Therapeutic Class Overview
β_2-Agonists Single Entity Agents

Therapeutic Class

- **Overview/Summary:** Respiratory β_2-agonists are primarily used to treat reversible airway disease. Their Food and Drug Administration (FDA)-approved indications include asthma, chronic obstructive pulmonary disease, exercise-induced asthma/bronchospasm, and/or and reversible bronchospasm. Respiratory β_2-agonists act preferentially on the β_2-adrenergic receptors. Activation of these receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.[1-20] The β_2-agonists can be divided into two categories: short-acting and long-acting. The short-acting respiratory β_2-agonists consist of albuterol, levalbuterol, metaproterenol, pirbuterol and terbutaline. The long-acting β_2-agonists include extended release albuterol, arformoterol, formoterol, indacaterol and salmeterol. Respiratory β_2-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.[1-20] As a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing and sale of all albuterol metered dose inhalers (MDIs) containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008. These inhalers were replaced by MDIs which use hydrofluoroalkanes (HFAs). There is no difference in the safety or efficacy of the HFA inhalers compared to the CFC inhalers; however, there may small differences in taste and/or feel with the HFA inhalers. The deadline for removal of the pirbuterol (Maxair®) CFC inhaler is December 31, 2013.[21]

Table 1. Current Medications Available in the Therapeutic Class[1-20]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Short-Acting β_2-agonists			
Albuterol (AccuNeb®*, ProAir HFA®, Proventil HFA®, Ventolin HFA®, Vospire ER®*)	Relief of bronchospasm in patients with asthma (inhalation solution, oral formulations only), treatment or prevention of bronchospasm in patients with reversible obstructive airway disease (meter dose inhaler), prevention of exercise-induced bronchospasm (meter dose inhaler only)	Meter dose aerosol inhaler (HFA): 120 µg albuterol sulfate (60 or 200 inhalations) Solution for nebulization: 0.63 mg 1.25 mg 2.5 mg 0.5% concentrated solution (3 mL unit dose vials) Sustained-release tablet: 4 mg 8 mg Syrup: 2 mg/5 mL	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Tablet: 2 mg 4 mg	
Levalbuterol (Xopenex®*, Xopenex HFA®)	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease	Meter dose aerosol inhaler (HFA): 59 µg (80 or 200 inhalations) Solution for nebulization: 0.31 mg 0.63 mg 1.25 mg (3 mL vials)	✔
Metaproterenol*	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg	✔
Pirbuterol (Maxair Autohaler®)	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease	Breath activated aerosol inhaler: 200 µg (80 or 400 inhalations)	-
Terbutaline* (Brethine®)	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Injection: 1 mg/mL (2 mL vial) Tablet: 2.5 mg 5 mg	✔
Long-Acting β_2-agonists			
Arformoterol (Brovana®)	Long-term, twice daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema	Solution for nebulization: 15 µg (2 mL)	-
Formoterol (Foradil®, Perforomist®)	Treatment of asthma and prevention of bronchospasm as concomitant therapy with a long-term asthma control medication in patients with reversible obstructive airways disease, including patients with nocturnal symptoms (dry powder inhaler only), long-term, twice daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema, prevention of exercise-induced bronchospasm (dry powder inhaler only)	Capsule for inhalation: 12 µg Solution for nebulization: 20 µg/2 mL	-
Indacaterol (Arcapta Neohaler®)	The long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	Capsule for inhalation: 75 µg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Salmeterol (Serevent Diskus®)	Treatment of asthma and prevention of bronchospasm as concomitant therapy with a long-term asthma control medication in patients with reversible obstructive airways disease, including patients with nocturnal symptoms, long-term, twice daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema, prevention of exercise-induced bronchospasm	Dry powder inhaler: 50 µg (28 or 60 inhalations)	-

COPD=chronic obstructive pulmonary disease, ER=extended release, HFA=hydrofluoroalkanes
*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials have demonstrated the efficacy of short-acting and long-acting β_2-agonists (SABAs and LABAs) in providing relief from asthma exacerbations, chronic obstructive pulmonary disease (COPD) exacerbations and exercise induced asthma (EIA).[22-79]
- In clinical trials that comparing albuterol to levalbuterol, inconsistent results have been reported and have not consistently demonstrated improved outcomes with levalbuterol compared to albuterol. Moreover, studies have shown no significant differences between the two agents in the peak change in forced expiratory volume in one second ($FEV_{1)}$ or the number and incidence of adverse events.[22-32]
- Salmeterol and formoterol have been found to improve FEV_1 in patients with mild to moderate asthma who require persistent use of SABAs. In a meta-analysis by Salpeter et al, 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.[33]
- A recent systematic review concluded that in patients with COPD, there was no difference in rate of mild exacerbation 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 (relative risk, 0.96; 95% CI, 0.89 to 1.02).[34]
- Overall, data from published clinical trials demonstrate 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.[35-44]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Short-acting β_2-agonists are recommended for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm.[80,81]
  - Short-acting β_2-agonists should be used on an as-needed or "rescue" basis.[80,81]
  - In the chronic management of asthma, the long-acting β_2-agonists should be used as add-on therapy in patients not adequately controlled on an inhaled corticosteroid.[80,81]
  - Long-acting β_2-agonists should not be used as monotherapy for the long-term control of asthma.[80,81]
  - Long-acting β_2-agonists can be used for exercise-induced bronchospasm and provide a longer period of coverage compared to short acting β_2-agonists.[80,81]
  - Long-acting β_2-agonists have a role in the treatment of chronic obstructive pulmonary disease (COPD), for patients who remain symptomatic even with current treatment with short-acting bronchodilators.[80,81]

  - Long-acting β_2-agonists can be added to other COPD treatment regimens, including an anticholinergic agent, in efforts to decrease exacerbations.[82,83]
- Other Key Facts:
  - The role of the short- and long-acting respiratory β_2-agonists in the treatment of asthma and COPD has been well established.
  - Studies have failed to consistently demonstrate significant differences between products.
  - Albuterol oral solution, oral tablets, and solution for nebulization, levalbuterol solution for nebulization, metaproterenol oral solution and oral tablets, and terbutaline oral tablets and solution for injection are available generically.
  - There are currently three branded albuterol hydrofluoroalkanes (HFA) inhalers; however, no generic equivalents are available.
  - None of the long-acting respiratory β_2-agonists are currently available generically.

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Therapeutic Class Review
β_2-Agonists Single Entity Agents

Overview/Summary

Respiratory β_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 and reversible bronchospasm. Activation β_2-adrenergic receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation, ultimately resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.[1-19] The β_2-agonists are classified as short- and long-acting agents. The short-acting β_2-agonists (SABAs) consist of albuterol (ProAir HFA®, Proventil HFA®, Ventolin HFA®), levalbuterol (Xopenex®, Xopenex HFA®), metaproterenol, pirbuterol (Maxair Autohaler®) and terbutaline (Brethine®). The long-acting β_2-agonists (LABAs) include extended-release albuterol (Vospire ER®), arformoterol (Brovana®), formoterol (Foradil®, Perforomist®), indacaterol (Arcapta Neohaler®) and salmeterol (Serevent Diskus®). The β_2-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.[1-20] Each SABA is available generically in at least one strength or formulation with the exception of pirbuterol. There are no generic formulations for the LABAs.

As a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing and sale of all albuterol metered dose inhalers (MDIs) containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008. These inhalers are to be replaced by MDIs which use hydrofluoroalkanes (HFAs). There is no difference in the safety or efficacy of the HFA inhalers compared to the CFC inhalers; however, there may small differences in taste and/or feel with the HFA inhalers. The deadline for discontinuation of production or dispensing of the pirbuterol CFC inhaler is December 31, 2013.[21]

According to the National Heart, Lung, and Blood Institute (NHLBI) and the Global Initiative for Asthma, inhaled corticosteroids (ICSs) are the most effective long-term control medications used for the treatment of asthma for patients of all ages. Alternative long-term control medications include leukotriene modifiers, mast-cell stabilizers and methylxanthines; however, these agents are considered less effective as monotherapy compared to ICSs. The LABAs should not be used as monotherapy for the management of asthma; however, they are considered the most effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Leukotriene modifiers, mast-cell stabilizers and methylxanthines may also be used as adjunctive therapies but are less effective than LABAs. Chronic administration of systemic corticosteroids is reserved for severe, difficult-to-control asthma patients and the use of immunomodulators is only indicated in asthma patients with severe disease and allergies.[22,23] The guidelines state that SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma.[22,23] Anticholinergics may also be used for the treatment of acute exacerbations but are considered less effective than SABAs. The addition of a systemic corticosteroid may be required if patients do not respond immediately to treatment with a SABA or if the exacerbation is severe. According to the NHLBI, the use of LABAs to treat acute symptoms or exacerbations of asthma is not recommended.[22,23]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, agents used to manage stable chronic obstructive pulmonary disease include inhaled bronchodilators and corticosteroids. The choice between bronchodilators, which are central to COPD symptom management, depends on patient response, the incidence of adverse events and availability. Bronchodilators, which include LABAs and SABAs, anticholinergics and methylxanthines, should be administered as needed or on a scheduled basis to relieve intermittent or worsening symptoms or to prevent or reduce persistent symptoms. Long-acting bronchodilators are more effective than short-acting bronchodilators; however,

short-acting bronchodilators should be considered initial empiric therapy.[24] According to the National Institute for Clinical Excellence, long-acting bronchodilators should be used to control symptoms of COPD in patients who continue to experience problems despite the use of short-acting bronchodilators.[25] Also, a combination of bronchodilators from different pharmacologic classes may increase the efficacy of the treatment regimen. The addition of an ICS to a treatment regimen reduces exacerbations and improves lung function.[24] Long-term treatment with oral corticosteroids is not recommended for the management of stable COPD.[24,25] Current GOLD guidelines also recommend the use of bronchodilators and corticosteroids for the management of acute COPD exacerbations.[24] An increase in the dose and/or frequency of short-acting bronchodilators as well as the addition of an anticholinergic is recommended until symptoms improve. The use of antibiotics in COPD is only recommended for the treatment of infectious exacerbations.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Short Acting β_2-agonists		
Albuterol (AccuNeb®*, ProAir HFA®, Proventil HFA®, Ventolin HFA®, Vospire ER®*)	β_2-agonist	✔
Levalbuterol (Xopenex®*, Xopenex HFA®)	β_2-agonist	✔
Metaproterenol*	β_2-agonist	✔
Pirbuterol (Maxair Autohaler®)	β_2-agonist	-
Terbutaline* (Brethine®)	β_2-agonist	✔
Long Acting β_2-agonists		
Arformoterol (Brovana®)	β_2-agonist	-
Formoterol (Foradil®, Perforomist®)	β_2-agonist	-
Indacaterol (Arcapta Neohaler®)	β_2-agonist	-
Salmeterol (Serevent Diskus®)	β_2-agonist	-

ER=extended release, HFA=hydrofluoroalkanes
*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-20]

Indication	Short-acting β_2 agonists					Long-acting β_2 agonists			
	Albuterol	Levalbuterol	Metaproterenol	Pirbuterol	Terbutaline	Arformoterol	Formoterol	Indacaterol	Salmeterol
Asthma									
Relief of bronchospasm in patients with asthma	✔ *§								
Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease	✔ †	✔ *†		✔					
Treatment of asthma and prevention of bronchospasm as concomitant therapy with a long-term asthma control medication in patients with reversible obstructive airways disease, including patients with nocturnal symptoms							✔ ‡		✔
Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema			✔		✔				
COPD									
Long-term, twice daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema						✔	✔		✔
The long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema								✔	
Exercised-Induced Bronchospasm									
Prevention of exercise-induced bronchospasm	✔ †						✔ ‡		✔

COPD=chronic obstructive pulmonary disease.
*Inhalation solution.
†Metered-dose inhaler.
‡Dry powder inhaler.
§Oral formulations.

Pharmacokinetics

Table 3. Pharmacokinetics[1-20]

Generic Name	Onset of Action (minutes)	Duration of Action (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Short Acting β_2-agonists					
Albuterol (HFA-propelled inhalation)	8.2 to 10.0* 6 to 7† 5.4 to 7.8‡	2.3 to 6.0	80 to 100	Yes	4.6 to 6.0
Albuterol (nebulized inhalation)	30 to 60	2.5 to 6.0	80 to 100	Yes	4.6 to 6.0
Albuterol (oral tablets)	2 to 3	6 to 8	76	Yes	5.0 to 7.2 (immediate release); 9.3 (extended release)
Levalbuterol	10 to 17 (levalbuterol); 4.5 to 10.2 (levalbuterol HFA)	5 to 8 (levalbuterol); 3 to 6 (levalbuterol HFA)	80 to 100	Yes	3.3 to 4.0 (levalbuterol); 5 to 7 (levalbuterol HFA)
Metaproterenol	30	4	Not reported	Not reported	Not reported
Pirbuterol	5	3 to 4	60	Yes	2 to 3
Terbutaline	30 to 45	4 to 8	24 to 60	No	3.4
Long Acting β_2-agonists					
Arformoterol	7 to 20	Not reported	63 to 67	No	26
Formoterol	1 to 3	8 to 12	1.1 to 28.0	No	7 to 10
Indacaterol	15	~24	1.2 <2	Not reported	40 to 56
Salmeterol	10 to 20	12	25	No	5.5

HFA=hydrofluoroalkanes
*ProAir HFA®
†Proventil HFA®
‡Ventolin HFA®

Clinical Trials

Clinical trials have demonstrated the efficacy of short-acting and long-acting β_2-agonists (SABAs and LABAs) in providing relief from asthma exacerbations, chronic obstructive pulmonary disease (COPD) exacerbations and exercise induced asthma (EIA).[26-93]

In clinical trials evaluating these products for the treatment of mild asthma, all SABAs have been shown to be efficacious in improving forced expiratory volume in 1 second (FEV_1). Inconsistent result have been reported in trials comparing albuterol to levalbuterol.[26-36] In two studies (one retrospective, one prospective), levalbuterol resulted in a significantly lower hospitalization rate compared to albuterol.[26,27] When the two agents were administered in the emergency department, there was no significant difference in the time to discharge.[29] Nowak et al also reported that there was no difference in the time to discharge from the emergency room with albuterol compared to levalbuterol (76.0 and 78.5 minutes; *P*=0.74).[30] In an unpublished study, the difference in peak FEV_1 was statistically significant for albuterol hydrofluoroalkanes (HFA) compared to levalbuterol HFA (*P*=0.018).[35] In addition, studies have shown no significant differences between the two agents in the peak change in FEV_1 and the number or incidence of adverse events.[26-36]

Salmeterol and formoterol have been found to improve FEV_1 in patients with mild to moderate asthma who require persistent use of SABAs. Results from the SMART trial found that salmeterol treatment was associated with significantly more occurrences of combined respiratory-related deaths or respiratory-related life-threatening experiences compared to placebo (P<0.05).[48] In a meta-analysis by Salpeter et al, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life threatening exacerbations and asthma-related deaths in adults and children when compared to placebo.[40] Due to the results of these studies, the labeling of salmeterol, formoterol, and arformoterol were updated to include a black box warning stating that these agents may increase the risk of asthma related deaths.[16-19]

The results of a recent systematic review demonstrated that in patients with COPD, there was no statistically significant difference in the rate of mild exacerbation between patients treated with an inhaled corticosteroid (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 (relative risk, 0.96; 95% CI, 0.89 to 1.02).[61]

The safety and efficacy of indacaterol were evaluated in randomized controlled trials compared to placebo and other agents used in the management of COPD.[73-83] Notably, these trials evaluated indacaterol in doses of 150, 300 and 600 µg once-daily, but not the Food and Drug Administration (FDA)-approved dosing (75 µg once-daily).[73-83] According to the FDA-approved labeling, dose selection for indacaterol in COPD was based on three dose ranging clinical trials, one of which included an asthmatic population. In the two COPD dose ranging trials (18.75, 37.5, 75 and 150 µg/day and 75, 150, 300 and 600 µg/day), a dose-response relationship in FEV_1 was observed; however, the effect did not clearly differ between the various doses.[3] Overall, data from published clinical trials demonstrate 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 (e.g., 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 significant “superiority” is not consistently achieved.[73-83] Placebo-controlled trials demonstrate that within five minutes after administration of indacaterol, significant improvements in bronchodilation are achieved.[78-81] These results have also been observed when comparing indacaterol to salmeterol, salmeterol/fluticasone and tiotropium.[77,81,82]

In two studies, patients diagnosed with COPD were treated with arformoterol, salmeterol or placebo. 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).[63,64] In a head-to-head study against salmeterol, formoterol was associated with a greater change from baseline in FEV_1 at five minutes postdose on day 28 (P=0.022).[66]

For the treatment of EIA, albuterol, metaproterenol, and formoterol have demonstrated an improvement in FEV_1 compared to placebo.[88-92] In one study, albuterol- and metaproterenol- treated patients had a lower incidence of exercise induced bronchospasm compared to placebo.[88] 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).[89]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Asthma				
Carl et al[26] Albuterol 2.5 mg via nebulization (every 20 minutes for 2 hours) vs levalbuterol 1.25 mg via nebulization (every 20 minutes for 2 hours)	DB, PRO, RCT Individuals 1 to 18 years of age with asthma presenting to the ED (1 patient had been using levalbuterol the remainder albuterol as rescue prior to presenting to the ED)	N=547 Varying duration of hospitalizations	Primary: Hospital admission rate Secondary: LOS, ED LOS, intensification, number of aerosols, requirement for oxygen and adverse events	Primary: Compared to the albuterol group, the levalbuterol group had a significantly lower hospitalization rate (36 vs 45%; *P*=0.02). Secondary: There were no significant differences between the albuterol and levalbuterol group concerning secondary outcomes, including adverse events (*P*=0.26 to *P*=0.94). No significant adverse events occurred in either group.
Schreck et al[27] Albuterol 2.5 mg via nebulization (plus standard treatment) vs levalbuterol 1.25 mg via nebulization (plus standard treatment)	CR, OS, RETRO, Individuals ≥1 year of age with an acute asthma presenting to the ED requiring nebulization with a SABA	N=736 9 months	Primary: Patient disposition, ED LOS, and objective measures of patient upon arrival Secondary: Not reported	Primary: There was a significantly lower hospitalization rate in the levalbuterol group compared to the albuterol group (4.7 vs 15.1%; *P*=0.0016). The rate of 15.1% is comparable to the hospitals average admission rate of 16.4%. There was no significant difference between the two treatment groups concerning ED LOS and other objective measures upon patient presentation (*P*=0.762). Due to a decrease in hospitalizations, treatment costs were lower in the levalbuterol treatment group (*P* value not reported). Secondary: Not reported
Qureshi et al[28] Albuterol 2.5 to 5 mg via nebulization (plus standard treatment as needed)	DB, PRO, RCT Children 2 to 14 years of age with a known history of asthma presenting to a pediatric ED	N=129 Study was complete after patient received 5 doses, was admitted, or	Primary: Changes from baseline in clinical asthma score and the percent of predicted FEV_1 after the first, third, and	Primary: No significant differences between the treatment groups were found (*P* value not reported). Secondary: No significant differences between the treatment groups were found (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs levalbuterol 1.25 to 2.5 mg via nebulization (plus standard treatment needed)	with an acute moderate or severe asthma exacerbation	discharged	fifth treatment Secondary: Number of treatments, length of ED care, rate of hospitalizations, changes in pulse rate and oxygen saturation	No significant differences between the treatment groups concerning adverse event were reported (*P* value not reported).
Skoner et al[29] Albuterol 1.25 mg via nebulization vs albuterol 2.5 mg via nebulization vs levalbuterol 0.31 mg via nebulization vs levalbuterol 0.63 mg via nebulization vs placebo	DB, MC, PC, PG, RCT Children 2 to 5 years of age with asthma for at least 30 days and no other underlying medical condition	N=211 4 weeks	Primary: Change from baseline in the total score on the PAQ Secondary: PEF, rescue medication use, and the Child Health Status Questionnaire	Primary: Decrease in the PAQ score was demonstrated in all treatment groups (*P* value not reported). Secondary: All treatment groups demonstrated an improvement in PEF compared to placebo (*P*<0.01 for all treatment groups). All treatment groups, including the placebo group, demonstrated a decrease in rescue medication use. There were no significant differences between the treatment groups (*P* value not reported). All treatment groups demonstrated and improvement from baseline in the Child Health Status Questionnaire (*P* value not reported). Overall, the incidence of adverse events was similar for each treatment group during the study period. Adverse events were mild (68.0%) to moderate (28.1%) in severity. Among all patients, significant increases in ventricular heart rates were demonstrated in the levalbuterol 0.63 mg and racemic albuterol 2.5 mg groups compared to placebo (*P* value not reported).
Nowak et al[30] Albuterol 2.5 mg via	DB, MC, PG, PRO, RCT	N=627 1 month	Primary: Time to meet ED discharge criteria	Primary: For the levalbuterol and albuterol groups the median time to discharge (76.0 and 78.5 minutes) was not statistically different (*P*=0.74).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nebulization (up to 6 doses in 3 hours) with prednisone 40 mg tablet vs levalbuterol 1.25 mg via nebulization (up to 6 doses in 3 hours) with prednisone 40 mg tablet	Individuals ≥18 years of age presenting to the ED or clinic with an acute asthma exacerbation		Secondary: Comparisons of FEV_1 change from baseline, the proportion of patients hospitalized, effect of plasma concentration of (*S*)-albuterol at presentation on FEV_1 response and hospitalization	Secondary: There was no significant difference (*P*=0.28) in the admission rate between the albuterol (9.3%) and levalbuterol (7.0%) groups. After dose one and cumulative doses over time there was a greater FEV_1 improvement following levalbuterol compared to albuterol (*P*=0.021). For individuals not taking corticosteroids chronically before the trial, there were significantly fewer hospitalizations in the levalbuterol group compared to the albuterol group (3.8 vs 9.3%; *P*=0.03). There was no significant difference in the overall frequency of adverse event in the two treatment groups (*P* value not reported).
Nelson et al[31] Albuterol 1.25 mg TID via nebulization vs albuterol 2.5 mg TID via nebulization vs levalbuterol 0.63 mg TID via nebulization vs levalbuterol 1.25 mg TID via nebulization vs	DB, PC, PG, RCT Patients ≥12 years of age who did not smoke and had ≥6 month history of chronic and stable asthma, demonstrating at ≥15% improvement in FEV_1 to a single dose of albuterol 2.5 mg via nebulization	N=362 4 weeks	Primary: Peak change in FEV_1 after four weeks Secondary: AUC and use of rescue racemic albuterol MDI	Primary: Change in peak FEV_1 in the combined levalbuterol group was not significantly greater than the combined albuterol group (0.84 and 0.74; *P* value not reported). Secondary: A similar trend was noticed when evaluating the AUC; after the first dose, levalbuterol treatment was significantly better (*P*=0.02) compared to albuterol; however, at week four, even though the AUC values were higher in the levalbuterol groups, the difference was not significant. There was a significant improvement (*P*=0.006) in predose FEV_1 in the combined levalbuterol arm compared to the combined albuterol arm in the subset of patients not taking corticosteroids. There was significantly less rescue medication used in the active treatment groups compared to placebo. Compared to baseline, there was a significant decrease in rescue-medication use in both the levalbuterol 1.25 mg arm (*P*<0.001) and the albuterol 2.5 mg arm (*P*=0.056).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				All active treatments were well tolerated with the percent of patients reporting nervousness or tremor in the low dose groups being statistically significantly lower (*P*=0.003) compared to the high dose groups.
Gawchik et al[32] Albuterol 1.25 mg via nebulization (1 dose) vs albuterol 2.5 mg via nebulization (1 dose) vs levalbuterol 0.16 mg via nebulization (1 dose) vs levalbuterol 0.31 mg via nebulization (1 dose) vs levalbuterol 0.63 mg via nebulization (1 dose) vs levalbuterol 1.25 mg via nebulization (1 dose) vs	DB, PC, RCT, XO Patients 3 to 11 years of age with asthma for ≥6 months and reversibility of 12% or more 30 minutes after 2.5 mg of albuterol administered by nebulization	N=43 4 treatment visits (2 to 8 days apart)	Primary: Differences in peak change in FEV_1, peak percent change in FEV_1 and AUC Secondary: Not reported	Primary: Differences in peak change in FEV_1, peak percent change in FEV_1 and AUC were significantly improved in all treatment arms (with the exception of albuterol 1.25 mg in AUC) compared to placebo (*P*<0.05). No significant differences between the treatment groups were found (*P*<0.55). The medications were well tolerated and all adverse events reported were mild or moderate in severity, with no significant difference seen across the treatment groups (*P* values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				
Milgrom et al[33] Albuterol 1.25 mg via nebulization vs albuterol 2.5 mg via nebulization vs levalbuterol 0.31 mg via nebulization vs levalbuterol 0.63 mg via nebulization vs placebo	DB, MC, PC, PG, RCT Patients 4 to 11 years of age mild or worse asthma with a reversibility of ≥15% to albuterol	N=338 3 weeks	Primary: Peak percent change in FEV_1 from baseline Secondary: Change in pulmonary function, percent of responders within 30 minutes after dose, time to peak improvement in FEV_1, use of rescue medications, symptoms, symptom-free days, asthma control days and adverse event	Primary: A significant improvement was seen in peak percent change in FEV_1 from baseline in all active treatment arms compared to placebo on day 21 (*P*<0.019). Secondary: Immediately after nebulization on days zero and 21 there were clinically significant changes for all groups except placebo (*P*<0.02) and, with the exception of the albuterol 1.25 mg group, more patients responded to active treatment in comparison to the placebo group on both days (*P*<0.02). On day zero significantly more patients responded to levalbuterol 0.31 mg (62.9%) than to albuterol 1.25 mg (41.8%), immediately after nebulization (*P*=0.12). Levalbuterol 0.31 mg achieved a significantly greater change in asthma control days compared to levalbuterol 0.63 mg and albuterol 1.25 mg (*P*<0.04 for each comparison). Compared to all active treatments, levalbuterol 0.31 mg produced significantly smaller changes in heart rate (*P*<0.02). A significant decrease in potassium levels was seen in all treatment groups compared to placebo (*P*<0.002).
Data on file[34] Albuterol 180 µg QID via HFA-MDI vs levalbuterol 90 µg QID via HFA-MDI	DB, PC, PG, RCT Patients ≥12 years of age with moderate to severe asthma and FEV_1 45 to 75% of the predicted value	N=445 9 weeks	Primary: Mean percent change in peak FEV_1 Secondary: Not reported	Primary: Levalbuterol and albuterol demonstrated a significant improvement in mean peak FEV_1 during the study period compared to placebo (25.63, 28.98 vs 13.94%, respectively; *P*<0.001). The difference in peak FEV_1 was statistically significant for albuterol compared to levalbuterol (*P*=0.018). Overall, the incidences in adverse events were similar between all treatment groups. The most commonly reported adverse events were headache, viral infection and asthma. The most common adverse event

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				leading to discontinuation was asthma that occurred in 5.5, 2.5 and 1.8% of patients in the levalbuterol, albuterol and placebo groups, respectively. Secondary: Not reported
Data on file[35] Albuterol 180 µg QID via HFA-MDI vs levalbuterol 90 µg QID via HFA-MDI vs placebo	DB, PC, PG, RCT Patients ≥12 years of age with moderate to severe asthma with a FEV_1 45 to 75% of the predicted value	N=303 9 weeks	Primary: Mean percent change in peak FEV_1 Secondary: Percentage of responders (patients achieving a FEV_1 >15% over the visit predose value)	Primary: Levalbuterol and albuterol demonstrated a significant improvement in mean peak FEV_1 during the study period compared to placebo (25.30, 26.14 vs 12.45%, respectively; *P*<0.001). Secondary: The percentage of responders was greater in each active treatment group compared to placebo at each visit. The time to 15% response was also significantly shorter for each active treatment group compared to placebo at visits two and six (*P*<0.001). Overall, the incidences in adverse events were similar between each treatment group (50.0 to 56.5%). Serious adverse events were slightly less common in the levalbuterol group (5.7%) compared to the albuterol (10.0%) and placebo (8.5%) groups. Adverse events leading to discontinuation occurred in 5.7, 10.0, and 6.8% of patients in the levalbuterol, albuterol and placebo groups, respectively.
Nowak et al[36] Albuterol 2.5 mg via nebulization (3 doses) vs albuterol 5 mg via nebulization (3 doses) vs levalbuterol 0.63 mg via	OL, PRO Adult asthmatics presenting to the ED with an acute asthma exacerbation	N=93 2 hours	Primary: FEV_1 percent change from baseline following the third nebulization Secondary: Change and percent change from baseline FEV_1 at each time point, the percent of	Primary: The median percent change in FEV_1 was greater for 1.25 mg levalbuterol (74%), compared to 2.5 mg albuterol, (39%), 0.63 mg levalbuterol (37%), and 3.75 mg levalbuterol (26%) after three doses (*P* value not reported). Secondary: At 60 minutes posttreatment, levalbuterol 1.25, 2.5, and 5 mg improved the median percent predicted FEV_1 by 33 to 38% compared to 12 to 24% with 2.5 and 5 mg doses of albuterol and 0.63 and 3.75 mg doses of levalbuterol (*P* value not reported). (*S*) albuterol levels were found to be significantly inversely correlated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nebulization (3 doses) vs levalbuterol 1.25 mg via nebulization (3 doses) vs levalbuterol 2.5 mg via nebulization (3 doses) vs levalbuterol 3.75 mg via nebulization (3 doses) vs levalbuterol 5 mg via nebulization (3 doses)			responders, and the time to achieve a 15% and 50% increase from baseline	with baseline FEV_1 (*P*=0.004), and percent change in FEV_1 60 minutes post dose (*P*=0.006).
Jat et al[37] Albuterol (doses varied) vs levalbuterol (doses varied)	MA (7 RCT) Patients of all ages with acute asthma	N=1,625 Duration not reported	Primary: Respiratory rate, oxygen saturation, FEV_1, PEFR, retractions, air entry, wheezing and adverse events Secondary: Hospital admission rate, need for mechanical ventilation and duration of hospital stay	Primary: Overall, no significant difference was identified between levalbuterol and albuterol with regard to final respiratory rate (mean difference, 0.37; 95% CI, 0.80 to 1.54), change in respiratory rate (mean difference, -0.42; 95% CI, -9.28 to 8.46) or combined respiratory rate (mean difference, 0.35; 95% CI, 0.81 to 1.51). There was no statistically significant difference between the treatments in final oxygen saturation (mean difference, -0.29; 95% CI, -0.68 to 0.10) or the change in oxygen saturation (mean difference, -0.38; 95% CI, -2.98 to 2.23). No statistically significant difference was observed between patients treated with levalbuterol compared to albuterol with regard to FEV_1 (mean difference, -28.3; 95% CI, -59.95 to 3.33) and PEFR (mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				difference, 0.53; 95% CI, -13.85 to 14.91). There was no statistically significant difference between treatments with regard to asthma symptom scores (air entry, wheezing, retractions) (mean difference, -1.01; 95% CI, -5.30 to 3.28). Secondary: No statistically significant differences in adverse events were reported between the treatment groups. There was no statistically significant difference between levalbuterol and albuterol treatment with regard to changes in heart rate (mean difference, -2.87; 95% CI, -12.24 to 6.50). The hospital admission rate was significantly lower in levalbuterol group compared to the albuterol group (OR, 0.76; 95% CI, 0.58 to 0.98); however, the duration of ED care was not different between the groups (mean difference, 1.44; 95% CI, -4.39 to 7.27). There were no data available related to need for mechanical ventilation.
Wolfe et al[38] Albuterol syrup 2 mg TID vs metaproterenol syrup 10 mg TID	IB, MC, PG, RCT Individuals 5 to 9 years of age with chronic asthma	N=65 4 weeks	Primary: Time to maximal response, maximum percent increase from baseline, peak flow measurements, heart rate, blood pressure and adverse event Secondary: Not reported	Primary: There was a significantly greater degree of bronchodilation with albuterol compared to metaproterenol from two to eight hours post dose (P<0.05). The peak percent improvement in FEV_1 from baseline was significantly greater for albuterol compared to metaproterenol (29.3 vs 20.6%; P<0.05). There were no significant differences in the mean change from baseline in systolic blood pressure in either group; however, with metaproterenol the chronotropic effect was significantly greater (P<0.05) at one hour on day one and 28 and 1.5 hours on day 28 compared to albuterol. There was no significant difference in the frequency of adverse event between the two groups (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Kemp et al[39] Albuterol via MDI vs formoterol via DPI vs placebo	MA (45 RCTs) Studies in which formoterol was administered either with or without an ICS or other adjunct therapy were included in this analysis	N=8,369 Duration not reported	Primary: Serous asthma exacerbations (asthma-related deaths, intubations and hospitalizations) Secondary: Not reported	Primary: Compared to placebo, the risk of a serious asthma exacerbation was highest in the formoterol group receiving 10 to12 µg daily (OR, 3.9; 95% CI, 1.5 to 10.3). Patients receiving formoterol 48 µg and 20/24 µg daily also had a greater risk of severe asthma exacerbations compared to placebo (OR, 2.9; 95% CI, 1.2 to 6.6 and OR, 1.8; 95% CI, 0.8 to 4.0, respectively). The risk of serious asthma exacerbation was also higher with albuterol compared to placebo (OR, 2.6; 95% CI, 1.0 to 6.6). In children, the risk of serious asthma exacerbations was higher among patients being treated with formoterol compared to placebo (OR, 8.4; 95% CI, 1.1 to 65.3). Formoterol use in adolescents and adults was not associated with an increased risk of serious asthma exacerbations (OR, 0.30; 95% CI, 0.03 to 3.50 and OR, 1.30; 95% CI, 0.4 to 3.7, respectively). Among adults who reported using concomitant ICS at baseline, a trend toward fewer serious asthma exacerbations was seen in those receiving formoterol compared to placebo (adolescents: OR, 0.8; 95% CI, 0.05 to 12.3; adults: OR, 0.6; 95% CI, 0.2 to 2.2). Children receiving concomitant ICS had greater odds of experiencing a serious asthma exacerbation (OR, 7.8; 95% CI, 1.0 to 61.3) when also using formoterol. Secondary: Not reported
Salpeter et al[40] LABAs (formoterol via DPI) vs placebo	MA (RCTs) Individuals diagnosed with asthma (15% of the participants were African American)	N=33,826 At least 3 months	Primary: Severe asthma exacerbations requiring hospitalizations, life-threatening asthma exacerbations, and asthma-related deaths	Primary: Treatment with LABAs (formoterol and salmeterol) resulted in an increase in severe exacerbations that required hospitalization (OR, 2.6; 95% CI, 1.6 to 4.3), life-threatening exacerbations (OR, 1.8; 95% CI, 1.1 to 2.9), and asthma-related deaths (OR, 3.5; 95% CI, 1.3 to 9.3) compared to placebo. The risks seen in adults and children were similar. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	
Boonsawat et al[41] Formoterol 18 µg administered at 0, 30, and 60 minutes via DPI vs albuterol 100 µg administered at 0, 30, and 60 minutes via MDI	DB, DD, PG, RCT Individuals 18 to 67 years of age with asthma presenting to the ED with acute bronchoconstriction	N=88 1 day	Primary: FEV_1 and asthma symptoms Secondary: Not reported	Primary: A nonsignificant increase in FEV_1 at 75 minutes compared to baseline was seen (37% in the formoterol group vs 28% in the albuterol group; *P*=0.18). There was a significant increase in the maximum FEV_1 between 75 to 240 and 15 to 45 minutes after the first and second dose of the medications in the formoterol group compared to the albuterol group (51 vs 36%; *P*<0.05). Subjective symptom score assessments decreased during the course of the study (*P* value not reported). Secondary: Not reported
Pauwels et al[42] Formoterol 4.5 µg administered as needed via DPI vs albuterol 200 µg administered as needed via MDI	MC, OL, RCT Individuals ≥6 years of age with asthma requiring the use of β_2-agonists as reliever medication	N=18,124 6 months	Primary: Asthma-related and non-asthma-related serious adverse events, discontinuation due to adverse events, and time to first exacerbation Secondary: Rescue reliever mediation	Primary: The number of adverse events reported was not statistically significant between the two groups (*P* value not reported). With formoterol there was a significantly higher number of asthma-related discontinuation due to adverse events (1.0 vs 0.5%; *P*<0.001). Compared to albuterol, there was a significantly longer time to first asthma exacerbation with formoterol (*P*<0.001). Secondary: Rescue inhaler use decreased in both groups over the course of the study with a significantly greater decrease seen in the formoterol group (*P*<0.001).
Molimard et al[43] Formoterol 12 µg via DPI and albuterol via MDI to	MC, OL, PG, RCT Individuals ≥18 years of age with	N=259 3 months	Primary: The mean change in morning predose PEF for the entire	Primary: Over three months, there was a significantly higher mean increase in the morning PEF in the formoterol group than in the albuterol group (25.7 and 4.5 L/minute (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
use as needed (administered as separate products) vs albuterol 100 µg via MDI to be used throughout the day as needed	moderate persistent asthma		treatment period Secondary: Mean increase in evening predose PEF for the entire treatment period, day and night use of albuterol and scores on the SGRQ	Secondary: At visits three and five, there was a significantly greater improvement in predose FEV_1 with formoterol compared to albuterol (P<0.01 and P<0.05). At three months, the mean changes from baseline in the number of puffs of albuterol during the day and night were -0.8 and -0.4 with formoterol and 0.1 and 0.1 for albuterol (P<0.0001). There was a significant increase in symptom-free days and nights in the formoterol group compared to albuterol (P<0.05 for both). A significant decrease was seen in the SGRQ score with formoterol compared to albuterol (-6.4 vs -3.5; P=0.05).
Pleskow et al[44] Formoterol 12 µg BID via DPI vs formoterol 24 µg BID via DPI vs albuterol 180 µg QID via MDI vs placebo	DB, DD, MC, PC, PG, RCT Individuals 12 to 75 years of age with mild to moderate asthma	N=554 12 weeks	Primary: FEV_1 at the 12-hour evaluation time point Secondary: AUC of FEV_1, and percent of predicted FEV_1	Primary: On the final visit at the 12-hour mark, both formoterol groups showed significant improvement in FEV_1 compared to placebo and albuterol (P<0.001 and P<0.002) with no statistical difference between albuterol and placebo at this time. Secondary: At the last visit, both formoterol groups showed significant improvement at all time points compared to placebo (P<0.001) with the exception of formoterol 12 µg at time zero. Both groups also showed significant improvement against albuterol at time zero, two to six hours, and 10 to 12 hours (P<0.001 and P<0.002). In the albuterol group there were also a significant difference compared to placebo at all points in time except zero, four to six and 10 to 12 hours (P<0.013). The AUC of FEV_1 was significantly different in favor of both formoterol groups compared to placebo (P<0.001), formoterol 24 µg compared to albuterol (P<0.001) and albuterol compared to placebo (P<0.008) at all visits. Both medications were well tolerated with no significant difference between them (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bouros et al[45] Formoterol 12 µg BID via DPI, added to current beclomethasone DPI treatment (500 µg QD; administered as separate products) vs beclomethasone 1,000 µg QD via DPI	MC, OL, PG, RCT Individuals ≥18 years of age who were symptomatic on 500 µg daily of inhaled beclomethasone	N=132 12 weeks	Primary: Mean PEF during final seven days of treatment Secondary: Overall PEF, asthma symptoms, rescue medication and safety	Primary: There was a treatment effect of 20.36 L/minute in the combination group over the patients receiving the double dose of ICS (*P*=0.021). Secondary: For the entire treatment period, the combination group had an overall evening premedication PEF that was significantly higher compared to the double dose of ICS (*P*<0.05). There was a decrease in day and night symptom scores in both groups but there was a significant difference in favor of the combination group (night; *P*=0.001, day; *P*<0.001). In both groups the number of puffs of rescue medication taken decreased during the study, with a significant improvement seen with the combination compared to the double dose of the ICS (night; *P*=0.003, day; *P*<0.001). There was no significant difference in adverse events in either group (*P* value not reported).
Tinkelman et al[46] Metaproterenol via MDI vs pirbuterol via MDI	DB, MC, PG Asthmatic patients	N=133 12 weeks	Primary: Onset of action, peak effect, adverse event and tolerance Secondary: Not reported	Primary: There was no clinical difference between the two treatment groups in the outcomes (*P* value not reported). Secondary: Not reported
Von Berg et al[47] Salmeterol 50 µg BID via DPI vs placebo	DB, PC, PG, RCT Individuals 6 to 15 years of age with a documented history of reversible airway obstruction requiring β_2-agonist	N=426 12 months	Primary: Change from baseline in mean morning PEF Secondary: Percent of symptom-free nights and days, percent of	Primary: Over the first six months of the study, the adjusted mean change above baseline in mean morning PEF was 341 minutes in patients treated with salmeterol compared to 171 minutes for placebo (*P*<0.001). This significant improvement was maintained throughout the second six months of the study (*P*=0.03). Over the first six months of the study, the adjusted mean change above baseline in mean evening PEF was 251 minutes in patients treated with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Both groups received albuterol MDI to use as needed.	treatment for symptomatic control		nights and days with no rescue inhaler and incidence of asthma exacerbations	salmeterol compared to 121 minutes for placebo (*P*<0.001). This significant improvement was maintained throughout the second six months of the study (*P*=0.05). Secondary: Although the number of symptom-free days was high (86%) in both groups, there was no statistically significant difference between the groups (*P* value not reported). There was a higher frequency distribution of the percentage of nights with no rescue inhaler use in patients receiving salmeterol compared to placebo that was significant throughout the 12-month treatment period (*P*<0.05). During the 12-month treatment period there was no statistically significant difference between the treatment in the number of patients with asthma exacerbations (*P*=0.2).
Nelson et al[48] Salmeterol 42 µg BID via DPI vs placebo Both groups received this treatment as a supplement, not a replacement to current treatment.	DB, MC, OS, PC, PG, RCT Individuals ≥12 years of age with asthma and currently using asthma medications	N=26,355 28 weeks	Primary: Occurrence of combined respiratory related deaths or respiratory related life-threatening experiences Secondary: All-cause deaths, combined asthma-related deaths or life-threatening experiences, asthma-related deaths, respiratory-related deaths, combined all-cause	Primary: There were three asthma-related deaths and 22 combined asthma-related deaths or life-threatening experiences in subjects receiving placebo compared to 13 asthma-related deaths and 37 combined asthma-related deaths or life-threatening experiences in subjects receiving salmeterol, a difference that was statistically significant (*P*<0.05). Secondary: There was no statistically significant difference seen in Caucasians in the primary or secondary end points (*P* value not reported). For the primary and two of the secondary end points there was a statistically significant difference in African Americans receiving salmeterol compared to placebo (*P*<0.05). Between the treatment groups there was a statistically significant difference for time to first serious adverse event causing discontinuation (placebo survival rate, 96.18%; salmeterol survival rate, 95.61%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			deaths or life-threatening experiences, and all-cause hospitalizations	*P*=0.022).
Boulet et al[67] Salmeterol 50 µg BID via DPI vs albuterol 200 µg QID via MDI	DB, MC, PG, RCT, Individuals ≥12 years of age with mild to moderate asthma for ≥6 months	N=228 15 weeks	Primary: FEV_1 Secondary: PEF, symptoms, use of rescue medication, and adverse events	Primary: Salmeterol resulted in a significantly greater mean improvement in FEV_1 compared to albuterol from hours three to six (*P*<0.001) and 10 to 12 (*P*<0.012) and this effect was maintained throughout the study. Secondary: A significant improvement in evening PEF was seen for salmeterol compared to albuterol (34 vs 6 L/minute; *P*<0.001). The average percent increase of symptom-free days in the salmeterol group was significantly greater than the albuterol group (29 vs 15%; *P*=0.012). There was no significant difference in rescue medication use between the two groups and both treatments were well tolerated (*P* value not reported).
Faurschou et al[50] Salmeterol 100 µg BID via DPI and as needed albuterol vs albuterol 400 µg QID via MDI and as needed albuterol All patients continued to receive their ICS dose.	DB, DD, MC, PG, RCT Individuals ≥18 years of age with chronic asthma currently receiving ICS	N=190 6 weeks	Primary: PEFR Secondary: Symptom scores, use of rescue inhaler, FEV_1 and patient and physician assessment of efficacy	Primary: The mean morning PEFR improved by 33 L/minute in the salmeterol group compared to 4 L/minute in the albuterol group at the conclusion of the study (*P*<0.001). There was a significant reduction in diurnal variation in the salmeterol group, from 39 to 22 L/minute compared to the albuterol group with a change from 34 to 37 L/minute (*P*<0.001). Secondary: Salmeterol increased FEV_1 after three and six weeks compared to baseline significantly more than albuterol (*P*<0.05 for both weeks). There was a significant improvement in symptom-free nights in the salmeterol group compared to the albuterol group *(P*<0.001); however, there was no significant difference in symptom-free days.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no difference in the number of rescue-free days between the groups; however, there was an increase in percent of rescue-free nights in the salmeterol group (*P*<0.04).
Vervloet et al[51] Salmeterol 50 µg BID via DPI vs formoterol 12 µg BID via DPI	MC, OL, PG, RCT Patients ≥18 years of age with moderate to severe reversible obstructive airway disease for ≥1 year and currently using regular ICS (no attempt was made to exclude patients with COPD)	N=482 6 months	Primary: Mean morning predose PEF during the last seven days of treatment Secondary: Mean morning and evening predose PEF during the last week before each clinic visit, overall mean morning and evening pre-dose PEF, day and night use of rescue medication and time symptoms score	Primary: The 95% CI for the treatment contrast formoterol minus salmeterol was -8.69, 9.84 L/minute during the last seven days of treatment and was included entirely in the predefined range of equivalence (*P* value not reported). Secondary: The estimated treatment contrasts showed a trend towards greater efficacy with formoterol over salmeterol for mean evening predose PEF, which became statistically significant at two, three and four months (*P*<0.05). Both treatments resulted in a mean decrease in rescue medication use to less than half compared to baseline and an improvement in mean symptom score but no significant difference between the groups was found (*P* value not reported). Both medications were found to be safe and well tolerated (*P* value not reported).
Condemi et al[52] Salmeterol 50 µg BID via DPI vs formoterol 12 µg BID via DPI	AC, MC, PG, OL Individuals 18 to 75 years of age with moderate to moderately severe asthma diagnosed at least 1 year prior and currently on ICS	N=528 6 months	Primary: Mean morning PEF measured five minutes after dosing Secondary: Mean morning and evening predose PEF, number of episode-free days, use and time of rescue medications, symptom score, overall mean	Primary: There was a significant increase in mean PEF values measured five minutes after dosing in patients receiving formoterol compared to salmeterol (393.4 vs 371.7 L/minute; *P*<0.001). Secondary: Individuals receiving formoterol reported using significantly fewer actuations of rescue medication/week within 30 minutes of dosing (1.4 vs 2.1; *P*<0.005), significantly fewer actuations between morning and evening doses (5.6 vs 7.7; *P*<0.03) and significantly fewer actuations between evening and morning doses (2.8 vs 4.2; *P*<0.03) all compared to salmeterol. Patients experienced significantly more episode free days in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			morning predose PEF and safety	formoterol group compared to the salmeterol group (9.5 vs 7.8; *P*<0.04). Mean morning predose PEF, mean evening predose PEF and nighttime or daytime symptom scores did not differ significantly between treatments (*P* value not reported).
Brambilla et al[53] Salmeterol 50 µg BID via DPI and as needed albuterol vs formoterol 12 µg BID via DPI and as needed albuterol vs as needed albuterol All patients continued to receive their ICS dose.	MC, OL, PG, RCT Patients ≥18 years of age with moderate to severe persistent asthma sub-optimally controlled on ICS with on demand albuterol with or without salmeterol	N=6,239 4 weeks	Primary: Difference in evening predose PEF between patients continued on salmeterol and these switched to formoterol Secondary: Morning predose PEF, daytime and nighttime asthma symptom score, use of rescue inhaler, and percent days with no asthma symptoms or albuterol use	Primary: A significant increase in mean evening predose PEF was seen in patients switched to formoterol from salmeterol or albuterol as needed compared to patients staying on salmeterol (402.9 vs 385.5 L/minute; *P*<0.001) and albuterol as needed (409.3 vs 385.0 L/minute; *P*<0.001). Secondary: In patients switched to formoterol compared to individuals who continued to receive salmeterol or on-demand albuterol, there was a significant increase in morning predose PEF, a significantly reduction in both daytime and nighttime asthma symptom score, a significant higher percent of symptom-free days, and a significant reduction in rescue medication use (all *P*<0.001). There was no significant difference in the incidence of adverse event between groups (*P* value not reported).
Martin et al[54] Salmeterol 42 µg two inhalations BID via DPI vs albuterol extended release tablets 4 mg in the morning and 8 mg in the evening	DB, DD, MC, RCT, XO Individuals 18 to 65 years of age with FEV_1 >50% and 12% improvement following inhaled albuterol	N=56 8 weeks	Primary: Morning peak flow, FEV_1 measurements Secondary: Nocturnal symptoms, nights without awakenings, rescue inhaler use, and safety	Primary: Improvements in PEF and FEV_1 were significantly improved in both groups (*P*<0.001) but did not differ significantly between groups (*P* value not reported). Secondary: A comparison of the adjusted treatment means for the percentage of nights without awakenings demonstrated a significant improvement with salmeterol compared to albuterol (84.6 vs 79.4; *P*=0.021). There was no statistical difference between the two groups concerning the percentage of patients who had no nocturnal awakenings (*P* value

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				not reported). A significant decrease in baseline puffs/day of a rescue inhaler was observed in both the salmeterol group (4.57 to 1.85; *P*<0.001) and the albuterol group (4.57 to 2.66; *P*<0.001). The decrease with salmeterol was significantly greater (*P*<0.001). Seventy eight percent of the patients treated with albuterol and 75.9% of patients treated with salmeterol listed adverse event during the study (*P* value not reported).
Brambilla et al[55] Salmeterol 50 µg BID via DPI vs terbutaline sustained release 5 mg tablets BID	DB, DD, MC, PG, RCT Individuals 18 to 67 years of age suffering from chronic asthma with >15% reversibility after inhaled albuterol	N=159 2 weeks	Primary: Number of awakening-free nights over the last week of treatment Secondary: Morning PEF, evening PEF, PEF diurnal variations, and nocturnal and diurnal rescue albuterol intake	Primary: In the salmeterol group the mean number of awakening-free nights over the last week of treatment was significantly higher compared to the terbutaline group (5.3 vs 4.6; *P*=0.006). Secondary: No significant difference was found concerning the mean evening PEF; however, salmeterol was more efficacious than terbutaline on morning PEF (*P*=0.04) and PEF daily variations (*P*=0.01). A significantly greater percent of individuals in the salmeterol group compared to the terbutaline group stopped using rescue albuterol during the day (30 vs 9%; *P*=0.004); however, there was no significant difference at night (*P* value not reported). Significantly fewer patients in the albuterol group reported adverse events (16 vs 29%; *P*=0.04).
Estelle et al[56] Salmeterol 50 µg BID via DPI vs beclomethasone 200 µg BID via DPI	DB, PC, PG, RCT Individuals 6 to 14 years of age with stable asthma	N=241 56 weeks	Primary: Airway hyper-responsiveness Secondary: PEF, rescue inhaler use, and adverse event	Primary: During months one to two of the study, there was significantly less airway hyperresponsiveness with beclomethasone compared to salmeterol (*P*=0.003) or placebo (*P*<0.001); however, this difference was lost two weeks after discontinuation of treatment. Secondary: In the beclomethasone group, the PEF varied significantly less when compared to the salmeterol and placebo groups (*P*=0.002 or *P*=0.02)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				with the similar effects seen with beclomethasone and salmeterol. Compared to the placebo group, individuals receiving beclomethasone required significantly less rescue medication and had fewer withdrawals due to exacerbations (*P*<0.001 or *P*=0.03); however, the difference between salmeterol and placebo was not significant (*P* value not reported). Height in the beclomethasone-treated children increased by 3.96 cm during months one to 12, which was significantly less than the height increase in the placebo-treated children (5.04 cm; *P*=0.018) and the salmeterol-treated children (5.40 cm; *P*=0.004).
Lazarus et al[57] Salmeterol 42 µg BID via MDI vs triamcinolone 400 µg BID via MDI vs placebo	DB, MC, PC, PG, RCT Individuals 12 to 65 years of age with persistent asthma	N=164 28 weeks	Primary: Change in morning PEF from the final week of the run in period to the final week of treatment Secondary: FEV_1, asthma symptom scores, rescue albuterol use, QoL scores, and number of exacerbations	Primary: No significant difference in morning PEF measures was seen between the groups; however, they were both more effective compared to placebo (*P* values not reported). Secondary: There was no significant difference between the salmeterol and triamcinolone groups in terms of asthma symptom scores, rescue inhaler use, or QoL; both treatment arms were more effective compared to placebo in these categories (*P* values not reported). There were significantly more group treatment failures in the salmeterol group than the triamcinolone group (25 vs 6%; *P*=0.004) as well as more exacerbations (20 vs 7%; *P*=0.04).
Tattersfield et al[58] Terbutaline 0.5 mg as needed via DPI vs formoterol 4.5 µg as needed via DPI	DB, PG, RCT Patients ≥18 years of age with asthma for ≥6 months and treated with a constant dose of ICS	N=362 12 weeks	Primary: Time to first severe exacerbation Secondary: Morning and evening peak flow rate, FEV_1, symptoms, number of inhalations of	Primary: In the formoterol group, patients experienced a longer time to the first severe exacerbation than in the terbutaline group (*P*=0.013) with the relative risk ratio for having an exacerbation first in the formoterol group compared to the terbutaline group of 0.55. Secondary: No significant difference was seen between the groups concerning daytime or nighttime symptoms (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			relief medication and safety	It was documented that pre-bronchodilator FEV_1 was greater in the formoterol group than the terbutaline group (*P* value not reported). Both groups experienced a decrease in rescue inhalations but it was to a greater extent in the formoterol group (1.15 vs 0.40; *P* value not reported).
Hermansson et al[59] Terbutaline 500 µg QID via DPI vs salmeterol 50 µg BID via DPI	MC, OL, PG, RCT Patients ≥18 years of age with mild to moderate asthma	N=243 4 weeks	Primary: Morning, evening and diurnal PEF, daytime and nighttime symptoms, use of rescue inhaler and FEV_1 Secondary: Not reported	Primary: Over four weeks, salmeterol produced significant improvements over terbutaline in morning and evening PEF and diurnal variation (*P*<0.001, *P*=0.045 and *P*<0.001). After four weeks there was a statistically significant difference in favor of the salmeterol group in daytime and nighttime asthma score, and percent of days and nights when a rescue medication was needed (*P*<0.001, *P*=0.008, *P*=0.002 and *P*=0.007). After four weeks of treatment there were no significant differences in FEV_1 or FVC between the two groups (*P*=0.598 and *P*=0.916). Secondary: Not reported
Hancox et al[60] Terbutaline 1,000 µg QID via DPI vs budesonide 400 µg BID via DPI vs terbutaline 1,000 µg QID and budesonide 400 µg BID via DPI	PC, RCT, XO Individuals 9 to 64 years of age with mild to moderate asthma with documented hyper-responsiveness	N=61 24 weeks	Primary: A rank order of treatment from worst [1] to best [4], and period of asthma control for each subject Secondary: PEF, nocturnal and daytime symptoms, use of rescue medication and compliance	Primary: Combined treatment was ranked significantly higher than each individual treatment and placebo (*P*<0.0001, *P*<0.0001 and *P*<0.01), budesonide ranked higher than placebo (*P*=0.025), and there was no significant difference between budesonide and terbutaline or terbutaline and placebo. Secondary: Mean morning peak flow was higher during combined treatment than budesonide alone (*P*<0.02), and both the combined treatment and budesonide were higher than either placebo or terbutaline (*P*<0.01). Mean evening peak flow was higher with all treatments (*P*<0.0003) and was higher with the combined treatment than either active medication alone (*P*<0.0002). No significant difference was seen between the two

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				active medications alone. Nocturnal awakenings and percent of days during which wheeze was reported were reduced significantly in all treatment groups compared to placebo (*P*<0.0001 and *P*<0.001), but did not differ significantly between the groups. Rescue inhaler use significantly decreased in all groups compared to placebo (*P*<0.001), but did not differ significantly between the groups. The self-reported compliance was above 90% for all groups and did not differ significantly (*P* value not reported).
Chronic Obstructive Pulmonary Disease				
Spencer et al[61] ICS/LABA combination treatment vs ICS alone Vs LABA alone	MA (7 RCT) Randomized controlled trials comparing ICS and LABA in the treatment of patients with stable COPD	N=5,997 6 months to 3 years	Primary: Moderate or severe exacerbations, hospitalization due to exacerbations and incidence of pneumonia Secondary: All-cause mortality, mild exacerbations, changes in FEV_1, QoL, symptom scores of breathlessness, rescue medication use, all cause hospitalizations and discontinuation rates	Primary: There was no difference in the rate of moderate or severe COPD exacerbations between ICS and LABA monotherapy use (RR, 0.96; 95% CI, 0.89 to 1.02). Moreover, there was no significant difference in the exacerbation risk between studies lasting more or less than one year (*P*=0.75). Exacerbations leading to hospitalizations were only reported in a single trial which showed that there was no significant difference in the risk of hospitalization due to exacerbation between treatment with fluticasone and salmeterol (RR, 1.07; 95% CI 0.91 to 1.26). Overall, there was an increased risk of pneumonia associated with ICS treatment compared to LABA (OR, 1.38; 95% CI 1.10 to 1.73; *P*=0.005). Specifically, there was an increased risk of pneumonia in patients treated with fluticasone compared to salmeterol (OR, 1.43; 95% CI, 1.13 to 1.81; *P*=0.003). There was no difference in the risk of developing pneumonia with budesonide compared to formoterol (OR, 0.84; 95% CI, 0.36 to 1.96; *P*=0.68). Secondary: The pooled result showed that there was no significant difference in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mortality rates between treatment with an ICS or LABA (OR, 0.98; 95% CI 0.59 to 1.64). Mild exacerbation rates were not significantly different between patients treated with an ICS or LABA (OR, 1.63; 95% CI, 0.49 to 5.39). There was no difference in the increase in FEV_1 with ICS compared to LABA treatment (mean difference, -17.36; 95% CI, -39.54 to 4.82). Patients treated with an ICS showed greater improvements in QoL compared to those treated with LABA (mean difference, -0.74; 95% CI, -1.42 to -0.06). This difference was small in relation to the threshold of four units for a clinically significant difference. There was no statistically significant difference between ICS and LABA using the four point dyspnea scale. There was no difference in the use of rescue medication during the treatment period with formoterol compared to ICS (mean difference, 0.56 puffs/24 h; 95% CI, 0.10 to 1.02). None of the included studies reported the number of patients admitted to hospital for any cause. There was no significant difference in the number of patients discontinuing therapy between patients on ICS and LABA (OR, 1.02; 95% CI, 0.92 to 1.14). Moreover, no statistically significant differences between fluticasone vs salmeterol (OR, 1.05; 95% CI, 0.92 to 1.18) and budesonide vs formoterol (OR, 0.96; 95% CI, 0.76 to 1.20) were observed.
Hanania et al[62] (abstract) Arformoterol 15 µg BID via nebulizer	DB, DD, MC, RCT Patients with COPD	N=443 6 months	Primary: Post-treatment adverse events, COPD exacerbations,	Primary: The proportion of patients with post-treatment adverse events in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 67.8, 76.2 and 66.7% respectively (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs arformoterol 25 µg BID via nebulizer vs formoterol 12 µg BID via DPI			pulmonary function, dyspnea, use of rescue SABAs and ipratropium, SGRQ Secondary: Not reported	The proportion of patients with COPD exacerbation in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 32.2, 30.6 and 22.4% respectively (*P* value not reported). Pulmonary function improved for all groups and was maintained throughout the study. The mean change from baseline in peak FEV_1 in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 0.30, 0.34 and 0.26 L respectively (*P* value not reported). The mean change from baseline in mean 24 hour trough FEV_1 in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 0.10 L, 0.14 L and 0.09 L respectively (*P* value not reported). The mean change from baseline in respiratory capacity in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 0.20, 0.37 and 0.23 L respectively (*P* value not reported). Dyspnea and use of rescue SABAs and ipratropium improved in all treatment groups. Health status as measured by the SGRQ improved in all treatment groups. Secondary: Not reported
Baumgartner et al[63] Arformoterol 15 µg BID via nebulizer vs arformoterol 25 µg BID via nebulizer	DB, MC, PC, RCT Patients ≥35 years of age with COPD and FEV_1 ≤65% predicted and >0.70 L, with Medical Research Council Dyspnea	N=717 12 weeks	Primary: Mean percentage change from baseline in morning trough FEV_1 averaged over 12-weeks Secondary:	Primary: Patients taking all three doses of arformoterol and salmeterol experienced statistically significant improvements in morning trough FEV_1 throughout 12 weeks of daily treatment compared to placebo (*P*<0.001). Secondary: Arformoterol 15 µg demonstrated significantly greater improvement in the percent change from pre-dose in the 12-hour FEV_1 $AUC_{0\text{-}12\ h}$

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs arformoterol 50 µg QD via nebulizer vs salmeterol 42 µg BID via MDI vs placebo Patients were allowed to use albuterol MDI as a rescue therapy and ipratropium MDI as a supplemental medication as needed.	Scale Score ≥2, an FEV_1/FVC ratio ≤70%, and a minimum smoking history of 15 pack-years at baseline		Percent change from baseline in FEV_1 AUC_{0-12}	compared to placebo (P<0.001). Greater improvement in FEV_1 AUC_{0-12} was also observed for the arformoterol group compared to the salmeterol group over the 12 week period (P<0.024). Compared to the 15 µg dose, higher doses did not provide sufficient additional benefit to support their use. Adverse events of the three doses of arformoterol were similar compared to salmeterol and placebo. The most serious adverse events were of respiratory and cardiovascular in nature.
Data on file[64] Arformoterol 15 µg BID via nebulizer vs arformoterol 25 µg BID via nebulizer vs arformoterol 50 µg QD via nebulizer	DB, PC, MC, RCT Patients ≥35 years of age with of COPD and FEV_1 ≤65% predicted and >0.70 L, with Medical Research Council Dyspnea Scale Score ≥2, an FEV_1/FVC ratio ≤70%, and a minimum smoking history of 15 pack-years at baseline	N=739 12 weeks	Primary: Mean percentage change from baseline in morning trough FEV_1 averaged over 12-weeks Secondary: Percent change from baseline in 12-hour FEV_1 AUC_{0-12}	Primary: Patients taking arformoterol and salmeterol experienced statistically significant improvements in morning trough FEV_1 throughout 12 weeks of daily treatment (P<0.001). Secondary: Arformoterol 15 µg demonstrated significantly greater improvement in the percent change from predose in the 12 hour FEV_1 $AUC_{0-12\ h}$ compared to placebo (P<0.001). Adverse events of the three doses of arformoterol were similar compared to salmeterol and placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs salmeterol 42 µg BID via MDI vs placebo Patients were allowed to use albuterol MDI as a rescue therapy and ipratropium MDI as a supplemental medication as needed.				
Benhamou et al[65] Formoterol 24 µg via DPI vs albuterol 400 µg via DPI vs placebo	DB, PC, RCT, XO Individuals 40 to 75 years of age with stable, reversible COPD	N=25 1 dose	Primary: AUC (zero to 30 minutes) of FEV_1 in one minute Secondary: AUC (zero to one hour) of FEV_1 in one minute, AUC (zero to three hours) of FEV_1 in one minute, maximal change in FEV_1 a percent of predicted value	Primary: There were no significant differences between formoterol (5.89) and salmeterol (6.06) in the primary endpoint, but both were statistically higher than placebo (*P*<0.0001). Secondary: There were no statistically significant differences between the two active medication groups in secondary endpoints, and each had a similar onset (five minutes; *P* value not reported). No serious adverse events or clinically relevant changes in vital sign were observed in any of the groups (*P* value not reported).
Cote et al[66] Formoterol 12 µg BID via DPI vs	AC, MC, OL, PG, RCT Patients ≥40 years of age who were current or previous smokers (>10	N=270 28 days	Primary: Change from baseline in FEV_1 five minutes postdose on day 28 Secondary:	Primary: Changes from baseline in FEV_1 at five minutes postdose on day 28 favored treatment with formoterol over salmeterol (0.13 vs 0.07 L; *P*=0.022). Secondary: Changes from baseline in FEV_1 on day 28 were significantly greater with

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salmeterol 50 µg BID via MDI	pack-years) with COPD, a prebronchodilator FEV_1 >35% of predicted normal, an FEV_1 ≤70% of FVC		Changes from baseline in FEV_1 at 30 and 60 minutes postdose on day 28, in distance walked in the 6MWT on day 28, and changes in Borg scores for perception of breathlessness after 6MWT	formoterol compared to salmeterol at 30 and 60 minutes postdose (*P*<0.001 and *P*=0.069, respectively). There was no difference between formoterol and salmeterol in regard to the change from baseline in distance walked during the 6MWT (65.2 vs 48.1 feet, respectively; *P*=0.412). There was no difference in Borg dyspnea scores after the 6MWT for patients who received formoterol or salmeterol (*P* value not reported).
Cazzola et al[67] Formoterol 12 µg, 12, and 24 µg via DPI vs albuterol 200 µg, 200, and 400 µg via MDI Doses administered on two consecutive days.	RCT, SB, XO Patients 51 to 77 years of age with COPD, having an acute exacerbation defined as sustained worsening of the condition from stable and beyond normal day-to-day variations, FEV_1 <70% of personal best that is acute in onset and necessitating a change in the medication regimen	N=16 2 days	Primary: Maximum FEV_1 value during the dose-response curve Secondary: Spirometric data (inspiratory capacity and FVC), pulse rate, SpO_2 values	Primary and Secondary: There was a significant increase in FEV_1, inspiratory capacity, and FVC in both the albuterol and formoterol groups compared to baseline after 48 µg of formoterol and 800 µg of albuterol (*P*<0.05). There was no significant difference between FEV_1, inspiratory capacity, and FVC values in the formoterol group compared to the albuterol group after 48 µg of formoterol and 800 µg of albuterol. There was a significant increase in FEV_1 values after 24 µg of formoterol compared to 48 µg of formoterol (*P*=0.022). There was no significant difference in pulse rate or SpO_2 values compared to baseline after 48 µg of formoterol or 800 µg of albuterol (*P*>0.05). SpO_2 values decreased below 90% in two patients after the highest dose of formoterol and in one patient after the highest dose of albuterol. The clinical significance of this finding was not reported.
Gross et al[68] Formoterol 20 µg via nebulizer vs	DB, MC, PC, PG, RCT Patients ≥40 years of age with COPD, a current or prior	N=351 12 weeks	Primary: Percent change from baseline in the standardized absolute AUC_{0-12} for FEV_1 measured	Primary: The percent change in from baseline in the standardized absolute AUC_{0-12} for FEV_1 measured over 12 hours following the morning dose at week 12 was significantly improved in the formoterol nebulizer group compared to the placebo group (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
formoterol 12 µg via DPI vs placebo	history of ≥10 pack-years of cigarette smoking, a post-bronchodilator FEV_1 30 to 70% of the predicted value, and a FEV_1/FVC ratio of <0.70		over 12 hours following the morning dose at week 12 Secondary: Change in the QoL from baseline in the total SGQR, symptom and impact scores, and rescue medication use	Peak FEV_1 remained higher in the formoterol nebulizer group compared to the placebo group throughout the study, with the least square mean difference of 0.247 L at week 12 (95% CI, 0.174 to 0.320; *P*<0.0001). The formoterol nebulizer group had similar results to the formoterol DPI group in FEV_1 AUC_{0-12}, 12-hour FEV_1 measurements, peak FEV_1, trough FEV_1, and FVC across all clinic visits. There were no statistically significant differences between the groups (*P* value not reported). Secondary: The formoterol nebulizer group demonstrated statistically significant improvements from baseline in the total SGRQ, symptom and impact scores compared to the placebo group (*P*≤0.03). There were no statistically significant differences between the formoterol nebulizer group and the formoterol DPI group in the total SGRQ or component scores (*P* value not reported). Albuterol use remained consistent throughout the study for the placebo group. There was a 42% decrease in albuterol use in the formoterol nebulizer group during the first assessment period, which was maintained throughout the study. The formoterol DPI group had similar results to the formoterol nebulizer group. Over half of the patients enrolled in the study reported at least one adverse event. The overall incidence of adverse events was similar across the treatment groups. The most commonly reported adverse events were headache, nausea, diarrhea and COPD exacerbation.
Sutherland et al[69] (abstract) Formoterol 20 µg BID via nebulizer vs ipratropium/albuterol MDI	OL, RCT, XO Patients with COPD	N=109 5 weeks	Primary: Morning pre-dose FEV_1 trough Secondary: Post-dose efficacy at six hours, patient satisfaction, patient perception of	Primary: Morning pre-dose FEV_1 was significantly improved in the formoterol group compared to the ipratropium/albuterol group (*P*=0.0015). Secondary: Post-dose efficacy at six hours was maintained in the formoterol group compared to the ipratropium/albuterol group (*P*≤0.0001). Patient satisfaction and perception of disease control were significantly

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			disease control, and dyspnea	greater in the formoterol group among older, male and more severe subgroups (*P* value not reported). Both groups resulted in meaningful changes in dyspnea but no significant differences between groups were observed.
Datta et al[70] Levalbuterol 1.25 mg via nebulizer vs albuterol 2.5 mg via nebulizer vs albuterol/ipratropium 2.5/0.5 mg via nebulizer vs placebo	DB, RCT, XO Patients with COPD, FEV_1 45 to 75% of predicted value, FEV_1/FVC ratio of <0.70, stable disease (absence of clinical exacerbation and no change in COPD medications in previous month),	N=30 4 days	Primary: FEV_1 Secondary: FVC, pulse rate, oxygen saturation (measured by pulse oximetry), hand tremor (rating scale zero to seven, rated by same blinded investigator for all patients)	Primary: Mean change in FEV_1 from baseline increased significantly in all three active groups compared to placebo at 0.5 hours and persisted at one hour (*P*<0.05). At two hours, only the albuterol/ipratropium group had a mean change in FEV_1 that was significantly better than placebo (*P*=0.04). This effect persisted at three hours for the albuterol/ipratropium group (*P*<0.05). There were no significant differences between active groups at any time during the study (*P* value not reported). The percentage of patients in exhibiting a positive bronchodilator response (defined as both a >12% increase and a 0.20 L increase in FEV_1) was significantly increased in all three active groups compared to placebo at 0.5 hours ($P \leq 0.03$) and one hour ($P \leq 0.03$). The percentage of patients in exhibiting a positive bronchodilator response at two and three hours was only significant compared to placebo in the albuterol/ipratropium group (*P*=0.03 at two hours and *P*=0.003 at three hours). Between-group comparisons were not reported. Secondary: All three active groups led to significant improvements in FVC compared to placebo at 0.5 hours (*P*<0.05) but remained significant at one hour only for the albuterol/ipratropium group (*P*<0.05). No significant differences between active treatment groups and placebo were noted from two hours on (*P* values not reported). Differences in FVC between active groups were similar (*P* values not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reported). Significant increases in pulse rate compared to placebo were noted at 0.5 hours in the albuterol and levalbuterol groups (*P*<0.01) but no differences were noted at one hour and beyond. No significant changes in oxygen saturation were noted in any group compared to placebo (*P* values not reported). No significant differences in hand tremor noted between groups (*P* values not reported).
Hanania et al[71] Fluticasone 250 µg BID via DPI vs salmeterol 50 µg BID via DPI vs fluticasone/salmeterol 250/50 µg BID via DPI vs placebo	DB, MC, PC, RCT Patients 40 to 87 years of age, current or former smokers with ≥20 pack year history, diagnosed with COPD, with an FEV_1/FVC ratio of ≤70%, baseline FEV_1 of <65% predicted normal value but >0.70 L (or if ≤0.70 L, then >40% predicted)	N=723 24 weeks	Primary: Morning pre-dose FEV_1 and two hour post-dose FEV_1 Secondary: Morning PEF values, TDI, CRDQ, CBSQ, exacerbations, and supplemental albuterol use	Primary: There was a statistically significant increase in pre-dose FEV_1 in the fluticasone/ salmeterol group compared to the salmeterol (*P*=0.012) and placebo (*P*<0.001) groups. No significant difference between the fluticasone/ salmeterol group and fluticasone group was noted. There was a statistically significant increase in two hour post-dose FEV_1 in the fluticasone/ salmeterol group compared to the salmeterol group (*P*<0.001), the placebo group (*P*<0.001) and the fluticasone group (*P*≤0.048). Secondary: There was a statistically significant increase in morning PEF values in the fluticasone/salmeterol group compared to the salmeterol group, placebo group, and fluticasone group (*P*≤0.034), though improvements were also seen from baseline in the salmeterol and fluticasone monotherapy groups (*P*<0.001). Statistically significant improvements in TDI occurred in the fluticasone/salmeterol group (*P*=0.023) compared to placebo, in addition to improvements in the fluticasone (*P*=0.057) and salmeterol (*P*=0.043) monotherapy groups compared to placebo. There was a statistically significant reduction in supplemental albuterol use in the fluticasone/salmeterol group compared to the fluticasone

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				monotherapy group (*P*=0.036) and placebo (*P*=0.002). There was a numerical reduction in supplemental albuterol use in the fluticasone/ salmeterol group compared to the salmeterol monotherapy group. There was a statistically significant increase in CRDQ scores in the fluticasone/ salmeterol group compared to placebo (*P*=0.006). There was a statistically significant increase in CRDQ scores in the fluticasone monotherapy group compared to placebo (*P*=0.002). There were a statistically significant increases in CBSQ scores in the fluticasone/salmeterol group and the fluticasone monotherapy group compared to placebo (*P*≤0.017).
Vogelmeier et al[72] Salmeterol 50 µg BID vs tiotropium 18 µg QD Patients receiving a fixed-dose ICS/LABA were instructed to switch to inhaled glucocorticoid monotherapy at the start of the treatment phase of the study. Patients were allowed to continue their usual medications for COPD, except for anticholinergic drugs and LABA, during the double-blind treatment phase.	AC, DB, DD, MC, PG, RCT Patients ≥40 years of age with a smoking history of ≥10 pack-years, a diagnosis of COPD with a FEV_1 after bronchodilation of ≤70% of the predicted value, a FEV_1/FVC ratio of ≤70%, and a documented history of ≥1 exacerbation leading to treatment with systemic glucocorticoids or	N=7,384 1 year	Primary: Time to the first exacerbation of COPD Secondary: Time-to-event end points, number-of-event end points, serious adverse events and death	Primary: Tiotropium increased the time to first exacerbation by 42 days compared to salmeterol (187 vs 145 days, [time until at least 25% of the patients had a first exacerbation]), resulting in a 17% reduction the risk of exacerbations with tiotropium (HR, 0.83; 95% CI, 0.77 to 0.90; *P*<0.001). Of note, less than 50% percent of patients experienced a COPD exacerbation; therefore it was not possible to calculate the median time to first exacerbation in this population. Secondary: Compared to salmeterol, treatment with tiotropium significantly reduced the risk of moderate exacerbations by 14% (HR, 0.86; 95% CI, 0.79 to 0.93; *P*<0.001) and of severe exacerbations by 28% (HR, 0.72; 95% CI, 0.61 to 0.85; *P*<0.001). Tiotropium reduced the risk of exacerbations leading to treatment with systemic glucocorticoids by 23% (HR, 0.77; 95% CI, 0.69 to 0.85; *P*<0.001), exacerbations leading to treatment with antibiotics by 15% (HR, 0.85; 95% CI, 0.78 to 0.92; *P*<0.001), and exacerbations leading to treatment with both systemic glucocorticoids and antibiotics by 24% (HR, 0.76; 95% CI, 0.68 to 0.86; *P*<0.001).

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	antibiotics or hospitalization within the previous year			The annual rate of exacerbations was 0.64 in the tiotropium group and 0.72 in the salmeterol group, representing a 11% reduction in the exacerbation rate with tiotropium (RR, 0.89; 95% CI, 0.83 to 0.96; *P*=0.002). Treatment with tiotropium significantly reduced the annual rate of moderate exacerbations by 7% (0.54 vs 0.59; RR, 0.93; 95% CI, 0.86 to 1.00; *P*=0.048) and the annual rate of severe exacerbations by 27% (0.09 vs 0.13; RR, 0.73; 95% CI, 0.66 to 0.82; *P*<0.001). The incidence of a serious adverse event was 14.7% compared to 16.5% in the tiotropium and salmeterol groups, respectively. The most common serious adverse event was COPD exacerbation. There were 64 exacerbations in the tiotropium group and 78 in the salmeterol group during the treatment period (HR for tiotropium, 0.81; 95% CI, 0.58 to 1.13).
Feldman et al[73] INLIGHT-1 Indacaterol 150 µg QD vs placebo Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was provided for use as needed.	DB, MC, PC, PG, RCT Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%	N=416 12 weeks	Primary: Trough FEV_1 at 12 weeks Secondary: Trough FEV_1 after one dose and at day 29, peak FEV_1 at day 1 and week 12, FEV_1 AUC five minutes to four hours, five minutes to one hour and one hour to hours after last dose at 12 weeks	Primary: Trough FEV_1 at 12 weeks was significantly higher with indacaterol compared to placebo, with a least-squares mean (±SEM) difference of 130±24 mL (*P*<0.001). Secondary: Indacaterol achieved significantly higher 24 hour post dose trough FEV_1 after the first dose, with a least-squares mean difference from placebo of 80±19 mL (*P*<0.001). Similar results were observed at day 29 (difference, 140±24 mL; *P*<0.001). Indacaterol achieved a significantly higher peak FEV_1 compared to placebo at day one and week 12, with mean differences of 190±28 mL (*P*<0.001) and 160±28 mL (*P*<0.001), respectively. The FEV_1 AUC measurements after 12 weeks were all significantly higher with indacaterol compared to placebo, with mean differences of 170±24, 180±24 and 170±24 mL, respectively (*P*<0.001 for all).
To et al[74] Indacaterol 150 µg QD	DB, PC, PG, RCT Patients ≥40 years	N=347 12 weeks	Primary: Trough FEV_1, TDI, SGRQ at week 12	Primary: Of the patients included, 59.7% had moderate, and 40.3% had severe COPD. Trough FEV_1 at week 12 was 0.19 L and 0.20 L in moderate

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs indacaterol 300 µg QD vs placebo	of age with moderate or severe COPD, a smoking history of ≥20 pack years, post-bronchodilator FEV_1 <80% and ≥30% predicted and FEV_1/FVC <70%		Secondary: Adverse events	COPD with indacaterol 150 and 300 µg, respectively and 0.15 L and 0.19 L in severe COPD (*P*<0.001 for both subgroups vs placebo). All of the differences exceeded the pre-specified MCID of 0.12 L. TDI total scores for both indacaterol doses vs placebo in both subgroups were statistically significant and clinically meaningful (at least one unit; *P*<0.05). The difference from placebo in SGRQ total score at week 12 exceeded the MCID of four units (-4.3 and -4.2 units for indacaterol 150 µg and 300 µg, respectively) (*P*< 0.01 for both). Secondary: Adverse event incidences were comparable between the two strengths of indacaterol and placebo. Both strengths of indacaterol were found to be safe, efficacious in improving lung function and dyspnea.
Kornmann et al[75] INLIGHT-2 Indacaterol 150 µg QD vs salmeterol 50 µg BID vs placebo Permitted concomitant medications included ICS, if the dose and regimen were stable for 1 month prior to screening. Patients previously on LABA/ICS combination products were switched to	AC, DB, DD, MC, PC, PG, RCT Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%	N=1,002 26 weeks	Primary: Trough FEV_1 at 12 weeks compared to placebo Secondary: Trough FEV_1 at 12 weeks compared to salmeterol, FEV_1 at day two and weeks 12 and 26, health status, diary assessments, dyspnea and safety	Primary: Trough FEV_1 at 12 weeks was significantly higher with indacaterol compared to placebo (*P*<0.001). Secondary: Trough FEV_1 at 12 weeks was significantly higher with indacaterol compared to salmeterol (treatment difference, 60 mL; *P*<0.001). Similar results were observed at 26 weeks (treatment difference, 70 mL; *P*<0.001). Indacaterol maintained a clinically significant increase in FEV_1 over placebo during the course of the trial, with an increase from 130 mL at day two to 170 mL at week 12 and 180 mL at week 26 (*P*<0.001 for all). The difference between salmeterol and placebo was smaller and did not increase with length of treatment (120, 110 and 110 mL at day two, week 12 and week 26, respectively; *P*<0.001 for all). Indacaterol was "superior" at weeks 12 and 26 compared to salmeterol (*P*<0.001 for both). Both indacaterol (treatment difference, -3.6, -4.1, -6.3 and -5.0 at weeks four, eight, 12 and 26; *P*<0.001 for all) and salmeterol (-2.5, -3.6, -4.2 and -4.1; *P*<0.01 for all) significantly improved SGRQ total scores

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ICS monotherapy at an equivalent dose. Salbutamol was provided for use as needed.				compared to placebo, with the differences between indacaterol and salmeterol significantly favoring indacaterol at 12 weeks (*P*<0.05). The odds of indacaterol achieving a clinically important improvement from baseline in SGRQ total scores (at least four units) was significantly greater compared to salmeterol by 12 weeks (OR, 1.59; 95% CI, 1.12 to 2.25; *P*<0.01). The mean percentage days of poor COPD control over 26 weeks was 34.10% with both indacaterol and salmeterol compared to 38.10% with placebo (*P*=0.058 and *P*=0.057). Compared to patients receiving salmeterol, patients receiving indacaterol used less salbutamol, had higher morning PEF measurements and had more days when they were able to perform usual activities. Adjusted mean total TDI scores at weeks four, eight, 12 and 26 were significantly higher with salmeterol (*P*<0.05) and indacaterol (*P*<0.001) compared to placebo. The mean differences compared to placebo were numerically larger with indacaterol than with salmeterol, with significance achieved at weeks four (0.95 vs 0.55; *P*<0.05) and 12 (1.45 vs 0.90; *P*<0.05). Patients receiving indacaterol were more likely to achieve a clinically important improvement from baseline in TDI total scores at all time points compared to patients receiving placebo (*P*<0.001 for all). The odds of this occurring with salmeterol compared to placebo only reached significance at weeks 12 and 26 (*P*≤0.001). The most commonly reported adverse events were COPD worsening, nasopharyngitis, upper and lower respiratory tract infections and back pain. The proportions of patients experiencing serious adverse events were similar among the treatments (8.8, 5.7 and 7.8%).
Dahl et al[76] INVOLVE Indacaterol 300 µg QD vs	DB, DD, PC, PG, RCT Patients ≥40 years of age with moderate to severe COPD,	N=129 1 year	Primary: Trough FEV_1 at 12 weeks Secondary: Days of poor COPD control, SGRQ	Primary: Trough FEV_1 at week 12 with both indacaterol doses was significantly higher compared to placebo (treatment difference, 170 mL; *P*<0.001) and formoterol (treatment difference, 100 mL; *P*<0.001). Over the remainder of the trial, improvements with indacaterol compared to placebo were maintained at a similar level, while the difference between formoterol and placebo diminished.

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indacaterol 600 µg QD vs formoterol 12 µg BID vs placebo Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was provided for use as needed. Other bronchodilators or ICSs were not allowed unless to treat a COPD exacerbation.	smoking history ≥20 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%		score, time to first exacerbation, spirometry, TDI score, exacerbation rates, BODE index, safety	Secondary: Both doses of indacaterol were significantly "superior" to placebo in decreasing the number of days of poor COPD control (treatment difference, -4.7; 95% CI, -8.4 to -1.0; *P*<0.05 and -8.3; 95% CI, -12.0 to -4.6; *P*<0.001). Formoterol was also significantly "superior" to placebo (-4.8; 95% CI, -8.5 to -1.1; *P*<0.05). Both doses of indacaterol were significantly "superior" to placebo in improving SGRQ scores at weeks 12 (treatment difference, -3.8; 95% CI, -5.6 to -2.1 and -4.1; 95% CI, -5.9 to -2.3; *P*<0.001 for both) and 52 (-4.7; 95% CI, -6.7 to -2.7 and -4.6; 95% CI, -6.6 to -2.6; *P*<0.001 for both). Formoterol was also significantly "superior" to placebo (-3.2; 95% CI, -5.0 to -1.5 and -4.0; 95% CI, -6.0 to -2.0; *P*<0.001 for both). There were too few events to calculate COPD exacerbation free time; however, both doses of indacaterol were significantly "superior" to placebo in improving the time to first COPD exacerbation (HR, 0.77; 95% CI, 0.606 to 0.975 and HR, 0.69; 95% CI, 0.538 to 0.882; *P*<0.05 for both). Formoterol was also significantly "superior" to placebo (HR, 0.77; 95% CI, 0.605 to 0.981; *P*<0.05). Both doses of indacaterol were significantly "superior" to placebo in improving change from baseline in morning and evening PEF (treatment difference, 28.3; 95% CI, 22.8 to 33.8; and 31.1; 95% CI, 25.6 to 36.7; *P*<0.001 for both [morning PEF], and 24.6; 95% CI, 19.2 to 30.1; and 28.3; 95% CI, 22.8 to 33.8; *P*<0.001 for both [evening PEF]). Formoterol achieved similar results (*P*<0.001 for both), and both doses of indacaterol were significantly "superior" to formoterol (*P*<0.001 for all comparisons). Both doses of indacaterol were significantly "superior" to placebo in improving TDI scores at week 12 (treatment difference, 1.17; 95% CI, 0.76 to 1.58 and 1.13; 95% CI, 0.71 to 1.54; *P*<0.001 for both) and week 52 (1.00; 95% CI, 0.53 to 1.47 and 0.98; 95% CI, 0.51 to 1.46; *P*<0.001 for both). Formoterol was also significantly "superior" to placebo (0.72;

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				95% CI, 0.300 to 1.013; *P*<0.001 and 0.71; 95% CI, 0.24 to 1.19; *P*<0.01). After 12 weeks, both doses of indacaterol were significantly "superior" to formoterol (*P*<0.05 for both doses). Exacerbations occurred at a rate of 0.60 (rate ratio, 0.82; 95% CI, 0.63 to 1.06; *P* value not significant vs placebo), 0.57 (0.74; 95% CI, 0.56 to 0.97; *P*<0.05 vs placebo) 0.56 (0.75; 95% CI, 0.58 to 0.99; *P*<0.05 vs placebo) and 0.74 per year with indacaterol 300 µg, 600 µg, formoterol and placebo. Both doses of indacaterol were significantly "superior" to placebo (least-squares mean, 2.67 and 2.90) in improving the BODE index at week 12 (treatment difference, -0.40; 95% CI, -0.56 to -0.25; *P*<0.001 and -0.24; 95% CI, -0.40 to -0.08; *P*<0.01) and week 52 (-0.55; 95% CI, -0.73 to 0.37 and -0.49; 95% CI, -0.68 to -0.31; *P*<0.001 for both). Formoterol was also significantly "superior" to placebo (-0.28; 95% CI, -0.43 to -0.12 and -0.53; 95% CI, -0.72 to -0.35; *P*<0.001 for both). COPD worsening and nasopharyngitis were the only adverse events reported by >10% of patients with any treatment. Eight patients died during the trial and four died during follow up (two due to cardiac arrest [indacaterol 300 µg and placebo], one due to multiorgan failure [formoterol], one due to respiratory failure [formoterol] and four due to sudden death [one, formoterol; three, placebo]). Tremor was reported in 0.2, 1.9, 1.2 and 0.5% of patients, while tachycardia was reported in 0.9, 0.7, 0.5 and 1.2% of patients. Cough observed within five minutes of drug administration was observed in 19.1, 0.8 and 1.8% of patients receiving indacaterol, formoterol and placebo. (*P* values not reported).
Korn et al[77] INSIST Indacaterol 150 µg QD vs salmeterol 50 µg BID	DB, DD, MC, PG, RCT Patients ≥40 years of age with moderate to severe COPD, smoking history	N=1,123 12 weeks	Primary: Change in FEV_1 AUC from five minutes post dose to 11 hours and 45 minutes postdose at 12 weeks	Primary: FEV_1 AUC measurements at 12 weeks were significantly higher with indacaterol compared to salmeterol, with an adjusted mean difference of 57 mL (95% CI, 35 to 79; *P*<0.001). The mean (percent) changes from baseline for indacaterol and salmeterol were 0.19 (16.6%) and 0.13 L (11.4%), respectively. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Permitted concomitant medications included ICS, if the dose and regimen were stable for 1 month prior to screening. Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was provided for use as needed.	≥10 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%		Secondary: Trough FEV_1, FEV_1 AUC five minutes to four hours, five minutes to eight hours and eight to 11 hours at 12 weeks, FVC at 12 weeks; dyspnea; safety	Trough FEV_1 significantly favored indacaterol compared to salmeterol after 12 weeks, (adjusted mean difference, 60 mL; 95% CI, 37 to 83; *P*<0.001). Indacaterol maintained significance over salmeterol at all visits (*P*<0.001), except on day two (*P* value not significant). Results for other FEV_1 AUC measurements after 12 weeks all significantly favored indacaterol over salmeterol (*P*<0.001 for all). The adjusted mean differences were 0.06 (95% CI, 0.03 to 0.08), 0.05 (95% CI, 0.03 to 0.08) and 0.07 L (95% CI, 0.04 to 0.09). FEV_1 at week 12 with indacaterol was significantly higher compared to salmeterol at all time points (*P*<0.001 for all). At 12 weeks, FVC with indacaterol was significantly higher compared to salmeterol at all time points (*P* values not reported). With regards to dyspnea, TDI total scores with indacaterol were significantly "superior" compared to salmeterol after 12 weeks (adjusted mean difference, 0.63; 95% CI, 0.30 to 0.97; *P*<0.001). There was also a significantly greater proportion of patients receiving indacaterol that achieved a clinically important improvement from baseline (at least one point) in TDI total score (69.4 vs 62.7%; OR, 1.41; 95% CI, 1.07 to 1.85; *P*<0.05). Over the 12 weeks, the use of rescue salbutamol was significantly lower with indacaterol (mean difference, -0.18 puffs/day; 95% CI, -0.36 to 0.00; *P*<0.05) and patients had a greater proportion of days with no rescue medication use (mean difference, 4.4 days; 95% CI, 0.6 to 8.2; *P*<0.05). Overall incidences of adverse events were similar between the two treatments; at least one adverse event was reported by 33.8 and 33.5% of patients receiving indacaterol and salmeterol. The most frequently reported adverse events were COPD worsening (4.5 vs 5.7%) and headache (3.6 vs 3.6%). Overall, 3.6 and 2.8% of patients experienced a serious adverse event, with cardiac disorders being the most

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				frequently reported (1.1 vs 0.4%; *P* values not reported).
Magnussen et al[78] INPUT Indacaterol 300 µg QD in the AM vs indacaterol 300 µg QD in the PM vs salmeterol 50 µg BID vs placebo Patients were randomly assigned to one of 12 treatment sequences, each comprising 3 DB, 14 day treatment periods, with each treatment period separated by a 14 day washout period. In each treatment sequence, patients received 3 of the 4 treatments listed above. Permitted concomitant medications included ICS,	DB, DD, PC, RCT, XO Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%	N=96 12 weeks	Primary: Trough FEV_1 at 14 days Secondary: FEV_1 at individual time points on day one of each treatment period, trough FVC at 14 days, patient-reported symptom assessment and safety	Primary: Trough FEV_1 was significantly higher with indacaterol PM (treatment difference, 200 mL; *P*<0.001) and indacaterol AM (200 mL; *P*<0.001) compared to placebo. The difference between indacaterol PM and AM (10 mL) was not significant (*P* value not reported). Trough FEV_1 was significantly higher with indacaterol PM compared to the evening dose of salmeterol (*P*<0.001). No significant difference between indacaterol AM and the morning dose of salmeterol was observed (*P* value not significant). Secondary: For individual time point FEV_1 values on day one, all active treatments produced significantly higher measurements compared to placebo at all time points. At five minutes, the differences between indacaterol AM and indacaterol PM compared to placebo were 150 and 140 mL (*P*<0.001 for both). The FEV_1 with both indacaterol AM and indacaterol PM was numerically higher compared to salmeterol at all time points. Significance was observed between indacaterol AM and salmeterol at all time points until the second salmeterol dose was administered (*P* values not reported). Similar results were observed for trough FVC. Over 14 days of treatment, both indacaterol AM and indacaterol PM significantly improved the proportion of nights with no awakenings (*P*<0.001 and *P*<0.01), days with no daytime symptoms (*P*<0.05 for both) and days able to perform usual activities (*P*<0.05 for both) compared to placebo. Improvements in all of these analyses were consistently in favor of indacaterol over salmeterol, with the difference reaching significance for indacaterol PM analysis of proportion of nights with no awakenings (*P*<0.05). No differences were observed between the two indacaterol regimens. The overall incidence of adverse events was comparable between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
if the dose and regimen were stable for 1 month prior to screening.				treatments (25.0, 23.1, 19.1 and 20.6%), with most being of mild to moderate severity. Cough was the most frequently reported suspected drug-related adverse event with indacaterol (5.9 and 7.7% compared to 1.5 and 0.0% with salmeterol and placebo). Serious adverse events were reported in two patients receiving indacaterol; neither was suspected to be drug-related.
Balint et al[79] INSURE Indacaterol 150 or 300 µg, administered as a single dose vs salbutamol 200 µg, administered as a single dose vs salmeterol/fluticasone 50 /500 µg, administered as a single dose vs placebo Permitted concomitant medications included ICS, if the dose and regimen were stable for 1 month prior to screening. Patients previously on	DB, MC, RCT, XO Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%	N=89 5 single dose treatment periods, separated by a 4 to 7 day washout period	Primary: FEV_1 at five minutes compared to placebo Secondary: FEV_1 at five minutes compared to salbutamol and salmeterol/ fluticasone; FEV_1 at other scheduled time points; proportion of patients with ≥10, 12 and 15% increase in FEV_1 from baseline to each scheduled time point; proportion of patients with ≥12% and 200 mL increase in FEV_1 from baseline to each scheduled time point; safety	Primary: FEV_1 was significantly higher with both doses of indacaterol compared to placebo (treatment difference, 100 and 200 mL; *P*<0.001 for both). Secondary: FEV_1 at five minutes was numerically higher with both doses of indacaterol compared to salbutamol (treatment difference, 10 and 30 mL; *P* value not reported), and significantly higher compared to salmeterol/fluticasone (50 and 70 mL; *P*=0.003 and *P*<0.001). FEV_1 at all time points were significantly higher with both doses of indacaterol compared to placebo (*P*<0.001 for all) and compared to salmeterol/fluticasone at five and 15 minutes (*P*<0.05 for both). Indacaterol 300 µg achieved significantly higher measurements at 30 minutes (*P* value not reported) and two hours (*P*<0.001) compared to salbutamol. The proportion of patients with ≥10, 12 or 15% increase in FEV_1 from baseline at five minutes were significantly greater with both doses of indacaterol compared to salmeterol/fluticasone (*P*<0.01 for all), and similar to salbutamol (*P* values not significant). After 30 minutes proportions with both doses of indacaterol were significantly greater compared to placebo (*P*<0.001 for all); however, only indacaterol 300 µg achieved significance compared to salmeterol/fluticasone (*P*<0.01, *P*<0.01 and *P*<0.001). The proportion of patients with ≥12% and 200 mL increase in FEV_1 from baseline at five minutes with both doses of indacaterol and salbutamol were significantly greater compared to salmeterol/fluticasone and placebo (*P*<0.05 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. The following medications were excluded at any time during the trial (unless an arm of the study): long and short acting anticholinergics, LABA/ICS combination products, SABA/short acting anticholinergic combination products, other LABAs, SABAs, xanthine derivatives and parenteral or oral corticosteroids.				Overall, adverse events were reported in 3.5, 3.4, 4.7, 6.8 and 4.6% of patients, respectively. All reported adverse events were mild or moderate in severity and none were suspected of being drug-related. There were no serious adverse events reported.
Donohue et al[80] INHANCE Indacaterol 150 µg QD vs indacaterol 300 µg QD vs tiotropium 18 µg QD vs placebo	DB, PC, RCT Patients ≥40 years of age with moderate to severe COPD and a smoking history ≥20 pack years	N=1,683 26 weeks	Primary: Trough FEV_1 at 12 weeks compared to placebo Secondary: Trough FEV_1 at 12 weeks compared to tiotropium, FEV_1 at five minutes on day one, TDI, diary card-derived symptom variables, SGRQ, time to first COPD exacerbation and safety	Primary: The difference between both doses of indacaterol and placebo in trough FEV_1 was 180 mL, which exceeded the prespecified MCID of 120 mL (*P* value not reported). Secondary: The 40 to 50 mL differences between indacaterol 150 and 300 µg compared to tiotropium in trough FEV_1 were significant when tested for superiority ($P \leq 0.01$) and noninferiority ($P < 0.001$). FEV_1 at five minutes on day one was increased relative to placebo by 120 mL (95% CI, 100 to 140) with both doses of indacaterol and by 60 mL (95% CI, 30 to 80) with tiotropium ($P < 0.001$ for all vs placebo and for indacaterol vs tiotropium). TDI total scores significantly increased relative to placebo ($P < 0.001$ for all) at all assessments with both doses of indacaterol and after four, 12

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients randomized to tiotropium received OL treatment. Albuterol was permitted for use as needed.				and 16 weeks with tiotropium, with significant differences between indacaterol 300 µg and tiotropium after four, eight and 12 weeks (*P*<0.05 for all). Over the 26 weeks, the change from baseline in mean daily number of puffs of as needed albuterol was significantly reduced with both doses of indacaterol compared to placebo (*P*<0.001 for both). Both doses of indacaterol were significantly "superior" to tiotropium (*P*≤0.001 for both). The proportion of days with no use of as needed albuterol was significantly lower with both doses of indacaterol compared to placebo (*P*<0.001 for both) and tiotropium (*P*≤0.001). The changes in baseline in morning and evening PEF (L/minute) were significantly greater with both doses of indacaterol compared to placebo (*P*<0.001 for all) and tiotropium (morning; *P*≤0.001 for both, evening; *P*<0.05 and *P*<0.01). The proportion of nights with no awakenings (*P*<0.01 for both), days with no daytime symptoms (*P*<0.05 for both) and days able to perform usual activities (*P*<0.01 for both) were all significantly greater with both doses of indacaterol compared to placebo. SGRQ total scores improved relative to placebo with both doses of indacaterol at all assessments (*P*<0.01 for all) but not with tiotropium (*P* value not reported). Analysis of time to first COPD exacerbation showed a reduced risk compared to placebo with indacaterol 150 µg (HR, 0.69; 95% CI, 0.51 to 0.94; *P*=0.019). Nonsignificant reductions were observed with indacaterol 300 µg (HR, 0.74; 95% CI, 0.55 to 1.01; *P*=0.05) and tiotropium (HR, 0.76; 95% CI, 0.56 to 1.03; *P*=0.08) compared to placebo. The rate of cough as an adverse event did not differ across treatments. Cough within five minutes was observed in an average of 16.6 and 21.3% of patients were receiving indacaterol 150 and 300 µg, 0.8% of patients receiving tiotropium and 2.4% of patients receiving placebo (*P* values not reported). Otherwise, adverse events were similar across

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treatment.
Vogelmeir et al[81] INTIME Indacaterol 150 µg QD vs indacaterol 300 µg QD vs tiotropium 18 µg QD vs placebo Permitted concomitant medications included ICS, if the dose and regimen were stable for 1 month prior to screening. Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was allowed for use as needed.	DB, DD, PC, RCT, XO Patients ≥40 years of age with moderate to severe COPD, smoking history ≥10 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%	N=169 12 weeks	Primary: Trough FEV_1 at 14 days vs placebo Secondary: Trough FEV_1 at 12 weeks vs tiotropium, trough FEV_1 after the first dose, FEV_1 at individual time points after the first dose and on day 14, safety	Primary: Trough FEV_1 was significantly higher with both doses of indacaterol compared to placebo (treatment difference, 170 mL; 95% CI, 120 to 220 and 150 mL; 95% CI, 100 to 200; *P*<0.001). Secondary: Both doses of indacaterol not only met the criterion for noninferiority compared to tiotropium, but also achieved numerically higher values, with differences compared to tiotropium of 40 and 30 mL, respectively. The *P* value for the statistical comparison of superiority between indacaterol 150 µg and tiotropium was 0.043, with a mean difference of 50 mL; this did not meet the requirement for superiority. FEV_1 after the first dose was significantly higher with both doses of indacaterol compared to placebo (*P*< 0.001 for all). No differences were noted between indacaterol and tiotropium (*P* value not reported). At all time points on day one and after 14 days, all active treatments achieved significantly higher FEV_1 measurements compared to placebo (*P*<0.05 for all). Indacaterol 300 µg achieved higher measurements compared to tiotropium at all time points, while indacaterol 150 µg only achieved higher measurements at the majority of time points. Both doses of indacaterol had a fast onset of action on day one, achieving a significantly higher FEV_1 after five minutes compared to placebo (treatment difference, 120 and 130 mL, respectively; *P*<0.001 for both) and tiotropium (50 mL; *P*<0.004). The overall incidences of adverse events were similar across all treatments and were predominantly mild or moderate in severity including cough, COPD worsening and nasopharyngitis.
Buhl et al[82] INTENSITY Indacaterol 150 µg QD	DB, DD, MC, PG, RCT Patients ≥40 years	N=1,593 12 weeks	Primary: Trough FEV_1 at 12 weeks	Primary: Trough FEV_1 was 1.44 and 1.43 L with indacaterol and tiotropium, respectively (treatment difference, 0 mL; 95% CI, -20 to 20); therefore, indacaterol was determined to be noninferior to tiotropium (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs tiotropium 18 µg QD Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was allowed for use as needed. No other bronchodilator use was permitted.	of age with moderate to severe COPD, smoking history ≥10 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%		Secondary: FEV_1 and FVC at individual time points, TDI, SGRQ, use of rescue medication, diary card-derived symptom variables and safety	Subsequent criteria for superiority were not met. Secondary: After five minutes on day one, FEV_1 was higher with indacaterol (treatment difference, 70 mL; 95% CI, 60 to 80; *P*<0.00), and the difference remained significant after 30 minutes (*P*<0.001) and one hour (*P*<0.01). FVC measurements followed a similar pattern and were significantly higher with indacaterol (*P*<0.001, *P*<0.001 and *P*<0.05). TDI total scores after 12 weeks revealed a significantly greater reduction in dyspnea with indacaterol (treatment difference, 0.58; *P*<0.001). Patients receiving indacaterol were significantly more likely to achieve a clinically relevant improvement in TDI total scores (OR, 1.49; *P*<0.001). SGRQ total scores after 12 weeks revealed significantly better health status with indacaterol (treatment difference, -2.1; *P*<0.001). Patients receiving indacaterol were significantly more likely to achieve a clinically relevant improvement in SGRQ total scores (OR, 1.43; *P*<0.001). Patients receiving indacaterol significantly reduced the use of daily, daytime and nighttime use of rescue medications (*P*<0.001), and had a significantly greater proportion of days without rescue medication use (*P*=0.004). Diary data revealed that indacaterol and tiotropium resulted in similar increases from baseline of 2.0 and 1.9, respectively, in the proportion of days with no daytime COPD symptoms, 7.5 and 4.6 in the proportion of nights with no awakenings and 6.2 and 3.1 in the proportion of days able to undertake usual activities (*P* values not reported). Overall incidences of adverse events were similar between the two treatments, with the most common events generally reflecting the type of disease characteristics of COPD. The incidence of COPD worsening was 10.7 vs 8.3%; most cases were mild to moderate in severity. Serious adverse events were reported in 2.8 and 3.8% of patients receiving indacaterol and tiotropium. (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chapman et al[83] INDORSE Indacaterol 150 µg QD vs indacaterol 300 µg QD vs placebo	DB, ES, MC, RCT Patients in the extension had completed the 26-week core study for which they were required to have moderate to severe COPD with postbronchodilator FEV_1 <80% and ≥30% predicted and postbronchodilator FEV_1 /FVC <70% and were aged ≥40 years with a ≥20 pack-years smoking history	N=415 52 weeks (26 week extension)	Primary: Trough FEV_1 at 52 weeks and time to first COPD exacerbation Secondary: FEV_1 at other time points, albuterol use, rate of exacerbations and SGRQ total score	Primary: Trough FEV_1 at week 52 was significantly higher for both indacaterol groups compared to placebo (170 mL; 95% CI, 110 to 230 mL and 180 mL; 95% CI, 120 to 240 mL, for the 150 µg and 300 µg doses, respectively; *P*<0.001). The percent change from baseline in trough FEV_1 at week 52 was 120 mL (10%), 130 mL (10%), and -40 mL (-3%) with indacaterol 150 µg, indacaterol 300 µg and placebo, respectively. The differences between indacaterol and placebo in trough FEV_1 were maintained at a similar level from week two to the end of the study, with differences of ≥160 mL with both doses compared to placebo at each time point (all *P*<0.001). There were not enough events in the study to evaluate the time to first exacerbation. The HR compared to placebo of 0.82 (95% CI, 0.51 to 1.34) and 0.86 (95% CI, 0.53 to 1.39) for indacaterol 150 µg and indacaterol 300 µg, respectively, suggested a trend toward improvement associated with indacaterol treatment but this was not statistically significant. Secondary: At five minutes postdose on day one, FEV_1 increased relative to placebo by 90 mL (95% CI, 40 to 140) with indacaterol 150 µg, and by 100 mL (95% CI, 50 to 150) with indacaterol 300 µg (both *P*<0.001). This bronchodilation at five minutes post-dosing was maintained at all subsequent assessments, with differences compared to placebo of 150 to 290 mL with indacaterol 150 µg, and 180 to 240 mL with indacaterol 300 µg (*P* value not reported). At 52 weeks, the use of daily albuterol decreased from baseline by 1.2 puffs with indacaterol 150 µg, and 1.4 puffs with indacaterol 300 µg, compared to placebo (*P*<0.001 for both comparisons). The proportions of days without albuterol use were 56% and 59% with 150 µg, and 300 µg of indacaterol, respectively, (*P*<0.05) compared to placebo (46% of days without albuterol).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The mean SGRQ total scores with both indacaterol doses were numerically higher at all assessments, and significantly higher at week 26 (150 µg, *P*=0.002; 300 µg, *P*=0.025) and week 44 (*P*=0.002 for both doses) compared to placebo.
Han et al[84] Indacaterol 75 to 300 µg QD vs placebo	MA (6 RCT) Patients with stable COPD who received indacaterol or placebo for 12 weeks or more	N=5,250 Up to 52 weeks	Primary: Odds of achieving an improvement of at least one point on TDI scale Secondary: Not reported	Primary: Patients treated with indacaterol 75 µg were significantly more likely to achieve an improvement in TDI score of at least one point compared to placebo (OR, 1.784; 95% CI, 1.282 to 2.482). Patients treated with indacaterol 150 µg were significantly more likely to achieve an improvement in TDI score of at least one point compared to placebo (OR, 2.149; 95% CI, 1.746 to 2.645). Patients treated with indacaterol 300 µg were significantly more likely to achieve an improvement in TDI score of at least one point compared to placebo (OR, 2.458; 95% CI, 2.010 to 3.006). Secondary: Not reported
Wang et al[85] Formoterol vs placebo or indacaterol vs placebo or	MA (17 RCT) Patients with COPD who were treated with LABA or placebo for at least 24 weeks	N=11,871 At least 24 weeks	Primary: COPD exacerbations and severe COPD exacerbations or withdrawals due to exacerbations Secondary: Not reported	Primary: Compared to placebo, statistically significant reductions in COPD exacerbations occurred with formoterol (OR, 0.83; 95% CI, 0.73 to 0.96), indacaterol (OR, 0.82; 95% CI, 0.69 to 0.97) or salmeterol (OR, 0.79; 95% CI, 0.70 to 0.90). Overall, LABA treatment was associated with a significantly lower risk of COPD exacerbation compared to placebo (OR, 0.81; 95% CI, 0.75 to 0.88). All LABA treatments significantly reduced COPD exacerbations when both the study arm and the placebo arm were exposed to ICS (OR, 0.79; 95% CI, 0.72 to 0.87). When both study arms were not exposed to ICS, there was no statistically significant reduction in COPD exacerbations for patients treated with formoterol compared to placebo (OR, 0.93; 95% CI, 0.75 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
salmeterol vs placebo				1.15). The odds of experiencing a severe COPD exacerbation or withdrawal owing to exacerbations was significantly lower with LABA treatment overall compared to placebo (OR, 0.74; 95% CI, 0.63 to 0.88) and for formoterol (OR, 0.85; 95% CI, 0.68 to 1.06), indacaterol (OR, 0.42; 95% CI, 0.21 to 0.83) and salmeterol (OR, 0.66; 95% CI, 0.49 to 0.89) individually. When both arms were exposed to ICS, there was no significant reduction in severe exacerbations or withdrawals owing to exacerbations with salmeterol compared to placebo (OR, 0.78; 95% CI, 0.53 to 1.13). Formoterol reduced severe exacerbations or withdrawals owing to exacerbations compared to placebo, but this reduction did not reach statistical significance. Secondary: Not reported
Rodrigo et al[86] Indacaterol vs LABA or tiotropium	SR (5 RCT) Patients >40 years of age with moderate to severe COPD	N=5,920 At least 4 weeks	Primary: Trough FEV_1 Secondary: Use of rescue medication, proportion of patients with an improvement of at least one point on TDI, proportion of patients with a decrease of at least four units on SGRQ, COPD exacerbations, withdrawals, all-cause mortality and	Primary: In two studies comparing indacaterol to tiotropium, there was no statistically significant difference in trough FEV_1 between the treatments (WMD, 0.01; 95% CI, 0.03 to -0.01; *P*=0.27). In three studies comparing indacaterol to BID LABA use, the trough FEV_1 was significantly higher following treatment with indacaterol (WMD, 0.08; 95% CI, 0.06 to 0.09; *P*=0.00001). Secondary: Statistically significant reductions in rescue medication use were reported with indacaterol compared to treatment with tiotropium (WMD, -0.57; 95% CI, -0.37 to -0.77) or BID LABA (WMD, -0.22; 95% CI, -0.42 to -0.02). The odds of achieving an improvement in TDI score of at least one point was significantly greater with indacaterol compared to treatment with tiotropium (OR, 1.43; 95% CI, 1.22 to 1.67) or BID LABA use (OR, 1.61;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			adverse events	95% CI, 1.13 to 2.28). The odds of achieving a decrease in SGRQ score of at least four units was significantly greater with indacaterol compared to tiotropium (OR, 1.43; 95% CI, 1.22 to 1.68) or BID LABA (OR, 1.21; 95% CI, 1.01 to 1.45). There was no statistically significant difference in the odds of a COPD exacerbation with indacaterol compared to tiotropium (*P*=0.81) or BID LABA (*P*=0.93). There was no statistically significant difference in total withdrawals between patients treated with indacaterol compared to tiotropium (*P*=0.78) or BID LABA treatment (*P*=0.60). All-cause mortality was not significantly different between the indacaterol treatment group and the tiotropium (*P*=0.13) or BID LABA treatment groups (*P*=0.86). The incidences of any adverse event or serious adverse events were not significantly different between patients treated with indacaterol compared to tiotropium or BID LABA (*P*>0.05 for all).
Lee et al[87] Exposure to ICS, ipratropium, LABAs, theophylline, and SABAs	Nested case-control Patients treated in the United States Veterans Health Administration health care system	N=145,020 Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	Primary: All-cause mortality, respiratory mortality, and cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	Primary: After adjusted for differences in covariates, ICS and LABAs were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICS and 0.92 (95% CI, 0.88 to 0.96) for LABAs was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15). Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared to the unexposed group (OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABAs (OR, 1.12; 95% CI, 0.97 to 1.30); however, the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with ICS (OR, 0.88; 95% CI, 0.79 to 1.00); however, this also did not reach statistical significance.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABAs (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths. Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICS, 1.08 for ipratropium, and 0.90 for LABAs. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICS with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; *P*<0.001). In the all-cause mortality group, ICSs were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with an elevated risk for death.
Exercise-Induced Bronchospasm				
Berkowitz et al[88] Albuterol 0.18 mg, two inhalations 15 minutes prior to exercise via MDI	RCT, SB, XO Patients 12 to 17 years of age with bronchial asthma and exercised-	N=18 4 days	Primary: Mean percentage increase in FEV_1 five minutes after medication, mean workload for	Primary: Differences between mean baseline FEV_1 were not statistically significant between the treatment groups; however, five minutes post administration of albuterol or metaproterenol the mean increase in percentage of predicted FEV_1 was significantly higher compared to placebo (*P*<0.0005). A significantly greater increase (*P*<0.01) was also

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs metaproterenol 1.3 mg, two inhalations 15 minutes prior to exercise via MDI vs placebo	induced bronchospasm (FEV_1 >20% of pre-exercise level) following a treadmill exercise test		exercise challenges, mean decrease in FEV_1 from baseline, and the number of patients in whom bronchoconstriction was blocked over time Secondary: Not reported	seen five minutes after the administration of metaproterenol when compared to albuterol. On the days when the subjects received the active medications, the mean workloads were not found to be significantly different. Following the initial post-medication exercise test, a majority of patients in the placebo group experienced exercise-induced spasm compared to both active ingredient groups. This was a significant difference (P<0.0005) between the placebo and active ingredient groups but not between the active ingredient groups themselves. Following the two-hour exercise challenge, the remainder of the placebo group experienced exercise-induced spasm and a greater number in the remaining metaproterenol group compared to the albuterol group experienced exercise-induced spasm. There was a greater decrease in mean maximum decrease in FEV_1 in the placebo group compared to the active ingredient groups, which was found to be statistically significant (P<0.001). Albuterol prevented exercise-induced bronchospasm in more patients and for a significantly longer time than metaproterenol (P<0.05). Secondary: Not reported
Shapiro et al[89] Albuterol 180 µg prior to exercise challenge via MDI vs formoterol 12 µg prior to exercise challenge via DPI vs	DD, XO Individuals 12 to 50 years of age with a baseline FEV_1 >70% and at least a 20% reduction in FEV_1 after 2 exercise challenges 4 hours apart	N=20 4 test sequences	Primary: Maximum percent decrease in FEV_1 after each exercise challenge Secondary: Length of coverage, rescue therapy, and tolerability	Primary: Both formoterol doses produced significantly greater inhibition of FEV_1 decrease compared to placebo at all points in time (P<0.01), and compared to albuterol at all points in time with the exception of 15 minutes post dose (P<0.01). The two formoterol dose groups were not statistically different from each other and the only point in time that the mean maximum percent decrease in FEV_1 with albuterol was statistically different from placebo was 15 minutes post dose (P<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
formoterol 24 µg prior to exercise challenge via DPI vs placebo				Eighty nine percent to 94% of patients given formoterol and 79% of patients receiving albuterol were protected within 15 minutes of administration. Additionally, 71% of patients receiving formoterol were protected 12 hours after dosing compared to 26% of patients receiving albuterol, a percentage close to the 29% of patients receiving placebo (*P* values not reported). Nineteen percent of the patients treated with albuterol required a rescue inhaler at least once compared to zero patients receiving formoterol (*P* value not reported). There was no statistical difference in the percent of patients experiencing adverse event in all of the groups (no *P* value reported).
Richter et al[90] Formoterol 12 µg prior to exercise challenge via DPI vs salmeterol 50 µg prior to exercise challenge via DPI vs terbutaline 500 µg prior to exercise challenge via DPI vs placebo	DB, DD, PC, RCT, XO Nonsmoking patients 25 to 48 years of age with mild to moderate asthma, a history of exercise-induced bronchoconstriction and a documented hyper-responsiveness to inhaled methacholine	N=25 13 visits	Primary: Percent increase in FEV_1 between the inhalation of the study medication and the initiation of exercise (five, 30, or 60 minutes), and AUC of percent change in FEV_1 from end of exercise to 90 minutes Secondary: Not reported	Primary: At five minutes there was a significantly stronger response with terbutaline than salmeterol (*P*<0.001) and at five, 15, 30, and 60 minutes after inhalation, formoterol provided greater bronchodilation than salmeterol (*P*<0.05). There was no significant difference between terbutaline and formoterol at any of the time points. Mean pre-exercise FEV_1 was significantly larger in all active medication groups compared to placebo at 30 and 60 minute intervals (*P*<0.01) and was significantly larger after terbutaline and formoterol compared to salmeterol and placebo at the five-minute interval (*P*<0.05). A statistically significant (*P*<0.01) decrease was seen in AUC with increasing time between inhalation and exercise with terbutaline, formoterol, and salmeterol; however, there was no difference between treatments. Secondary: Not reported
Edelman et al[91] Montelukast 10 mg orally once in the evening	DB, PG, RCT Patients 15 to 45 years of age who	N=191 8 weeks	Primary: Change from baseline in the maximal percentage	Primary: In both treatment groups spirometry before exercise resulted in a small, non-significant change from baseline FEV_1 at first treatment visit at weeks four and eight, the groups did not differ statistically (*P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs salmeterol 100 µg, two inhalations BID via DPI	had been nonsmokers for at least 1 year and had a smoking history of less than 15 pack-years; patients had a history of chronic asthma and a decrease in FEV_1 of at least 20% after a standardized exercise challenge on two occasions during the baseline period		decrease in FEV_1 at the end of eight weeks of treatment Secondary: Change from baseline for maximal percent decrease in FEV_1 at days one to three and week four, the time required after maximal decrease to return to within 5% of pre challenge values, AUC at all visits, the number and percent of patients requiring rescue medication during or at the conclusion of exercise test, and the number and percent of patients whose decrease in FEV_1 from pre-exercise levels was <10%, 10 to 20%, 20 to 40% and >40%	reported). No statistical difference was seen at baseline in the maximal percent decrease in FEV_1. Improvement in maximal percent decrease in FEV_1 observed was maintained at week eight for the montelukast group, compared to the salmeterol group (*P*=0.002). Secondary: No statistical difference was seen at baseline in the post exercise AUC or time to recovery within five minutes. Improvement in maximal percent decrease in FEV_1 was similar in both groups between days one to three and was maintained at week four in the montelukast group but not in the salmeterol group (*P*=0.015). A similar trend was also seen when evaluating the time required after maximal decrease to return to within 5% of pre challenge values and the AUC at all visits. The effect of salmeterol diminished while that of montelukast was maintained (*P*<0.001, *P*<0.001, *P*=0.010, *P*<0.001). Twenty five of 96 (26%) patients in the montelukast group required rescue doses of medication after exercise challenge at any post treatment visit compared to 37 of 93 (40%)patients in the salmeterol group, a difference that was statistically significant (*P*=0.044). After eight weeks 62 of 93 (66.7%) of patients in the montelukast group achieved a decrease in FEV_1 of <20% after exercise challenging compared to 41 of 90 (45.6%) of patients receiving salmeterol (*P*=0.028). Both medications were generally well tolerated.
Storms et al[92] Montelukast 10 mg orally QD in the evening vs	DB, MC, PG, RCT Patients 15 to 45 years of age with at least a 1-year history of asthma,	N=122 4 weeks	Primary: Effect on the maximum FEV_1 after β_2-agonists administered to	Primary: The maximum post-rescue medication FEV_1 after four weeks improved in the montelukast and placebo groups but not in the salmeterol group (1.5, 1.2 and -3.9%). This maximum FEV_1 was significantly less in the salmeterol group compared to the montelukast (*P*<0.001) and placebo groups (*P*<0.001). Results were similar to those obtained after one week

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
salmeterol 50 µg BID via DPI vs placebo	documentation of exercise-induced bronchospasm in the past year, and were uncontrolled on ICS for ≥2 months		patients with four weeks of treatment with placebo, montelukast, or salmeterol Secondary: Effects of treatment on pre-exercise FEV_1, exercise exacerbation, rescue bronchodilation, time to recovery to pre exercise FEV_1 level and average CEAQ	of therapy and the difference between the montelukast and placebo groups was not significant. Secondary: There was a significant improvement in the in the mean change from baseline in pre-exercise FEV_1 in the salmeterol group compared to the placebo (at week one; *P*<0.001) and montelukast groups (at weeks one and four; *P*=0.010). In addition, there was no difference between the montelukast and placebo groups. Montelukast significantly decreased exercise induced bronchospasm at week four compared to placebo (*P*=0.008), however, there was no significant difference between the salmeterol and placebo groups or the salmeterol and montelukast groups. Compared to both placebo and salmeterol, after four weeks of treatment montelukast permitted significantly faster rescue with β_2-agonists (*P*=0.036, *P*=0.005). After four weeks, there was a significant difference in the CEAQ score immediately and 10 minutes after exercise with montelukast compared to placebo (*P*<0.020). Both medications were generally well tolerated.
Miscellaneous Studies				
Huchon et al[93] Fenoterol/ipratropium via HFA134a-MDI vs fenoterol/ipratropium CFC-MDI	MC, OL, PG, RCT Patients 18 to 80 years of age with chronic airway obstruction or mixed conditions, stable chronic airway obstruction with no hospital admissions for an	N=2,027 (HFA=1,348 CFC=679) 12 weeks	Primary: Adverse events Secondary: Additional use of the study drug as rescue medication and the number of chronic airway obstruction exacerbations	Primary: The incidence of adverse events in the 2,027 randomized patients was comparable between the two treatment groups with 36.4% (N=491) in the HFA-MDI group and 37.1% (242) in the CFC-MDI group reporting at least one adverse event during the randomized phase. In addition, the rates of potential systemic effects of the trial drug, based on the incidence of cardiovascular events, mouth dryness or tremor, were balanced across both formulations. The most commonly reported adverse events were respiratory disorders

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	exacerbation and no major change in medication for at least 4 weeks prior to screening visit, and an initial FEV_1 of ≥40% of the predicted value when not receiving a bronchodilator			including asthma or COPD exacerbations, bronchitis, cough, and dyspnea. There were no statistically significant difference between formulations for each of the most clinically important adverse events; with the exception of COPD exacerbations (4.1% for the CFC-MDI group vs 2.4% in the HFA-MDI group; *P*=0.04). There was one death during the run in period of the trial (lung cancer), five deaths during the randomized phase: four of the 1,348 patients in HFA-MDI group (one from a heart attack, three myocardial infarction), and one of 679 patients in the CFC-MDI group. There was no difference between the two groups in the incidence of serious adverse events and adverse events leading to withdrawal. Secondary: The use of rescue medication was similar in each group. The analysis of FEV_1 and FVC showed that a fixed combination dose of fenoterol/ipratropium delivered via HFA-MDI produced a comparable efficacy profile to delivery by CFC-MDI.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active control, CI=confidence interval, CR=case review, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, IB=investigational blinded, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blinded, XO=crossover
Miscellaneous abbreviations: 6MWT=six-minute walk test, AUC=area under the curve, BODE index= body-mass index, airflow obstruction, dyspnea, and exercise capacity index, CBSQ=chronic bronchitis symptom questionnaire, CEAQ=clinic exercise-assessment questionnaire, CFC=chlorofluorocarbons, COPD=chronic obstructive pulmonary disease, CRDQ=chronic respiratory disease questionnaire, DPI=dry powered inhaler, ED=emergency department, FEV1=forced expiratory volume in 1 second, FVC=forced vital capacity, HFA=hydrofluoroalkane, ICS=inhaled corticosteroid, LABA=long acting β2-agonists, LOS=length of stay, MCID=minimal clinically important difference, MDI=metered dose inhaler, PAQ=pediatric asthma questionnaire, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, QoL=quality of life, SABA=short acting β2-agonists, SEM=standard error of the mean, SGRQ=St. George's Hospital Respiratory Questionnaire, TDI=total dyspnea index, WMD=weighted mean difference

Special Populations

Table 5. Special Populations[1-20]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Short Acting β_2-agonists					
Albuterol	Limit initial dose to 2 mg three to four times daily in the elderly population (oral dosage forms). Not studied in the elderly population (inhalation dosage forms). Approved for use in children two years of age and older (oral and solution for nebulization dosage forms). Approved for use in children four years of age and older (ProAir® HFA Ventolin® HFA). Approved for use in children 12 years of age and older (Proventil® HFA). Approved for use in children six years of age and older (oral extended-release tablet dosage form).	No dosage adjustment required.	No dosage adjustment required.	C	Unknown
Levalbuterol	Not sufficiently studied in patients 65 years of age and older. Approved for use in children four years of age and older (HFA inhaler dosage form). Approved for use in children six years of age and older (solution for nebulization dosage form).	Decrease in racemic albuterol clearance. Caution should be used when administering levalbuterol to patients with renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Metaproterenol	Not sufficiently studied in patients 65 years of age and older.	Not reported.	Not reported.	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Approved for use in children six years of age and older.				
Pirbuterol	Not sufficiently studied in patients 65 years of age and older. Approved in children 12 years of age and older.	Not reported.	Not reported.	C	Unknown
Terbutaline	Not sufficiently studied in patients 65 years of age and older. Approved in children 12 years of age and older.	Patients with moderate renal dysfunction should receive 50% of the usual dose. Avoid use in patients with severe renal impairment.	Not reported.	C	Unknown
Long Acting β_2-agonists					
Arformoterol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	Use with caution in patients with hepatic dysfunction.	C	Unknown
Formoterol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved in children five years of age and older (Foradil®). Safety and efficacy in children have not been established (Perforomist®).	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Indacaterol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Not studied in renal dysfunction.	No dosage adjustment required; not studied in severe	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in children have not been established.		hepatic dysfunction.		
Salmeterol	Dosage adjustment not required in the elderly population. Approved in children four years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown

HFA=hydrofluoroalkane

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-20]

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Cardiovascular																
Angina	✔	✔	-	✔	✔	✔	✔	-	-	✔	✔	-	-	-	-	-
Arrhythmias	✔	-	-	✔	<2	✔	✔	-	✔	✔	✔	-	-	✔	-	-
Arteriosclerosis	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Chest pain	<1	<1	0.9 to 1.7	<3	7	1.9 to 3.2	-	-	<2	✔	-	0.2	1.3	-	-	1.3 to 1.5
Congestive heart failure	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Electrocardiogram abnormal	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-	-
Electrocardiogram change	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-	-
Extrasystoles ventricular	-	-	-	<3	-	-	-	-	-	-	-	-	-	-	1.5	-
Heart block	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Hypertension	✔	✔	1	✔	✔	✔	✔	-	<2	✔	✔	0.4	-	4	-	-
Hypotension	-	-	-	✔	✔	✔	✔	-	<2	-	✔	-	<1	-	-	-
Myocardial infarction	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Pallor	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Palpitations	<1	2.4 to 5.0	-	<3	✔	✔	✔	-	-	-	✔	3.8	1.3 to 1.7	✔	5	7.8 to 22.9
QT prolongation	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Syncope	-	-	-	-	-	-	-	-	<2	-	-	0.4	<1	-	-	-
Tachycardia	1 to 2	2.7 to 5.0	1	3 to 7	✔	✔	✔	-	2.7 to 2.8	✔	6.1	17.1	1.2 to 1.3	✔	3.5	1.3 to 1.5
Vasodilations	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	1	-
Central Nervous System																
Agitation	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Anxiety	-	-	-	<3	-	1.5	-	-	2.7	-	-	-	<1	≥1	1	-
Asthenia	-	-	-	-	≥2	-	-	-	3	-	-	-	-	-	2	-
Ataxia	-	-	-	<3	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Cerebral infarct	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Central nervous system stimulation	✔	✔	-	✔	✔	-	-	-	-	✔	-	-	-	-	-	-
Confusion	-	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-
Depression	-	-	-	<3	-	-	-	-	-	-	-	-	<1	-	-	-
Dizziness	3	1.5 to 2.0	4	3	✔	1.6	2.4	-	1.4 to 2.7	2.7	✔	2.4	0.6 to 1.2	4	3.5	1.3 to 10.2
Excitement	2 to 20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fatigue	1	-	-	-	✔	✔	✔	-	-	-	✔	1.4	<1	-	-	11.7-9.8
Hallucinations	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Headache	4	7.0 to 18.8	3	7	≥2	✔	✔	5.1	7.6 to 11.9	✔	1.1	7	1.3 to 2.0	13 to 17	7.5	7.8 to 8.8
Hyperactivity	2	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Hyperkinesia	4	-	-	<3	-	-	-	-	-	-	-	-	<1	-	-	-
Hypokinesia	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Insomnia	1 to 2	2.0 to 2.4	1	✔	✔	1.5	2.4	-	<2	✔	✔	1.8	<1	-	1.5	-
Irritable behavior	<1	<1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Migraine	-	-	0.9 to 1.7	-	-	-	-	-	<2.7	-	-	-	-	≥1	-	-
Nervousness	9 to 15	8.5 to 20.0	-	7	≥2	✔	✔	-	2.8 to 9.6	✔	4.8	20.2	4.5 to 6.9	✔	35	16.9 to 30.7
Numbness in extremities	-	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-
Paralysis	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Paresthesia	-	-	-	-	<2	-	-	-	<2	-	-	-	-	✔	<1	-
Restlessness	-	<1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rigors	-	-	-	<3	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Sensory disturbances	-	-	-	-	-	-	-	-	-	-	-	0.2	-	✔	-	-
Shakiness	9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Somnolence	1	<1	-	<3	<2	-	-	-	-	-	-	0.6	-	-	5.5	9.8 to 11.7
Sweating	<1	-	-	<3	-	-	-	-	-	-	-	0.2	-	-	1	2.4
Tremor	10	20.0 to 24.2	-	7	≥2	1.9	✔	-	6.8	✔	1.6	16.9	1.3 to 6.0	✔	15	7.8 to 38.0
Vertigo	✔	✔	-	✔	-	-	-	-	-	✔	-	-	-	-	-	-
Weakness	<1	2	-	-	-	-	-	-	-	-	-	0.2	<1	-	-	0.5 to 1.3
Dermatological																
Acne	-	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-
Angioedema	✔	✔	-	✔	-	-	-	-	✔	✔	-	-	-	✔	-	-
Bruising	-	-	-	-	-	-	-	-	-	-	-	-	0.6	-	-	-
Contact dermatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Dry skin	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Eczema	-	-	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Flushing	-	✔	-	-	-	-	-	-	-	-	-	-	<1	-	-	2.4
Herpes simplex	-	-	-	-	<2	-	-	-	-	<2	-	-	-	-	-	-
Herpes zoster	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Hives	-	-	-	-	-	-	-	-	-	-	-	0.2	-	-	-	-
Photodermatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	>1	-	-
Pruritus	-	-	-	-	-	1.5	-	-	-	-	-	0.4	<1	-	-	-
Rash	✔	✔	-	<3	4	1.1	-	-	7.5	✔	-	-	<1	4	<1	-
Skin/appendage infection	-	-	1.7	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin discoloration	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Skin hypertrophy	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Skin reaction	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urticaria	✔	✔	0.9 to	✔	-	-	-	-	3	✔	-	-	-	3	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
			1.7													
Endocrine and Metabolic																
Decrease glucose intolerance	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diabetes	-	-	-	<3	-	-	-	>2	-	-	-	-	-	-	-	-
Hyperglycemia	-	-	-	✔	✔	✔	✔	>2	-	-	-	-	-	≥1	-	-
Hypoglycemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hyperlipidemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Metabolic acidosis	-	-	-	✔	✔	✔	✔	-	-	-	-	-	-	-	-	-
Weight gain	-	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-
Gastrointestinal																
Abdominal pain	-	-	-	-	-	✔	-	-	1.5	-	-	-	<1	-	-	-
Anorexia	-	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-
Constipation	-	-	-	-	<2	-	-	-	-	<2	-	-	-	-	-	-
Diarrhea	-	-	-	<3	6	-	4.9	-	1.5 to 6.0	-	-	1.2	1.3	-	-	-
Dry mouth	-	-	-	<3	✔	1.2	3.3	-	<2	-	✔	0.4	1.3	-	1.5	-
Dyspepsia	-	-	1	-	-	✔	-	-	1.4 to 2.7	-	-	-	-	-	-	-
Dyspeptic symptoms	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Epigastric pain	<1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Eructation	-	-	-	<3	-	-	-	-	-	-	-	-	-	-	-	-
Flatulence	-	-	-	<3	-	-	-	-	-	-	-	-	-	-	-	-
Gastritis	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Gastroenteritis	-	-	0.9 to 3.4	-	-	✔	-	-	<2	<2	-	-	-	-	-	-
Gastrointestinal infections	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Gastrointestinal symptoms/ distress	2	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-
Hyposalivation	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Increased appetite	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Loss of appetite	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Melena	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Nausea	-	2.0 to 4.2	0.9 to 1.7	10	✔	✔	4.9	2.4	<2	✔	1.3	3.6	1.3 to 1.7	3	3	1.3 to 3.9
Oral candidiasis	-	-	-	-	<2	-	-	-	-	-	-	-	-	≥1	-	-
Periodontal abscess	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Rectal hemorrhage	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Stomatitis	-	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-
Taste changes	✔	✔	-	4	-	-	-	-	-	-	-	0.8	0.6	-	-	-
Vomiting	✔	4.2	-	7	≥2	-	2.4	-	-	10.5	-	0.8	<1	3	<1	1.3 to 3.9
Genitourinary																
Calcium crystalluria	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Cystitis	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Difficulty in micturition	-	<1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Glycosuria	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Hematuria	-	-	-	-	<2	-	-	-	-	<2	-	-	-	-	-	-
Kidney calculus	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Nocturia	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Prostate specific antigen increase	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Pyuria	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Urinary tract infection	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-	-
Urine abnormality	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Vaginal moniliasis	-	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-
Hematologic																
Dysmenorrhea	-	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-
Leukocytosis	-	-	-	-	≥2	-	-	-	-	-	-	-	-	-	-	-
Laboratory Test Abnormalities																
Hyperkalemia	-	-	-	-	≥2	-	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Hypokalemia	-	-	-	✔	✔	✔	✔	-	-	-	-	-	-	-	-	-
Liver enzyme elevation	-	-	-	-	-	✔	-	-	-	-	-	-	-	-	✔	-
Metabolic acidosis	-	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-
Musculoskeletal																
Arthralgia	-	-	-	-	<2	-	-	-	-	-	-	-	-	>1	-	-
Arthritis	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Articular rheumatism	-	-	-	-	-	-	-	-	-	-	-	-	-	>1	-	-
Bone disorder	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Clonus on flexing foot	-	-	-	-	-	-	-	-	-	-	-	0.2	-	-	-	-
Hypertonia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Leg cramps	-	-	-	-	4	1.7	-	-	2.7	-	-	-	-	-	-	-
Muscle cramps	-	2.7 to 3.0	-	✔	✔	1.7	✔	>2	-	-	-	-	-	3	-	-
Muscle spasm	-	-	-	-	-	-	-	-	-	-	-	0.2	-	3	-	-
Muscle stiffness	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Muscle tightness	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Muscle rigidity	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Musculoskeletal inflammation	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Myalgia	-	-	-	-	-	✔	-	-	<2	<2	-	-	-	≥1	-	-
Neck rigidity	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Pain	-	-	-	3 to 5	8	-	-	>2	1.4 to 3.0	4	-	0.2	-	12	-	-
Rheumatoid arthritis	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Tendinous contracture	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Respiratory																
Asthma exacerbation	-	-	11.1 to13. 0	✔	-	0.6 to 4.7	-	-	9.0 to 9.1	9.4	-	2	-	3 to 4	-	-
Bronchitis	-	-	0.9 to 1.7	-	≥2	4.6	-	-	-	2.6	-	✔	-	7	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Bronchospasm	✔	✔	-	✔	-	-	-	-	-	-	-	✔	-	✔	-	-
Carcinoma of the lung	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Chest infection	-	-	-	-	-	2.7	-	-	-	-	-	-	-	-	-	-
Chronic obstructive pulmonary disease	-	-	-	-	≥2	-	-	-	-	-	-	-	-	-	-	-
Cough	<1	-	-	5	-	-	-	6.5	1.4 to 4.1	✔	-	0.2	1.2	5	-	-
Drying of oropharynx	✔	✔	-	✔	-	-	-	-	-	✔	-	-	-	-	-	-
Dysphonia	-	-	-	<3	-	1	-	-	-	-	-	-	-	-	-	-
Dyspnea	-	-	-	<3	4	2.1	-	-	✔	✔	-	✔	-	-	-	2
Epistaxis	1	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-
Hoarseness	✔	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Increased sputum	-	-	-	-	-	1.5	-	-	-	-	-	-	-	-	-	-
Influenza	-	-	-	-	-	-	-	-	-	-	-	-	-	5	-	-
Laryngeal irritation	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Laryngeal spasm	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Laryngeal swelling	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Laryngitis	-	-	-	<3	-	-	-	-	-	-	-	-	-	-	-	-
Lung disorder	-	-	-	-	2	-	-	-	-	<2	-	-	-	-	-	-
Nasal congestion	-	-	-	-	-	-	-	-	-	-	-	-	-	9	-	-
Nasopharyngitis	-	-	-	✔	-	-	3.3	5.3	-	-	-	-	-	-	-	-
Oral mucosal abnormality	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Oropharyngeal edema	✔	✔	-	<3	-	-	-	-	-	-	-	-	-	-	-	-
Oropharyngeal pain	-	-	-	-	-	-	-	2.2	-	-	-	-	-	-	-	-
Pharyngitis	-	-	-	14	-	3.5	-	-	3.0 to 10.4	6.6 to 7.9	-	-	-	6	-	-
Respiratory disorder	-	-	-	5	-	-	-	-	-	-	-	-	-	-	-	-
Rhinitis	-	-	-	16	-	✔	-	-	2.7 to 11.1	7.4	-	-	-	4	-	-
Sinusitis	-	-	-	-	5	2.7	-	>2	1.4 to	-	-	-	-	4	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
									4.2							
Throat irritation	-	-	-	10	-	-	-	-	-	-	-	-	-	7	-	-
Turbinate edema	-	-	-	-	-	-	-	-	1.4 to 2.8	-	-	-	-	-	-	-
Upper respiratory tract infection	-	-	-	21	-	7.4	-	>2	-	-	-	-	-	≥3	-	-
Viral respiratory infection	-	-	-	7	-	-	-	-	6.9 to 12.3	-	-	-	-	5	-	-
Voice alteration	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Wheezing	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other																
Abnormal vision	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Abscess	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Accidental injury	-	-	-	-	-	-	-	-	2.7	9.2	-	-	-	-	-	-
Allergic reaction	-	-	0.9 to 3.4	-	-	-	-	-	-	-	-	-	-	-	-	-
Alopecia	-	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-
Anaphylaxis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Back pain	-	-	-	4	6	4.2	-	-	-	-	-	-	-	-	-	-
Blurred vision	-	-	-	-	-	-	-	-	-	-	-	0.2	-	-	-	-
Chattiness	-	-	-	-	-	-	-	-	-	-	-	0.2	-	-	-	-
Chills	-	-	-	-	-	-	-	-	<2	-	-	0.2	-	-	-	-
Cold symptoms	-	-	3.4	-	-	-	-	-	-	-	-	-	-	-	-	-
Conjunctivitis	1	-	-	-	-	-	-	-	-	<2	-	-	-	≥1	-	-
Digitalis intoxication	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Dilated pupils	<1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear pain	-	-	-	<3	-	-	-	-	-	<2	-	-	-	-	-	-
Ear signs	-	-	-	-	-	-	-	-	-	-	-	-	-	4	-	-
Edema	-	-	-	<3	-	-	-	>2	-	-	-	-	<1	≥1	-	-
Emotional lability	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Eye itch	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-	-
Fever	-	-	-	6	≥2	2.2	-	-	3.0 to 9.1	-	-	0.4	-	✔	-	-
Flu syndrome	-	-	2.6	-	3	-	-	-	1.4 to 4.2	-	-	0.2	-	-	-	-
Glaucoma	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Glossitis	-	-	-	<3	-	-	-	-	-	-	-	-	<1	-	-	-
Hernia	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Hypersensitivity vasculitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✔	-
Keratitis	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Lymphadenopathy	-	-	0.9 to 2.6	-	-	-	-	-	3	-	-	-	-	-	-	-
Malaise	-	-	-	-	✔	-	✔	-	-	-	✔	-	-	-	-	-
Neoplasm	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Otitis media	-	-	0.9 to 4.3	-	-	-	-	-	-	-	-	-	-	-	-	-
Pelvic pain	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Peripheral edema	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-
Retroperitoneal hemorrhage	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Tonsillitis	-	-	-	-	-	1.2	-	-	-	-	-	-	-	-	-	-
Trauma	-	-	-	-	-	1.2	-	-	-	-	-	-	-	-	-	-
Viral infection	-	-	-	-	-	17.2	-	-	7.6 to 9.0	<2	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported.
* Oral syrup formulation.
† Oral tablet formulation.
‡ Inhalation solution formulation.
§ Aerosol inhalation formulation.
¶ HFA aerosol inhalation formulation.
# Dry powder inhaler.
** Injection.

Contraindications/Precautions

All Long-acting β_2 adrenergic agonists are contraindicated in patients with asthma without use of a long-term asthma control medication. In addition all β_2-agonists are contraindicated in patients with a history of hypersensitivity to any components of a particular product.[1-20]

In some patients, the use of β_2-agonists have been reported to produce electrocardiogram changes such as flattening of the T-wave, prolongation of the QTc interval and ST segment depression. All β_2-agonists can potentially produce clinically significant cardiovascular effects in some patients (i.e., increase pulse rate and blood pressure).[1-20]

In some patients, the use of β_2-agonists can produce paradoxical bronchospasm, which may be life threatening. Immediate discontinuation of the medication and alternate therapy is indicated if paradoxical bronchospasm is suspected.[1-20]

Immediate hypersensitivity reactions may occur after administration of β_2-agonists as demonstrated by anaphylaxis, urticaria, angioedema, rash and bronchospasm.[1-20]

The use of β_2-agonists alone may not be adequate to control asthma symptoms. Early consideration should be given to adding anti-inflammatory agents to the therapeutic regimen.[1-20]

The use of β_2-agonists may produce significant hypokalemia in some patients. The decrease is usually transient.[1-20]

The use of β_2-agonists may aggravate preexisting diabetes mellitus and ketoacidosis and should be used with caution in patients with diabetes.[1-20]

Indacaterol has not been evaluated in patients with acutely deteriorating chronic obstructive pulmonary disease, which may be a life-threatening condition; therefore, it should not be initiated in such patients. Indacaterol has also not been evaluated in the relief of acute symptoms; therefore, should not be used for the relief of such symptoms. Acute symptoms should be treated with an inhaled short acting β_2-adrenergic agonist.[1]

There have been rare reports of seizures in patients taking terbutaline. Seizures did not recur after the drug was discontinued.[14,15]

Boxed Warning for Arformoterol[16]

WARNING
Asthma-related death: Long-acting beta-2 adrenergic agonists may increase the risk of asthma-related death. Data from a large placebo-controlled United States study that compared the safety of another long-acting beta-2 adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of long-acting beta-2 agonists, including arformoterol. The safety and efficacy of arformoterol in patients with asthma have not been established. All long-acting beta-2 agonists, including arformoterol, are contraindicated in patients with asthma without use of a long-term asthma control medication.

Boxed Warning for Formoterol[18,19]

WARNING
Long-acting beta-2 adrenergic agonists increase the risk of asthma-related death. Data from a large placebo-controlled United States study that compared the safety of another long-acting beta-2 adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of long-acting beta-2 adrenergic agonists. Currently available data are inadequate to

WARNING
determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from long-acting beta-2 adrenergic agonists. Because of this risk, use of formoterol inhalation powder for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use formoterol only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue formoterol) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use formoterol for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. The safety and efficacy of formoterol inhalation solution in patients with asthma have not been established. Pediatric and adolescent patients: Available data from controlled clinical trials suggest that long-acting beta-2 adrenergic agonists increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require the addition of a long-acting beta-2 adrenergic agonist to an inhaled corticosteroid, a fixed-dose combination product containing an inhaled corticosteroid and long-acting beta-2 adrenergic agonist should ordinarily be considered to ensure adherence with both drugs. In cases in which use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and long-acting beta-2 adrenergic agonist is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be ensured, a fixed-dose combination product containing an inhaled corticosteroid and long-acting beta-2 adrenergic agonist is recommended.

Boxed Warning for Indacaterol[3]

WARNING
Asthma-related death: Long-acting beta-2 adrenergic agonists increase the risk of asthma-related death. Data from a large, placebo-controlled United States study that compared the safety of another long-acting beta-2 adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of long-acting beta-2 adrenergic agonists, including indacaterol. The safety and efficacy of indacaterol in patients with asthma have not been established. Indacaterol is not indicated for the treatment of asthma.

Boxed Warning for Salmeterol[19]

WARNING
Long-acting beta-2 adrenergic agonists, such as salmeterol, increase the risk of asthma-related death. Data from a large placebo-controlled United States study that compared the safety of salmeterol or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol vs 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from long-acting beta-2 adrenergic agonists. Because of this risk, use of salmeterol for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use salmeterol only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is

WARNING
achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue salmeterol) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use salmeterol for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. Children and adolescents: Available data from controlled clinical trials suggest that long-acting beta-2 adrenergic agonists increase the risk of asthma-related hospitalization in children and adolescents. For children and adolescents with asthma who require addition of a long-acting beta-2 adrenergic agonist to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a long-acting beta-2 adrenergic agonist should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a long-acting beta-2 adrenergic agonist is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be ensured, a fixed-dose combination product containing both an inhaled corticosteroid and a long-acting beta-2 adrenergic agonist is recommended.

Boxed Warning for Terbutaline[14,15]

WARNING
Prolonged tocolysis: Terbutaline has not been approved and should not be used for acute or maintenance tocolysis. In particular, do not use terbutaline for maintenance tocolysis in the outpatient or home setting. Serious adverse reactions, including death, have been reported after administration of terbutaline to pregnant women. In mothers, these adverse reactions include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration.

Drug Interactions

Table 7. Drug Interactions[1-20]

Generic Name	Interacting Medication or Disease	Potential Result
β_2-agonists (all)	Diuretics (i.e., loop diuretics, thiazide diuretics)	Electrocardiogram changes or hypokalemia may potentially be worsened with the addition of a β_2-agonist, particularly when the recommended dose is exceeded.
β_2-agonists (all)	Monoamine oxidase inhibitors	Monoamine oxidase is an enzyme that metabolizes catecholamines. When given with an indirect acting sympathomimetic, hypertensive crisis may occur.
β_2-agonists (all)	Nonselective β_2-antagonists	β-blockers inhibit the therapeutic effects of β_2 agonists and may produce bronchospasm in patients with asthma and chronic obstructive pulmonary disease.
β_2-agonists (all)	Tricyclic antidepressants	Tricyclic antidepressant may potentiate the cardiovascular effects of β_2-agonists.

Dosage and Administration

Table 8. Dosing and Administration[1-20]

Generic Name	Adult Dose	Pediatric Dose	Availability
Short Acting β_2-agonists			
Albuterol	Relief of bronchospasm in patients with asthma, treatment or prevention of bronchospasm	Relief of bronchospasm in patients with asthma, treatment or prevention of	Meter dose aerosol inhaler (HFA): 120 µg albuterol

Generic Name	Adult Dose	Pediatric Dose	Availability
	in patients with reversible obstructive airway disease: Meter dose aerosol inhaler (HFA): 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations/day Solution for nebulization: 2.5 mg TID to QID times daily Sustained-release tablet: 4 to 8 mg BID; maximum, 32 mg/day Syrup, tablet: 2 to 4 mg TID to QID; maximum, 8 mg QID Prevention of exercise-induced bronchospasm: Meter dose aerosol inhaler (HFA): 2 inhalations 15 to 30 minutes before exercise	bronchospasm in patients with reversible obstructive airway disease in patients four years of age and older: Meter dose aerosol inhaler (HFA): 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations/day Relief of bronchospasm in patients with asthma, treatment or prevention of bronchospasm in patients with reversible obstructive airway disease in patients two years of age and older: Solution for nebulization: 0.63 to 1.25 mg TID to QID; maximum, 2.5 mg TID to QID Syrup: 2 to 6 years of age: 0.1 mg/kg of body weight TID; maximum, 4 mg TID; 6 to 14 years of age: 2 mg TID to QID; maximum, 24 mg/day Relief of bronchospasm in patients with asthma, treatment or prevention of bronchospasm in patients with reversible obstructive airway disease in patients six years of age and older: Sustained-release tablet: 4 mg BID; maximum, 24 mg/day Tablet: 2 mg TID to QID; maximum 24 mg/day Prevention of exercise-induced bronchospasm in patients four years of age and older: Meter dose aerosol inhaler (HFA): 2 inhalations 15 to 30 minutes before exercise	sulfate* (60^{T} or 200 inhalations) Solution for nebulization: 0.63 mg 1.25 mg 2.5 mg 0.5% concentrated solution (3 mL unit dose vials) Sustained-release tablet: 4 mg 8 mg Syrup: 2 mg/5 mL Tablet: 2 mg 4 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
Levalbuterol	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease : Meter dose aerosol inhaler (HFA): 1 to 2 inhalations every 4 to 6 hours Solution for nebulization: 0.63 mg TID every 6 to 8 hours; maximum, 1.25 mg TID	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease in patients four years of age and older: Meter dose aerosol inhaler (HFA): 1 to 2 inhalations every 4 to 6 hours Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease in patients six years of age and older: Solution for nebulization: 0.31 mg TID; maximum, 0.63 mg TID	Meter dose aerosol inhaler (HFA): 59 µg‡ (80 or 200 inhalations) Solution for nebulization: 0.31 mg 0.63 mg 1.25 mg (3 mL vials)
Metaproterenol	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema: Syrup, tablet: 20 mg TID to QID	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema in children six years of age and older (or weight under 60 lbs): Syrup, tablet: 10 mg TID to QID	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg
Pirbuterol	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease: 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations daily	Safety and efficacy in children less than 12 years of age have not been established.	Breath activated aerosol inhaler: 200 µg (80 or 400 inhalations)
Terbutaline	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema: Injection: 0.25 mg SQ in the lateral deltoid area, may repeat in 15 to 30 minutes if improvement does not occur; maximum, 0.5 mg in 4 hours Tablet: 2.5 to 5 mg TID, 6 hours apart; maximum, 15 mg in 24 hours	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema: Injection: Safety and efficacy in children less than 12 years of age have not been established. Tablet: 12 to 15 years of age: 2.5 mg TID, 6 hours apart; maximum, 7.5 mg in 24 hours	Injection: 1 mg/mL (2 mL vial) Tablet: 2.5 mg 5 mg
Long Acting β_2-agonists			
Arformoterol	Long-term, twice daily, maintenance treatment of	Safety and efficacy in children have not been	Solution for nebulization:

Generic Name	Adult Dose	Pediatric Dose	Availability
	bronchospasm associated with COPD, including chronic bronchitis and emphysema: Solution for nebulization: 15 µg BID	established.	15 µg (2 mL)
Formoterol	Treatment of asthma and prevention of bronchospasm as concomitant therapy with a long-term asthma control medication in patients with reversible obstructive airways disease, including patients with nocturnal symptoms: Capsule for inhalation: 12 µg capsule inhaled BID; maximum, 24 µg/day (Foradil®) Prevention of exercise-induced bronchospasm: Capsule for inhalation: 12 µg capsule inhaled at least 15 minutes before exercise (Foradil®) Long-term, twice daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema: Capsule for inhalation: 12 µg capsule inhaled BID; maximum, 24 µg/day (Foradil®) Solution for nebulization: 20 µg BID; maximum 40 µg/day (Perforomist®)	Treatment of asthma and prevention of bronchospasm as concomitant therapy with a long-term asthma control medication in patients with reversible obstructive airways disease, including patients with nocturnal symptoms in patients five years of age and older: Capsule for inhalation: 12 µg capsule inhaled BID; maximum, 24 µg/day (Foradil®) Prevention of exercise-induced bronchospasm in patients five years of age and older: Capsule for inhalation: 12 µg capsule inhaled at least 15 minutes before exercise (no repeat dose) (Foradil®)	Capsule for inhalation: 12 µg Solution for nebulization: 20 µg/2 mL
Indacaterol	The long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema: Capsule for inhalation: 75 µg QD	Safety and efficacy in children have not been established.	Capsule for inhalation: 75 µg
Salmeterol	Treatment of asthma and prevention of bronchospasm as concomitant therapy with a long-term asthma control medication in patients with reversible obstructive airways disease, including patients with nocturnal symptoms: Dry powder inhaler: 1 inhalation	Treatment of asthma and prevention of bronchospasm as concomitant therapy with a long-term asthma control medication in patients with reversible obstructive airways disease, including patients with nocturnal	Dry powder inhaler: 50 µg (28 or 60 inhalations)

Generic Name	Adult Dose	Pediatric Dose	Availability
	BID Prevention of exercise-induced bronchospasm: Dry powder inhaler: 1 inhalation at least 30 minutes before exercise Long-term, twice daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema: Dry powder inhaler: 1 inhalation BID	symptoms in patients four years of age and older: Dry powder inhaler: 1 inhalation BID Prevention of exercise-induced bronchospasm in patients four years of age and older: Dry powder inhaler: 1 inhalation at least 30 minutes before exercise	

BID=two times daily, COPD=chronic obstructive pulmonary disease, HFA=hydrofluoroalkanes, QID=four times daily, SQ=subcutaneously, TID=three times daily
*Delivering 108 µg of albuterol (90 µg albuterol base).
†Ventolin® available as 60 and 200 inhalations.
‡Delivering 45 µg levalbuterol base.

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guidelines	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2014)**[24]	Diagnosis • A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking. • A diagnosis of COPD should be confirmed by spirometry. • COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio. • The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and COPD. • A detailed medical history should be obtained for all patients suspected of developing COPD. • Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications. • Chest radiograph may be useful to rule out other diagnoses. • Arterial blood gas measurements should be performed in advanced COPD. • Screening for α_1-antitrypsin deficiency should be performed in patients of Caucasian decent who develop COPD at 45 years of age or younger. • Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis. Treatment • Patients should be instructed to avoid the exacerbating exposure. This includes assisting the patient in smoking cessation attempts and counseling the patient on how to avoid pollutant exposures. • The management of COPD should be individualized to address symptoms and improve the patient's quality of life.

Clinical Guidelines	Recommendations
	• None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. • Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations. • Principle bronchodilators include β_2-agonists, anticholinergics and theophylline used as monotherapy or in combination. • The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. • For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators. • Combining bronchodilators of different pharmacological classes may improve efficacy and decrease adverse effects compared to increasing dose of a single bronchodilator • In patients with an FEV_1 <60% of the predicted value, regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function and quality of life as well as reduces exacerbations. • Long term therapy ICS as monotherapy is not recommended. • Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. • COPD patients should receive an annual influenza vaccine. • The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1 <40% of the predicted value. • Exercise training programs should be implemented for all COPD patients. • Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. <u>Management of exacerbations</u> • The most common causes of an exacerbation are respiratory tract infections. • Inhaled short-acting β_2-agonists, with or without short-acting anticholinergics are the preferred bronchodilators for treatment for exacerbations of COPD. • Roflumilast may also be used to reduce exacerbations for patients with chronic bronchitis, severe to very severe airflow limitation and frequent exacerbations not adequately controlled by long-acting bronchodilators. • Antibiotics are recommended in patients with increased dyspnea, increased sputum volume or increased sputum purulence; or increase sputum purulence and increased dyspnea or increased sputum volume, or patients that require mechanical ventilation.
Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2012)**[23]	<u>Treatment</u> • Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages. • Measures to prevent the development of asthma, asthma symptoms, and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented whenever possible. • Controller medications are administered daily on a long-term basis and include inhaled and systemic corticosteroids, leukotriene modifiers, LABAs in combination with ICSs, sustained-released theophylline, chromones and anti-immunoglobulin E (IgE). • Reliever medications are administered on an as-needed basis to reverse

Clinical Guidelines	Recommendations
	bronchoconstriction and relieve symptoms and include rapid-acting inhaled β_2-agonists, inhaled anticholinergics, short-acting theophylline and short-acting β_2-adrenergic agonists (SABAs). Controller medications • ICSs are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages. • ICSs differ in potency and bioavailability, but few studies have been able to confirm the clinical relevance of these differences. • Most clinical benefit from an ICS in adults is achieved at relatively low doses, equivalent to 400 µg of budesonide daily. Higher doses provide little further benefit but increase the risk of adverse events. • To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of the ICS. • Leukotriene modifiers are generally less effective than low doses of ICSs therefore may be used as an alternative treatment in patients with mild persistent asthma. • Some patients with aspirin-sensitive asthma respond well to leukotriene modifiers. • Leukotriene modifiers used as add-on therapy may reduce the dose of the ICS required by patients with moderate to severe asthma, and may improve asthma control in adult patients whose asthma is not controlled with low or high doses of ICSs. • Several studies have demonstrated that leukotriene modifiers are less effective than LABAs as add-on therapy. • LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation. • When a medium dose of the ICS fails to achieve control, the addition of a LABA is the preferred treatment. • Controlled studies have shown that delivering an ICS and LABA in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers are more convenient, may increase compliance, and ensure that the LABA is always accompanied by an ICS. • Although the guideline indicates that combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance, this use is not approved by the Food and Drug Administration (FDA). • Tiotropium has been evaluated in adults with uncontrolled asthma compared to double-dose ICSs and salmeterol. Study results are conflicting and no effect on asthma exacerbations has been demonstrated. • Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on ICSs alone. Furthermore, withdrawal of sustained-release theophylline has been associated with worsening asthma control. • Cromolyn and nedocromil are less effective than a low dose of ICSs. • Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed. • Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE. • Long-term oral corticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse event. • Other anti-allergic compounds have limited effect in the management of asthma.

Clinical Guidelines	Recommendations

Reliever medications

- Rapid-acting inhaled β_2-agonists are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise-induced bronchoconstriction, in patients of all ages.
- Rapid-acting inhaled β_2-agonists should be used only on an as-needed basis at the lowest dose and frequency required.
- Although the guidelines state that formoterol, a LABA, is approved for symptom relief due to its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with ICSs, the use of this agent as a rescue inhaler is not approved by the FDA.
- Ipratropium, an inhaled anticholinergic, is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists.
- Short-acting theophylline may be considered for relief of asthma symptoms.
- Short-acting oral β_2-agonists (tablets, solution, etc.) are appropriate for use in patients who are unable to use inhaled medication however they are associated with a higher prevalence of adverse event.
- Systemic corticosteroids are important in the treatment of severe acute exacerbations.

Assessment, treatment, and monitoring

- The goal of asthma treatment is to achieve and maintain clinical control.
- To aid in clinical management, a classification of asthma by level of control is recommended: controlled, partly controlled, or uncontrolled.
- Treatment should be adjusted in a continuous cycle driven by the patient's asthma control status and treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down.
- Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.
- The management approach based on control is outlined below:

Step 1	Step 2	Step 3	Step 4	Step 5
Asthma education and environmental control				
As needed rapid-acting β_2-agonist				
Controller options	Select one	Select one	Add one or more	Add one or both
	Low-dose ICS	Low-dose ICSs + LABA	Medium- or high-dose ICS + LABA	Oral corticosteroid
	Leukotriene modifier	Medium- or high-dose ICS	Leukotriene modifier	Anti-IgE treatment
	-	Low-dose ICS +leukotriene modifier	-	-
	-	Low-dose ICS +sustained-release theophylline	-	-

Management of exacerbations

- Repeated administration of rapid-acting inhaled β_2-agonists is the best method of achieving relief for mild to moderate exacerbations. Systemic corticosteroids should be considered if the patient does not immediately respond to rapid-acting inhaled β_2-agonists or if the episode is severe.

Clinical Guidelines	Recommendations
The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: **Guidelines for the Diagnosis and Management of Asthma (2007)**[22]	Diagnosis • To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction and alternative diagnoses must be excluded. • The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility and additional studies to exclude alternative diagnoses. • A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections and symptoms that occur or worsen at night. • Spirometry is needed to establish a diagnosis of asthma. • Additional studies such as pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. Treatment • Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations and reverse airflow obstruction. • The initial treatment of asthma should correspond to the appropriate asthma severity category. • 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. • Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing. • Quick relief medications include SABAs, anticholinergics and systemic corticosteroids. Long-term control medications • ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. • Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma. • When patients ≥12 years of age require more than a low-dose ICS, the addition of a LABA is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton. • Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventatively prior to exercise or unavoidable exposure to known allergens. • Omalizumab, an immunomodulator, is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy. • Leukotriene receptor antagonists (montelukast and zafirlukast) are

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
alternative therapies for the treatment of mild persistent asthma.
• LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma.
• LABAs should continue to be considered for adjunctive therapy in patients five years of age or older who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA.
• Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma.
• Tiotropium is a long-acting inhaled anticholinergic indicated once-daily for COPD and has not been studied in the long-term management of asthma.

Quick-relief medications
• SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm.
• There is inconsistent data regarding the efficacy of levalbuterol compared to albuterol. Some studies suggest an improved efficacy while other studies fail to detect any advantage of levalbuterol.
• Anticholinergics may be used as an alternative bronchodilator for patients who do not tolerate SABAs and provide additive benefit to SABAs in moderate-to-severe asthma exacerbations.
• Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations.
• The use of LABAs is not recommended to treat acute symptoms or exacerbations of asthma.

Assessment, treatment and monitoring
• A stepwise approach to managing asthma is recommended to gain and maintain control of asthma.
• Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control.
• The stepwise approach for managing asthma is outlined below:
<table>
<tr><th>Inter-mittent Asthma</th><th colspan="5">Persistent Asthma: Daily Medication</th></tr>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th><th>Step 6</th></tr>
<tr><td>Preferred
SABA as needed</td><td>Preferred
Low-dose ICS

Alternative
Cromolyn, leukotriene receptor antagonists, nedocromil, or theophylline</td><td>Preferred
Low-dose ICS+LABA or medium-dose ICS

Alternative
Low-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td>Preferred
Medium-dose ICS+LABA

Alternative
Medium-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td>Preferred
High-dose ICS+ LABA and consider omalizu-mab for patients who have allergies</td><td>Preferred
High-dose ICS+LABA+ oral steroid and consider omalizumab for patients who have allergies</td></tr>
</table>

Management of exacerbations
• Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is
</td></tr>
</table>

Clinical Guidelines	Recommendations
	recommended. Special populations • For exercise-induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. Leukotriene receptor antagonists may also attenuate exercise-induced bronchospasm, and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention; however, they are not as effective as SABAs. • The addition of cromolyn to a SABA is helpful in some individuals who have exercise-induced bronchospasm. • Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery. • Albuterol is the preferred SABA in pregnant women because of an excellent safety profile. • ICSs are the preferred treatment for long-term control medication in pregnant women. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.
National Institute for Health and Clinical Excellence: **Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)**[25]	Diagnosis • Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze. • The primary risk factor is smoking. • Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1 <80% predicted and FEV_1/FVC <70%. Treatment • Smoking cessation should be encouraged for all patients with COPD. • Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation. • Long-acting bronchodilators (β_2 agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators. • Once-daily long-acting anticholinergic antagonists are preferred compared to four-times-daily short-acting anticholinergic antagonists in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with an anticholinergic antagonist. o FEV_1 ≥50% predicted: LABA or long-acting anticholinergic antagonist. o FEV_1 < 50% predicted: either LABA with an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist. • In patients with stable COPD and FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist when ICSs are not tolerated or declined. • Consider a long-acting anticholinergic antagonist in patients remaining breathless or having exacerbations despite therapy with LABA and ICSs and vice versa. • Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects

Clinical Guidelines	Recommendations
	and costs. • In most cases, inhaled bronchodilator therapy is preferred. • Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation. • Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Combination therapy with β_2-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy. • Pulmonary rehabilitation should be made available to patients. • Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. <u>Management of exacerbations</u> • Patients with exacerbations should be evaluated for hospital admission. • Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial. • Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. • Oxygen should be given to maintain oxygen saturation above 90%. • Patients should receive invasive and noninvasive ventilation as necessary. • Respiratory physiotherapy may be used to help remove sputum. • Before discharge, patients should be evaluated by spirometry. • Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.

Conclusions

The single-entity respiratory β_2-agonists are Food and Drug Administration (FDA)-approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), reversible airway obstruction and/or exercise-induced asthma.[1-19] The agents in this class are classified as short-acting or long-acting β_2-agonists due to their pharmacokinetic differences. These agents are available in a variety of dosage forms, including solution for nebulization, aerosol inhaler, capsule for inhaler, dry powder inhaler, oral solution, tablet and solution for injection. Each of the short-acting respiratory β_2-agonists is available generically in at least one strength or formulation with the exception of pirbuterol (Maxair Autohaler®); however, there are no generic formulations for the long-acting β_2-agonists.[89] The short-acting β_2-agonists are generally dosed multiple times per day for the relief of asthma related symptoms. When used for maintenance treatment of COPD, the long-acting β_2-agonists are typically dosed twice daily, with the exception of indacaterol (Arcapta Neohaler®), which is administered once daily.[3,16-19]

The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program guidelines, as well as other national and international guidelines, recommend the use of short-acting β_2-agonists for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm. These medications should be used on an as-needed or “rescue” basis. Guidelines recommend that in the chronic management of asthma, long-acting β_2-agonists should be used as add-on therapy in patients not adequately controlled on an inhaled corticosteroid as an alternative to maximizing the dose of the inhaled corticosteroid. Long-acting β_2-agonists can also be used for exercise-induced bronchospasm and provide a longer period of coverage (typically 12 hours or more) compared to the short-acting β_2-agonists.[22,23]

The Global Initiative for Chronic Obstructive Lung Disease and National Institute for Clinical Excellence guidelines state that long-acting β_2-agonists also have a role in the treatment of COPD for patients who remain symptomatic even with current treatment with short-acting bronchodilators (i.e., short acting β_2-agonists and anticholinergics). The long acting β_2-agonists can be added to other regimens, including an anticholinergic agent, in efforts to decrease exacerbations.[24,25]

Overall, short-acting β_2-agonists have demonstrated similar efficacy and safety.[25-35] Guidelines do not recommend one long-acting agent over another, and head-to-head clinical trials have been inconclusive to determine "superiority" of any one agent. However, in the treatment of asthma, long-acting β_2-agonists should not be used as monotherapy or as rescue medications due to the potential risk of asthma-related deaths.[40,48]

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