizer) has been studied in children ages 5 years and older for the prevention and treatment of asthma and prevention of EIB; recommended dosage is the same as for older children. Salmeterol (Serevent) is indicated for the prevention and treatment of asthma and prevention of EIB in children as young as 4 years.

Safety and effectiveness of indacaterol (Arcapta), arformoterol (Brovana), formoterol (Perforomist), and oloaterol (Striverdi) have not been established in children.

Pregnancy

All agents in this category are Pregnancy Category C.
### DOSAGES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Adult Dosage</th>
<th>Prevention of EIB</th>
<th>Usual Pediatric Dose</th>
<th>Availability</th>
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<tr>
<td></td>
<td></td>
<td><strong>Long Acting Inhalation Agents</strong></td>
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<tr>
<td><strong>arformoterol</strong></td>
<td><strong>inhalation solution</strong> (Brovana)</td>
<td>15 mcg twice daily</td>
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<td><strong>inhalation powder in capsules</strong> (Foradil Aerolizer)</td>
<td>1 inhalation every 12 hours</td>
<td>1 inhalation 15 minutes prior to exercise</td>
<td>Ages 5 years and up: 1 inhalation every 12 hours</td>
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<tr>
<td><strong>formoterol</strong></td>
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<td>20 mcg every 12 hours</td>
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<tr>
<td><strong>indacaterol</strong></td>
<td><strong>inhalation powder</strong> (Arcapta Neohaler)</td>
<td>75 mcg inhaled once daily using the Neohaler inhaler</td>
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<tr>
<td><strong>olodaterol</strong></td>
<td><strong>inhalation spray</strong> (Striverdi Respimat)</td>
<td>2 inhalations once daily</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>salmeterol DPI</strong></td>
<td><strong>(Serevent Diskus)</strong></td>
<td>1 inhalation every 12 hours</td>
<td>1 inhalation 30 minutes before exercise; not to administer a second dose within 12 hours</td>
<td>Ages 4 years and up: 1 inhalation every 12 hours</td>
</tr>
</tbody>
</table>

A FDA Public Health Advisory issued in March 2008 emphasized the correct use of formoterol (Foradil) inhalation capsules, which are to be used in the Aerolizer device. These capsules should not be swallowed.80

### CLINICAL TRIALS

#### Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.
Asthma

*formoterol DPI inhalation powder (Foradil) versus salmeterol DPI (Serevent) versus terbutaline MDI (Brethine)*

Twenty-five subjects with asthma and a history of exercise-induced bronchoconstriction (EIB) were enrolled in a double-blind, double-dummy, placebo-controlled, randomized, 4-period crossover study. Exercise challenge was performed after 12 days at 5, 30, or 60 minutes after inhalation of a single dose of formoterol dry powder inhaler (DPI) 12 mcg, salmeterol DPI 50 mcg, terbutaline metered-dose inhaler (MDI) 500 mcg, or placebo. EIB did not differ significantly among the active treatments at 5, 30, or 60 minutes postdose. In contrast, the onset of bronchodilation was slower after salmeterol DPI compared to terbutaline MDI (p<0.05) and formoterol DPI (p<0.05), both of which showed a similar time course. At all time points between 5 and 60 minutes, formoterol DPI provided significantly greater bronchodilation than salmeterol DPI (p<0.05). Terbutaline MDI is not currently marketed in the United States.

COPD

Indacaterol (Arcapta Neohaler) has demonstrated superiority over placebo in 6 randomized, double-blinded clinical trials in 5,474 patients COPD. Olopatadine (Striverdi) also demonstrated superiority over placebo in 8 randomized, double-blind clinical trials in 3,533 patients with COPD.

*formoterol (Brovana) versus salmeterol (Serevent) MDI*

A 12-week, double-blind, randomized, double-dummy, placebo- and active-controlled trial in the U.S. compared formoterol and salmeterol in 717 patients with COPD. Patients were randomized to formoterol 15 mcg twice daily, 25 mcg twice daily, or 50 mcg daily via nebulizer, salmeterol 42 mcg twice daily via MDI, or placebo. Groups were similar at baseline and had a mean baseline FEV$_1$ of 1.2 L (41% predicted). Mean improvement in trough FEV$_1$ over 12 weeks was significantly greater with all 3 formoterol doses (15 mcg twice daily, +16.9%; 25 mcg twice daily, +18.9%; 50 mcg daily, +14.9%) and for salmeterol (+17.4%) relative to placebo (+6%; p<0.001). There were significantly greater improvements in the mean percentage change in FEV$_1$ area under the curve from 0 to 12 hours (AUC$_{0-12h}$) from the predose value over 12 weeks (formoterol 15 mcg twice daily, 12.7%; 25 mcg twice daily, 13.9%; 50 mcg daily, 18.9%; salmeterol, 9.8%) versus placebo (2.7%; p<0.001); all doses of formoterol were statistically different from salmeterol for this endpoint (p=0.024). Adverse effects and COPD exacerbations (defined as worsening respiratory status requiring a change in medication or an unscheduled provider visit) were similar in frequency across groups, including placebo.

*formoterol (Brovana) versus salmeterol MDI (Serevent) versus placebo*

Data were pooled from 2, identical, 12-week, double-blind, randomized trials to determine the effect of nebulized formoterol on airway function in adult patients with COPD. Patients were randomized to 1 of the following 5 treatment groups: formoterol 15 mcg twice daily (n=147), 25 mcg twice daily (n=149), or 50 mcg daily (n=147); salmeterol 42 mcg twice daily via MDI (n=146); or placebo (n=150). Both formoterol and salmeterol showed an improvement in trough FEV$_1$ over 12 weeks greater than placebo. The formoterol groups showed the following improvements in trough FEV$_1$: 15 mcg (11.4%); 25 mcg (15.4%); and 50 mcg (10.9%), respectively. The salmeterol group had an 11.6% improvement in trough FEV$_1$. Also, after 12 weeks, 78% to 87% of formoterol patients had at least a 10% increase in
FEV\textsubscript{1} compared to 56% for the salmeterol and 44% for the placebo groups. The study was conducted and funded by the manufacturer of arformoterol.

**albuterol MDI (Proventil, Ventolin) versus formoterol DPI (Foradil) versus salmeterol DPI (Serevent)**

A cross-over, randomized, double-blind, placebo-controlled study was carried out on 20 patients with COPD.\textsuperscript{86} Patients underwent pulmonary function testing and dyspnea evaluation at baseline and 5, 15, 30, 60, and 120 minutes after bronchodilator (albuterol MDI 200 mcg, formoterol DPI 12 mcg, salmeterol DPI 50 mcg, or oxitropium 200 mcg) or placebo administration. Oxitropium was used in this study, but it is not available in the U.S. The results indicated that, in patients with COPD with decreased baseline inspiratory capacity (IC), there was a much greater increase of inspiratory capacity after bronchodilator administration compared to placebo which correlated closely with the improvement of dyspnea sensation at rest. Albuterol and formoterol caused significant increases in IC compared to placebo within 5 minutes while salmeterol and oxitropium caused increases within 15 to 30 minutes, respectively. Changes in FEV\textsubscript{1} were significantly increased in time measures ≥ 30 minutes for the beta-agonist agents compared to oxitropium (p=0.01). Likewise, formoterol resulted in a more marked improvement in IC than salmeterol and oxitropium (p<0.05 for both).

**formoterol inhalation powder (Foradil) versus salmeterol DPI (Serevent)**

Researchers compared the effects of single doses of formoterol 12 and 24 mcg and salmeterol DPI 50 and 100 mcg in a randomized, double-blind, placebo-controlled, crossover study of 47 patients with moderate-to-severe COPD.\textsuperscript{87} The primary efficacy parameter was the area under the curve of FEV\textsubscript{1} in the first hour after drug inhalation in the morning. The estimates of treatment difference in absolute terms (0.086 L; p=0.0044) and percentage change from predose baseline (7.8%; p=0.0021) were greater for formoterol than for salmeterol.

**formoterol inhalation solution (Perforomist) versus formoterol inhalation powder (Foradil) versus placebo**

A 12-week, randomized, double-blind, double-dummy study of 351 patient with COPD (mean FEV\textsubscript{1}=1.3L, 44% predicted) were randomized to receive nebulized formoterol fumarate 20 mcg, formoterol inhalation powder 12 mcg, or placebo to determine the comparative efficacy and safety associated with nebulized therapy in COPD patients.\textsuperscript{88} Efficacy was assessed with 12-hour pulmonary function tests, and quality of life was assessed before and after treatment with the St. George’s Respiratory Questionnaire (SGRQ). At the 12-week endpoint, formoterol inhalation solution significantly increased FEV\textsubscript{1} versus placebo (p<0.0001). There was no evidence of tachyphylaxis since the FEV\textsubscript{1} AUC was maintained and rescue albuterol use was reduced throughout treatment. The SGRQ assessment at week 12 demonstrated significant and clinically meaningful improvements in total, symptom, and impact scores when comparing formoterol inhalation solution to placebo (p=0.0067). No significant differences in efficacy were observed between the 2 active treatments. The safety profile was comparable between the formoterol inhalation solution and the formoterol inhalation powder.

**META-ANALYSES**

A systematic review of pertinent randomized, controlled, clinical trials was undertaken using MEDLINE, EmBase, and the Cochrane Library databases to determine if a difference in efficacy and adverse effects exists among the various aerosol delivery devices (MDI versus DPI versus nebulizers) used in the
management of asthma and COPD exacerbations. A total of 254 outcomes were tabulated. Of the 131 studies that met the eligibility criteria, only 59 (primarily those that tested beta₂-agonists) proved to have useable data. None of the pooled meta-analyses showed a significant difference among devices in any efficacy outcome in any patient group for each of the clinical settings that were investigated. The adverse effects that were reported were minimal and were related to the increased drug dose that was delivered. Each of the delivery devices provided similar outcomes in patients using the correct technique for inhalation.

A Cochrane review of 33 randomized controlled trials (RCTs) assessing the efficacy and safety of adding a LABA to an ICS in 6,381 children and adolescents with asthma found that the LABA addition did not result in a significant reduction in exacerbation rate requiring systemic corticosteroids (risk ratio [RR], 0.95; 95% confidence interval [CI], 0.7 to 1.28; 12 RCTs; 1,669 children; moderate quality evidence) but did find superiority in improving lung function compared to the same or higher doses of ICS monotherapy (FEV₁, morning PEF, reduction in use of daytime rescue inhalations, and reduction in use of nighttime rescue inhalations). No significant differences were found in adverse effects; however, there was lower linear growth velocity in the higher ICS monotherapy group compared to the ICS/LABA group.

SUMMARY

Arformoterol (Brovana), formoterol (Perforomist), salmeterol (Serevent Diskus), indacaterol (Arcapta Neohaler), and olodaterol (Striverdi Respimat) are long-acting beta₂-agonist (LABA) bronchodilators. Another LABA, formoterol (Foradil Aerolizer) has been discontinued but some product may still be available. The main difference between formoterol, arformoterol, indacaterol, and olodaterol compared to salmeterol is that the former have an earlier onset of action. Whether this translates to a clinically significant effect is unknown. Indacaterol and olodaterol are not indicated for use in the treatment of asthma nor should they be used in patients during rapidly deteriorating or potentially life-threatening episodes of chronic obstructive lung disease (COPD). Arformoterol (Brovana) and formoterol (Perforomist) are LABAs for nebulization indicated for the twice-daily, long-term maintenance treatment of bronchoconstriction in patients with COPD, which includes chronic bronchitis and emphysema. The nebulized form may prove beneficial for patients who have difficulty synchronizing breath and actuation using the other existing LABAs available as dry powder inhalers (Foradil Aerolizer [discontinued], Arcapta Neohaler, and Serevent Diskus) or an inhalational spray (Striverdi Respimat). There are no comparative data to suggest that arformoterol (Brovana) or formoterol (Perforomist) are superior in efficacy or safety to the other agents. Olodaterol and indacaterol offer once-daily administration. None of the LABAs have demonstrated an impact on delaying the progression of disease or improving survival of patients with COPD.

Consideration should be made to the boxed warning which appears in the labeling for all LABAs and may discourage the use of these agents, particularly in the African American population.

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4 Arcapta [package insert]. East Hanover, NJ; Novartis; September 2012.
5 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; June 2016.
35 Perforomist [package insert]. Napa, CA; Dey; March 2013.
36 Foradil [package insert]. Whitehouse Station, NJ; Merck/Schering ; March 2012.
38 Arcapta [package insert]. East Hanover, NJ; Novartis; September 2012.
39 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; June 2016.
43 Perforomist [package insert]. Napa, CA; Dey; March 2013.
44 Foradil [package insert]. Whitehouse Station, NJ; Merck/Schering; September 2013.
45 Arcapta [package insert]. East Hanover, NJ; Novartis; September 2012.


56 Perforomist [package insert]. Napa, CA; Dey; March 2013.
58 Foradil [package insert]. Whitehouse Station, NJ; Merck/Schering; March 2012.
60 Brovana [package insert]. Marlborough, MA; Sunovion; February 2014.
61 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; June 2016.
63 Perforomist [package insert]. Napa, CA; Dey; March 2013.
64 Foradil [package insert]. Whitehouse Station, NJ; Merck/Schering; September 2013.
65 Arcapta [package insert]. East Hanover, NJ; Novartis; September 2012.
66 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; June 2016.
68 Perforomist [package insert]. Napa, CA; Dey; March 2013.
70 Foradil [package insert]. Whitehouse Station, NJ; Merck/Schering; September 2013.
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73 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; June 2016.
75 Perforomist [package insert]. Napa, CA; Dey; March 2013.
76 Foradil Aerolizer [package insert]. Whitehouse Station, NJ; Merck/Schering; March 2012.
77 Arcapta [package insert]. East Hanover, NJ; Novartis; September 2012.
78 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; June 2016.
82 Arcapta [package insert]. East Hanover, NJ; Novartis; September 2012.
83 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; June 2016.
Bronchodilators, Short-Acting Beta-Agonists
Therapeutic Class Review (TCR)

November 29, 2016

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## FDA-APPROVED INDICATIONS

<table>
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<tr>
<th>Drug Name</th>
<th>Manufacturer</th>
<th>Reversible Bronchospasm</th>
<th>Prevention and Treatment</th>
<th>Prevention of Exercise Induced Bronchospasm</th>
<th>Chronic Obstructive Pulmonary Disease (COPD)</th>
<th>Age of Use (years)</th>
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<td>albuterol DPI (ProAir RespiClick®)¹</td>
<td>Teva</td>
<td>X</td>
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DPI=dry powder inhaler, HFA=hydrofluoroalkane

## OVERVIEW

Beta₂-agonist bronchodilators are the medications of choice for the treatment and prevention of bronchospasm associated with asthma and prophylaxis of exercise-induced bronchospasm (EIB) in adults and children. They are also used in the treatment of chronic obstructive pulmonary disease (COPD).¹⁶

In some patients with chronic asthma, a clear distinction between asthma and COPD may be difficult. Differing features between asthma and COPD include: the onset of asthma is usually in childhood,
while onset of COPD is in mid-life; asthma symptoms vary from day to day and time during the day, COPD symptoms progress slowly; allergy, rhinitis and/or eczema are usually present in asthma patients. There may be a genetic link with asthma; COPD is due to tobacco smoke, indoor/outdoor and occupational pollutants.\textsuperscript{17}

**Asthma**

Prevalence of asthma in the United States continues to rise. In 2010, total asthma prevalence was estimated to be 8.4\% of the population, or approximately 25.7 million Americans.\textsuperscript{18} Further, the National Health Statistics Report shows that asthma appears to disproportionately affect minority groups, females, children, and individuals of low socioeconomic status which can place significant pressure on public health systems.\textsuperscript{19} The National Asthma Education and Prevention Program (NAEPP) of the National Heart Lung and Blood Institute (NHLBI) has defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.\textsuperscript{20} In susceptible individuals, inflammation may cause recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These episodes are usually associated with airflow obstruction that is often reversible, either spontaneously or with treatment. The inflammation also causes an increase in bronchial hyperresponsiveness to a variety of stimuli.

Medications to treat asthma are classified as controllers or relievers. Controllers are medications taken daily on a long-term basis to maintain asthma control. Relievers are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve symptoms.\textsuperscript{21}

Short-acting beta\textsubscript{2}-agonists (SABAs) have a rapid onset of action and are useful for temporary relief of bronchoconstriction and the accompanying acute symptoms such as wheezing, chest tightness, and cough. Short-acting agents have not been shown to be as beneficial as the long-acting controller medications for chronic asthma management.\textsuperscript{22} Also, increased use of reliever medications is a warning of deterioration in asthma control that indicates a need to reassess treatment.

In 2007 the NAEPP released a summary of the third report of the Expert Panel (EPR-3) that emphasizes the importance of asthma control, and identifies asthma severity as the intrinsic intensity of the disease process.\textsuperscript{23} The EPR-3 advises of the need to first assess severity as the basis of initial therapy and then assess control to adjust therapy. The NAEPP recommends that inhaled SABAs are the drug of choice for treating acute asthma symptoms and exacerbations and for preventing EIB. Regularly scheduled, daily, chronic use of a SABA is not recommended. Use of a short-acting agent greater than 2 days per week for symptom relief is indicative of inadequate asthma control; anti-inflammatory medication should be started or intensified. These guidelines also state that the inhaled route is preferred due to faster onset of action, fewer adverse effects, and increased efficacy. Likewise, agents less selective for the beta\textsubscript{2} receptor, including metaproterenol, are not recommended due to excessive cardiac stimulation.

The 2016 Global Initiative for Asthma (GINA) report defines asthma as a heterogeneous disease, usually characterized by chronic airway inflammation.\textsuperscript{24} GINA categorizes asthma severity based on the level of treatment required to control symptoms. Mild asthma is well-controlled with as-needed SABA or low dose inhaled corticosteroid (ICS). Moderate and severe asthma is controlled with low to moderate dose ICS and long-acting beta\textsubscript{2} agonists (LABAs). GINA provides a 5-step treatment approach which offers flexibility to step up treatment if control is lost or to step down treatment when asthma is controlled. The 2016 GINA guidelines center on the diagnosis and management of asthma in the
clinical practice setting, and offer a control-based management plan to adjust treatment in a continuous cycle of assessment, treatment, and review of the patient’s response as it relates to symptom control, future risk of exacerbations, and side effects. Equally important in this process is identifying the patient’s own goals regarding their asthma management to ensure improved outcomes. During this continuous cycle, a stepwise treatment approach is offered to achieve control using the patient’s current level of control as the baseline. If the patient is not controlled on the current regimen, treatment should be stepped up until control is achieved. If control is maintained for at least 3 months on the current regimen, treatment can be stepped down to the lowest step and dosage that maintains control. At each step, use of a reliever medication for as-needed use, such as a SABA, is recommended. High usage of SABAs is a risk factor for asthma exacerbations; furthermore, excessive usage (e.g., more than 200 doses/month) is a risk factor for asthma-related death.

**COPD**

The 2017 edition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report defines chronic obstructive pulmonary disease (COPD) as a common, preventable, and treatable disease in which its pulmonary component is characterized by persistent respiratory symptoms and airflow limitation that is usually progressive and is associated with airway and/or alveolar abnormalities caused by exposure to noxious particles or gases. It is estimated that the number of Americans with a COPD diagnosis exceeds 15 million. However, the U.S. Preventive Services Task Force recommends against routine screening for COPD in asymptomatic adults.

Bronchodilator medications are central to the symptomatic management of COPD. They improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance. Regular bronchodilation with these drugs does not modify the decline of function in mild COPD or the prognosis of the disease. The principal bronchodilator treatments are beta2-agonists, anticholinergics, and theophylline. These may be given either as monotherapy or in combination. While SABAs can be used on an as-needed basis in mild COPD, regular treatment with a long-acting agent is required as the disease progresses.

The 2017 GOLD updated Global Strategy for the Diagnosis, Management, and Prevention of COPD report, stresses that a diagnosis of COPD should be considered in any individual who has dyspnea, chronic cough/sputum production, and a history of exposure to risk factors specific to the disease. Spirometry is required to effectively establish a clinical diagnosis of COPD. A postbronchodilator forced expiratory volume in 1 second to forced vital capacity ratio (FEV1/FVC) < 0.7 confirms presence of airflow limitation and a diagnosis of COPD. The assessment of FEV1 alone is a poor descriptor of disease status. Therefore, individual assessment of the patient’s symptoms, future risks of exacerbations, severity of airflow limitation, and presence of comorbidities is essential in guiding therapy. The GOLD Classification of Airflow Limitation, which is divided into 4 grades (GOLD 1 [mild] to GOLD 4 [very severe]), utilizes these airflow limitation grades in addition to the number of exacerbations/hospitalizations to describe a patient’s disease severity. A COPD exacerbation is defined as an acute event characterized by worsening of the patient’s respiratory symptoms that varies from the normal daily variations and requires additional therapy. Hospitalization for a COPD exacerbation signifies a poor prognosis and increased risk of death. The COPD Assessment Test (CAT, 0-40) or the Clinical COPD Questionnaire (CCQ) is recommended for a comprehensive assessment of symptoms. The Modified British Medical Research Council (mMRC) questionnaire may be used but only assesses
breathlessness. The St. George’s Respiratory Questionnaire (SGRQ) is comprehensive but is considered too complex for routine practice.

Previously, patient groups were classified into an alphabetic (ABCD) classification system based on exacerbation risk and symptoms in combination with airway limitation. However, patients are now classified separately by both their GOLD severity (airflow limitations) and exacerbation/symptom assessment (e.g., GOLD grade 4, group D). Therefore, exacerbation risk and symptoms alone are used to define the ABCD classification. The patient groups, for which the definitions of airflow limitation and numerical values for exacerbations/symptoms have not changed, are summarized as follows:

- **Assessment of Airflow Limitation:**
  - GOLD 1: mild, FEV\(_1\) ≥ 80% predicted
  - GOLD 2: moderate, FEV\(_1\) 50% to 79% predicted
  - GOLD 3: severe, FEV\(_1\) 30% to 49% predicted
  - GOLD 4: very severe, FEV\(_1\) < 30% predicted

- **Assessment of Exacerbation Risk and Symptoms:**
  - Patient Group A – Low Risk, Less Symptoms: 0 to 1 exacerbations per year (not leading to hospitalization); and CAT score < 10 or mMRC grade 0 to 1
  - Patient Group B – Low Risk, More Symptoms: 0 to 1 exacerbations per year (not leading to hospitalization); and CAT score ≥ 10 or mMRC grade ≥ 2
  - Patient Group C – High Risk, Less Symptoms: ≥ 2 exacerbations per year or ≥ 1 exacerbation leading to hospitalization; and CAT score < 10 or mMRC grade 0 to 1
  - Patient Group D – High Risk, More Symptoms: ≥ 2 exacerbations per year or ≥ 1 exacerbation leading to hospitalization; and CAT score ≥ 10 or mMRC grade ≥ 2

The 2011 American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (ACP/ACCP/ATS/ERS) guidelines include a fifth category, namely “At Risk”, which is based on the presence (FEV\(_1\)/FVC ratio < 0.7 and FEV\(_1\) ≥ 50% predicted) or absence (FEV\(_1\)/FVC ratio ≥ 0.7) of mild to moderate airflow obstruction in asymptomatic individuals and risk factors including smoking or exposure to pollutants with cough, sputum, or dyspnea, or a family history of respiratory disease.\(^36\) These guidelines support the idea that history or physical examinations alone are poor predictors of airflow obstruction. Airway obstruction, as indicated by a post-bronchodilator ratio of FEV\(_1\)/FVC < 0.7, can be predicted by the presence of wheezing on auscultation, smoking history greater than 55 pack years, and patient self-report of wheezing. Spirometry is a key diagnostic tool to determine respiratory disease and the severity of airflow obstruction.

Pharmacotherapy for COPD is used to decrease symptoms, reduce the frequency and severity of exacerbations and hospitalizations, and improve health status and exercise tolerance. The 2017 GOLD report recommends treatment plans for COPD based on the aforementioned patient group categories, identified by symptoms/exacerbation risk, but and emphasizes individualized therapy.\(^37\) Bronchodilator medications continue to be central to symptom management in COPD across all groups. While the guidelines review multiple medications and state that bronchodilators are generally effective in their medication overview, GOLD notes that long-acting antimuscarinics (LAMAs) have a greater effect on exacerbation reduction and hospitalizations compared to LABAs in more severe patients (Evidence A and B, respectively). Likewise, they generally state that combination treatment with bronchodilators
(e.g., beta_2-agonist and anticholinergic) is more effective than bronchodilator monotherapy. In regards to antiinflammatory therapy, the addition of an ICS to a LABA is more effective than a LABA alone (Evidence A). Also, triple therapy (ICS/LAMA/LABA) is more effective compared to an ICS/LABA or LAMA monotherapy (Evidence, A-B); however, data on triple therapy are limited. For the treatment of stable COPD with bronchodilators, LABAs and LAMAs are preferred over short-acting agents except in cases of only occasional dyspnea (Evidence A). Inhaled therapy is also preferred over oral therapy (Evidence A). Patients may be initiated on either bronchodilator monotherapy or dual bronchodilator therapy (LAMA/LABA); those initiated on monotherapy with persistent symptoms should be escalated to dual bronchodilator therapy (Evidence A). For the treatment of stable COPD with ICS, monotherapy with an ICS is not recommended (Evidence A), but long-term treatment with an ICS may be considered in addition to a LABA in patients with a history of exacerbations despite bronchodilator therapy (Evidence A). For the treatment of acute exacerbations, GOLD recommends the use of a SABA with or without a short-acting anticholinergic agent (Evidence C).

Following these general medication recommendations, GOLD provides a treatment algorithm based on the patient’s ABCD exacerbation/symptom assessment.\(^\text{38}\) Previously, GOLD had focused on recommendations for preferred and alternative initial therapy. In the revised guidelines, Group A patients should be initiated on a bronchodilator (short- or long-acting). Following an efficacy assessment, the patient may be continued on that bronchodilator or could be switched to an alternative bronchodilator class (e.g., LAMA to LABA). Patients in Group B should be initiated on a LABA or LAMA and, if symptoms persist, therapy may be escalated to LABA + LAMA combination therapy. If combination therapy does not provide an additional benefit, monotherapy should be resumed. No specific long-acting bronchodilator class is preferred in this population. Patients in Group C should be initiated on a LAMA, and if they have further exacerbations, treatment can be escalated to LAMA + LABA combination therapy (preferred) or a LABA + ICS combination therapy. Finally, Group D patients should be initiated on a LAMA + LABA (preferred), LAMA monotherapy, or a LABA + ICS (may be preferred in patients with asthma comorbidity). Patients with persistent symptoms and/or further exacerbations can have treatment escalated to triple therapy (LAMA + LABA +ICS; preferred) or switched to a LABA + ICS if they were not initially receiving this therapy. If further exacerbations occur following triple therapy, additional treatments may be considered (e.g., roflumilast or macrolide in select patients).

In 2015, ACCP published a joint guideline with the Canadian Thoracic Society (CTS) regarding the prevention of acute exacerbations of COPD.\(^\text{39}\) To prevent moderate to severe exacerbations in patients with moderate to severe COPD, they recommend use of a LABA or a LAMA over no therapy (placebo) (Grade 1B and 1A, respectively). In this same group, they recommend the use of a LAMA over a LABA (Grade 1C) and a LAMA over a SAMA (Grade 1A). To prevent mild to moderate exacerbations in patients with moderate to severe COPD, they recommend use of a SAMA over a SABA (Grade 2C) and a SAMA + LABA over a LABA alone (Grade 2C). In patients with moderate to severe COPD, they recommend use of a SAMA + SABA over SABA monotherapy (Grade 2B) to prevent acute moderate exacerbations and use of a LABA over a SAMA to prevent acute exacerbations (Grade 2C). In patients with stable moderate to very severe COPD, ACCP recommends maintenance therapy with an ICS + LABA over placebo, ICS monotherapy, and LABA monotherapy (Grade 1B, 1B, and 1C, respectively) to prevent acute exacerbations. For patients with stable COPD, they recommend either combination LAMA/LABA therapy or LAMA monotherapy as both are effective for exacerbations (Grade 1C). Likewise, in stable patients, either ICS/LABA or LAMA monotherapy is recommended (Grade 1C) and
either a LAMA + ICS + LABA or LAMA monotherapy is recommended to prevent exacerbations (Grade 2C).

The 2011 ACP/ACCP/ATS/ERS guidelines do not support routine treatment with bronchodilators in the asymptomatic “At Risk” group as there are limited data to support that such treatment influences the trajectory of the disease.40

Devices, Delivery, and Deposition

In 2005, the American College of Chest Physicians (ACCP) and the American College of Allergy, Asthma, and Immunology (ACAAI) issued joint evidence-based guidelines for selecting aerosol delivery devices for use in asthma or COPD.41 The authors performed a systematic review of randomized controlled trials comparing the efficacy and adverse effects of treatment using nebulizers versus pressurized metered-dose inhalers (MDIs) with or without a spacer/holding chamber versus dry powder inhalers (DPIs) as delivery systems for beta₂-agonists, anticholinergic agents, and corticosteroids in several commonly encountered clinical settings and patient populations. DPIs, including the Respiciick® device, are breath-actuated devices that release the medicine in the form of a dry powder when the user inhales. The authors conclude that devices used for the delivery of bronchodilators and steroids can be equally efficacious. The 2016 GINA guidelines state DPIs may be used to deliver SABAs as an alternative to a pressurized MDI and spacer during worsening asthma or exacerbations; however, the available studies did not include patients with severe acute asthma.42

The 2016 GINA update also maintains that inhaled therapy constitutes the cornerstone of asthma treatment in children 5 years of age and younger.43 Similar improvement in lung function has been shown in patients with mild to moderate asthma treated with a SABA administered via an MDI and a spacer as compared to a nebulizer. Since the dose may vary considerably from one spacer device to another, a spacer that has documented efficacy in young children is recommended. The choice of inhaler device for use in children should be based on the child’s age and capability. The preferred delivery system is a pressurized MDI with a valved spacer with a face mask for children younger than 4 years of age and a mouthpiece for most children 4 to 5 years old. Nebulizers should be reserved for the minority of children who cannot be taught effective use of a spacer device. Factors such as arthritis, muscle weakness, impaired vision and inspiratory flow should be considered in choosing an inhaler device for older patients.

The 2017 GOLD guidelines place a greater focus on the assessment of inhaler technique to improve therapeutic outcomes.44

PHARMACOLOGY45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60

Beta-agonists stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3’5’ adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity, especially from mast cells. Beta₂-agonists relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma, COPD, or bronchiectasis. Bronchodilation may additionally facilitate expectoration.61,62 Albuterol is a moderately selective beta₂ receptor agonist. Levalbuterol (Xopenex) is the R-enantiomer form of racemic albuterol. The R-enantiomer is responsible for the bronchodilatory effects of albuterol.
Metaproterenol is neither as β₂-selective nor as long-acting as albuterol. Another β₂-agonist, terbutaline, is more β₂-selective than metaproterenol.

Although there are both β₁ and β₂ receptors in the heart, the latter are more predominant in the lungs, where they serve as the primary adrenergic receptors in bronchial smooth muscle. In order to reduce cardiac toxicities (e.g., tachyarrhythmias), in the treatment of bronchospasm, the use of β₂ specific agonists to nonselective agents (e.g., epinephrine, isoproterenol [Isuprel®], racepinephrine [Asthmanefrin™]) is preferred. In 2012, the FDA revised the labeling of over-the-counter (OTC) bronchodilator products (e.g. ephedrine, epinephrine, and racepinephrine HCl), including revising the indication (for temporary relief of mild symptoms of intermittent asthma) and maximum dosage guidance. To further reduce cardiac toxicities, non-systemic dosage forms given by inhalation are preferred to oral dosage forms.

Non-ozone-depleting propellants, such as hydrofluoroalkane (HFA), for use in pressurized MDIs have replaced the older chlorofluorocarbon (CFC)-containing devices. In clinical studies HFA MDIs have been shown to be equivalent, in terms of efficacy and tolerability, to the original CFC MDIs. The FDA completed its phase-out of inhalers using ozone-depleting CFCs as propellants in 2013.

**PHARMACOKINETICS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative β₂ Specificity</th>
<th>Onset of Action (minutes)</th>
<th>Duration of Action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-Acting Inhalation Agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>albuterol DPI (ProAir RespiClick)</td>
<td>β₂ &gt;&gt; β₁</td>
<td>5 – 15</td>
<td>3 – 6</td>
</tr>
<tr>
<td>albuterol HFA (ProAir HFA, Proventil HFA, Ventolin HFA)</td>
<td>β₂ &gt;&gt; β₁</td>
<td>5.4 – 8.2</td>
<td>3 – 6</td>
</tr>
<tr>
<td>albuterol inhalation solution (generic, AccuNeb)</td>
<td>β₂ &gt;&gt; β₁</td>
<td>5 – 15</td>
<td>3 – 6</td>
</tr>
<tr>
<td>levalbuterol HFA (Xopenex HFA)</td>
<td>β₂ &gt;&gt; β₁</td>
<td>5 – 10</td>
<td>3 – 6</td>
</tr>
<tr>
<td>levalbuterol inhalation solution (Xopenex)</td>
<td>β₂ &gt;&gt; β₁</td>
<td>10 – 17</td>
<td>5 – 8</td>
</tr>
<tr>
<td>Oral Agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>albuterol syrup, tablets</td>
<td>β₂ &gt;&gt; β₁</td>
<td>30</td>
<td>4 – 8</td>
</tr>
<tr>
<td>metaproterenol syrup, tablets</td>
<td>β₂ &gt; β₁</td>
<td>30</td>
<td>≥4</td>
</tr>
<tr>
<td>terbutaline tablet</td>
<td>β₂ &gt;&gt; β₁</td>
<td>30</td>
<td>4 – 8</td>
</tr>
</tbody>
</table>
CONTRAINDICATIONS/WARNINGS

No specific contraindications exist for the short-acting beta₂-agonists (SABAs).

Warnings that are common to the SABAs include: paradoxical bronchospasm (can be life threatening), cardiovascular effects (e.g., effects on blood pressure and pulse rate), excessive dose and usage, acute deterioration of asthma and use of anti-inflammatory agents (e.g., corticosteroids). SABAs should be used with caution in patients with heart disease, seizure disorder, diabetes, and hyperthyroidism.

There have been rare reports of seizures in patients receiving terbutaline; seizures did not recur in these patients after the drug was discontinued.

DRUG INTERACTIONS

Monoamine Oxidase (MAO) Inhibitors and Tricyclic Antidepressants

All beta₂-agonists should be administered with extreme caution to patients being treated with MAO inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because these agents may potentiate the action of adrenergic agonists on the cardiovascular system. Allow 2 weeks after discontinuation of MAO inhibitors before initiating therapy with agents in this category.

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, such as prevention of myocardial re-infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma or COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

Electrocardiogram (ECG) changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta₂-agonists, especially when the recommended dose of the beta₂-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta₂-agonists with non-potassium-sparing diuretics. Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

Digoxin

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear; nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are concurrently receiving digoxin with albuterol or levalbuterol.
**ADVERSE EFFECTS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Headache</th>
<th>Nausea/Vomiting</th>
<th>Nervousness</th>
<th>Palpitations</th>
<th>Tachycardia</th>
<th>Tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-Acting Inhalation Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>albuterol DPI (ProAir RespiClick)</td>
<td>reported</td>
<td>nr</td>
<td>nr</td>
<td>reported</td>
<td>nr</td>
<td>reported</td>
</tr>
<tr>
<td>albuterol HFA (ProAir HFA, Proventil HFA, Ventolin HFA)</td>
<td>7 – 20</td>
<td>7 – 10</td>
<td>7</td>
<td>&lt; 3</td>
<td>&lt; 3 – 7</td>
<td>2 – 7</td>
</tr>
<tr>
<td>albuterol inhalation solution (generic, AccuNeb)</td>
<td>reported</td>
<td>1.7/0.9</td>
<td>reported</td>
<td>reported</td>
<td>nr</td>
<td>reported</td>
</tr>
<tr>
<td>levalbuterol HFA (Xopenex HFA)</td>
<td>reported</td>
<td>10.5</td>
<td>reported</td>
<td>reported</td>
<td>reported</td>
<td>reported</td>
</tr>
<tr>
<td>levalbuterol inhalation solution (Xopenex)</td>
<td>7.6 – 11.9</td>
<td>&lt; 2</td>
<td>2.8 – 9.6</td>
<td>reported</td>
<td>2.7 – 2.8</td>
<td>0 – 6.8</td>
</tr>
<tr>
<td><strong>Oral Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>albuterol syrup</td>
<td>4</td>
<td>&lt; 1 – 2</td>
<td>9 – 15</td>
<td>&lt; 1</td>
<td>1 – 2</td>
<td>10</td>
</tr>
<tr>
<td>albuterol tablets</td>
<td>7</td>
<td>2</td>
<td>20</td>
<td>5</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>metaproterenol syrup</td>
<td>1.1</td>
<td>1.3</td>
<td>4.8</td>
<td>&lt; 1</td>
<td>6.1</td>
<td>1.6</td>
</tr>
<tr>
<td>metaproterenol tablets</td>
<td>7</td>
<td>0.8 – 3.6</td>
<td>20.2</td>
<td>3.8</td>
<td>17.1</td>
<td>16.9</td>
</tr>
<tr>
<td>terbutaline tablets</td>
<td>7.8 – 10</td>
<td>1.3 – 10</td>
<td>&lt; 5 – 31</td>
<td>&lt; 23</td>
<td>1.3 – 3</td>
<td>&lt; 5 – 38</td>
</tr>
</tbody>
</table>

Adverse effects data are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive.

nr = not reported.

**SPECIAL POPULATIONS**

**Pediatrics**

Most of the short-acting beta-agonists (SABAs) have been studied in pediatric patients and shown to be safe and effective in children as young as 2 years of age. Levalbuterol (Xopenex HFA) is approved in patients ≥ 4 years of age. Additionally, ProAir RespiClick is intended for patients 4 years of age and older. There is insufficient clinical data to establish safety and efficacy of terbutaline sulfate; therefore, it is not recommended for patients under the age of 12 years.

**Pregnancy**

There are no adequate and well-controlled studies of these agents in pregnant women. Terbutaline is Pregnancy Category B. All of the SABAs are Pregnancy Category C. They should only be used during pregnancy if the potential benefit outweighs the potential risk.

**Geriatrics**

These agents have not been studied in a geriatric population. Special caution should be observed when using these agents in elderly patients with coexisting conditions like impaired renal function and cardiovascular disease that could be adversely affected by this class of drug.
**Hepatic Impairment**

No dosage adjustments are needed in hepatically impaired patients who use albuterol, albuterol HFA, or levalbuterol.

**Renal Impairment**

Exercise caution and monitor patients with renal impairment who use albuterol, albuterol HFA, or levalbuterol. No special monitoring or dosage adjustments are needed in patients with renal impairment who use metaproterenol.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Adult Dosage</th>
<th>Usual Pediatric Dose</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-Acting Inhalation Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>albuterol DPI (ProAir RespiClick)</td>
<td>2 inhalations every 4 to 6 hours as needed</td>
<td>Prevention of exercise-induced bronchospasm (EIB): 2 inhalations 15 to 30 minutes prior to exercise</td>
<td>Do not use in patients under 4 years of age 108 mcg per actuation from the mouth piece (117 mcg from device reservoir) with dose counter (breath activated device)</td>
</tr>
<tr>
<td>albuterol HFA (Proventil HFA, Ventolin HFA, ProAir HFA)</td>
<td>2 inhalations every 4 to 6 hours as needed</td>
<td>2 inhalations every 4 to 6 hours as needed</td>
<td>90 mcg per actuation (Ventolin HFA and ProAir HFA have dose counters attached to the actuator)</td>
</tr>
<tr>
<td>albuterol inhalation solution (generic, AccuNeb)</td>
<td>2.5 mg every 6 to 8 hours as needed</td>
<td>0.63 to 2.5 mg 4 to 4 times daily as needed</td>
<td>generic: 2.5 mg/3 mL, 5 mg/mL AccuNeb or low-dose generic: 0.63 mg/3 mL, 1.25 mg/3 mL</td>
</tr>
<tr>
<td>levalbuterol HFA (Xopenex HFA)</td>
<td>2 inhalations every 4 to 6 hours as needed</td>
<td>2 inhalations every 4 to 6 hours as needed</td>
<td>45 mcg per actuation</td>
</tr>
<tr>
<td>levalbuterol inhalation solution (Xopenex)</td>
<td>0.63 to 1.25 mg 3 times daily</td>
<td>0.31 to 0.63 mg 3 times daily</td>
<td>0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL, 1.25 mg/0.5 mL (concentrate)</td>
</tr>
<tr>
<td><strong>Oral Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>albuterol oral syrup</td>
<td>2 to 4 mg every 6 to 8 hours</td>
<td>0.1 to 0.2 mg/kg every 8 hours</td>
<td>2 mg/5 mL</td>
</tr>
<tr>
<td>albuterol oral tablets</td>
<td>2 to 4 mg every 6 to 8 hours</td>
<td>2 mg every 6 to 8 hours</td>
<td>Immediate Release: 2 mg, 4 mg Extended Release: 4 mg, 8 mg (one generic formulation is available under the trade name VoSpire ER)</td>
</tr>
<tr>
<td>metaproterenol oral syrup</td>
<td>20 mg 3 to 4 times daily</td>
<td>10 mg 3 to 4 times daily</td>
<td>10 mg/5 mL</td>
</tr>
<tr>
<td>metaproterenol oral tablets</td>
<td>20 mg 3 to 4 times daily</td>
<td>Age 6 – 9 years old or weight &lt; 60 lbs: 10 mg 3 to 4 times daily Age &gt; 9 years old or weight &gt; 60 lbs: 20 mg 3 to 4 times daily</td>
<td>10 mg, 20 mg</td>
</tr>
<tr>
<td>terbutaline tablets</td>
<td>2.5 to 5 mg 3 times daily</td>
<td>2.5 mg 3 times daily</td>
<td>2.5 mg, 5 mg</td>
</tr>
</tbody>
</table>
**CLINICAL TRIALS**

**Search Strategy**

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

While some historical data have demonstrated efficacy of oral agents in the treatment of asthma or COPD, their adverse effect profile, decreased efficacy compared to inhaled formulations, and slower onset of action limit their role as primary treatments for these disorders. As a result, current comparative data focuses on inhaled beta-agonists.

**Asthma**

*albuterol inhalation solution (Proventil, Ventolin) versus levalbuterol inhalation solution (Xopenex)*

In a randomized, double-blind, placebo-controlled, crossover study, 20 adults with mild-to-moderate asthma received single doses of levalbuterol inhalation solution (0.31, 0.63, and 1.25 mg) and albuterol inhalation solution (2.5 mg). All doses of active treatment produced a significantly greater degree of bronchodilation (measured by change in forced expiratory volume in 1 second [FEV$_1$]) than placebo, and there were no significant differences between any of the active treatment arms. The bronchodilator response of levalbuterol 1.25 mg and albuterol 2.5 mg showed similar efficacy over the 6 hour evaluation period, except for a slightly longer duration of action after administration of levalbuterol 1.25 mg. Systemic beta adrenergic adverse effects were observed with all active doses. Levalbuterol 1.25 mg produced a slightly higher rate of systemic beta adrenergic adverse effects than the albuterol 2.5 mg dose. This study was funded by the manufacturer of levalbuterol.

A multicenter, randomized, double-blind, placebo- and active-controlled study was conducted in 338 children with mild-to-moderate asthma. Following a 1-week placebo run-in period, subjects were randomized to nebulized levalbuterol 0.31 or 0.63 mg, albuterol 1.25 or 2.5 mg, or placebo given 3 times daily for 3 weeks. Of the 338 patients who were randomized, 316 patients completed the study. Efficacy, measured by mean peak change in FEV$_1$, was demonstrated for all active treatment regimens compared with placebo (p<0.001). The onset and duration of effect of levalbuterol are consistent with those of albuterol.

A randomized, double-blind, controlled trial was conducted in children age 1 to 18 years (n=482) in the emergency department (ED) and inpatient asthma care unit of an urban tertiary children's hospital.
Patients received a nebulized solution of either 2.5 mg racemic albuterol or 1.25 mg levalbuterol every 20 minutes (maximum 6 doses). Patients admitted to the asthma care unit were treated in a standardized fashion by using the same blinded drug assigned in the ED. Hospitalization rate was the primary outcome. Hospitalization rate was significantly lower in the levalbuterol group (36%) than in the racemic albuterol group (45%, p=0.02). The adjusted relative risk of admission in the racemic group compared with the levalbuterol group was 1.25 (95% confidence interval (CI), 1.01 to 1.57). Hospital length of stay was not significantly shorter in the levalbuterol group (levalbuterol, 44.9 hours; racemic albuterol, 50.3 hours; p=0.63). No significant adverse events occurred in either group.

A randomized, double-blind, controlled trial was conducted in 99 children aged 6 to 17 years in the emergency department (ED). Inclusion criteria included a history of asthma, ED presentation consistent with asthma exacerbation, and an initial FEV1 of less than 70% predicted. Patients were randomized to receive via continuous nebulization either 7.5 mg of albuterol or 3.75 mg of levalbuterol over a 1 hour period, in addition to standard asthma therapies. Spirometry and asthma scoring were performed at the end of the first hour, and a second hour-long nebulization with the same drug was administered if deemed necessary. Spirometry and asthma scoring were again performed and recorded. As a second, optional part of the study, baseline serum albuterol levels were collected on some patients prior to treatment. Baseline characteristics were similar except that the albuterol group had a higher baseline asthma score. Children in the albuterol group had a greater improvement in their FEV1 (p=0.043) as well as in their asthma scores (p=0.01) after 1 hour of continuous treatment compared to the levalbuterol group. The greater improvement in asthma scores was maintained after the second hour of continuous therapy in the albuterol group (p=0.008) but not for FEV1 measurements (p=0.57). There were no differences between groups for changes in heart rate, respiratory rate, oxygen saturation, or rates of admission. The authors concluded that at the doses used, albuterol appears to be superior to levalbuterol with respect to changes in FEV1 and asthma score. There was no significant difference between the drugs with respect to admission rates or side-effect profile.

**COPD**

*albuterol MDI (Proventil, Ventolin) versus formoterol DPI (Foradil) versus salmeterol DPI (Serevent) in COPD*

A cross-over, randomized, double-blind, placebo-controlled study was carried out on 20 patients with COPD. Patients underwent pulmonary function testing and dyspnea evaluation in basal condition and at 5, 15, 30, 60, and 120 minutes after bronchodilator (albuterol metered-dose inhaler (MDI), formoterol dry powder inhaler [DPI], or salmeterol DPI) or placebo administration. The results indicated that in COPD patients with decreased baseline inspiratory capacity, there was a much greater increase of inspiratory capacity after bronchodilator administration, which correlated closely with the improvement of dyspnea sensation at rest. On average, formoterol DPI elicited the greatest increase in inspiratory capacity than the other bronchodilators used.

**META-ANALYSES**

A systematic review of pertinent randomized, controlled, clinical trials was undertaken using MEDLINE, Embase, and the Cochrane Library databases to determine if a difference in efficacy and adverse effects exists among the various aerosol delivery devices (metered-dose inhalers [MDIs] versus dry powder inhalers [DPIs] versus nebulizers) used in the management of asthma and COPD.
exacerbations. A total of 254 outcomes were tabulated. Of the 131 studies that met the eligibility criteria, only 59 (primarily those that tested beta₂-agonists) proved to have useable data. None of the pooled meta-analyses showed a significant difference among devices in any efficacy outcome in any patient group for each of the clinical settings that were investigated. The adverse effects that were reported were minimal and were related to the increased drug dose that was delivered. Each of the delivery devices provided similar outcomes in patients using the correct technique for inhalation.

**SUMMARY**

The 2016 Global Initiative for Asthma (GINA) guidelines for asthma recommend an inhaled short-acting beta₂-agonist (SABA) as the medication of choice for quick relief of asthma symptoms and bronchoconstriction including in acute exacerbations and for exercise-induced bronchoconstriction. Due to its rapid onset of action, relative lack of adverse systemic effects, and availability of multiple dosage forms, albuterol remains the most commonly used SABA bronchodilator. Merck (Proventil HFA), Teva (ProAir HFA), and GlaxoSmithKline (Ventolin HFA) produce albuterol inhalers using HFA propellant. Teva (ProAir RespiClick) also manufactures albuterol inhalers using dry powder meters. Inhaled SABAs also used in the treatment of chronic obstructive pulmonary disease (COPD), particularly for the treatment of acute dyspnea or exacerbations.

In general, oral dosage forms of albuterol are less utilized than the inhaled forms due to systemic beta-adrenergic stimulation of the former, especially in patients sensitive to these effects, such as those with cardiovascular disease. Metaproterenol is neither as beta₂ selective nor as long acting as albuterol, and, therefore, should not be considered for first-line therapy. Another beta₂-agonist, terbutaline, is more beta₂ selective than metaproterenol but is available only as oral tablets. The short duration of action of terbutaline reduces its value in the treatment of bronchoconstriction.

Levalbuterol (Xopenex) is the R-enantiomer form of albuterol. Levalbuterol inhalation solution has similar efficacy to albuterol inhalation solution when given in equivalent doses. In addition, an HFA-propelled inhaler containing the enantiomer of albuterol is available as levalbuterol HFA (Xopenex HFA). There are no significant differences in adverse effects between albuterol and levalbuterol formulations.

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