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

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Reversible Bronchospasm		Prevention of Exercise-Induced Broncho-constriction	Chronic Obstructive Pulmonary Disease (COPD)	Age of Use (years)
		Prevention and Treatment	Relief			
arformoterol inhalation solution (Brovana®)[1]	generic, Sunovion	--	--	--	X	≥ 18
formoterol inhalation solution (Perforomist®)[2]	generic, Mylan	--	--	--	X	≥ 18
olodaterol inhalation spray (Striverdi® Respimat®)[3]	Boehringer Ingelheim	--	--	--	X	≥ 18
salmeterol DPI (Serevent® Diskus®)[4]	GlaxoSmithKline	X	--	X	X	≥ 4

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

Arformoterol (Brovana), formoterol (Perforomist), and olodaterol (Striverdi) are not indicated for the treatment of acute deteriorations of chronic obstructive pulmonary disease (COPD) or the management of asthma.

Salmeterol (Serevent Diskus) is only approved for use in patients with asthma when used in combination with an inhaled corticosteroid (ICS).

In March 2020, Sunovion discontinued indacaterol (Arcapta Neohaler) production.[5]

OVERVIEW

Beta$_2$-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 Pulmonary Disease (COPD).[6,7]

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; and allergies, rhinitis and/or eczema, as well as obesity, are usually present in asthma patients. [8,9] While there may be a genetic link with asthma, COPD is generally due to tobacco smoke and occupational pollutants.

Asthma

In 2020, total asthma prevalence in the US was estimated to be 7.8% of the population (25 million people), including 5.8% of people < 18 years and 8.4% for people ≥ 18 years.[10] While recent data show some improvements in asthma outcomes over time, the National Health Interview Survey maintains that asthma appears to disproportionately affect minority groups, females, children, and individuals of low socioeconomic status.[11] The National Asthma Education and Prevention Program (NAEPP) has defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play

a role.[12,13] 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.[14] 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. The mainstay of asthma therapy is the use of inhaled corticosteroids (ICS) alone or in combination with long-acting beta$_2$-agonists (LABAs) as controller medications.[15,16] While the corticosteroid reduces inflammation, the LABA acts principally to dilate the airways by relaxing airway smooth muscle. These agents lead to improvements in lung function and symptoms and reduce the need for short-acting beta$_2$-agonists (SABAs) for quick relief. Due to the increased risk of severe exacerbations with regular or frequent use, SABA-only treatment is no longer recommended.[17] Likewise, LABAs are not to be used as monotherapy for controlling asthma. For most asthma patients, treatment can be initiated with an as-needed low dose ICS-formoterol, daily low dose ICS, or low dose ICS taken whenever a SABA is taken.

The 2022 Global Initiative for Asthma (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.[18] Equally important in this process is identifying the patient's own goals regarding their asthma management to ensure improved outcomes. In patients whose asthma is not adequately controlled on the preferred controller despite good adherence and correct technique, a step up in treatment may be added until control is achieved. This can be a short-term or sustained step up in therapy. 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. Patients should be started on treatment based on symptoms, with infrequent symptoms beginning at Step 1, and patients with the most frequent, severe, or debilitating symptoms beginning at Step 4. The stepwise approach for asthma control in the GINA guidelines is described below. Notably, reliever therapy can be considered for symptom management prior to exercise, if needed. The GINA 2022 guidelines describe 2 treatment tracks: Track 1 and Track 2. In Track 1, which is the preferred approach, the reliever is as-needed low dose ICS-formoterol. In Track 2, the reliever is an as-needed SABA, which is the alternative approach when Track 1 is not an option or if a patient's asthma is stable with good adherence and no exacerbations on current therapy in the past 12 months.

Stepwise Approach to Asthma Control from 2022 GINA Guidelines – Controller and Reliever Therapy in Patients ≥ 12 Years Old[19]

Step	Track 1	Track 2	Other Controller Options
1	▪ As-needed low dose ICS/formoterol	▪ Low dose ICS (whenever SABA is taken) ▪ With as-needed SABA	--
2	▪ As-needed low dose ICS/formoterol	▪ Low dose maintenance ICS ▪ With as-needed SABA	▪ Low dose ICS whenever SABA is taken, or daily LTRA, or add HDM SLIT
3	▪ Low dose maintenance ICS/formoterol ▪ With as-needed low dose ICS/formoterol	▪ Low dose maintenance ICS/LABA ▪ With as-needed SABA	▪ Medium dose ICS, or add LTRA, or add HDM SLIT
4	▪ Medium dose maintenance ICS/formoterol ▪ With as-needed low dose ICS/formoterol	▪ Medium/high dose maintenance ICS/LABA ▪ With as-needed SABA	▪ Add LAMA, or LTRA or HDM SLIT, or switch to high dose ICS
5	▪ Add on LAMA ▪ Refer for phenotypic assessment ▪ Consider high dose maintenance ICS/formoterol ± anti-IgE (omalizumab), anti-IL-5/5R (mepolizumab, reslizumab, benralizumab), anti-IL4R (dupilumab), or anti-TSLP (tezepelumab) ▪ With as-needed low dose ICS/formoterol	▪ Add on LAMA ▪ Refer for phenotypic assessment ▪ Consider high dose maintenance ICS/LABA ± anti-IgE (omalizumab), anti-IL-5/5R (mepolizumab, reslizumab, benralizumab), anti-IL4R (dupilumab), or anti-TSLP (tezepelumab) ▪ With as-needed SABA	▪ Add azithromycin (adults) or add LTRA ▪ As a last resort, add low dose oral corticosteroid (considering adverse effects)

HDM SLIT = house dust mite sublingual immunotherapy; ICS = inhaled corticosteroid; IgE = Immunoglobulin E; IL-5 = interleukin-5; LABA = long-acting beta$_2$-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; SABA = short-acting beta$_2$-agonist; TSLP = thymic stromal lymphopoietin

Stepwise Approach to Asthma Control from 2022 GINA Guidelines – Controller and Reliever Therapy in Patients 6 to 11 Years Old[20]

Step	Preferred Controller	Other Controller Options	Reliever
1	▪ Low dose ICS whenever SABA is taken	▪ Consider daily low dose ICS	▪ As needed SABA
2	▪ Daily low dose ICS	▪ Daily LTRA or low dose ICS whenever SABA is taken	▪ As needed SABA
3	▪ Low dose ICS/LABA, or medium dose ICS, or very low dose ICS/formoterol MART	▪ Low dose ICS + LTRA	▪ As needed SABA (or ICS/formoterol for MART)
4	▪ Medium dose ICS/LABA, or low dose ICS/formoterol MART; refer for expert advice	▪ Add tiotropium or LTRA	▪ As needed SABA (or ICS/formoterol for MART)
5	▪ Refer for phenotypic assessment ± higher dose ICS/LABA or add-on therapy (e.g., anti-IgE [omalizumab], anti-IL-4R [dupilumab])	▪ Add-on anti-IL-5, or as last resort, add low dose oral corticosteroid (considering adverse effects)	▪ As needed SABA

ICS = inhaled corticosteroid; IgE = Immunoglobulin E; IL-4R = interleukin-4 receptor; IL-5 = interleukin-5; LABA = long-acting beta$_2$-agonist; LTRA = leukotriene receptor antagonist; MART = maintenance and reliever therapy; SABA = short-acting beta$_2$-agonist

Assessment of Asthma Control from 2022 GINA Guidelines[21]

Characteristic	Well Controlled (all of the following)	Partly Controlled (any present in past week)	Uncontrolled
A. Assessment of symptom control (preferably over 4 weeks)			
Daytime symptoms more than twice per week	None of these criteria	1 to 2 of these criteria	≥ 3 of these criteria
Limitations of activity due to asthma			
Nocturnal symptoms/awakening due to asthma			
Need for reliever/rescue treatment with a SABA more than twice per week			
B. Risk factors for poor asthma outcomes			
Assess at diagnosis and periodically at least every 1 to 2 years (and during exacerbations); assess forced expiratory volume in 1 second (FEV_1) after 3 to 6 months of controller treatment, and periodically thereafter			
Independent risk factors for exacerbations include (≥ 1 of these risk factors increases risk for exacerbations despite well-controlled symptoms): ▪ Uncontrolled asthma symptoms, excessive SABA use, inadequate ICS, low FEV_1, exposure to cigarette smoke/allergens, poor adherence, incorrect inhaler technique, major psychological or socioeconomic problems, obesity, chronic rhinosinusitis, gastroesophageal reflux disease (GERD), pregnancy, confirmed food allergy, sputum or blood eosinophilia, intensive care unit (ICU) admission or prior intubation for asthma, ≥ 1 severe exacerbation in past year, and high bronchodilator reversibility			
Fixed air flow limitation risk factors include: ▪ Lack of ICS treatment, tobacco/chemical/occupational exposures, chronic mucus hypersecretion, low weight at birth/pre-term birth, sputum or blood eosinophilia, and low FEV_1			
Risk factors for medication side effects include: ▪ Frequent oral corticosteroid use, long-term/high-dose ICS, cytochrome P450 inhibitor use, and poor inhaler technique			

FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; SABA = short-acting beta$_2$-agonist

The NAEPP Expert Panel Report-3 (EPR-3) report released in 2007 by the National Heart, Lung, and Blood Institute (NHLBI) also recommends a similar classification of asthma severity and control to guide the initiation and adjustment of therapy, respectively.[22] A focused update to these guidelines was released in 2020.[23] The group emphasizes the importance of asthma control and identifying asthma severity as the intrinsic intensity of the disease process. The group recommends a stepwise approach to asthma management, which is detailed in the table below. In addition, all asthma patients should have a SABA inhaler for use on an as-needed basis. As-needed ICS with formoterol is recommended instead for patients 5 to 11 years of age at steps 3 and 4 (as low-dose or medium-dose, respectively), but a SABA is recommended as an alternative. For combinations of an ICS and a LABA for patients ≥ 5 years of age, the group states a single inhaler is preferable. Additional information on the role of biologics for more severe

disease is detailed in another Therapeutic Class Review. For EIB, LABAs may be used for prevention; however, it is noted that frequent or chronic use may disguise poorly controlled persistent asthma.

Stepwise Approach for Managing Persistent Asthma from the NAEPP Expert Panel Report-3 and 2020 Focused Update[24,25]

Severity of Asthma	Adults and Children ≥ 12 Years	Children 5 to 11 Years of Age	Children from Birth to 4 Years of Age
Step 1 Intermittent Asthma	SABA as needed (no daily medications needed)	SABA as needed (no daily medications needed)	SABA as needed (no daily medications needed) Add short course of ICS at start of RTI
Step 2 Persistent Asthma	Low-dose ICS Alternative: cromolyn, LTRA, nedocromil, zileuton, or theophylline	Low-dose ICS Alternative: cromolyn, LTRA, nedocromil, or theophylline	Low-dose ICS Alternative: cromolyn or montelukast
Step 3 Persistent Asthma	Low-dose ICS + formoterol Alternative: medium-dose ICS, low-dose ICS + LABA, low-dose ICS + LAMA, low-dose ICS + LTRA, low-dose ICS + theophylline, or low-dose ICS + zileuton	Low-dose ICS + formoterol Alternative: low-dose ICS + LABA, low-dose ICS + LTRA, or ICS + theophylline	Medium-dose ICS
Step 4 Persistent Asthma	Medium-dose ICS + formoterol Alternative: medium-dose ICS + LABA, medium-dose ICS + LAMA, medium-dose ICS and 1 of the following: LTRA, theophylline, or zileuton	Medium-dose ICS + formoterol Alternative: medium-dose ICS + LABA, medium-dose ICS + LTRA, or medium-dose ICS + theophylline	Medium-dose ICS + LABA Alternative: medium-dose ICS + montelukast
Step 5 Persistent Asthma	Medium-dose ICS + LABA + LAMA Alternative: Medium-high-dose ICS + LABA, high-dose ICS + LTRA	High-dose ICS + LABA Alternative: high-dose ICS + LTRA, or high-dose ICS + theophylline	High-dose ICS + LABA Alternative: high-dose ICS + montelukast
Step 6 Persistent Asthma	High-dose ICS + LABA + oral corticosteroid	High-dose ICS + LABA + oral corticosteroid Alternative: high-dose ICS + LTRA + oral corticosteroid, high-dose ICS + theophylline + oral corticosteroid	High-dose ICS + LABA + oral systemic corticosteroid Alternative: high-dose ICS + montelukast + oral corticosteroid

ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; LTRA = leukotriene receptor antagonist or leukotriene modifier; RTI = respiratory tract infection; SABA = short-acting beta$_2$-agonist

The American Academy of Allergy, Asthma, and Immunology (AAAAI) issued a practice parameter regarding EIB in 2016.[26] They state that SABAs should be prescribed to protect against EIB and to accelerate recovery of lung function when it is compromised (Strong recommendation, Evidence level A). They state that a single dose of SABA, LABA, or both on an intermittent basis (e.g., < 4 times/week) may protect against or mitigate symptoms of EIB (Strong recommendation, Evidence level A); however, prescribers should be cautious with daily use of inhaled beta-agonists, with or without an ICS, as this may lead to tolerance or decreased efficacy (Strong recommendation, Evidence level A).

In August 2020, Choosing Wisely, an initiative of the American Board of Internal Medicine (ABIM), released guidance for the management of pediatric asthma based on information from the American Academy of Pediatrics.[27] Choosing Wisely recommends a thorough evaluation of medication adherence, technique, and device appropriateness prior to stepping up asthma therapy in pediatric patients. Additionally, the guidance recommends against the use of LABA/ICS combination inhalers as initial therapy in pediatric patients with intermittent or mild persistent asthma and states that typically a single agent, such as a low-dose ICS or leukotriene modifier, is sufficient to maintain asthma control.

COPD

The 2023 edition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines defines chronic obstructive pulmonary disease (COPD) as a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent and often progressive airflow obstruction.[28] It is estimated that the number of Americans with a COPD diagnosis is approximately 16 million.[29] However, the US Preventive Services Task Force (USPSTF) recommends against routine screening for COPD in asymptomatic adults (Grade D).[30]

Pharmacotherapy for COPD is used to decrease symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.[31] Bronchodilator therapy (e.g., beta$_2$-agonists, anticholinergics, and methylxanthines) is central to symptom management in COPD, and the inhaled route is preferred. Data suggest that pharmacotherapy has the potential to reduce the rate of decline of lung function, but additional research is needed to identify which patients are likely to benefit. The principal bronchodilator treatments are beta$_2$-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.

In their 2023 updated Global Strategy for the Diagnosis, Management, and Prevention of COPD, GOLD stresses that a diagnosis of COPD should be considered in any individual who has dyspnea, chronic cough/sputum production, and/or a history of exposure to risk factors specific to the disease.[32] Spirometry is required to effectively establish a clinical diagnosis of COPD. A post-bronchodilator forced expiratory volume in 1 second to forced vital capacity ratio (FEV_1/FVC) < 0.7 confirms presence of airflow limitation and a diagnosis of COPD. The assessment of FEV_1 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, including those leading to hospitalizations, to describe a patient's disease severity. COPD exacerbation is defined as an event characterized by increased dyspnea and/or cough and sputum that worsens in < 14 days, which may present with tachypnea and/or tachycardia, and which is often associated with increased inflammation from infection, pollution, or other insult to the airways. Hospitalization for a COPD exacerbation signifies a poor prognosis and increased risk of death. The COPD Assessment Test (CAT™; score range, 0 to 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 Chronic Respiratory Questionnaire (CRQ) and the St. George's Respiratory Questionnaire (SGRQ) are comprehensive measures of health status but are considered too complex for routine practice. Notably, GINA uses the term asthma-COPD overlap to describe patients with features

of both disease states; however, the GOLD guidelines address them as different disorders, regardless of overlapping symptoms.[33,34]

Patients are classified separately by both their GOLD severity (airflow limitation) and exacerbation/symptom assessment (e.g., GOLD grade 2, group B).[35] The patient groups are summarized as follows:

- **Assessment of Airflow Limitation:**
  - GOLD 1: mild, $FEV_1 \geq 80\%$ 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:**

		Symptoms	
Moderate or Severe Exacerbation History		mMRC grade 0 to 1; CAT< 10	mMRC grade ≥ 2; CAT ≥ 10
	0 to 1 moderate exacerbations per year (not leading to hospitalization)	Group A	Group B
	≥ 2 moderate exacerbations per year or ≥ 1 exacerbation leading to hospitalization	Group E	

The 2023 GOLD guidelines recommend treatment plans for COPD based on the aforementioned patient group categories, identified by symptoms/exacerbation risk, and focus on individualized therapy.[36] Inhaled bronchodilator medications continue to be central to symptom management in COPD (Evidence A). While the guidelines review multiple medications and state that bronchodilators are generally effective, GOLD notes that LAMAs, also known as long-acting anticholinergics, have a greater effect on exacerbation reduction and decreased hospitalizations compared to LABAs (Evidence A and B, respectively). Likewise, they generally state that combination treatment with long-acting bronchodilators (e.g., $beta_2$-agonist and anticholinergic) is more effective at reducing exacerbations and symptoms than bronchodilator monotherapy (Evidence B and A, respectively). In regard to anti-inflammatory therapy, the addition of an inhaled corticosteroid (ICS) to a LABA is more effective than a LABA alone (Evidence A); however, regular treatment with ICS increases the risk of pneumonia especially in those with severe disease (Evidence A). Triple therapy (ICS/LAMA/LABA) is more effective compared to an ICS/LABA, LABA/LAMA, or LAMA monotherapy (Evidence A). 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 bronchodilator 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). Monotherapy with an ICS for the treatment of stable COPD is not recommended (Evidence A), and the use of a LABA/ICS combination is not encouraged; the combination of a LABA/LAMA/ICS is preferred when indicated. 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 ABE exacerbation/symptom assessment.[37] Group A patients should be initiated on a

bronchodilator (short- or long-acting). Patients in Group B should be initiated on LABA + LAMA combination therapy. If LABA/LAMA combination therapy is not appropriate, there is no specific long-acting bronchodilator class that is preferred in this population. Group E patients should be initiated on a LAMA + LABA, provided there are no issues with cost, availability, or side effects. If there is an indication for an ICS (e.g., eosinophils ≥ 300 cells/µL), LABA + LAMA + ICS is preferred; the use of a LABA + ICS is not encouraged. The use of an ICS is required in patients who have concomitant asthma. Treatment escalation for each group is based on symptoms. If symptoms include dyspnea or persistent exacerbations and the patient is on a LABA or LAMA, escalating to a LABA/LAMA combination is recommended. For patients who develop further exacerbations on LABA/LAMA therapy, triple therapy with LABA + LAMA + ICS is recommended for patients with eosinophil counts ≥ 100 cells/µL. If patients on triple therapy continue to experience exacerbations, roflumilast or a macrolide (e.g., azithromycin) may be appropriate based on patient-specific factors. If there is a lack of clinical improvement after the addition of an ICS or if pneumonia develops regardless of symptom type, the provider should consider discontinuing the ICS. Furthermore, step-down therapy should also be considered based on symptoms. GOLD states that the choice of inhaler device should be individually tailored based on access, cost, prescriber, patient ability, and patient preference. Inhaler technique and adherence to therapy should be assessed before concluding the current therapy is insufficient. In addition, spirometry should be repeated at least annually.

In 2017, The American Thoracic Society (ATS) and European Respiratory Society (ERS) published joint guidelines on the prevention of COPD exacerbations.[38] They suggest treatment with an oral mucolytic agent to prevent future exacerbations in patients who have COPD with moderate or severe airflow obstruction and exacerbations despite optimal inhaled therapy (conditional recommendation, low quality of evidence). For patients who have COPD with moderate or severe airflow obstruction and a history of ≥ 1 COPD exacerbation during the previous year, they recommend use of a LAMA over LABA monotherapy to prevent future exacerbations (strong recommendation, moderate quality of evidence). For patients with severe or very severe airflow obstruction and COPD exacerbations despite optimal inhaled therapy, they suggest a macrolide antibiotic (also for moderate airflow obstruction) or roflumilast (select patients with chronic bronchitis) to prevent future exacerbations (conditional recommendation, low [macrolide] and moderate [roflumilast] quality of evidence).

In 2015, the American College of Chest Physicians (CHEST) published a joint guideline with the Canadian Thoracic Society (CTS) regarding the prevention of acute exacerbations of COPD.[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 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, CHEST 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).

In 2020, the ATS released additional guidelines for the pharmacologic management of COPD.[40] These guidelines focus on addressing specific questions developed by an ATS panel regarding significant COPD management issues. The panel strongly recommends the use of dual LABA/LAMA therapy over LABA or LAMA monotherapy in COPD patients who complain of exercise intolerance or dyspnea, based on pooled evidence demonstrating decreased hospital admissions and exacerbations and improvements in patient quality of life and dyspnea. Additionally, in patients who complain of dyspnea or exercise intolerance despite dual therapy with LABA/LAMA, the ATS suggests triple therapy (ICS/LABA/LAMA) in patients with a history of ≥ 1 exacerbation requiring hospitalization, oral steroids, or antibiotics in the past year who, despite LABA/LAMA dual therapy, complain of exercise intolerance or dyspnea. Further, for patients receiving triple combination therapy who experience no exacerbations over the course of 1 year, the ATS suggests that ICS therapy may be discontinued. Additional management recommendations regarding treatment approaches outside of this therapeutic class review are detailed in the guidelines.

Devices

In children 5 years of age and younger, the 2022 GINA update maintains that inhaled therapy constitutes the cornerstone of asthma treatment.[41] The preferred delivery system is a pressurized MDI with a valved spacer (with face mask for children < 3 years old and mouthpiece for most 3- to 5-year-old children). 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.

Diskus (salmeterol [Serevent]) is a breath-activated DPI. 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. [42] Respimat (olodaterol [Striverdi]) 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.[43,44] 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 2023 GOLD guidelines place a focus on the assessment of inhaler technique and adherence to improve therapeutic outcomes; these should be assessed regularly.[45]

PHARMACOLOGY[46,47,48,49]

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. $Beta_2$-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.[50,51]

Although there are both $beta_1$ and $beta_2$ 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 beta$_2$ 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[52,53,54,55]

Drug	Relative ß$_2$ Specificity	Onset of Action (minutes)	Duration of Action (hours)
Long Acting Inhalation Agents			
arformoterol inhalation solution (Brovana)	ß$_2$ >>> ß$_1$	7-20	12
formoterol inhalation solution (Perforomist)	ß$_2$ >>> ß$_1$	11-13	12
olodaterol inhalation spray (Striverdi Respimat)	ß$_2$ >>> ß$_1$	5-20	24
salmeterol inhalation dry powder (Serevent Diskus)	ß$_2$ >>> ß$_1$	30-48	12

CONTRAINDICATIONS/WARNINGS[56,57,58,59]

Salmeterol DPI (Serevent Diskus) contains a boxed warning about a small, but significant, increased risk of life-threatening asthma episodes or asthma-related deaths when used as monotherapy. 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.[60] This boxed warning was removed from labeling for arformoterol (Brovana), formoterol (Perforomist), and olodaterol (Striverdi) in May 2019. Nonetheless, labeling for all agents states that LABAs are contraindicated in patients with asthma without an ICS, as this is associated with an increased risk of asthma-related death and asthma-related hospitalizations. Fixed-dose combinations of ICS/LABA do not show a significant increase in the risk of serious asthma-related events compared with ICS alone.

In 2010, the FDA issued recommendations on the safe use of LABAs in the treatment of asthma.[61] 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 a LABA to an ICS should use a combination product containing both an ICS and a LABA to ensure compliance with both medications. In December 2017, the FDA removed the asthma death risk warning from ICS/LABA combination inhalers.[62] The removal of this warning follows the results from 4 large clinical safety trials in which no increase in serious asthma-related adverse effects or asthma-related deaths were observed with the ICS/LABA fixed-dose products compared to the ICS agents alone.

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, diabetes, hypokalemia, hepatic impairment, or with sensitivity to sympathomimetic drugs.

Agents in this class should not be used in patients with known sensitivity to the active component (including a racemic mixture, when applicable) or any of its components.

Salmeterol (Serevent) contains lactose with trace levels of milk proteins. Allergic reactions to products containing milk proteins may occur in patients with severe milk protein allergy.

DRUG INTERACTIONS[63,64,65,66]

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 events, the concomitant use of salmeterol with these agents is not recommended.

ADVERSE EFFECTS[67,68,69,70]

Drug	Headache	Nausea/ Vomiting	Nervousness	Palpitations	Tachycardia	Tremor
arformoterol inhalation solution (Brovana)	reported	reported	reported	< 2	< 2	< 2
formoterol inhalation solution (Perforomist)	nr	4.9/2.4 (2.6/1.8)	nr	nr	nr	nr
olodaterol inhalation spray (Striverdi Respimat)	nr	nr	nr	nr	nr	nr
salmeterol DPI (Serevent Diskus)	13-17 (9-14)	3 (3)	reported	reported	reported	reported

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.

Common adverse effects reported with arformoterol (reported ≥ 5% and twice as often as placebo) include back pain (6%).

Common adverse effects reported with salmeterol (reported ≥ 5% and twice as often as placebo) include influenza (5%).

SPECIAL POPULATIONS[71,72,73,74]

Pediatrics

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 arformoterol (Brovana), formoterol (Perforomist), and olodaterol (Striverdi) have not been established in children.

Pregnancy

The labeling for all agents in this category has been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and now contains descriptive text rather than an assigned Pregnancy Category. The labeling states data are too limited to inform of a drug-associated risk of adverse developmental outcomes; however, beta-agonists may interfere with uterine contractility.

DOSAGES[75,76,77,78]

Drug	Usual Adult Dosage	Prevention of EIB	Usual Pediatric Dose	Availability
Long Acting Inhalation Agents				
arformoterol inhalation solution (Brovana)	15 mcg twice daily	--	--	15 mcg/2 mL inhalation solution
formoterol inhalation solution (Perforomist)	20 mcg every 12 hours	--	--	20 mcg/2 mL inhalation solution
olodaterol inhalation spray (Striverdi Respimat)	2 inhalations once daily	--	--	2.5 mcg per actuation inhalation spray
salmeterol DPI (Serevent Diskus)	1 inhalation every 12 hours	1 inhalation 30 minutes before exercise; not to administer a second dose within 12 hours	Ages 4 years and up: 1 inhalation every 12 hours	50 mcg per actuation inhalation powder (breath-activated device)

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

Salmeterol DPI (Serevent Diskus) is the only agent within this class approved for asthma when used with inhaled corticosteroids. Its efficacy for this indication was demonstrated in 4 randomized, double-blind trials in 1,922 adolescents and adults. Its efficacy versus placebo in pediatric patients 4 to 11 years of age has also been demonstrated.[79]

formoterol DPI inhalation powder versus salmeterol DPI (Serevent Diskus) 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.[80] 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 post-dose. 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 (US). Formoterol DPI inhalation powder, once marketed as Foradil®, is no longer available in the US.

COPD

All agents in this class have demonstrated superiority over placebo in clinical trials; however, within class, high-quality, comparative trials are lacking. Formoterol fumarate (Perforomist) has demonstrated superiority over placebo in a randomized, double-blind clinical trial that included 351 patients with COPD and has demonstrated noninferiority to placebo in a randomized, double-blind, noninferiority postmarketing study that included 1,071 patients with COPD assessed over a 1-year treatment period. Both olodaterol (Striverdi) and salmeterol (Serevent) have also demonstrated superiority over placebo in patients with COPD: olodaterol in 8 randomized, double-blind clinical trials consisting of 3,533 patients, and salmeterol in 2 clinical trials randomized, double-blind clinical trials consisting of 702 patients.[81,82,83]

arformoterol (Brovana) versus placebo with salmeterol (Serevent) MDI as an active comparator

A 12-week, double-blind, randomized, double-dummy, placebo- and active-controlled trial in the US compared arformoterol and salmeterol in 717 patients with COPD.[84] Patients were randomized to arformoterol 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 arformoterol 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 pre-dose value over 12 weeks (arformoterol 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 arformoterol 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.

Data were pooled from 2 identical, 12-week, double-blind, randomized trials to determine the effect of nebulized arformoterol on airway function in adult patients with COPD.[85] Patients were randomized to 1 of the following 5 treatment groups: arformoterol 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 arformoterol and salmeterol showed an improvement in trough FEV_1 over 12 weeks greater than

placebo. The arformoterol 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 a 11.6% improvement in trough FEV_1. Also, after 12 weeks, 78% to 87% of arformoterol patients had at least a 10% increase in FEV_1 compared to 56% for the salmeterol and 44% for the placebo groups. The study was conducted and funded by the manufacturer of arformoterol.

Exercised-Induced Bronchospasm

Salmeterol DPI (Serevent Diskus) is the only agent within this class approved for exercise-induced bronchospasm (EIB). Its efficacy for this indication was demonstrated in 2 randomized, single-dose, crossover trials in 52 adolescents and adults and in 2 randomized trials, single-dose studies in 50 children aged 4 to 11 years.[86]

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.[87] A total of 254 outcomes were tabulated. Of the 131 studies that met the eligibility criteria, only 59 (primarily those that tested $beta_2$-agonists) proved to have usable 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 (FEV_1, morning peak expiratory flow [PEF], reduction in use of daytime rescue inhalations, and reduction in use of nighttime rescue inhalations).[88] 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. Another Cochrane review assessed the addition of formoterol to an ICS and found no difference in all-cause or asthma-related death; however, this risk cannot be completely ruled out.[89] Of note, formoterol is only approved for use in asthma in select fixed-dose ICS/LABA combination inhaler products.

A Cochrane review of controlled clinical trials compared the mortality and non-fatal serious adverse effects of formoterol and salmeterol, each as add-on therapy to an ICS in patients with asthma who were of any age (adult/adolescents: 7 formoterol/budesonide versus salmeterol/fluticasone [n=7,764], 6 formoterol/beclomethasone versus salmeterol/fluticasone [n=1,923], 2 formoterol/mometasone versus salmeterol/fluticasone [n=1,126], 2 formoterol/fluticasone versus salmeterol/fluticasone [n=790], and 1 formoterol/budesonide versus salmeterol/budesonide [n=229]; children: 2 formoterol/fluticasone versus salmeterol/fluticasone [n=723]).[90] Overall, 5 deaths not attributed to asthma were reported among adults and adolescents, and there were 201 reports of non-fatal adverse events. No deaths or

asthma-related serious adverse events were reported in children. No statistically significant differences were found, and data were too limited for any conclusions.

SUMMARY

Arformoterol (Brovana), formoterol (Perforomist), salmeterol (Serevent Diskus), and olodaterol (Striverdi Respimat) are long-acting beta$_2$-agonist (LABA) bronchodilators. The main difference between formoterol, arformoterol, and olodaterol compared to salmeterol is that the first 3 have an earlier onset of action than salmeterol. Whether this translates to a clinically significant effect is unknown.

Olodaterol (Striverdi Respimat) is not indicated for use in the treatment of asthma, nor should it be used in patients during rapidly deteriorating or potentially life-threatening episodes of chronic obstructive pulmonary 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 a dry powder inhaler (Serevent Diskus) or an inhalational spray (Striverdi Respimat). There are no comparative data to suggest that either arformoterol (Brovana) or formoterol (Perforomist) is superior in efficacy or safety to the other agents in this class. Olodaterol (Striverdi Respimat) offers once-daily administration.

None of the LABAs have demonstrated an impact on delaying the progression of disease or improving survival of patients with COPD. The boxed warning that has previously appeared in the labeling for all agents within this class and the contraindication for the use of all single-component LABAs without an ICS may discourage the use of these agents, particularly in the African American population. In December 2017; however, the FDA removed the boxed warning from the inhaled corticosteroids (ICS)/LABA combination inhalers. Furthermore, in May 2019, the FDA removed the boxed warning from the labeling for arformoterol (Brovana), formoterol (Perforomist), and olodaterol (Striverdi). The warning remains in the labeling of salmeterol (Serevent Diskus).

REFERENCES

1 Brovana [package insert]. Marlborough, MA; Sunovion; May 2019.
2 Perforomist [package insert]. Morgantown, WV; Mylan; May 2019.
3 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2021.
4 Serevent Diskus [package insert]. Durham, NC; GlaxoSmithKline; October 2022.
5 Food and Drug Administration. Current and resolved drug shortages and discontinuations: Arcapta Neohaler. 2020. Available at https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm. Accessed January 9, 2023.
6 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 9, 2023.
7 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 9, 2023.
8 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 9, 2023.
9 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 9, 2023.
10 Centers for Disease Control and Prevention. Most recent asthma data. May 25, 2022. Available at: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm . Accessed January 9, 2023.
11 Centers for Disease Control and Prevention. Asthma surveillance - United States, 2006–2018. Available at: https://www.cdc.gov/mmwr/volumes/70/ss/ss7005a1.htm?s_cid=ss7005a1_w. Accessed January 9, 2023.
12 National Heart, Lung, and Blood Institute. National Heart, Lung, and Blood Institute. 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Available at: https://www.nhlbi.nih.gov/health-topics/asthma-for-health-professionals. Accessed January 9, 2023.

13 National Heart, Lung, and Blood Institute. Guidelines for the diagnosis and management of asthma (EPR-3) – 2007. Available at: https://www.nhlbi.nih.gov/health-topics/asthma-for-health-professionals. Accessed January 9, 2023.
14 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 9, 2023.
15 National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. Full report 2007. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/index.htm. Accessed January 9, 2023.
16 National Heart, Lung, and Blood Institute. 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Available at: https://www.nhlbi.nih.gov/health-topics/asthma-for-health-professionals. Accessed January 26, 2023.
17 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 9, 2023.
18 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 9, 2023.
19 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 9, 2023.
20 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 9, 2023.
21 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 9, 2023.
22 National Heart, Lung, and Blood Institute. Guidelines for the diagnosis and management of asthma (EPR-3) – 2007. Available at: https://www.nhlbi.nih.gov/health-topics/asthma-for-health-professionals. Accessed January 10, 2023.
23 National Heart, Lung, and Blood Institute. 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Available at: https://www.nhlbi.nih.gov/health-topics/asthma-for-health-professionals. Accessed January 10, 2023.
24 National Heart, Lung, and Blood Institute. Guidelines for the diagnosis and management of asthma (EPR-3) – 2007. Available at: https://www.nhlbi.nih.gov/health-topics/asthma-for-health-professionals. Accessed January 10, 2023.
25 National Heart, Lung, and Blood Institute. 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Available at: https://www.nhlbi.nih.gov/health-topics/asthma-for-health-professionals. Accessed January 10, 2023.
26 Weiler JM, Brannan JD, Randolph CC, et al. Exercise-induced bronchoconstriction update-2016. J Allergy Clin Immunol. 2016 Nov;138(5):1292-1295.e36. DOI: 10.1016/j.jaci.2016.05.029. Available at: https://www.aaaai.org/practice-resources/statements-and-practice-parameters/practice-parameter-guidelines. Accessed January 10, 2023.
27 Choosing Wisely. American Academy of Pediatrics – Section on pediatric pulmonology and sleep medicine. Five things physicians and patients should question. 2020. Available at https://www.choosingwisely.org/societies/. Accessed January 10, 2023.
28 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 10, 2023.
29 Chronic Obstructive Pulmonary Disease (COPD). Available at: http://www.cdc.gov/copd/index.html. Accessed January 10, 2023.
30 Chronic Obstructive Pulmonary Disease: Screening. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/chronic-obstructive-pulmonary-disease-screening?ds=1&s=copd. Accessed January 10, 2023.
31 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 10, 2023.
32 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 10, 2023.
33 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 10, 2023.
34 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 10, 2023.
35 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 10, 2023.
36 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 10, 2023.
37 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 10, 2023.
38 Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2017; 50: 1602265. DOI: 10.1183/13993003.02265-2016. Available at: https://www.thoracic.org/statements/copd.php. Accessed January 10, 2023.
39 Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society guideline. Chest. 2015; 147(4): 894-942. DOI: 10.1378/chest.14-1676. Available at: https://www.chestnet.org/Guidelines-and-Resources/CHEST-Guideline-Topic-Areas/Airway-Disorders. Accessed January 10, 2023.
40 Nici L, Mammen M, Charbek E, et al. Pharmacologic management of chronic obstructive pulmonary disease. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020; 201(9): e56-e69. DOI: 10.1164/rccm.202003-0625ST. Available at https://www.thoracic.org/statements/copd.php. Accessed January 10, 2023.
41 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 10, 2023.

42 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 10, 2023.
43 Schurmann W, Schmidtmann S, Moroni P, et al. Respimat soft mist Inhaler versus hydrofluoroalkane metered dose inhaler; patient preference and satisfaction. Treat Respir Med. 2005; 4(1):53-61. DOI: 10.2165/00151829-200504010-00006.
44 Anderson P. Use of Respimat soft mist inhaler in COPD patients. Int J Chron Obstruct Pulmon Dis. 2006; 1(3): 251–259. DOI: 10.2147/copd.2006.1.3.251.
45 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 10, 2023.
46 Brovana [package insert]. Marlborough, MA; Sunovion; May 2019.
47 Perforomist [package insert]. Morgantown, WV; Mylan; May 2019.
48 Serevent Diskus [package insert]. Durham, NC; GlaxoSmithKline; October 2022.
49 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2021.
50 Sharma G. Pediatric asthma treatment and medication. Updated December 20, 2021. Available at: http://emedicine.medscape.com/article/1000997-treatment. Accessed January 10, 2023.
51 Kleinschmidt P. Chronic obstructive pulmonary disease (COPD) and emphysema in emergency medicine treatment and medication. Updated November 13, 2020. Available at: http://emedicine.medscape.com/article/807143-treatment. Accessed January 10, 2023.
52 Brovana [package insert]. Marlborough, MA; Sunovion; May 2019.
53 Perforomist [package insert]. Morgantown, WV, CA; Mylan; May 2019.
54 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2021.
55 Serevent Diskus [package insert]. Durham, NC; GlaxoSmithKline; October 2022.
56 Perforomist [package insert]. Morgantown, WV; Mylan; May 2019.
57 Brovana [package insert]. Marlborough, MA; Sunovion; May 2019.
58 Serevent Diskus [package insert]. Durham, NC; GlaxoSmithKline; October 2022.
59 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2021.
60 Food and Drug Administration. FDA Talk Paper: Labeling changes for drug products that contain salmeterol. August 2003.
61 Koshak EA. New FDA safety warnings for LABAs: A call for asthma guidelines revisit for solo beta agonist. Ann Thorac Med. 2010; 5(2): 65–66. Ann Thorac Med. 2010 Apr-Jun; 5(2): 65–66. DOI: 10.4103/1817-1737.62468.
62 FDA removes asthma death risk warning from ICS/LABA drugs. Medpage Today. December 21, 2017. Available at: https://www.medpagetoday.com/pulmonology/asthma/70043?xid=NL_breakingnews_2017-12-21&eun=g776714d0r. Accessed January 10, 2023.
63 Perforomist [package insert]. Morgantown, WV; Mylan; May 2019.
64 Brovana [package insert]. Marlborough, MA; Sunovion; May 2019.
65 Serevent Diskus [package insert]. Durham, NC; GlaxoSmithKline; October 2022.
66 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2021.
67 Brovana [package insert]. Marlborough, MA; Sunovion; May 2019.
68 Perforomist [package insert]. Morgantown, WV; Mylan; May 2019.
69 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2021.
70 Serevent Diskus [package insert]. Durham, NC; GlaxoSmithKline; October 2022.
71 Perforomist [package insert]. Morgantown, WV; Mylan; May 2019.
72 Brovana [package insert]. Marlborough, MA; Sunovion; May 2019.
73 Serevent Diskus [package insert]. Durham, NC; GlaxoSmithKline; October 2022.
74 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2021.
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77 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2021.
78 Serevent Diskus [package insert]. Durham, NC; GlaxoSmithKline; October 2022.
79 Serevent Diskus [package insert]. Durham, NC; GlaxoSmithKline; October 2022.
80 Richter K, Janicki S, Jorres RA, et al. Acute protection against exercise-induced bronchoconstriction by formoterol, salmeterol and terbutaline. Eur Respir J. 2002; 19:865-71. DOI: 10.1183/09031936.02.00228502.
81 Striverdi Respimat [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2021.
82 Serevent Diskus [package insert]. Durham, NC; GlaxoSmithKline; October 2022.
83 Hanania NA, Sethi S, Koltun A, et al. Long-term safety and efficacy of formoterol fumarate inhalation solution in patients with moderate-to-severe COPD. Int J Chron Obstruct Pulmon Dis. 2018 Dec 27;14:117-127. DOI: 10.2147/COPD.S173595
84 Baumgartner RA, Hanania NA, Calhoun WJ, et al. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. Clin Ther. 2007; 29(2):261-278. DOI: 10.1016/j.clinthera.2007.02.009.
85 Hanrahan J, Hanania N, Calhoun W, et al. Effect of nebulized arformoterol on airway function in COPD: results from two randomized trials. COPD. 2008; 5(1):25-34. DOI: 10.1080/15412550701816187.
86 Serevent Diskus [package insert]. Durham, NC; GlaxoSmithKline; October 2022.
87 Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest. 2005; 127:335-371. DOI: 10.1378/chest.127.1.335.
88 Chauhan BF, Chartrand C, Ni Chroinin M, et al. Addition of long-acting beta2-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev. 2015;11:CD007949. DOI: 10.1002/14651858.CD007949.pub2.
89 Janjua S, Schmidt S, Ferrer M, et al. Inhaled steroids with and without regular formoterol for asthma: serious adverse events. Cochrane Database Syst Rev. 2019;9:CD006924. DOI: 10.1002/14651858.CD006924.pub4.
90 O'Shea O, Stovold, E, Cates CJ. Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2021;4(4):CD007694. DOI: 10.1002/14651858.CD007694.pub3.

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

January 11, 2023

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FDA-APPROVED INDICATIONS

Drug Name	Manufacturer	Reversible Bronchospasm		Prevention of Exercise Induced Broncho-spasm	Chronic Obstructive Pulmonary Disease (COPD)	Age of Use (years)
		Prevention and Treatment	Relief			
Short-Acting Inhalation Agents						
albuterol DPI (ProAir RespiClick®, ProAir® Digihaler®)[1,2]	Teva	X	X	X	–	≥ 4
albuterol HFA (ProAir® HFA*, Proventil® HFA, Ventolin® HFA)[3,4,5,]	generic†, Teva, Sandoz, GlaxoSmithKline	X	X	X	–	≥ 4
albuterol inhalation solution[6,7]	generic	–	X	–	–	≥ 2
albuterol low-dose inhalation solution[8]	generic	–	X	–	–	children 2 to 12 years and adolescents
levalbuterol HFA (Xopenex® HFA)[9]	generic‡, Sunovion	X	–	–	–	≥ 4
levalbuterol inhalation solution (Xopenex)[10,11]	generic, Akorn	X	–	–	–	≥ 6
Oral Agents						
albuterol oral syrup[12]	generic	–	X	–	–	≥ 2
albuterol oral tablets[13,14]	generic, Mylan	–	X	–	–	≥ 6
metaproterenol oral syrup[15]	Silarx/Lannett	X	–	–	X	≥ 6
terbutaline tablets[16]	generic	–	X	–	X	≥ 12

DPI = dry powder inhaler, HFA = hydrofluoroalkane

* Teva has discontinued ProAir HFA as of October 1, 2022; product may remain until supply is depleted.[17]

† Generics are available for ProAir HFA and Proventil HFA. An authorized generic for Ventolin HFA is available from Prasco.

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

OVERVIEW

Beta$_2$-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 Pulmonary Disease (COPD).[18,19]

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; and allergies, rhinitis and/or eczema, as well as obesity, are usually present in asthma patients. [20,21] While there may be a genetic link with asthma, COPD is generally due to tobacco smoke and occupational pollutants.

Asthma

In 2020, total asthma prevalence in the US was estimated to be 7.8% of the population (25 million people), including 5.8% of people < 18 years and 8.4% for people ≥ 18 years.[22] While recent data show some improvements in asthma outcomes over time, the National Health Interview survey maintains that asthma appears to disproportionately affect minority groups, females, children, and individuals of low socioeconomic status..[23] The National Asthma Education and Prevention Program (NAEPP) has defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.[24,25] 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. [26] 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. The mainstay of asthma therapy is the use of inhaled corticosteroids (ICS) alone or in combination with long-acting beta$_2$-agonists (LABAs) as controller medications.[27,28] While the corticosteroid reduces inflammation, the LABA acts principally to dilate the airways by relaxing airway smooth muscle. These agents lead to improvements in lung function and symptoms and reduce the need for short-acting beta$_2$-agonists (SABAs) for quick relief, which have historically been recommended for symptomatic treatment. Due to the increased risk of severe exacerbations with regular or frequent use, short-acting beta agonist (SABA)-only treatment is no longer recommended.[29] Likewise, LABAs are not to be used as monotherapy for controlling asthma. For most asthma patients, treatment can be initiated with an as-needed low dose ICS-formoterol, daily low dose ICS, or low dose ICS taken whenever a SABA is taken.

The 2022 Global Initiative for Asthma (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.[30] Equally important in this process is identifying the patient's own goals regarding their asthma management to ensure improved outcomes. In patients whose asthma is not adequately controlled on the preferred controller despite good adherence and correct technique, a step up in treatment may be added until control is achieved. This can be a short-term or sustained step up in therapy. 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. Patients should be started on treatment based on symptoms, with infrequent symptoms beginning at Step 1, and patients with the most frequent, severe, or debilitating symptoms beginning at Step 4. The stepwise approach for asthma control in the GINA guidelines is described below. Notably, reliever therapy can be considered for symptom management prior to exercise, if needed. The 2022 GINA guidelines describe 2 treatment tracks: Track 1 and Track 2. In Track 1, which is the preferred approach, the reliever is as-needed low dose ICS-formoterol. In Track 2, the reliever is an as-needed SABA, which is the alternative approach when Track 1 is not an option or if a patient's asthma is stable with good adherence and no exacerbations on current therapy in the past 12 months.

Stepwise Approach to Asthma Control from 2022 GINA Guidelines – Controller and Reliever Therapy in Patients ≥ 12 Years Old[31]

Step	Track 1	Track 2	Other Controller Options
1	▪ As-needed low dose ICS/formoterol	▪ Low dose ICS (whenever SABA is taken) ▪ With as-needed SABA	--
2	▪ As-needed low dose ICS/formoterol	▪ Low dose maintenance ICS ▪ With as-needed SABA	▪ Low dose ICS (whenever SABA is taken), or daily LTRA, or add HDM SLIT
3	▪ Low dose maintenance ICS/formoterol ▪ With as-needed low dose ICS/formoterol	▪ Low dose maintenance ICS/LABA ▪ With as-needed SABA	▪ Medium dose ICS, or add LTRA, or add HDM SLIT
4	▪ Medium dose maintenance ICS/formoterol ▪ With as-needed low dose ICS/formoterol	▪ Medium/high dose maintenance ICS/LABA ▪ With as-needed SABA	▪ Add LAMA, or LTRA or HDM SLIT, or switch to high dose ICS
5	▪ Add on LAMA ▪ Refer for phenotypic assessment ▪ Consider high dose ICS/formoterol ± anti-IgE (omalizumab), anti-IL-5/5R (mepolizumab, reslizumab, benralizumab), anti-IL4R (dupilumab), or anti-TSLP (tezepelumab) ▪ With as-needed low dose ICS/formoterol	▪ Add on LAMA ▪ Refer for phenotypic assessment ▪ Consider high dose ICS/LABA ± anti-IgE (omalizumab), anti-IL-5/5R (mepolizumab, reslizumab, benralizumab), anti-IL4R (dupilumab), or anti-TSLP (tezepelumab) ▪ With as-needed SABA	▪ Add azithromycin (adults) or add LTRA ▪ As a last resort, add low dose oral corticosteroid (considering adverse effects)

HDM SLIT = house dust mite sublingual immunotherapy; ICS = inhaled corticosteroid; IgE = Immunoglobulin E; IL-5 = interleukin-5; LABA = long acting beta$_2$-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; SABA = short acting beta$_2$-agonist; TSLP = thymic stromal lymphopoietin

Stepwise Approach to Asthma Control from 2022 GINA Guidelines – Controller and Reliever Therapy in Patients 6 to 11 Years Old[32]

Step	Preferred Controller	Other Controller Options	Reliever
1	▪ Low dose ICS whenever SABA is taken	▪ Consider daily low dose ICS	▪ As needed SABA
2	▪ Daily low dose ICS	▪ Daily LTRA or low dose ICS whenever SABA is taken	▪ As needed SABA
3	▪ Low dose ICS/LABA, or medium dose ICS, or very low dose ICS/formoterol MART	▪ Low dose ICS + LTRA	▪ As needed SABA (or ICS/formoterol for MART)
4	▪ Medium dose ICS/LABA, or low dose ICS/formoterol MART; refer for expert advice	▪ Add tiotropium or LTRA	▪ As needed SABA (or ICS/formoterol for MART)
5	▪ Refer for phenotypic assessment ± higher dose ICS/LABA or add-on therapy (e.g., anti-IgE [omalizumab], anti-IL-4R [dupilumab])	▪ Add-on anti-IL-5, or as last resort, add low dose oral corticosteroid (considering adverse effects)	▪ As needed SABA

ICS = inhaled corticosteroid; IgE = Immunoglobulin E; IL-4R = interleukin-4 receptor; IL-5 = interleukin-5; LABA = long acting beta$_2$-agonist; LTRA = leukotriene receptor antagonist; MART = maintenance and reliever therapy; SABA = short acting beta$_2$-agonist

Assessment of Asthma Control from 2022 GINA Guidelines[33]

Characteristic	Well Controlled (all of the following)	Partly Controlled (any present in past week)	Uncontrolled
A. Assessment of symptom control (preferably over 4 weeks)			
Daytime symptoms more than twice per week	None of these criteria	1 to 2 of these criteria	≥ 3 of these criteria
Limitations of activity due to asthma			
Nocturnal symptoms/awakening due to asthma			
Need for reliever/rescue treatment with a SABA more than twice per week			
B. Risk factors for poor asthma outcomes			
Assess at diagnosis and periodically at least every 1 to 2 years (and during exacerbations); assess forced expiratory volume in 1 second (FEV_1) after 3 to 6 months of controller treatment, and periodically thereafter			
Independent risk factors for exacerbations include (≥ 1 of these risk factors increases risk for exacerbations despite well-controlled symptoms): ▪ Uncontrolled asthma symptoms, excessive SABA use, inadequate ICS, low FEV_1, exposure to cigarette smoke/allergens, poor adherence, incorrect inhaler technique, major psychological or socioeconomic problems, obesity, chronic rhinosinusitis, gastroesophageal reflux disease (GERD), pregnancy, confirmed food allergy, sputum or blood eosinophilia, intensive care unit (ICU) admission or prior intubation for asthma, ≥ 1 severe exacerbation in past year, and high bronchodilator reversibility			
Fixed air flow limitation risk factors include: ▪ Lack of ICS treatment, tobacco/chemical/occupational exposures, chronic mucus hypersecretion, low weight at birth/pre-term birth, sputum or blood eosinophilia, and low FEV_1.			
Risk factors for medication side effects include: ▪ Frequent oral corticosteroid use, long-term/high-dose ICS, cytochrome P450 inhibitor use, and poor inhaler technique			

FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; SABA = short-acting beta$_2$-agonist

The NAEPP Expert Panel Report-3 (EPR-3) report released in 2007 by the National Heart, Lung, and Blood Institute (NHLBI) also recommends a similar classification of asthma severity and control, to guide the initiation and adjustment of therapy, respectively.[34] A focused update to these guidelines was released in 2020.[35] The group emphasizes the importance of asthma control and identifying asthma severity as the intrinsic intensity of the disease process. The group recommends a stepwise approach to asthma management, which is detailed in the table below. The NAEPP continues to recommend that inhaled SABAs are the drugs of choice for treating acute asthma symptoms and exacerbations and for preventing exercise-induced bronchospasm (EIB). Thus, in addition to the table below, all asthma patients should have a SABA inhaler for use on an as-needed basis, although there are a few exceptions in which it is not the preferred choice. As-needed ICS with formoterol is recommended instead for patients 5 to 11 years of age at steps 3 and 4 (as low-dose or medium-dose, respectively), but a SABA is recommended as an alternative. 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 (e.g., 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 $beta_2$ receptor, including metaproterenol, are not recommended due to excessive cardiac stimulation. For combinations of an ICS and a LABA for patients ≥ 5 years of age, the group states a single inhaler is preferable. Additional information on the role of biologics for more severe disease is detailed in another Therapeutic Class Review.

Stepwise Approach for Managing Persistent Asthma from the NAEPP Expert Panel Report-3 and 2020 Focused Update[36,37]

Severity of Asthma	Adults and Children ≥ 12 Years	Children 5 to 11 Years of Age	Children from Birth to 4 Years of Age
Step 1 Intermittent Asthma	SABA as needed (no daily medications needed)	SABA as needed (no daily medications needed)	SABA as needed (no daily medications needed) Add short course of ICS at start of RTI
Step 2 Persistent Asthma	Low-dose ICS Alternative: cromolyn, LTRA, nedocromil, zileuton, or theophylline	Low-dose ICS Alternative: cromolyn, LTRA, nedocromil, or theophylline	Low-dose ICS Alternative: cromolyn or montelukast
Step 3 Persistent Asthma	Low-dose ICS + formoterol Alternative: medium-dose ICS, low-dose ICS + LABA, low-dose ICS + LAMA, low-dose ICS + LTRA, low-dose ICS + theophylline, or low-dose ICS + zileuton	Low-dose ICS + formoterol Alternative: low-dose ICS + LABA, low-dose ICS + LTRA, or ICS + theophylline	Medium-dose ICS
Step 4 Persistent Asthma	Medium-dose ICS + formoterol Alternative: medium-dose ICS + LABA, medium-dose ICS + LAMA, medium-dose ICS and 1 of the following: LTRA, theophylline, or zileuton	Medium-dose ICS + formoterol Alternative: medium-dose ICS + LABA, medium-dose ICS + LTRA, or medium-dose ICS + theophylline	Medium-dose ICS + LABA Alternative: medium-dose ICS + montelukast
Step 5 Persistent Asthma	Medium-dose ICS + LABA + LAMA Alternative: Medium-high-dose ICS + LABA, high-dose ICS + LTRA	High-dose ICS + LABA Alternative: high-dose ICS + LTRA, or high-dose ICS + theophylline	High-dose ICS + LABA Alternative: high-dose ICS + montelukast
Step 6 Persistent Asthma	High-dose ICS + LABA + oral corticosteroid	High-dose ICS + LABA + oral corticosteroid Alternative: high-dose ICS + LTRA + oral corticosteroid, high-dose ICS + theophylline + oral corticosteroid	High-dose ICS + LABA + oral corticosteroid Alternative: high-dose ICS + montelukast + oral corticosteroid

ICS = inhaled corticosteroid; LABA = long-acting $beta_2$-agonist; LTRA = leukotriene receptor antagonist or leukotriene modifier; RTI = respiratory tract infection; SABA = short-acting $beta_2$-agonist

The American Academy of Allergy, Asthma, and Immunology (AAAAI) issued a practice parameter regarding EIB in 2016.[38] They state that SABAs should be prescribed to protect against EIB and to accelerate recovery of lung function when it is compromised (Strong recommendation, Evidence level A). They state that a single dose of SABA, LABA, or both on an intermittent basis (e.g., < 4 times/week) may protect against or mitigate symptoms of EIB (Strong recommendation, Evidence level A); however, prescribers should be cautious with daily use of inhaled beta-agonists, with or without an ICS, as this may lead to tolerance or decreased efficacy (Strong recommendation, Evidence level A).

In August 2020, Choosing Wisely, an initiative of the American Board of Internal Medicine (ABIM), released guidance for the management of pediatric asthma based on information from the American Academy of Pediatrics.[39] Choosing Wisely recommends a thorough evaluation of medication adherence, technique, and device appropriateness prior to stepping up asthma therapy in pediatric patients. Additionally, the guidance recommends against the use of LABA/ICS combination inhalers as initial therapy in pediatric patients with intermittent or mild persistent asthma and state that typically a single agent, such as a low-dose ICS or leukotriene modifier, is sufficient to maintain asthma control.

COPD

The 2023 edition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines defines chronic obstructive pulmonary disease (COPD) as a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent and often progressive airflow obstruction.[40] It is estimated that the number of Americans with a COPD diagnosis is approximately 16 million.[41] However, the US Preventive Services Task Force (USPSTF) recommends against routine screening for COPD in asymptomatic adults (Grade D).[42]

Pharmacotherapy for COPD is used to decrease symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.[43] Bronchodilator therapy (e.g., $beta_2$-agonists, anticholinergics, and methylxanthines) is central to symptom management in COPD, and the inhaled route is preferred. Data suggest that pharmacotherapy has the potential to reduce the rate of decline of lung function, but additional research is needed to identify which patients are likely to benefit. The principal bronchodilator treatments are $beta_2$-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.

In their 2023 updated Global Strategy for the Diagnosis, Management, and Prevention of COPD, GOLD stresses that a diagnosis of COPD should be considered in any individual who has dyspnea, chronic cough/sputum production, and/or a history of exposure to risk factors specific to the disease.[44] Spirometry is required to effectively establish a clinical diagnosis of COPD. A post-bronchodilator forced expiratory volume in 1 second to forced vital capacity ratio (FEV_1/FVC) < 0.7 confirms presence of airflow limitation and a diagnosis of COPD. The assessment of FEV_1 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, including those leading to hospitalizations, to identify a patient's disease severity. COPD exacerbation is defined as an event

characterized by increased dyspnea and/or cough and sputum that worsens in < 14 days, which may present with tachypnea and/or tachycardia, and which is often associated with increased inflammation from infection, pollution, or other insult to the airways. Hospitalization for a COPD exacerbation signifies a poor prognosis and increased risk of death. The COPD Assessment Test (CAT™; score range, 0 to 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 Chronic Respiratory Questionnaire (CRQ) and the St. George's Respiratory Questionnaire (SGRQ) are comprehensive measures of health status but are considered too complex for routine practice. Notably, GINA uses the term asthma-COPD overlap to describe patients with features of both disease states; however, the GOLD guidelines address them as different disorders, regardless of overlapping symptoms.[45, 46]

Patients are classified separately by both their GOLD severity (airflow limitation) and exacerbation/symptom assessment (e.g., GOLD grade 2, group B).[47] The patient groups are summarized as follows:

- **Assessment of Airflow Limitation:**
  - GOLD 1: mild, $FEV_1 \geq 80\%$ 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:**

		Symptoms	
Moderate or Severe Exacerbation History		mMRC grade 0 to 1; CAT< 10	mMRC grade ≥ 2; CAT ≥ 10
	0 to 1 moderate exacerbations per year (not leading to hospitalization)	Group A	Group B
	≥ 2 moderate exacerbations per year or ≥ 1 exacerbation leading to hospitalization	Group E	

The 2023 GOLD guidelines recommend treatment plans for COPD based on the aforementioned patient group categories, identified by symptoms/exacerbation risk, and focus on individualized therapy.[48] Inhaled bronchodilator medications continue to be central to symptom management in COPD (Evidence A). Regular and as-needed use of a SABA or a short-acting anticholinergic agent, also known as a short-acting muscarinic agent (SAMA), improves symptoms and FEV_1 (Evidence A). Combinations of SABA and SAMA are superior to either treatment alone in improving symptoms and FEV_1 (Evidence A). For the treatment of stable COPD with bronchodilators, LABAs and long-acting anticholinergics, also known as long-acting muscarinic agents (LAMAs), are preferred over short-acting agents except in cases of only occasional dyspnea (Evidence A). Following their general medication recommendations for all relevant treatment classes, GOLD provides a treatment algorithm based on the patient's ABE exacerbation/symptom assessment; however, SABAs are not addressed in this chronic management algorithm. For the treatment of acute exacerbations, GOLD recommends the use of a SABA with or without a SAMA (Evidence C). Notably, GOLD states that the choice of inhaler device should be individually tailored based on access, cost, prescriber, patient ability, and patient preference.

Inhaler technique and adherence to therapy should be assessed before concluding the current therapy is inadequate. In addition, spirometry should be repeated at least annually.

The 2011 American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (ACP/CHEST/ATS/ERS) COPD 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.[49] These guidelines support the idea that history or physical examination 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 > 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 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.

The 2017 American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines provide answers to specific questions pertaining to COPD exacerbation prevention and management.[50,51] 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 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* corticosteroid course of ≤ 14 days and an antibiotic are both advised.

In 2015, the American College of Chest Physicians (CHEST) published a joint guideline with the Canadian Thoracic Society (CTS) regarding the prevention of acute exacerbations of COPD.[52] 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, CHEST 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).

In 2020, the American Thoracic Society (ATS) released additional guidelines for the pharmacologic management of COPD.[53] These guidelines focus on addressing specific questions developed by an ATS panel regarding significant COPD management issues, but they do not make formal recommendations regarding the role of short-acting bronchodilators. Additional management recommendations regarding treatment approaches outside of this therapeutic class review are detailed in the guidelines.

Devices, Delivery, and Deposition

In 2005, the American College of Chest Physicians (CHEST) 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.[54] 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 beta$_2$-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 concluded that devices used for the delivery of bronchodilators and steroids can be equally efficacious.

In children 5 years of age and younger, the 2022 GINA update maintains that inhaled therapy constitutes the cornerstone of asthma treatment.[55] The preferred delivery system is a pressurized MDI with a valved spacer (with face mask for children < 3 years old and mouthpiece for most 3- to 5-year-old children). 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. The 2022 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.

The 2023 GOLD guidelines place a focus on the assessment of inhaler technique and adherence to improve therapeutic outcomes; these should be assessed regularly.[56] 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.

PHARMACOLOGY[57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72]

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 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. Beta$_2$-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.[73,74] Albuterol is a moderately selective beta$_2$ 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 beta$_2$-selective nor as long-acting as albuterol. Another beta$_2$-agonist, terbutaline, is more beta$_2$-selective than metaproterenol.

Although there are both beta$_1$ and beta$_2$ 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 beta$_2$ 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.[75] To further reduce cardiac toxicities, non-systemic dosage forms given by inhalation are preferred to oral dosage forms.

PHARMACOKINETICS[76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91]

Drug	Relative ß$_2$ Specificity	Onset of Action (minutes)	Duration of Action (hours)
Short-Acting Inhalation Agents			
albuterol DPI (ProAir RespiClick, ProAir Digihaler)	ß$_2$ >> ß$_1$	5 – 15	3 – 6
albuterol HFA (ProAir HFA, Proventil HFA, Ventolin HFA)	ß$_2$ >> ß$_1$	5.4 – 8.2	3 – 6
albuterol inhalation solution	ß$_2$ >> ß$_1$	5 – 15	3 – 6
levalbuterol HFA (Xopenex HFA)	ß$_2$ >> ß$_1$	5.5 – 10.2	3 – 6
levalbuterol inhalation solution (Xopenex)	ß$_2$ >> ß$_1$	10 – 17	5 – 8
Oral Agents			
albuterol syrup, tablets	ß$_2$ >> ß$_1$	30	6 – 12
metaproterenol syrup	ß$_2$ > ß$_1$	30	2 – 6
terbutaline tablets	ß$_2$ >> ß$_1$	30	4 – 8

CONTRAINDICATIONS/WARNINGS[92,93,94,95,96,97,98,99,100,101,102,103,104,105, 106,107]

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[108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123]

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 $beta_2$-agonists, especially when the recommended dose of the $beta_2$-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of $beta_2$-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[124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139]

Drug	Headache	Nausea/ Vomiting	Nervousness	Palpitations	Tachycardia	Tremor
Short-Acting Inhalation Agents						
albuterol DPI (ProAir RespiClick, ProAir Digihaler)	reported	nr	nr	reported	nr	reported
albuterol HFA (ProAir HFA, Proventil HFA, Ventolin HFA)	7 – 20	7 – 10	7	< 3	< 3 – 7	2 – 7
albuterol inhalation solution	reported	1.7/0.9	reported	reported	nr	reported
levalbuterol HFA (Xopenex HFA)	reported	10.5	reported	reported	reported	reported
levalbuterol inhalation solution (Xopenex)	7.6 – 11.9	< 2	2.8 – 9.6	reported	2.7 – 2.8	0 – 6.8
Oral Agents						
albuterol syrup	4	< 1 – 2	9 – 15	< 1	1 – 2	10
albuterol tablets	7	2	20	5	5	20
metaproterenol syrup	1.1	1.3	4.8	< 1	6.1	1.6
terbutaline tablets	7.8 – 10	1.3 – 10	< 5 – 31	≤ 23	1.3 – 3	< 5 – 38

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[140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155]

Pediatrics

Most of the SABAs have been studied in pediatric patients and have been 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. There are insufficient clinical data to establish safety and efficacy of terbutaline sulfate; therefore, it is not recommended for patients < 12 years of age.

Pregnancy

There are no adequate and well-controlled studies of these agents in pregnant women. Terbutaline is Pregnancy Category B. All of the SABAs still assigned a Pregnancy Category 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 albuterol (Ventolin HFA, Proair HFA) and levalbuterol (Xopenex HFA, Xopenex) 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.

DOSAGES[156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171]

Drug	Usual Adult Dosage	Usual Pediatric Dose	Availability
Short-Acting Inhalation Agents			
albuterol DPI (ProAir RespiClick, ProAir Digihaler)	Bronchospasm: 2 inhalations every 4 to 6 hours as needed Prevention of EIB: 2 inhalations 15 to 30 minutes prior to exercise	Do not use in patients under 4 years of age	90 mcg per actuation* from the mouthpiece in a box containing 200 actuations; contains dose counter (breath activated device)
albuterol HFA (ProAir HFA, Proventil HFA, Ventolin HFA)	Bronchospasm: 2 inhalations every 4 to 6 hours as needed Prevention of EIB: 2 inhalations 15 to 30 minutes prior to exercise	Bronchospasm: 2 inhalations every 4 to 6 hours as needed Prevention of EIB: 2 inhalations 15 to 30 minutes prior to exercise	90 mcg per actuation* from the mouthpiece in a canister containing 200 actuations (Proventil HFA, Ventolin HFA and ProAir HFA have dose counters attached to the actuator)
albuterol inhalation solution	2.5 mg every 6 to 8 hours as needed	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 > 12 years of age: 2.5 mg nebulized 3 to 4 times daily	generic: 2.5 mg/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
levalbuterol HFA (Xopenex HFA)	2 inhalations every 4 to 6 hours as needed	2 inhalations every 4 to 6 hours as needed	45 mcg per actuation in a canister containing 200 actuations (with dose counter)
levalbuterol inhalation solution (Xopenex)	0.63 to 1.25 mg 3 times daily	0.31 to 0.63 mg 3 times daily	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

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

† Available from Nephron Pharmaceuticals only

Dosages (continued)

Drug	Usual Adult Dosage	Usual Pediatric Dose	Availability
Oral Agents			
albuterol oral syrup	2 to 4 mg every 6 to 8 hours	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	2 mg/5 mL
albuterol oral tablets	Immediate-release: 2 to 4 mg every 6 to 8 hours Extended-release: 8 mg every 12 hours	Immediate-release: 6 to 12 years: 2 mg every 6 to 8 hours > 12 years: 2 mg every 6 to 8 hours Extended-release: 6 to 12 years of age: 4 mg every 12 hours > 12 years of age: 8 mg every 12 hours	Immediate-release: 2 mg, 4 mg Extended-release‡: 4 mg, 8 mg
metaproterenol oral syrup	20 mg 3 to 4 times daily	10 mg 3 to 4 times daily	10 mg/5 mL
terbutaline tablets	2.5 to 5 mg 3 times daily	2.5 mg 3 times daily	2.5 mg, 5 mg

‡ ER formulation available from Mylan only.

Authorized generic products have the same functionality as the branded product (e.g., dose counter).

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. ProAir Digihaler should not be used with a spacer or volume holding chamber. ProAir Digihaler does not need to be primed.

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.[172,173,174] As a result, current comparative data focus 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 mg, 0.63 mg, and 1.25 mg) and albuterol inhalation solution (2.5 mg).[175] All doses of active treatment produced a significantly greater degree of bronchodilation (measured by change in 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.[176] Following a 1-week placebo run-in period, subjects were randomized to nebulized levalbuterol 0.31 mg or 0.63 mg, albuterol 1.25 mg 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 aged 1 to 18 years (n=482) in the emergency department (ED) and inpatient asthma care unit of an urban tertiary children's hospital.[177] 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 $FEV_1 < 70\%$ predicted.[178] 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.[179] Patients underwent pulmonary function testing and dyspnea evaluation in basal condition and at 5, 15, 30, 60, and 120 minutes after bronchodilator (albuterol MDI, formoterol 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 compared with 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.[180] A total of 254 outcomes were tabulated. Of the 131 studies that met the eligibility criteria, only 59 (primarily those that tested $beta_2$-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 2022 Global Initiative for Asthma (GINA) guidelines for asthma recommend an inhaled short-acting $beta_2$-agonist (SABA) as one option for quick relief of asthma symptoms and bronchoconstriction, including in acute exacerbations and for exercise-induced bronchoconstriction. Due to the increased risk of severe exacerbations with regular or frequent use, however, SABA-monotherapy is no longer

recommended. For most asthma patients, treatment can be initiated with an as-needed low dose inhaled corticosteroid (ICS)/formoterol, daily low dose ICS, or low dose ICS taken whenever a SABA is taken. Either a SABA or a low dose inhaled ICS/formoterol is the preferred as needed medication, with details on preference of one over another based on advising organization, individual factors, and asthma severity. Inhaled SABAs are also used in the treatment of chronic obstructive pulmonary disease (COPD), particularly for the treatment of acute dyspnea or exacerbations.

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. Sandoz (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. In addition, Teva introduced a 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. 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.

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.

Metaproterenol is neither as $beta_2$ selective nor as long acting as albuterol, and, therefore, should not be considered for first-line therapy. Another $beta_2$-agonist, terbutaline, is more $beta_2$ 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.

REFERENCES

1 ProAir RespiClick [package insert]. Horsham, PA; Teva; September 2020.
2 ProAir Digihaler [package insert]. Parsippany, NJ; Teva; November 2022.
3 ProAir HFA [package insert]. Parsippany, NJ; Teva; September 2022.
4 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; July 2018.
5 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2021.
6 Albuterol sulfate inhalation solution 0.083% [package insert]. Morgantown, WV; Mylan; January 2013.
7 Albuterol sulfate inhalation solution 0.5% [package insert]. West Columbia, SC; Nephron; January 2021.
8 Albuterol low dose inhalation solution [package insert]. Morgantown, WV; Mylan; October 2021.
9 Xopenex HFA [package insert]. Marlborough, MA; Sunovion; February 2017.
10 Xopenex inhalation solution [package insert]. Lake Forest, IL; Akorn; December 2018.
11 Xopenex inhalation solution concentrate [package insert]. Lake Forest, IL; Akorn; January 2019.
10 Albuterol sulfate syrup [package insert]. Parsippany, NJ; Actavis; November 2020.
11 Albuterol sulfate tablet [package insert]. Morgantown, WV; Mylan; July 2020.
14 Albuterol sulfate extended-release tablets. Clinical Pharmacology. Available at: https://www.clinicalkey.com/pharmacology/. Accessed January 11, 2023.
15 Metaproterenol sulfate syrup [package insert]. Carmel Valley, NY; Silarx; June 2014.
16 Terbutaline tablet [package insert]. Baudette, MN; ANI; September 2018.
17 Available at: https://www.proair.com/hfa. Accessed January 29, 2023.
18 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 11, 2023.
19 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 11, 2023.

20 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 11, 2023.
21 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 11, 2023.
22 Centers for Disease Control and Prevention. Asthma Surveillance – United States, 2006–2018. September 17, 2021. Available at: https://www.cdc.gov/mmwr/volumes/70/ss/ss7005a1.htm?s_cid=ss7005a1_w. Accessed January 11, 2023.
23 Centers for Disease Control and Prevention. Asthma surveillance- United States, 2006–2018. Available at: https://www.cdc.gov/mmwr/volumes/70/ss/ss7005a1.htm?s_cid=ss7005a1_w .Accessed January 11, 2023.
24 National Heart, Lung, and Blood Institute. National Heart, Lung, and Blood Institute. 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Available at: https://www.nhlbi.nih.gov/health-topics/asthma-for-health-professionals. Accessed January 11, 2023.
25 National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. Full report 2007. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/index.htm. Accessed January 11, 2023.
26 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 11, 2023.
27 National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. Full report 2007. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/index.htm. Accessed January 11, 2023.
28 National Heart, Lung, and Blood Institute. 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Available at: https://www.nhlbi.nih.gov/health-topics/asthma-for-health-professionals. Accessed January 11, 2023.
29 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 11, 2023.
30 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 11, 2023.
31 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 11, 2023.
32 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 11, 2023.
33 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 11, 2023.
34 NHLBI. Guidelines for the diagnosis and management of asthma (EPR-3) – 2007. Available at: https://www.nhlbi.nih.gov/health-topics/asthma-for-health-professionals. Accessed January 11, 2023.
35 National Heart, Lung, and Blood Institute. 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Available at: https://www.nhlbi.nih.gov/health-topics/asthma-for-health-professionals. Accessed January 11, 2023.
36 National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. Full report 2007. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/index.htm. Accessed January 11, 2023.
37 National Heart, Lung, and Blood Institute. 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Available at: https://www.nhlbi.nih.gov/health-topics/asthma-for-health-professionals. Accessed January 11, 2023.
38 Weiler JM, Brannan JD, Randolph CC, et al. Exercise-induced bronchoconstriction update-2016. J Allergy Clin Immunol. 2016 Nov;138(5):1292-1295.e36. DOI: 10.1016/j.jaci.2016.05.029.
39 Choosing Wisely. American Academy of Pediatrics – Section on pediatric pulmonology and sleep medicine. Five things physicians and patients should question. 2020. Available at https://www.choosingwisely.org/societies/. Accessed January 11, 2023.
40 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 11, 2023.
41 Chronic Obstructive Pulmonary Disease (COPD). Available at: http://www.cdc.gov/copd/index.html. Accessed January 11, 2023.
42 Chronic Obstructive Pulmonary Disease: Screening. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/chronic-obstructive-pulmonary-disease-screening?ds=1&s=copd. Accessed January 11, 2023.
43 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 11, 2023.
44 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 11, 2023.
45 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 11, 2023.
46 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 11, 2023.
47 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 11, 2023.
48 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 11, 2023.
49 Qaseem A, Wilt TJ, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: A clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Int Med. 2011; 155:179-191. Available at: https://www.thoracic.org/statements/. Accessed January 11, 2023.

50 Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2017; 50: 1602265. Available at: https://www.thoracic.org/statements/copd.php. Accessed January 11, 2023.
51 Papi A, Rabe KF, Rigau D, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2017; 49: 1600791. Available at: https://www.thoracic.org/statements/copd.php. Accessed January 11, 2023.
52 Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society guideline. Chest. 2015; 147(4): 894-942. DOI: 10.1378/chest.14-1676. Available at: https://www.chestnet.org/Guidelines-and-Resources. Accessed January 11, 2023.
53 Nici L, Mammen M, Charbek E, et al. Pharmacologic management of chronic obstructive pulmonary disease. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020; 201(9): e56-e69. DOI: 10.1164/rccm.202003-0625ST. Available at https://www.thoracic.org/statements/copd.php. Accessed January 11, 2023.
54 Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest. 2005; 127:335-371.
55 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health; 2022. Available at: http://ginasthma.org/. Accessed January 11, 2023.
56 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2023. Available at: http://goldcopd.org/. Accessed January 11, 2023.
57 ProAir RespiClick [package insert]. Horsham, PA; Teva; September 2020.
58 ProAir Digihaler [package insert]. Parsippany, NJ; Teva; November 2022.
59 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; July 2018.
60 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2021.
61 ProAir HFA [package insert]. Parsippany, NJ; Teva; September 2022.
62 Albuterol sulfate inhalation solution 0.083% [package insert]. Morgantown, WV; Mylan; January 2013.
63 Albuterol sulfate inhalation solution 0.5% [package insert]. West Columbia, SC; Nephron; January 2021.
64 Albuterol low dose inhalation solution [package insert]. Morgantown, WV; Mylan; October 2021.
65 Xopenex HFA [package insert]. Marlborough, MA; Sunovion; February 2017.
66 Xopenex inhalation solution [package insert]. Lake Forest, IL; Akorn; December 2018.
67 Xopenex inhalation solution concentrate [package insert]. Lake Forest, IL; Akorn; January 2019.
68 Albuterol sulfate syrup [package insert]. Parsippany, NJ; Actavis; November 2020.
69 Albuterol sulfate tablet [package insert]. Morgantown, WV; Mylan; July 2020.
70 Albuterol sulfate extended-release tablets. Clinical Pharmacology. Available at: https://www.clinicalkey.com/pharmacology/. Accessed January 11, 2023.
71 Metaproterenol sulfate syrup [package insert]. Carmel Valley, NY; Silarx; June 2014.
72 Terbutaline tablet [package insert]. Baudette, MN; ANI; September 2018.
73 Sharma G. Pediatric asthma treatment & management. Updated December 20, 2021. Available at: http://emedicine.medscape.com/article/1000997-treatment. Accessed January 11, 2023.
74 Kleinschmidt P. Chronic obstructive pulmonary disease (COPD) and emphysema in emergency medicine treatment & medication. Updated November 13, 2020. Available at: http://emedicine.medscape.com/article/807143-treatment. Accessed January 11, 2023.
75 Department of Health and Human Services: Food and Drug Administration. 21 CFR Parts 201 and 341: Labeling for bronchodilators to treat asthma; cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter human use. Available at: http://www.gpo.gov/fdsys/pkg/FR-2011-07-26/pdf/2011-18347.pdf. Accessed January 11, 2023.
76 ProAir RespiClick [package insert]. Horsham, PA; Teva; September 2020.
77 ProAir Digihaler [package insert]. Parsippany, NJ; Teva; November 2022.
78 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; July 2018.
79 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2021.
80 ProAir HFA [package insert]. Parsippany, NJ; Teva; September 2022.
81 Albuterol sulfate inhalation solution 0.083% [package insert]. Morgantown, WV; Mylan; January 2013.
82 Albuterol sulfate inhalation solution 0.5% [package insert]. West Columbia, SC; Nephron; January 2021.
83 Albuterol low dose inhalation solution [package insert]. Morgantown, WV; Mylan; October 2021.
84 Xopenex HFA [package insert]. Marlborough, MA; Sunovion; February 2017.
85 Xopenex inhalation solution [package insert]. Lake Forest, IL; Akorn; December 2018.
86 Xopenex inhalation solution concentrate [package insert]. Lake Forest, IL; Akorn; January 2019.
87 Albuterol sulfate syrup [package insert]. Parsippany, NJ; Actavis; November 2020.
88 Albuterol sulfate tablet [package insert]. Morgantown, WV; Mylan; July 2020.
89 Albuterol sulfate extended-release tablets. Clinical Pharmacology. Available at: https://www.clinicalkey.com/pharmacology/. Accessed January 11, 2023.
90 Metaproterenol sulfate syrup [package insert]. Carmel Valley, NY; Silarx; June 2014.
91 Terbutaline tablet [package insert]. Baudette, MN; ANI; September 2018.
92 ProAir RespiClick [package insert]. Horsham, PA; Teva; September 2020.
93 ProAir Digihaler [package insert]. Parsippany, NJ; Teva; November 2022.
94 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; July 2018.
95 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2021.
96 ProAir HFA [package insert]. Parsippany, NJ; Teva; September 2022.
97 Albuterol sulfate inhalation solution 0.083% [package insert]. Morgantown, WV; Mylan; January 2013.
98 Albuterol sulfate inhalation solution 0.5% [package insert]. West Columbia, SC; Nephron; January 2021.
99 Albuterol low dose inhalation solution [package insert]. Morgantown, WV; Mylan; October 2021.
100 Xopenex HFA [package insert]. Marlborough, MA; Sunovion; February 2017.

101 Xopenex inhalation solution [package insert]. Lake Forest, IL; Akorn; December 2018.
102 Xopenex inhalation solution concentrate [package insert]. Lake Forest, IL; Akorn; January 2019.
103 Albuterol sulfate syrup [package insert]. Parsippany, NJ; Actavis; November 2020.
104 Albuterol sulfate tablet [package insert]. Morgantown, WV; Mylan; July 2020.
105 Albuterol sulfate extended-release tablets. Clinical Pharmacology. Available at: https://www.clinicalkey.com/pharmacology/. Accessed January 11, 2023.
106 Metaproterenol sulfate syrup [package insert]. Carmel Valley, NY; Silarx; June 2014.
107 Terbutaline tablet [package insert]. Baudette, MN; ANI; September 2018.
108 ProAir RespiClick [package insert]. Horsham, PA; Teva; September 2020.
109 ProAir Digihaler [package insert]. Parsippany, NJ; Teva; November 2022.
110 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; July 2018.
111 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2021.
112 ProAir HFA [package insert]. Parsippany, NJ; Teva; September 2022.
113 Albuterol sulfate inhalation solution 0.083% [package insert]. Morgantown, WV; Mylan; January 2013.
114 Albuterol sulfate inhalation solution 0.5% [package insert]. West Columbia, SC; Nephron; January 2021.
115 Albuterol low dose inhalation solution [package insert]. Morgantown, WV; Mylan; October 2021.
116 Xopenex HFA [package insert]. Marlborough, MA; Sunovion; February 2017.
117 Xopenex inhalation solution [package insert]. Lake Forest, IL; Akorn; December 2018.
118 Xopenex inhalation solution concentrate [package insert]. Lake Forest, IL; Akorn; January 2019.
119 Albuterol sulfate syrup [package insert]. Parsippany, NJ; Actavis; November 2020.
120 Albuterol sulfate tablet [package insert]. Morgantown, WV; Mylan; July 2020.
121 Albuterol sulfate extended-release tablets. Clinical Pharmacology. Available at: https://www.clinicalkey.com/pharmacology/. Accessed January 11, 2023.
122 Metaproterenol sulfate syrup [package insert]. Carmel Valley, NY; Silarx; June 2014.
123 Terbutaline tablet [package insert]. Baudette, MN; ANI; September 2018.
124 ProAir RespiClick [package insert]. Horsham, PA; Teva; September 2020.
125 ProAir Digihaler [package insert]. Parsippany, NJ; Teva; November 2022.
126 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; July 2018.
127 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2021.
128 ProAir HFA [package insert]. Parsippany, NJ; Teva; September 2022.
129 Albuterol sulfate inhalation solution 0.083% [package insert]. Morgantown, WV; Mylan; January 2013.
130 Albuterol sulfate inhalation solution 0.5% [package insert]. West Columbia, SC; Nephron; January 2021.
131 Albuterol low dose inhalation solution [package insert]. Morgantown, WV; Mylan; October 2021.
132 Xopenex HFA [package insert]. Marlborough, MA; Sunovion; February 2017.
133 Xopenex inhalation solution [package insert]. Lake Forest, IL; Akorn; December 2018.
134 Xopenex inhalation solution concentrate [package insert]. Lake Forest, IL; Akorn; January 2019.
135 Albuterol sulfate syrup [package insert]. Parsippany, NJ; Actavis; November 2020.
136 Albuterol sulfate tablet [package insert]. Morgantown, WV; Mylan; July 2020.
137 Albuterol sulfate extended-release tablets. Clinical Pharmacology. Available at: https://www.clinicalkey.com/pharmacology/. Accessed January 11, 2023.
138 Metaproterenol sulfate syrup [package insert]. Carmel Valley, NY; Silarx; June 2014.
139 Terbutaline tablet [package insert]. Baudette, MN; ANI; September 2018.
140 ProAir RespiClick [package insert]. Horsham, PA; Teva; September 2020.
141 ProAir Digihaler [package insert]. Parsippany, NJ; Teva; November 2022.
142 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; July 2018.
143 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2021.
144 ProAir HFA [package insert]. Parsippany, NJ; Teva; September 2022.
145 Albuterol sulfate inhalation solution 0.083% [package insert]. Morgantown, WV; Mylan; January 2013.
146 Albuterol sulfate inhalation solution 0.5% [package insert]. West Columbia, SC; Nephron; January 2021.
147 Albuterol low dose inhalation solution [package insert]. Morgantown, WV; Mylan; October 2021.
148 Xopenex HFA [package insert]. Marlborough, MA; Sunovion; February 2017.
149 Xopenex inhalation solution [package insert]. Lake Forest, IL; Akorn; December 2018.
150 Xopenex inhalation solution concentrate [package insert]. Lake Forest, IL; Akorn; January 2019.
151 Albuterol sulfate syrup [package insert]. Parsippany, NJ; Actavis; November 2020.
152 Albuterol sulfate tablet [package insert]. Morgantown, WV; Mylan; July 2020.
153 Albuterol sulfate extended-release tablets. Clinical Pharmacology. Available at: https://www.clinicalkey.com/pharmacology/. Accessed January 11, 2023.
154 Metaproterenol sulfate syrup [package insert]. Carmel Valley, NY; Silarx; June 2014.
155 Terbutaline tablet [package insert]. Baudette, MN; ANI; September 2018.
156 ProAir RespiClick [package insert]. Horsham, PA; Teva; September 2020.
157 ProAir Digihaler [package insert]. Parsippany, NJ; Teva; November 2022.
158 Proventil HFA [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; July 2018.
159 Ventolin HFA [package insert]. Research Triangle Park, NC; GlaxoSmithKline; August 2021.
160 ProAir HFA [package insert]. Parsippany, NJ; Teva; September 2022.
161 Albuterol sulfate inhalation solution 0.083% [package insert]. Morgantown, WV; Mylan; January 2013.
162 Albuterol sulfate inhalation solution 0.5% [package insert]. West Columbia, SC; Nephron; January 2021.

163 Albuterol low dose inhalation solution [package insert]. Morgantown, WV; Mylan; October 2021.
164 Xopenex HFA [package insert]. Marlborough, MA; Sunovion; February 2017.
165 Xopenex inhalation solution [package insert]. Lake Forest, IL; Akorn; December 2018.
166 Xopenex inhalation solution concentrate [package insert]. Lake Forest, IL; Akorn; January 2019.
167 Albuterol sulfate syrup [package insert]. Parsippany, NJ; Actavis; November 2020.
168 Albuterol sulfate tablet [package insert]. Morgantown, WV; Mylan; July 2020.
169 Albuterol sulfate extended-release tablets. Clinical Pharmacology. Available at: https://www.clinicalkey.com/pharmacology/. Accessed January 11, 2023.
170 Metaproterenol sulfate syrup [package insert]. Carmel Valley, NY; Silarx; June 2014.
171 Terbutaline tablet [package insert]. Baudette, MN; ANI; September 2018.
172 Clinical Pharmacology. Available at: https://www.clinicalpharmacology.com/. Accessed January 11, 2023.
173 National Asthma Education and Prevention Program Expert Panel Report: Guidelines for the diagnosis and management of asthma. Expert panel report 3. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed January 11, 2023.
174 Nathan RA. Beta 2 agonist therapy: oral versus inhaled delivery. J Asthma 1992; 29(1): 49-54. DOI: 10.3109/02770909209110640.
175 Handley DA, Tinkelman D, Noonan M, et al. Dose-response evaluation of levalbuterol verses racemic albuterol in patients with asthma. J Asthma. 2000; 37:319-27. DOI: 10.3109/02770900009055455.
176 Milgrom H, Skoner DP, Bensch G, et al. Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. J Allergy Clin Immunol. 2001; 108:938-45. DOI: 10.1067/mai.2001.120134.
177 Carl JC, Myers TR, Kirchner HL, et al. Comparison of racemic albuterol and levalbuterol for treatment of acute asthma. J Pediatr. 2003; 143(6):731-6. DOI: 10.1067/S0022-3476(03)00493-1.
178 Wilkinson M, Bulloch B, Garcia-Filion P, et al. Efficacy of racemic albuterol versus levalbuterol used as a continuous nebulization for the treatment of acute asthma exacerbations: a randomized, double-blind, controlled trial. J Asthma. 2011; 48(2): 188-93. DOI: 10.3109/02770903.2011.554939.
179 Di Marco F, Milic-Emili J, Boveri B, et al. Effect of inhaled bronchodilators on inspiratory capacity and dyspnoea at rest in COPD. Eur Respir J. 2003; 21:86-94. DOI: 10.1183/09031936.03.00020102.
180 Dolovich MB, Ahrens RC, Hess DR, et al. Device Selection and Outcomes of Aerosol Therapy: Evidence-Based Guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest. 2005; 127:335-371. DOI: 10.1378/chest.127.1.335.