Therapeutic Class Overview
Respiratory Beta-Agonists

INTRODUCTION

- Respiratory beta$_2$-agonists are primarily used to treat reversible airway disease. They are Food and Drug Administration (FDA)-approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), exercise-induced asthma/bronchospasm, and/or reversible bronchospasm.
- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In 2018, asthma affected an estimated 19.2 million adults and 5.5 million children in the United States (U.S.). The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (*Centers for Disease Control and Prevention [CDC] 2020, National Heart, Lung, and Blood Institute [NHLBI] Web site*).
- Current pharmacologic options for asthma management are categorized as: (1) control medications to achieve and maintain control of persistent asthma or prevent exacerbations, and (2) quick-relief medications used to treat acute symptoms and exacerbations (*NHLBI 2007, Global Initiative for Asthma [GINA] 2020*).
  - Control medications include:
    - Corticosteroids (inhaled corticosteroids [ICSs], or oral corticosteroids for severe exacerbations)
    - Long-acting beta$_2$-agonists (LABAs)
    - Leukotriene receptor antagonists (LTRAs)
    - Methylxanthines (ie, theophylline)
    - Cromolyn sodium and nedocromil
    - Add-on immunomodulators (ie, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) in patients with severe asthma
    - Add-on tiotropium in patients whose asthma is not well-controlled with ICS/LABA
    - Add-on azithromycin in patients whose asthma is not well-controlled with moderate-high dose ICS/LABA
  - Quick-relief/reliever medications include:
    - Short-acting beta$_2$-agonists (SABAs) for relief of acute symptoms and prevention of exercise-induced bronchospasm
    - ICS-formoterol (per GINA recommendations on the basis of the safety concerns about SABA-only treatment and the fact that ICS and ICS/LABA already have an effective safety record)
    - Anticholinergics (ie, ipratropium bromide) as an alternative bronchodilator for those not tolerating a SABA
    - Systemic corticosteroids, although not short-acting, are used for moderate and severe exacerbations as part of initial treatment.
  - In recent years, additional medications have been made available for select subsets of patients with asthma, including the interleukin-5 (IL-5) antagonists benralizumab, mepolizumab, and reslizumab, and the interleukin-4 (IL-4) antagonist dupilumab, for the management of severe asthma with an eosinophilic phenotype (*Prescribing information: Cinqair 2020, Dupixent 2019, Fasenra 2019, Nucala 2019*). Additionally, tiotropium, long used for COPD, has been FDA-approved for the treatment of asthma (*Spiriva Respimat prescribing information 2019*).
  - ICSs are the most effective and most commonly recommended long-term control medications used for the treatment of asthma. The updated 2020 GINA Report on Global Strategy for Asthma Management and Prevention recommends initial treatment based on a patient's presenting symptoms. Step 1 therapy (for patients with infrequent asthma symptoms) includes preferred controller therapy with low dose ICS-formoterol, with adjustments to the dose of ICS based on control of asthma symptoms (*GINA 2020*).
  - LABAs should not be used as monotherapy for the management of asthma due to increased risk for serious adverse events, including death; however, they can be used as adjunctive therapy in patients who are not adequately controlled with an ICS alone (*GINA 2020, NHLBI 2007*).
  - SABA-only treatment (without an ICS) is no longer recommended by GINA; a low dose ICS should be taken whenever a SABA is taken. In adults and adolescents, low dose ICS-formoterol is the preferred reliever medication, while as-needed SABAs are the only option for reliever medications in children (*GINA 2020*).

- Theophylline and mast-cell stabilizers have weak to low efficacy in asthma. Theophylline has an unfavorable side-effect profile and may be life-threatening at high doses. Mast-cell stabilizers have a more favorable safety profile. Tiotropium is an option for add-on therapy in patients ≥ 6 years of age with a history of exacerbations. Azithromycin may be added in patients experiencing symptomatic asthma despite using ICS and LABA. An IL-5, IL-4, or immunoglobulin E (IgE) antagonist may be added if patients require a higher level of care. Omalizumab, an IgE antagonist, is used in patients with moderate to severe allergic asthma while IL-5 antagonists are used for severe eosinophilic asthma (*GINA 2020, NHLBI 2007*).

- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions of each component vary between patients. The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2020a*).
  - COPD affects 6.4% of the U.S. population and is a major contributor to mortality from chronic lower respiratory diseases, the fourth leading cause of death in the U.S. (*CDC 2019*). Globally, COPD is responsible for 3 million deaths annually and is expected to cause 5.4 million annual deaths by 2060; the burden of COPD continues to increase due to continued exposure to risk factors and aging of the population (*GOLD 2020a*).
  - Cigarette smoking is the main risk factor for COPD; other risk factors include biomass fuel exposure (such as from cooking and heating in poorly ventilated dwellings) and air pollution. Host factors such as genetic abnormalities, abnormal lung development, and accelerated aging can predispose individuals to COPD development (*GOLD 2020a*).
  - Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (*GOLD 2020a*).
  - Pharmacologic therapy for COPD can reduce symptoms, reduce the frequency and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristics of COPD (*GOLD 2020a*).
  - Pharmacologic options for COPD treatment comprise several classes, including beta$_2$-agonists, anticholinergics, methylxanthines, ICSs, various combination products, antibiotics, mucolytic agents, and the phosphodiesterase (PDE)-4 inhibitor, roflumilast. Pharmacologic treatments should be individualized based on symptom severity, risk of exacerbations, side effects, comorbidities, drug availability, and cost, as well as the patient's response, preference, and ability to use various drug delivery devices (*GOLD 2020a*).
  - Inhaled bronchodilators are central to COPD symptom management and are usually administered on a regular basis to prevent or reduce symptoms. Several short-acting and long-acting inhaled bronchodilators are available. Long-acting muscarinic antagonists (LAMAs) and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea, and for immediate relief of symptoms in patients already receiving long-acting bronchodilators for maintenance therapy (*GOLD 2020a*).
  - Beta$_2$-agonists differ in their dosing requirements, pharmacokinetic parameters, and potential adverse effects. Several of the SABAs are available generically in at least 1 strength or formulation; however, there are no generic formulations for the LABAs.
- This review includes the single-agent inhaled and oral beta$_2$-agonists. Although several agents are also available in combination inhalers along with an ICS or an anticholinergic, the combination products are not included in this review.
  - Tables in this review are organized by whether the drug product is short- or long-acting. Note that extended-release albuterol is categorized as short-acting for the purposes of this review, along with the other albuterol products.
- Medispan class/subclass: Respiratory sympathomimetics/beta adrenergics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Short-acting beta$_2$-agonists (SABAs) (oral and inhaled)	
albuterol inhalation aerosols and powder (ProAir HFA, ProAir Digihaler dry powder inhaler*, ProAir RespiClick dry powder inhaler, Proventil HFA, Ventolin HFA)	-†
albuterol solution for nebulization	✔
albuterol, oral tablets, extended-release tablets, and syrup	✔
levalbuterol inhalation aerosol (Xopenex HFA and generic)	-‡
levalbuterol solution for nebulization (Xopenex and generics)	✔

Drug	Generic Availability
metaproterenol syrup	✔
terbutaline, oral tablets and injection	✔
Long-acting beta$_2$-agonists (LABAs) (inhaled)§	
Arcapta Neohaler (indacaterol) inhalation powder	-
Brovana (arformoterol) solution for nebulization	-
Perforomist (formoterol) solution for nebulization‖	-
Serevent Diskus (salmeterol) inhalation powder	-
Striverdi Respimat (olodaterol) inhalation spray	-

Abbreviation: HFA = hydrofluoroalkane
*ProAir Digihaler is a digital dry powder inhaler with built-in sensors to detect when it is used and to measure inspiratory flow, and is designed to be used with a companion mobile app. It has not yet launched at the time of this review but is expected to become commercially available in 2020.
†No A-rated generics have been approved by the FDA for Proventil HFA or Ventolin HFA; however, authorized generics are available for these products. Two A-rated generics for ProAir HFA were approved in early 2020. No generics are available for ProAir Digihaler or ProAir RespiClick.
‡No A-rated generics are approved by the FDA for Xopenex-HFA; however, a generic product is available for this product.
§The inhaled LABA, Arcapta Neohaler (indacaterol), was discontinued by the manufacturer effective April 1, 2020 for business reasons (*OINDP news 2020*). At the time of this review, Arcapta Neohaler was active in Medispan.
‖Formoterol was previously available as a dry powder inhaler (Foradil Aerolizer); however, this formulation is no longer marketed.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Generic Name	Treatment and/or prevention of bronchospasm in patients with asthma/reversible obstructive airway disease	Prevention of exercise-induced bronchospasm	Maintenance treatment of bronchoconstriction/ airflow obstruction in patients with COPD	Treatment of reversible bronchospasm occurring in association with emphysema and bronchitis
Short-acting beta$_2$-agonists				
albuterol	✔ *	✔ *†		
levalbuterol	✔ ‡			
metaproterenol	✔			✔
terbutaline	✔ §			✔ §
Long-acting beta$_2$-agonists				
arformoterol			✔	
formoterol			✔	
indacaterol			✔ **	
olodaterol			✔ **	
salmeterol	✔ ‖ ¶	✔ ¶	✔	

Abbreviations: COPD = chronic obstructive pulmonary disease; HFA = hydrofluoroalkane
*Age ≥ 4 years (HFA inhalation aerosols and dry powder inhaler); age ≥ 2 (solution for nebulization); age ≥ 2 years (syrup); age ≥ 6 years (tablets and extended-release tablets)
†Inhalation aerosols and dry powder inhalers only
‡Age ≥ 4 years (Xopenex HFA); age ≥ 6 years (Xopenex inhalation solution)
§Age ≥ 12 years
‖Only as a concomitant therapy with a long-term asthma control medication, such as an ICS
¶Age ≥ 4 years
**Indicated for long-term, once-daily maintenance treatment

(*Prescribing information: albuterol solution 2017, albuterol syrup 2016, albuterol tablets 2019, albuterol extended-release tablets 2015, Arcapta Neohaler 2019, Brovana 2019, metaproterenol syrup 2019, Perforomist 2019, ProAir HFA 2019, ProAir Digihaler 2019, ProAir RespiClick 2018, Proventil HFA 2018, Serevent Diskus 2020, Striverdi Respimat 2019, terbutaline injection 2011, terbutaline tablets 2018, Ventolin HFA 2019, Xopenex HFA 2017, Xopenex inhalation solution 2019*)

- Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials have demonstrated the efficacy of SABAs and LABAs in providing relief from asthma exacerbations, COPD exacerbations and exercise-induced asthma (EIA).

SABAs: Asthma and COPD

- In the clinical trials that evaluated SABAs for the treatment of mild asthma, all SABAs have been shown to be efficacious in improving forced expiratory volume in 1 second (FEV_1). In the clinical trials that compared albuterol to levalbuterol, inconsistent results were found (*Carl et al 2003, Gawchik et al 1999, Milgrom et al 2001, Nelson et al 1998, Nowak et al 2004, Nowak et al 2006, Qureshi et al 2005, Schreck et al 2005, Sepracor Trial 1, Sepracor Trial 2, Skoner et al 2001*).
  - In 2 studies (1 retrospective, 1 prospective), levalbuterol resulted in a significantly lower hospitalization rate compared to albuterol (*Carl et al 2003, Schreck et al 2005*).
  - In another trial, when the 2 agents were given in the emergency department, there was no significant difference in the time to discharge (*Skoner et al 2001*).
  - *Nowak et al* also reported that there was no difference in the time to discharge from the emergency room with albuterol compared to levalbuterol (76 and 78.5 minutes; p = 0.74) (*Nowak et al 2006*).
  - Overall, studies have shown no significant differences between the 2 agents in the peak change in FEV_1 and the number and incidence of adverse events experienced (*Carl et al 2003, Gawchik et al 1999, Milgrom et al 2001, Nelson et al 1998, Nowak et al 2004, Nowak et al 2006, Qureshi et al 2005, Schreck et al 2005, Sepracor Trial 1, Sepracor Trial 2, Skoner et al 2001*).
    - In an unpublished study, the difference in peak FEV_1 was statistically significant for albuterol hydrofluoroalkanes (HFA) compared to levalbuterol HFA (p = 0.018) (*Sepracor Trial 2*).
- Albuterol dry powder inhaler (ProAir RespiClick) was compared to placebo dry powder inhaler in patients with asthma maintained on ICS treatment (*Raphael et al 2014*). Patients treated with albuterol dry powder inhaler had significantly improved FEV_1 area under the curve compared to placebo. In patients with exercise-induced bronchoconstriction undergoing treadmill exercise challenge, placebo-treated patients had a greater decrease in FEV_1 compared with albuterol dry powder inhaler-treated patients (*Ostrom et al 2014*). In a cumulative-dose, crossover study, albuterol dry powder inhaler (ProAir RespiClick) was compared with albuterol HFA with similar between-group improvements in FEV_1 at 30 minutes (*Miller et al 2014*). Additionally, albuterol dry power inhaler (ProAir RespiClick) demonstrated favorable FEV_1 improvement in EIA compared to placebo in a crossover study (*Ostrom et al 2015*). Approval of ProAir Digihaler was based on efficacy data from studies with ProAir RespiClick (*ProAir Digihaler prescribing information 2019*).

LABAs: Asthma

- The LABAs salmeterol and formoterol have been found to improve FEV_1 in patients with mild to moderate asthma who require persistent use of SABAs. However, the SMART trial found that salmeterol had significant occurrences of combined respiratory-related deaths or respiratory-related life-threatening experiences compared to placebo ($p < 0.05$) (*Nelson et al 2006*). In a meta-analysis, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life-threatening exacerbations and asthma-related deaths in adults and children alike when compared to placebo (*Salpeter et al 2006*). Due to the results of these studies, all LABAs have a boxed warning stating that these agents may increase the risk of asthma-related death.

LABAs: COPD

- A systematic review concluded that in patients with COPD, there was no difference in the rate of mild exacerbations between patients treated with an ICS or LABA (odds ratio, 1.63; 95% confidence interval [CI], 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (rate ratio, 0.96; 95% CI, 0.89 to 1.02) (*Spencer et al 2011*).
- The safety and efficacy of indacaterol were evaluated in randomized controlled trials that compared it to placebo and other agents used in the management of COPD (*Balint et al 2010, Buhl et al 2011, Chapman et al 2011, Dahl et al 2010, Donohue et al 2010, Feldman et al 2010, Korn et al 2011, Kornmann et al 2011, Magnussen et al 2010, Vogelmeier et al 2010*). Notably, most of these trials evaluated indacaterol in doses of 150, 300 and 600 mcg once daily, rather than the FDA-approved dosing of 75 mcg once daily (*Balint et al 2010, Buhl et al 2011, Chapman et al 2011, Dahl et al 2010, Donohue et al 2010, Feldman et al 2010, Korn et al 2011, Kornmann et al 2011, Magnussen et al 2010, Vogelmeier et al*

2010). However, results from placebo-controlled trials of indacaterol 75 mcg have also been published, lending support to the use of the 75 mcg dose (*Gotfried et al 2012, Kerwin et al 2011*).

- Overall, data from published clinical trials demonstrated that treatment with indacaterol consistently results in significantly higher mean trough FEV_1 after 12 weeks of treatment compared to placebo, formoterol, salmeterol and tiotropium. Patients treated with indacaterol also achieved significant improvements in COPD symptoms, as well as health-related quality of life compared to those treated with placebo. Compared to placebo, indacaterol significantly reduces the use of rescue medications, increases the days of no rescue medication use, and improves diary card-derived symptom variables (eg, nights with no awakenings, days with no daytime symptoms, days able to perform usual activities). In general, treatment with indacaterol is favored over other long-acting bronchodilators for these outcomes, but statistical superiority is not consistently achieved (*Balint et al 2010, Buhl et al 2011, Chapman et al 2011, Dahl et al 2010, Donohue et al 2010, Feldman et al 2010, Gotfried et al 2012, Kerwin et al 2011, Korn et al 2011, Kornmann et al 2011, Magnussen et al 2010, Vogelmeier et al 2010*). Recent meta-analyses comparing indacaterol to tiotropium and to twice-daily LABAs (salmeterol or formoterol) demonstrated that patients treated with indacaterol had higher trough FEV_1 and greater improvements in the use of rescue medications and achieving improvements in dyspnea and health status compared to the alternative treatments. However, the trials included in this meta-analysis used indacaterol doses higher than FDA-approved daily doses of 75 mcg (*Cope et al 2013, Rodrigo et al 2012*).
- Placebo-controlled trials demonstrate that within 5 minutes after administration of indacaterol, significant improvements in bronchodilation are achieved (*Balint et al 2010, Donohue et al 2010, Gotfried et al 2012, Kerwin et al 2011, Magnussen et al 2010, Vogelmeier et al 2010*). These results have also been observed when comparing indacaterol to salmeterol, salmeterol/fluticasone, and tiotropium (*Buhl et al 2011, Korn et al 2011, Vogelmeier et al 2010*).
- In 2 studies, patients diagnosed with COPD were treated with arformoterol, salmeterol, or placebo. These studies found that both arformoterol and salmeterol significantly improved morning trough FEV_1 throughout the 12 weeks of daily treatment compared to placebo ($p < 0.001$ in both trials) (*Baumgartner et al 2007, Sepracor, 2005*). In a head-to-head study against salmeterol, formoterol was associated with a greater change from baseline in FEV_1 at 5 minutes post-dose on day 28 ($p = 0.022$) (*Cote et al 2009*). Currently, there is a lack of head-to-head randomized, double-blind clinical trials to determine a preferential status of one agent over another for the treatment of COPD.
- Two replicate, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 studies investigated the long-term efficacy and safety of once-daily olodaterol via Respimat soft-mist inhaler vs placebo and formoterol over 48 weeks in patients with moderate to very severe COPD receiving usual-care background therapy. Patients were randomized to receive once-daily olodaterol 5 or 10 mcg, twice-daily formoterol 12 mcg, or placebo. Co-primary endpoints were FEV_1 area under the curve from 0 to 3 hours (AUC_{0-3}), trough FEV_1, and Mahler transition dyspnea index (TDI) total score after 24 weeks. Overall, in Study 1222.13 (N = 904) and Study 1222.14 (N = 934), patients who received treatment with olodaterol had significantly improved FEV_1 AUC_{0-3} vs placebo in both studies ($p < 0.0001$ for all comparisons) and trough FEV_1 vs placebo ($p < 0.01$). Formoterol also showed statistically significant differences in both Study 1222.13 ($p < 0.01$) and Study 1222.14 ($p < 0.05$) (*Koch et al 2014*).
- Two replicate, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 trials investigated the long-term safety and efficacy of olodaterol in patients with moderate to very severe COPD receiving usual-care background therapy. Patients received olodaterol 5 mcg or 10 mcg or placebo once daily for 48 weeks. Co-primary endpoints were FEV_1 AUC_{0-3} (change from baseline) and trough FEV_1 at 12 weeks. Overall, Study 1222.11 (N = 624) and Study 1222.12 (N = 642) showed that olodaterol 5 mcg and 10 mcg significantly improved the FEV_1 AUC_{0-3} response ($p < 0.0001$) and trough FEV_1 (Study 1222.11, $p < 0.0001$; Study 1222.12, $p < 0.05$, post hoc) at week 12. The incidence of adverse events was comparable with that of placebo (*Ferguson et al 2014*).
- Two replicate, multicenter, randomized, double-blind, double-dummy, placebo-controlled, 4-way cross-over group, Phase 3 studies investigated the long-term efficacy and safety of once-daily olodaterol via Respimat soft-mist inhaler vs placebo and formoterol over 6 weeks in patients with moderate to very severe COPD receiving usual-care background therapy. Patients were randomized to receive once-daily olodaterol 5 or 10 mcg, twice-daily formoterol 12 mcg, or placebo. Co-primary endpoints were FEV_1 area under the curve from 0 to 12 hours (AUC_{0-12}) and FEV_1 area under the curve from 12 to 24 hours (AUC_{12-24}) after 6 weeks. Overall, in Study 1222.24 (N = 99) and Study 1222.25 (N = 100), patients who received treatment with both doses of olodaterol and formoterol had significantly improved FEV_1 profiles (co-primary endpoints of FEV_1 AUC_{0-12} and FEV_1 AUC_{12-24} and the key secondary endpoint [FEV_1 AUC_{0-24}]) vs placebo in both studies (for all comparisons $p < 0.0001$). No statistically significant differences were reported between the 3 active comparators (*Feldman et al 2014*).

- A meta-analysis that compared LABAs (salmeterol, formoterol, and indacaterol) to tiotropium demonstrated that tiotropium was more effective than LABAs as a group in preventing COPD exacerbations and disease-related hospitalizations. However, overall hospitalization rates, mortality, symptom improvement, and changes in lung function were similar among groups (*Chong et al 2012*). Another meta-analysis compared the use of LABAs plus tiotropium to the use of either LABAs alone or tiotropium alone. The analysis demonstrated that there was a significant improvement in FEV_1 with combination therapy compared to tiotropium alone. There was also a small mean improvement in health-related quality of life for patients receiving a LABA plus tiotropium compared to tiotropium alone, but the clinical significance of this small difference is unclear. Hospital admissions and mortality were not significantly different between groups. Data comparing LABA plus tiotropium to LABA alone were somewhat limited, but demonstrated a significant improvement in health-related quality of life, FEV_1 and exacerbations (*Farne et al 2015*).

EIA

- For the treatment of EIA, albuterol, metaproterenol, and formoterol have demonstrated an improvement in FEV_1 compared to placebo (*Berkowitz et al 1986, Bonini et al 2013, Edelman et al 2000, Richter et al 2002, Shapiro et al 2002, Storms et al 2004*).
  - In 1 study, albuterol- and metaproterenol-treated patients had a lower incidence of exercise-induced bronchospasm compared to placebo (*Cote et al 2009*).
  - In another study comparing albuterol, formoterol and placebo for EIA, both active treatment groups provided a statistically significant decrease in mean maximum percent of FEV_1 compared to placebo ($p < 0.01$) (*Shapiro et al 2002*).

CLINICAL GUIDELINES

Asthma

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICSs are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (*NHLBI 2007*).
  - LABAs are used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma.
  - Of the adjunctive treatments available, a LABA is the preferred option to combine with an ICS in patients 12 years of age and older. This combination is also an option in selected patients 5 to 12 years of age.
- The 2020 GINA report also provides a stepwise approach to asthma management. It recommends as-needed low-dose ICS-formoterol as a preferred controller to prevent exacerbations and control asthma symptoms in adult or adolescent patients with infrequent asthma symptoms (eg, < twice a month). If patients remain uncontrolled, an ICS or ICS/LABA is the next preferred controller options. The choice of a specific dose and combination depends on the age of the patient and step within the therapy. As-needed ICS-formoterol is also the preferred reliever medication for adults and adolescents, while as-needed SABAs are the only option for reliever medications in children; of note, a low dose ICS should be taken whenever a SABA is taken. At the highest step, the patient should be referred for add-on treatment (eg, tiotropium, azithromycin, omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab) (*GINA 2019, GINA 2020*).
- The 2020 GINA report provides interim guidance on the management of asthma in the context of the coronavirus disease 2019 (COVID-19) pandemic. Patients with asthma should continue their prescribed asthma medications, including ICS with or without LABA and add-on therapies, during the pandemic. Use of nebulizers should be avoided when possible to prevent transmission of the virus to other patients or healthcare workers (*GINA 2020*).
- In 2019, recommendations were published in the Annals of Allergy, Asthma, and Immunology (AAAI) for stepping down asthma controller therapy in patients whose asthma has been well-controlled, based on the stepwise approach to asthma treatment. For steps 2 through 5, the authors provided specific recommendations for stepping down therapy to a step below the patient's current level of care. In general, step-down strategies at each level recommend lowering the

dose of the ICS as an initial strategy; however, implementation of a step-down in treatment will vary, and patient-specific factors must be considered (*Chipps et al 2019*).

- A European Respiratory Society/American Thoracic Society guideline on the management of severe asthma recommends the addition of tiotropium for patients with uncontrolled asthma despite GINA step 4 or 5 or NAEPP step 5 therapy, and a trial of chronic macrolide therapy to reduce exacerbations in patients who require additional control despite GINA step 5 or NAEPP step 5 therapy (*Holguin et al 2020*).

COPD

- The 2020 GOLD guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and future risk of exacerbations; the risk of exacerbations is based on a patient's exacerbation history. Of note, the 2020 GOLD guidelines no longer recognize the phrase "asthma-COPD overlap," instead, emphasize that asthma and COPD are unique disease states with some similar signs and symptoms. Key recommendations from the GOLD guidelines are as follows (*GOLD 2020a*):
  - Inhaled bronchodilators are central to symptom management in COPD and commonly given on a regular basis to prevent or reduce symptoms. Inhaled bronchodilators are recommended over oral bronchodilators.
- LAMAs and LABAs significantly improve lung function, dyspnea, and health status, and reduce exacerbation rates.
  - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea, and for immediate relief of symptoms in patients already receiving long-acting bronchodilators for maintenance therapy.
  - LAMAs have a greater effect on exacerbation reduction compared to LABAs and decrease hospitalizations.
- Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on 1 bronchodilator, treatment should be escalated to 2.
  - Combination treatment with a LABA and LAMA:
    - Reduces exacerbations compared to monotherapy or ICS/LABA.
    - Increases FEV_1 and reduces symptoms compared to monotherapy.
- Long-term monotherapy with ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators. Long-term treatment with ICS may cause pneumonia in patients with severe disease.
- Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3).
  - Group A: Patients should be offered bronchodilator treatment (short- or long-acting), based on its effect on breathlessness. This should be continued if symptomatic benefit is documented.
  - Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of 2 bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with 2 bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator; switching to another device or molecules can also be considered.
  - Group C: Initial therapy should be a LAMA.
  - Group D: In general, it is recommended to start therapy with a LAMA. For patients with more severe symptoms, especially dyspnea and/or exercise limitation, LAMA/LABA may be considered for initial treatment. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap or blood eosinophil count ≥ 300 cells/µL.
  - Follow-up treatments: The follow-up treatments apply to any patients receiving maintenance treatment irrespective of the patient GOLD group.
    - For persistent dyspnea: The use of 2 bronchodilators is recommended in patients receiving 1 long-acting bronchodilator and experiencing persistent breathlessness or exercise limitation. Patients with persistent dyspnea symptoms on LABA + ICS may benefit from LAMA + LABA + ICS.
    - For exacerbations: Patients with persistent exacerbations on long-acting bronchodilator monotherapy may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA. For patients who have a history and/or findings suggestive of asthma or blood eosinophil count ≥ 300 cells/µL, ICS + LABA is preferred. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS if eosinophil count ≥ 100 cells/µL or addition of roflumilast or azithromycin if eosinophil count < 100 cells/µL. In patients with additional exacerbations on LABA + ICS, patients should try LAMA + LABA + ICS therapy. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

- Patients with COPD should continue their usual therapy, including inhaled or oral corticosteroids during the coronavirus disease 2019 (COVID-19) pandemic (*GOLD 2020b*).

Table 3. Assessment of symptoms and risk of exacerbations to determine GOLD patient group

Exacerbation history	Symptoms	
	mMRC 0 to 1 CAT < 10	mMRC ≥ 2 CAT ≥10
≥ 2 (or ≥ 1 leading to hospital admission)	C	D
0 or 1 (not leading to hospital admission)	A	B

Abbreviations: CAT = COPD assessment test; mMRC = modified Medical Research Council questionnaire

- Guidelines for the prevention of acute exacerbations of COPD from the American College of Chest Physicians and the Canadian Thoracic Society state that a LAMA is recommended over either a short-acting muscarinic antagonist or a LABA. The guidelines state that certain combination bronchodilators or bronchodilator/ICS combinations may reduce exacerbations, but does not state that any combination is superior to LAMA monotherapy in patients with stable COPD (*Criner et al 2015*).

Exercise-induced bronchoconstriction

- For exercise-induced bronchoconstriction, guidelines from the American Thoracic Society recommend administration of an inhaled SABA 15 minutes prior to exercise. The guidelines also recommend a controller agent added whenever SABA therapy is used at least once daily. Additional guidelines are set forth for patients with symptoms despite using an inhaled SABA before exercise (*Parsons et al 2013*). Joint guidelines from the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology state that beta$_2$-agonists (SABAs or LABAs) are most effective at short-term protection against exercise-induced bronchoconstriction and for accelerating recovery from exercise-induced bronchoconstriction. However, daily use of a SABA or LABA will lead to tolerance. Additional or adjunctive options include daily use of leukotriene inhibitors or ICSs, cromolyn sodium before exercise, or ipratropium for patients who have not responded to other agents (*Weiler et al 2016*).

SAFETY SUMMARY

- Contraindications:
  - Serevent Diskus, ProAir Digihaler, and ProAir RespiClick, are contraindicated in patients with a severe hypersensitivity to milk proteins.
  - LABAs should generally not be used as a primary treatment of status asthmaticus or other acute episodes of asthma or COPD that require intensive measures; this is listed as a contraindication for Serevent Diskus.
  - All LABAs are contraindicated for use in patients with asthma without concomitant use of a long-term asthma control medication.
- Key warnings and precautions:
  - Salmeterol has a boxed warning for asthma-related deaths and should be prescribed only as an additional therapy to ICS.
  - All LABAs have a warning describing the increased risk of asthma-related deaths and asthma-related hospitalizations (mainly in pediatric and adolescent patients) when used as monotherapy. The fixed-dose combinations of LABA and ICS do not increase serious asthma-related events compared with ICS alone. The use of a LABA without an ICS is contraindicated in patients with asthma. Patients with COPD do not experience increased mortality with the use of LABAs.
  - Beta$_2$-agonists may also lead to:
    - paradoxical bronchospasm
    - fatalities with excessive use
    - cardiovascular effects such as increased heart rate, blood pressure, and/or electrocardiogram changes
    - central nervous system effects and/or seizures

- LABAs should not be used to treat acute symptoms or initiated in the setting of acutely deteriorating asthma or COPD.

- Adverse events
  - Commonly-reported adverse events (≥ 5% for at least 1 medication in the class) include chest pain, palpitations, tachycardia, dizziness, excitement, fatigue, headache, nervousness, shakiness, somnolence, tremor, rash, diarrhea, nausea, vomiting, pain, asthma exacerbation, bronchitis, cough, influenza, nasal congestion, nasopharyngitis/pharyngitis, respiratory disorder, rhinitis, throat irritation, upper respiratory tract infection, viral respiratory infection, accidental injury, fever, and viral infection.
- Albuterol solution, syrup, tablets, and extended-release tablets, metaproterenol, terbutaline injection, and indacaterol are Pregnancy Category C; arformoterol, levalbuterol, ProAir HFA, Proventil HFA, ProAir Digihaler, ProAir HFA, ProAir RespiClick, Ventolin HFA, formoterol, olodaterol, salmeterol, and terbutaline tablets are not assigned a Pregnancy Category.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Generic Name	Available Formulations	Route	Usual Recommended Frequency	Comments
Short-acting beta$_2$-agonists				
albuterol	Inhalation: metered dose aerosol inhaler (HFA), metered dose dry powder inhaler, solution for nebulization Oral: extended-release tablets, syrup, tablets	Inhalation, oral	Treatment or prevention of bronchospasm in patients with asthma: • Aerosol/dry powder inhaler: 1 to 2 inhalations every 4 to 6 hours • Solution for nebulization: 3 to 4 times daily • Extended-release tablets: twice daily • Syrup, tablets: 3 to 4 times daily Exercise-induced bronchospasm: • Aerosol/dry powder inhaler: 2 inhalations 15 to 30 minutes before exercise	
levalbuterol	Metered dose aerosol inhaler (HFA), solution for nebulization	Inhalation	Treatment or prevention of bronchospasm in patients with asthma: • Aerosol inhaler: 1 to 2 inhalations every 4 to 6 hours • Solution for nebulization: 3 times daily	
metaproterenol	Syrup	Oral	3 to 4 times daily	
terbutaline	Injection, tablets	Subcutaneous injection, oral	• Injection: 1 subcutaneous injection, may repeat in 15 to 30 minutes if improvement does not occur; maximum, 0.5 mg in 4 hours • Tablets: 3 times daily, 6 hours apart	Injection: Safety and efficacy in children < 12 years of age have not been established.
Long-acting beta$_2$-agonists				
arformoterol	Solution for nebulization	Inhalation	Twice daily	Safety and efficacy in children have not been established.

Generic Name	Available Formulations	Route	Usual Recommended Frequency	Comments
formoterol	Solution for nebulization	Inhalation	Twice daily	Safety and efficacy in children have not been established.
indacaterol	Capsule for inhalation	Inhalation	Once daily	Safety and efficacy in children have not been established.
olodaterol	Inhalation spray	Inhalation	Once daily	Safety and efficacy in children have not been established.
salmeterol	Dry powder inhaler	Inhalation	Treatment or prevention of bronchospasm in patients with asthma/maintenance treatment of bronchoconstriction in COPD 1 inhalation twice daily Exercise-induced bronchospasm: 1 inhalation at least 30 minutes before exercise; at least 12 hours should elapse between doses	

Abbreviations: COPD = chronic obstructive pulmonary disease; HFA = hydrofluoroalkane

See the current prescribing information for full details.

CONCLUSION

- Single-entity respiratory beta$_2$-agonist agents are FDA-approved for the treatment of asthma, COPD, reversible airway obstruction and/or exercise-induced bronchospasm.
  - Beta$_2$-agonists are classified as short- or long-acting based on their onset and duration of action, and are available in various dosage forms, including solution for nebulization, aerosol inhaler, dry powder inhaler, oral solution, immediate- and extended-release tablets, and solution for injection.
  - SABAs are generally dosed multiple times per day for the treatment or prevention of symptoms.
  - LABAs are typically administered twice daily for COPD, with the exception of indacaterol and olodaterol, which are administered once daily.
- Overall, SABAs have demonstrated similar efficacy and safety. Similarly, for LABAs, head-to-head clinical trials have not determined the superiority of any one agent.
- All LABAs (salmeterol also has a boxed warning) have a warning describing the increased risk of asthma-related deaths and asthma-related hospitalizations (mainly in pediatric and adolescent patients) when used as monotherapy.
  - In the treatment of asthma, LABAs should not be used as monotherapy, but rather added on to another long-acting controller medication such as an ICS.
- According to GINA and NHLBI guidelines, as-needed SABAs may provide symptomatic relief in patients with asthma, including children, adolescents, and adults. The GINA guideline advises against the use of SABAs without ICS; a low dose ICS should be taken whenever a SABA is taken. In adults and adolescents, low dose ICS-formoterol is the preferred reliever medication. For chronic management of asthma, the preferred controller options consist of ICS-formoterol (on as-needed basis), ICS, or ICS/LABA depending on the age of a patient and severity of symptoms.
- GOLD guidelines state that inhaled bronchodilators are a key component of COPD treatment, and long-acting agents are generally preferred over short-acting agents for maintenance therapy.
  - Depending on the COPD patient subtype, initial COPD management may include use of a beta$_2$-agonist and/or an anticholinergic agent.

- The majority of the current asthma or COPD treatment guidelines do not recommend the use of one specific inhaled beta$_2$-agonist product over another, except for the GINA guideline which lists low-dose ICS-formoterol as the preferred controller and reliever medication in adults and adolescents.
  - Administration instructions and inhalation devices vary among products and should be considered in product selection.

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Publication Date: June 22, 2020