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

February 12, 2019

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# FDA-APPROVED INDICATIONS

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Manufacturer</th>
<th>Reversible Bronchospasm</th>
<th>Prevention and Treatment</th>
<th>Relief</th>
<th>Prevention of Exercise Induced Bronchospasm</th>
<th>Chronic Obstructive Pulmonary Disease (COPD)</th>
<th>Age of Use (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>albuterol DPI (ProAir® RespiClick®, ProAir® Digihaler™)¹,²</td>
<td>Teva</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>≥ 4</td>
<td></td>
</tr>
<tr>
<td>albuterol HFA (ProAir® HFA, Proventil® HFA, Ventolin® HFA)³,⁴,⁵</td>
<td>generic*, Merck Sharp &amp; Dohme, GlaxoSmithKline, Teva</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>–</td>
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<td></td>
</tr>
<tr>
<td>albuterol inhalation solution⁶,⁷</td>
<td>generic</td>
<td>–</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>≥ 2</td>
<td></td>
</tr>
<tr>
<td>albuterol low-dose inhalation solution⁸</td>
<td>generic</td>
<td>–</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>children 2 to 12 years and adolescents</td>
<td></td>
</tr>
<tr>
<td>levalbuterol HFA (Xopenex® HFA)⁹</td>
<td>generic†, Sunovion</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>≥ 4</td>
<td></td>
</tr>
<tr>
<td>levalbuterol inhalation solution (Xopenex)¹⁰,¹¹</td>
<td>generic, Akorn</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>≥ 6</td>
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</table>

## Oral Agents

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Manufacturer</th>
<th>Reversible Bronchospasm</th>
<th>Prevention and Treatment</th>
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<th>Chronic Obstructive Pulmonary Disease (COPD)</th>
<th>Age of Use (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>albuterol oral syrup¹²</td>
<td>Hi-Tech/Akorn</td>
<td>–</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>≥ 2</td>
<td></td>
</tr>
<tr>
<td>albuterol oral tablets¹³,¹⁴</td>
<td>generic</td>
<td>–</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>≥ 6</td>
<td></td>
</tr>
<tr>
<td>metaproterenol oral syrup¹⁵</td>
<td>Silarx/Lannett</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>X</td>
<td>≥ 6</td>
<td></td>
</tr>
<tr>
<td>metaproterenol oral tablets¹⁶</td>
<td>Par</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>≥ 6</td>
<td></td>
</tr>
<tr>
<td>terbutaline tablets¹⁷</td>
<td>generic</td>
<td>–</td>
<td>X</td>
<td>–</td>
<td>X</td>
<td>≥ 12</td>
<td></td>
</tr>
</tbody>
</table>

DPI = dry powder inhaler, HFA = hydrofluoroalkane

* An authorized generic for Proventil HFA is available from Prasco, and an authorized generic for Ventolin HFA is available from Teva.

† An authorized generic for Xopenex HFA is available by Actavis/Teva.
OVERVIEW

Beta\textsubscript{2}-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).\textsuperscript{18}

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 widely from day to day and are generally worse at night/early mornings, COPD symptoms progress slowly; allergy, rhinitis and/or eczema, as well as obesity are usually present in asthma patients. There may be a genetic link with asthma; COPD is generally due to tobacco smoke and occupational pollutants.\textsuperscript{19}

Asthma

Prevalence of asthma in the United States continues to rise. More than \textbf{26 million} Americans have asthma, and approximately \textbf{6 million} of these are children.\textsuperscript{20} 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{21} 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{22} 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 hyper-responsiveness 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{23}

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{24} Also, increased use of reliever medications is a warning of deterioration in asthma control that indicates a need to reassess treatment.

The 2018 Global Initiative for Asthma (GINA) report characterizes asthma as a heterogeneous disease, usually with chronic airway inflammation.\textsuperscript{25} 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). The 2018 GINA guidelines focus on the diagnosis and management of asthma in the clinical practice setting, and offer a 5-step 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.\textsuperscript{26} 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, as-needed use of a reliever medication such as a SABA, is recommended. High utilization 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. The stepwise approach for asthma control in the GINA guidelines is described below.

**Stepwise Approach to Asthma Control from 2018 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 addition of low dose ICS (controller option)</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
</tr>
<tr>
<td>▪ Preferred controller: low-dose ICS</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 options for adolescents and adults: low-dose ICS AND a LABA as maintenance plus as-needed SABA OR ICS/formoterol maintenance and reliever therapy†</td>
</tr>
<tr>
<td>▪ Preferred option for children 6 to 11 years of age: moderate dose ICS + as-needed SABA</td>
</tr>
<tr>
<td>▪ Alternative controllers: medium dose ICS, OR low-dose ICS + leukotriene modifier, OR low-dose ICS + low-dose sustained-release theophylline*</td>
</tr>
<tr>
<td>▪ Sublingual immunotherapy (SLIT) may be considered in adults with allergic rhinitis or house dust mite sensitivity and exacerbations despite ICS use</td>
</tr>
<tr>
<td><strong>Step 4</strong></td>
</tr>
<tr>
<td>▪ Preferred option for adolescents and adults: medium/high-dose ICS/LABA plus as-needed SABA OR low-dose ICS/formoterol maintenance and reliever therapy†</td>
</tr>
<tr>
<td>▪ Preferred option 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>▪ For adults and adolescents: high-dose ICS/LABA, OR medium-dose ICS + LABA and/or leukotriene modifier or sustained release theophylline*; OR add-on tiotropium‡</td>
</tr>
<tr>
<td>▪ Sublingual immunotherapy (SLIT) may be considered in adults with allergic rhinitis or house dust mite sensitivity and exacerbations despite ICS use</td>
</tr>
<tr>
<td><strong>Step 5</strong></td>
</tr>
<tr>
<td>▪ In addition to Step 4 treatment, refer for add-on therapy:</td>
</tr>
<tr>
<td>▪ Tiotropium‡</td>
</tr>
<tr>
<td>▪ Monoclonal antibody treatment (omalizumab [anti-IgE therapy]) in patients aged ≥ 6 years with moderate or severe allergic asthma</td>
</tr>
<tr>
<td>▪ Anti-IL-5 therapy (benralizumab, mepolizumab, reslizumab) in patients with severe eosinophilic asthma§</td>
</tr>
<tr>
<td>▪ Low-dose oral corticosteroids,</td>
</tr>
<tr>
<td>▪ Sputum guided therapy based on eosinophilia (&gt;3%) in induced sputum</td>
</tr>
</tbody>
</table>

ICS = inhaled corticosteroid; LABA = long acting beta_2-agonist; SABA = short acting beta_2-agonist

* For children < 12 years of age, theophylline is not recommended.
† For patients prescribed low dose budesonide/formoterol of low dose beclomethasone/formoterol for maintenance and reliever therapy. In at-risk patients, the ICS/formoterol maintenance and reliever regimen significantly reduces
exacerbations and provides similar levels of asthma control at relatively low doses of ICS, compared with a fixed-dose of ICS/LABA as maintenance treatment or a higher dose of ICS, both with as-needed SABA (Evidence A). For maintenance treatment with as-needed SABA, adding LABA to ICS in a combination inhaler provides additional improvements in symptoms and lung function with a reduced risk of exacerbations compared with the same dose of ICS, (Evidence A) but there is only a small reduction in reliever use.

‡ An add-on treatment option for patients with a history of exacerbations

§ Benralizumab or mepolizumab for patients aged ≥ 12 years; reslizumab for patients aged ≥ 18 years

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. 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 drugs of choice for treating acute asthma symptoms and exacerbations and for preventing exercise induced bronchospasm (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 and the need for a step-up in treatment (i.e. 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 beta2 receptor, including metaproterenol, are not recommended due to excessive cardiac stimulation.

**COPD**

The 2019 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, approximately 6.4% of the US population. However, the US 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 hospitalizations, 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 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 2019 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 or 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. Notably, both GINA and GOLD use the term asthma-COPD overlap to describe patients with features of both disease states. Due to the overlapping features, these patient populations are often excluded from clinical trials.

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, 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, namely “At Risk”, which is based on 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 and 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 2019 GOLD guidelines recommend treatment plans for COPD based on the aforementioned patient group categories, identified by symptoms/exacerbation risk and focus on individualized therapy. Inhaled bronchodilator medications continue to be central to symptom management in COPD across all groups and are commonly given on a regular basis to prevent or reduce symptoms (Evidence A). While the guidelines review multiple medications and state that bronchodilators are generally effective in their medication overview, GOLD notes that LAMAs, also known as long-acting anticholinergics, have a greater effect on exacerbation reduction and decrease hospitalizations compared to LABAs (Evidence A and B, respectively). Likewise, GOLD generally states that combination treatment with bronchodilators (e.g., beta2-agonist and anticholinergic) is more effective than bronchodilator monotherapy. In regards to anti-inflammatory therapy, the addition of an ICS to a LABA is more effective than a LABA alone (Evidence A); however, regular treatment with ICS increase the risk of pneumonia especially in those with severe disease (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). Blood eosinophil count can help identify patients who may be more likely to respond to ICS treatment. 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. 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). Patients in Group B should be initiated on a LABA or LAMA. Patients in Group C should be initiated on a LAMA, and Group D patients should be initiated on a LAMA + LABA (if symptomatic), LAMA monotherapy, or a LABA + ICS (may be preferred in patients with elevated eosinophils). For follow-up pharmacologic treatment, GOLD bases recommendations on the predominant treatable trait, either dyspnea or exacerbations. For dyspnea in patients on a LABA or LAMA, the next step is a LABA plus LAMA, and if dyspnea persists, a device or drug switch should be considered, along with investigation and treatment of other causes of dyspnea. For those on a LABA plus ICS, escalation to triple therapy can be considered. Likewise, de-escalation of the ICS component or a switch to LABA plus LAMA may be considered if there is a lack of response to the ICS or adverse effects (e.g., pneumonia). For targeting exacerbations, those on a LABA or LAMA can have treatment escalated to LABA plus LAMA, and subsequently, triple therapy (LABA/LAMA/ICS) in patients with an elevated eosinophil count (≥ 100 cells/μL). For those on a LABA or LAMA with a select eosinophil count (≥ 300 cells/μL or ≥ 100 cells/μL plus ≥ 2 moderate exacerbations or 1 hospitalization), treatment with a LABA plus ICS is recommended, followed by triple therapy if needed. If further escalation is needed or escalation is needed in those with an eosinophil count < 100 ≥ 100 cells/μL, the
addition of roflumilast or azithromycin can be considered in select patients. Similar to targeting dyspnea, de-escalation also should be considered, particularly of the ICS component or a switch to LABA plus LAMA in those on triple therapy may be considered if there is a lack of response to the ICS or adverse effects (e.g., pneumonia).

The 2017 American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines provide answers to specific questions pertaining to COPD exacerbations prevention and management. To prevent COPD exacerbations in patients with severe/very severe airflow obstruction, treatment with roflumilast and a macrolide antibiotic are suggested, in addition to optimal inhaled therapy. In those with moderate/severe airflow obstruction, a long-acting muscarinic antagonist (LAMA) is preferred over LABA monotherapy; treatment with an oral mucolytic drug and a macrolide are also recommended. Fluoroquinolones should not be used to solely prevent recurrent COPD exacerbations. To manage COPD exacerbations, an oral corticosteroids course of ≤ 14 days and an antibiotic are both advised.

In 2015, ACCP published a joint guideline with the Canadian Thoracic Society (CTS) regarding the prevention of acute exacerbations of COPD. 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 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.

Devices, Delivery, and Deposition

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.

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, including the Respiclick® 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 2018 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.51

The 2018 GINA update also maintains that inhaled therapy constitutes the cornerstone of asthma treatment in children 5 years of age and younger.52 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 2019 GOLD guidelines place a great focus on the assessment of inhaler technique and adherence to improve therapeutic outcomes; these should be assessed regularly.53

**PHARMACOLOGY**54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70

Beta-agonists stimulate adenylyl 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 from inflammatory cells, especially from mast cells. This increase of cyclic AMP also results in activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, leading to relaxation. 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.71,72 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 bronchodilator effects of albuterol. Metaproterenol is neither as beta₂-selective nor as long-acting as albuterol. Another beta₂-agonist, terbutaline, is more beta₂-selective than metaproterenol.

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), in the treatment of bronchospasm, the use of beta₂ specific agonists to nonselective agents (e.g., epinephrine, isoproterenol [Isuprel®], racpinephrine [Asthmanefrin™]) is preferred. In 2012, the FDA revised the labeling of over-the-counter (OTC) bronchodilator products (e.g. ephedrine, epinephrine, and racpinephrine HCl), including revising the indication (for temporary relief of mild symptoms of intermittent asthma) and maximum dosage guidance.73 To further reduce cardiac toxicities, non-systemic dosage forms given by inhalation are preferred to oral dosage forms.
**PHARMACOKINETICS**

<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><strong>Short-Acting Inhalation Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>albuterol DPI (ProAir RespiClick, ProAir Digihaler)</td>
<td>$\beta_2 &gt;&gt; \beta_1$</td>
<td>5 – 15</td>
<td>3 – 6</td>
</tr>
<tr>
<td>albuterol HFA (ProAir HFA, Proventil HFA, Ventolin HFA)</td>
<td>$\beta_2 &gt;&gt; \beta_1$</td>
<td>5.4 – 8.2</td>
<td>3 – 6</td>
</tr>
<tr>
<td>albuterol inhalation solution</td>
<td>$\beta_2 &gt;&gt; \beta_1$</td>
<td>5 – 15</td>
<td>3 – 6</td>
</tr>
<tr>
<td>levalbuterol HFA (Xopenex HFA)</td>
<td>$\beta_2 &gt;&gt; \beta_1$</td>
<td>5.5 – 10.2</td>
<td>3 – 6</td>
</tr>
<tr>
<td>levalbuterol inhalation solution (Xopenex)</td>
<td>$\beta_2 &gt;&gt; \beta_1$</td>
<td>10 – 17</td>
<td>5 – 8</td>
</tr>
<tr>
<td><strong>Oral Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>albuterol syrup, tablets</td>
<td>$\beta_2 &gt;&gt; \beta_1$</td>
<td>30</td>
<td>6 – 12</td>
</tr>
<tr>
<td>metaproterenol syrup, tablets</td>
<td>$\beta_2 &gt; \beta_1$</td>
<td>30</td>
<td>2 – 6</td>
</tr>
<tr>
<td>terbutaline tablet</td>
<td>$\beta_2 &gt;&gt; \beta_1$</td>
<td>30</td>
<td>4 – 8</td>
</tr>
</tbody>
</table>

**CONTRAINDICATIONS/WARNINGS**

Severe hypersensitivity to milk proteins is a contraindication to albuterol DPI (ProAir RespiClick, ProAir Digihaler). Pre-existing cardiac arrhythmias associated with tachycardia is a contraindication to metaproterenol.

Acute or maintenance tocolysis is a contraindication for terbutaline.

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, glaucoma, hypokalemia, renal impairment, 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 beta$_2$-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, ProAir Digihaler)</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</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 and ProAir Digihaler are 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, excluding levalbuterol concentrate, are Pregnancy Category C. They should only be used during pregnancy if the potential benefit outweighs the potential risk. As product labeling is updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR), assigned Pregnancy Categories have been replaced with descriptive text. No longer considered Pregnancy Category C, labeling for levalbuterol (Xopenex HFA and Xopenex concentrate) now states that there are no adequate and well-controlled studies in pregnant women to inform of a drug-related risk to the fetus.

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, ProAir Digihaler)</td>
<td>Bronchospasm: 2 inhalations every 4 to 6 hours as needed</td>
<td>Do not use in patients under 4 years of age</td>
<td>90 mcg per actuation* from the mouth piece in a box containing 200 actuations; contains dose counter (breath activated device)</td>
</tr>
<tr>
<td></td>
<td>Prevention of EIB: 2 inhalations 15 to 30 minutes prior to exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>albuterol HFA (ProAir HFA, Proventil HFA, Ventolin HFA)</td>
<td>Bronchospasm: 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* from the mouth piece in a canister containing 200 actuations (Proventil HFA, Ventolin HFA and ProAir HFA have dose counters attached to the actuator)</td>
</tr>
<tr>
<td></td>
<td>Prevention of EIB: 2 inhalations 15 to 30 minutes prior to exercise</td>
<td>Prevention of EIB: 2 inhalations 15 to 30 minutes prior to exercise</td>
<td></td>
</tr>
<tr>
<td>albuterol inhalation solution</td>
<td>2.5 mg every 6 to 8 hours as needed</td>
<td>2 to 12 years of age: 0.1 to 0.15 mg/kg (not to exceed 2.5 mg) nebulized 3 to 4 times a day &gt;12 years of age: 2.5 mg nebulized 3 to 4 times daily</td>
<td>generic: 2.5 mL/0.5 mL (0.5%) and 2.5 mg/3 mL (0.083%) in unit-dose vials; 5 mg/mL in multi-dose bottles low-dose generic: 0.63 mg/3 mL (0.021%) and 1.25 mg/3 mL (0.042%) in unit-dose vials</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 in a canister containing 200 actuations (with dose counter)</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, and 1.25 mg/0.5 mL (concentrate) in unit-dose vials</td>
</tr>
</tbody>
</table>

* 90 mcg of albuterol is equivalent to 108 mcg of albuterol sulfate

ProAir Digihaler is a multi-dose breath-actuated dry powder inhaler with a built-in electronic module that detects, records, and stores data on inhaler events, including peak inspiratory flow rate (L/min). Data can be transmitted via a wireless connection to a companion mobile application (App) that categorizes inhaler events and can be shared with a healthcare provider. Use of the App is not required for administration of albuterol sulfate to the patient. There is, however, no evidence that using the App results in improved clinical outcomes. Do not use ProAir Digihaler with a spacer or volume holding chamber. ProAir Digihaler does not need to be primed.
<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>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>2 to 6 years of age: 0.1 to 0.2 mg/kg every 8 hours 6 to 12 years of age: 2 mg 3 to 4 times a day</td>
<td>2 mg/5 mL</td>
</tr>
<tr>
<td>albuterol oral tablets</td>
<td>Immediate-release: 2 to 4 mg every 6 to 8 hours  Extended-release: 8 mg every 12 hours</td>
<td>Immediate-release 6 to 12 years: 2 mg every 6 to 8 hours &gt; 12 years: 2 mg every 6 to 8 hours Extended-release 6 to 12 years of age: 4 mg every 12 hours &gt; 12 years of age: 8 mg every 12 hours</td>
<td>Immediate-release: 2 mg, 4 mg Extended-release: 4 mg, 8 mg†</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>

† ER formulation available from Mylan.
**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 \([\text{FEV}_1]\)) 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 FEV$_1$ 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 FEV$_1$ (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 FEV$_1$ 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 FEV$_1$ 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. However, proper technique is a key component for optimal drug delivery and desired therapeutic outcome. 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 2018 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 also manufactures albuterol inhalers (ProAir RespiClick, ProAir Digihaler) using dry powder meters. Teva also introduced an albuterol inhaler is a multi-dose breath-actuated dry powder albuterol inhaler (ProAir Digihaler) that contains a built-in electronic module to detect inhaler usage and measure inspiratory flow. The data from the device can be transmitted to a companion mobile application (App) and shared with a healthcare provider. Inhaled SABAs are 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.

**REFERENCES**

1 ProAir RespiClick [package insert]. Horsham, PA; Teva; April 2018.
2 ProAir Digihaler [package insert]. Frazer, PA; Teva; December 2018.
5 ProAir HFA [package insert]. Horsham, PA; Teva; February 2019.
6 Albuterol sulfate inhalation solution 0.083% [package insert]. Morgantown, WV; Mylan; January 2013.
7 Albuterol sulfate inhalation solution 0.5% [package insert]. Tampa, FL; Bausch & Lomb; February 2017.
10 Xopenex inhalation solution [package insert]. Lake Forest, IL; Akorn; June 2017.


54. ProAir RespiClick [package insert], Horsham, PA; Teva; April 2018.

55. Proventil HFA [package insert], Whitehouse Station, NJ; Merck Sharp & Dohme; September 2017.


57. ProAir HFA [package insert], Horsham, PA; Teva; February 2019.

58. Albuterol sulfate inhalation solution 0.083% [package insert], Morgantown, WV; Mylan; January 2013.

59. Albuterol sulfate inhalation solution 0.5% [package insert], Tampa, FL; Bausch & Lomb; February 2017.

60. AccuNeb inhalation solution [package insert], Napa, CA; Mylan; January 2013.

61. Xopenex HFA [package insert], Marlborough, MA; Sunovion; February 2017.

62. Xopenex inhalation solution [package insert], Lake Forest, IL; Akorn; June 2017.

63. Xopenex inhalation solution concentrate [package insert], Lake Forest, IL; Akorn; January 2019.

64. Albuterol sulfate syrup [package insert], Sellersville, PA; Teva; August 2017.


66. Albuterol sulfate extended-release tablets [package insert], Morgantown, WV; Mylan; March 2015.

67. Metaproterenol sulfate syrup [package insert], Carmel Valley, NY; Silax; June 2014.

68. Metaproterenol sulfate tablet [package insert], Chestnut Ridge, NY; PAR; April 2016.

69. Terbutaline tablet [package insert], Hayward, CA; Impax; January 2017.


74. ProAir RespiClick [package insert], Horsham, PA; Teva; April 2018.

75. ProAir Digihaler [package insert], Frazer, PA; Teva; December 2018.

76. Proventil HFA [package insert], Whitehouse Station, NJ; Merck Sharp & Dohme; September 2017.

77. Ventolin HFA [package insert], Research Triangle Park, NC; GlaxoSmithKline; May 2017.

78. ProAir HFA [package insert], Horsham, PA; Teva; February 2019.

79. Albuterol sulfate inhalation solution 0.083% [package insert], Morgantown, WV; Mylan; January 2013.

80. Albuterol sulfate inhalation solution 0.5% [package insert], Tampa, FL; Bausch & Lomb; February 2017.

81. AccuNeb inhalation solution [package insert], Napa, CA; Mylan; January 2013.

82. Xopenex HFA [package insert], Marlborough, MA; Sunovion; February 2017.

83. Xopenex inhalation solution [package insert], Lake Forest, IL; Akorn; June 2017.

84. Albuterol sulfate syrup [package insert], Sellersville, PA; Teva; August 2017.

85. Albuterol sulfate tablet [package insert], Morgantown, WV; Mylan; January 2010.

86. Albuterol sulfate tablet [package insert], Morgantown, WV; Mylan; January 2010.

87. Albuterol sulfate extended-release tablets [package insert], Morgantown, WV; Mylan; March 2015.

88. Metaproterenol sulfate syrup [package insert], Carmel Valley, NY; Silax; June 2014.

89. Metaproterenol sulfate tablet [package insert], Chestnut Ridge, NY; PAR; April 2016.

90. Terbutaline tablet [package insert], Hayward, CA; Impax; January 2017.


92. ProAir RespiClick [package insert], Horsham, PA; Teva; April 2018.

93. ProAir Digihaler [package insert], Frazer, PA; Teva; December 2018.

94. Proventil HFA [package insert], Whitehouse Station, NJ; Merck Sharp & Dohme; September 2017.


96. ProAir HFA [package insert], Horsham, PA; Teva; February 2019.

97. Albuterol sulfate inhalation solution 0.083% [package insert], Morgantown, WV; Mylan; January 2013.

98. Albuterol sulfate inhalation solution 0.5% [package insert], Tampa, FL; Bausch & Lomb; February 2017.


100. Xopenex HFA [package insert], Marlborough, MA; Sunovion; February 2017.

101. Xopenex inhalation solution [package insert], Lake Forest, IL; Akorn; January 2019.

102. Xopenex inhalation solution [package insert], Lake Forest, IL; Akorn; June 2017.
169 Albuterol sulfate inhalation solution 0.083% [package insert]. Morgantown, WV; Mylan; January 2013.
170 Albuterol sulfate inhalation solution 0.5% [package insert]. Tampa, FL; Bausch & Lomb; February 2017.
173 Xopenex inhalation solution [package insert]. Lake Forest, IL; Akorn; June 2017.
175 Albuterol sulfate syrup [package insert]. Sellersville, PA; Teva; August 2017.