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.[1-19] 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 effects.[1-19,20] 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 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 removal of the pirbuterol (Maxair®) CFC inhaler is December 31, 2013.[21]

Table 1. Current Medications Available in 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®*)	Treatment or prevention of bronchospasm in patients with asthma, prevention of exercise-induced bronchospasm	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 Tablet: 2 mg 4 mg	a
Levalbuterol (Xopenex®*, Xopenex® concentrate*,	Treatment or prevention of bronchospasm in patients with asthma	Meter dose aerosol inhaler (HFA): 59 µg§ (80 or 200 inhalations) Solution for nebulization:	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Xopenex HFA®)		0.31 mg 0.63 mg 1.25 mg (3 mL vials)	
Meta-proterenol*	Treatment or prevention of bronchospasm in patients with asthma, treatment of reversible bronchospasm occurring in association with emphysema and bronchitis	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg	a
Pirbuterol (Maxair Autohaler®)	Treatment or prevention of bronchospasm in patients with asthma	Breath activated aerosol inhaler: 200 µg (80 or 400 inhalations)	-
Terbutaline*	Treatment or prevention of bronchospasm in patients with asthma, treatment of reversible bronchospasm occurring in association with emphysema and bronchitis	Injection: 1 mg/mL (2 mL vial) Tablet: 2.5 mg 5 mg	a
Long Acting β_2-agonists			
Arformoterol (Brovana®)	Maintenance treatment of bronchoconstriction in patients with COPD	Solution for nebulization: 15 µg (2 mL)	-
Formoterol (Foradil®, Perforomist®)	Treatment or prevention of bronchospasm in patients with asthma, prevention of exercise-induced bronchospasm (Foradil®), maintenance treatment of bronchoconstriction in patients with COPD (Foradil®, Perforomist®)	Capsule for inhalation: 12 µg Solution for nebulization: 20 µg/2 mL	-
Indacaterol (Arcapta Neohaler®)	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease	Capsule for inhalation: 75 µg	-
Salmeterol (Serevent Diskus®)	Treatment or prevention of bronchospasm in patients with asthma, prevention of exercise-induced bronchospasm, maintenance treatment of bronchoconstriction in patients with COPD	Dry powder inhaler: 50 µg (28 or 60 inhalations)	-

COPD=chronic obstructive pulmonary disease, HFA=hydrofluoroalkanes
*Generic available in at least one dosage form or strength.
†Delivering 108 µg of albuterol (90 µg albuterol base).
‡Ventolin® available as 60 and 200 inhalations.
‡Delivering 45 µg levalbuterol base.

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 the clinical trials that compared albuterol to levalbuterol, inconsistent results were reported and have not consistently demonstrated improved outcomes with levalbuterol over albuterol. Moreover, studies have shown no significant differences between the two agents in the peak change in FEV_1 and the number and incidence of adverse events experienced.[22-32]
- The LABAs salmeterol and formoterol have been found to improve FEV_1 in patients with mild to moderate asthma who require persistent use of SABAs. 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 (OR, 1.63; 95% CI, 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (RR, 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. Respiratory β_2-agonists act predominantly 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, 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-acting and long-acting agents. The short-acting β_2-agonists (SABAs) consist of albuterol (ProAir HFA®, Proventil HFA®, Ventolin HFA®), levalbuterol (Xopenex®), 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 effects.[1-20] 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.

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 removal 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 the 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 also 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.[4] 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. For patients with a baseline forced expiratory volume in one second <50% predicted, the addition of oral corticosteroids is recommended for the management of acute exacerbations. 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	a
Levalbuterol (Xopenex®*, Xopenex® concentrate, Xopenex HFA®)	β_2-agonist	a
Metaproterenol*	β_2-agonist	a
Pirbuterol (Maxair Autohaler®)	β_2-agonist	-
Terbutaline* (Brethine®)	β_2-agonist	a
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[1-19]

Generic Name	Treatment or Prevention of Bronchospa-sm in Patients with Asthma	Prevention of Exercise-induced Bronchospa-sm	Maintenance Treatment of Bronchoconstri-ction in Patients with Chronic Obstructive Pulmonary Disease	Maintenance Treatment of Airflow Obstruction in Patients with Chronic Obstructive Pulmonary Disease	Treatment of Reversible Bronchospas-m Occurring in Association with Emphysema and Bronchitis
Short Acting β_2-agonists					
Albuterol	a	a			
Levalbuterol	a				
Metaproterenol	a				a
Pirbuterol	a				
Terbutaline	a				a
Long Acting β_2-agonists					

Generic Name	Treatment or Prevention of Bronchospa-sm in Patients with Asthma	Prevention of Exercise-induced Bronchospa-sm	Maintenance Treatment of Bronchoconstri-ction in Patients with Chronic Obstructive Pulmonary Disease	Maintenance Treatment of Airflow Obstruction in Patients with Chronic Obstructive Pulmonary Disease	Treatment of Reversible Bronchospas-m Occurring in Association with Emphysema and Bronchitis
Arformoterol			a		
Formoterol	a * (Foradil®)	a † (Foradil®)	a		
Indacaterol				a	
Salmeterol	a *	a	a		

*Only as concomitant therapy with a long-term control medication such as an inhaled corticosteroid.
†When administered on an occasional, as-needed basis.

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). Current treatment guidelines recognize the efficacy of these agents for their respective indications and note that all available agents are equally efficacious and give no preferential status to one agent over another.[22-25]

In the clinical trials that evaluated 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). In the clinical trials that compared albuterol to levalbuterol, inconsistent results were found.[26-36] In two studies (one retrospective, one prospective), levalbuterol resulted in a significantly lower hospitalization rate compared to albuterol.[26,27] In another trial, when the two agents were given 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] Additionally, studies have shown no significant differences between the two agents in the peak change in FEV_1 and the number and incidence of adverse events experienced.[26-36]

The LABAs salmeterol and formoterol have been found to improve FEV_1 in patients with mild to moderate asthma who require persistent use of SABAs. The SMART trial found that salmeterol had significant occurrences of combined respiratory-related deaths or respiratory-related life-threatening experiences compared to placebo (*P*<0.05).[37] 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.[38] Due to the results of these studies, salmeterol, formoterol, and arformoterol are assigned a black box warning stating that these agents may increase the risk of asthma related deaths.[16-19]

For the treatment of COPD, treatment guidelines state that no medication has been shown to modify the long-term decline in lung function associated with the disease. National guidelines recommend that treatment should focus on reducing the symptoms and complications of the disease.[24,25] All agents used in the treatment of COPD (i.e., inhaled corticosteroids, inhaled anticholinergics, β_2-agonists, and methylxanthines) can improve symptoms, exacerbations and complications of the disease. Long-acting bronchodilators are more effective and convenient than short-acting bronchodilators; however, short-acting bronchodilators should be considered initial empiric therapy.[24,25] 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 (OR, 1.63; 95% CI, 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (RR, 0.96; 95% CI, 0.89 to 1.02).[39]

The safety and efficacy of indacaterol were evaluated in randomized controlled trials that compared it to placebo and other agents used in the management of COPD.[40-49] 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).[40-49] 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 forced expiratory volume in one second (FEV_1) was observed; however, the effect did not clearly differ among the various doses evaluated.[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.[40-49]

Placebo-controlled trials demonstrate that within five minutes after administration of indacaterol, significant improvements in bronchodilation are achieved.[44-47] These results have also been observed when comparing indacaterol to salmeterol, salmeterol/fluticasone and tiotropium.[43,47,48]

In two studies, patients diagnosed with COPD were treated with arformoterol, salmeterol or placebo. These studies found that both arformoterol and salmeterol significantly improved morning trough FEV_1 throughout the 12 weeks of daily treatment compared to placebo (P<0.001 in both trials).[50,51] 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).[52] Currently, there are a lack of head-to-head randomized, double blind clinical trials to determine a preferential status of one agent over another for the treatment of COPD.

For the treatment of EIA, albuterol, metaproterenol, and formoterol have demonstrated an improvement in FEV_1 compared to placebo.[53-57] In one study, albuterol- and metaproterenol-treated patients had a lower incidence of exercise induced bronchospasm compared to placebo.[52] 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).[54]

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 diagnosed with asthma presenting to the ED (1 patient had been using levalbuterol the remainder albuterol as rescue prior to presenting to the emergency department)	N=547 Varying duration of hospitalizations	Primary: Hospital admission rate Secondary: LOS, ED LOS, intensification, number of aerosols, requirement for oxygen, and adverse effects	Primary: Compared with the albuterol group (45%), the levalbuterol group (36%) had a significantly lower hospitalization rate (*P*=0.02). Secondary: There were no significant differences between the albuterol and levalbuterol group concerning secondary outcomes, including adverse effects (*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 or older with a diagnosis of 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 and 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	DB, PRO, RCT Children 2 to 14 years of age with a known history of	N=129 Study was complete after patient received	Primary: Changes from baseline in clinical asthma score and the percent of	Primary: No significant differences between the treatment groups were found (*P* value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
needed) vs levalbuterol 1.25 to 2.5 mg via nebulization (plus standard treatment needed)	asthma presenting to a pediatric ED with an acute moderate or severe asthma exacerbation	5 doses, was admitted, or discharged	predicted FEV_1 after the first, third, and 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 were found (*P* value not reported). No significant differences between the treatment groups concerning adverse effects 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 who had been diagnosed with asthma for at least 30 days and had 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 scores 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 rate were demonstrated in the levalbuterol 0.63 mg and racemic albuterol 2.5 mg groups compared to placebo (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Nowak et al[30] Albuterol 2.5 mg via 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	DB, MC, PG, PRO, RCT Individuals 18 years of age and older presenting to the ED or clinic with an acute asthma exacerbation	N=627 1 month	Primary: Time to meet ED discharge criteria Secondary: Comparisons of FEV_1 change from baseline, the proportion of patients hospitalized, and the effect of plasma concentration of (*S*)-albuterol at presentation on FEV_1 response and hospitalization	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). 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 effects 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	DB, PC, PG, RCT Patients 12 years of age and older who did not smoke and had at least a 6-month history of chronic and stable asthma, demonstrating at least a 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, 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
vs 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 a history of asthma for at least 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 was 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 (1 dose)				
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 with documented diagnosis of at least mild asthma with a reversibility of at least 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 effects	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 and older with moderate to severe asthma with a 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. However, the most common

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				adverse event 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 and older 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 (defined as 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 with 2.5 mg albuterol, (39%), 0.63 mg levalbuterol (37%), and 3.75 mg levalbuterol (26%) after three doses (*P* value not reported). Secondary: Compared to baseline at 60 minutes post treatment, levalbuterol 1.25, 2.5, and 5 mg improved the median percent predicted FEV_1 by 33%-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).
Wolfe et al[58] 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 effects Secondary: Not reported	Primary: There was a significantly greater degree of bronchodilation with albuterol compared to metaproterenol from 2 to 8 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 effects 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[59] Albuterol via MDI vs formoterol via DPI vs placebo	MA, 45 AC or PC, RCT Studies in which formoterol was administered either with or without an ICS or other adjunct therapy were included in this analysis	N=8,369	Primary: Serous asthma exacerbations defined as (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 (from aerolizer or certihaler) of formoterol 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 with 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, 0.3; 95% CI, 0.03 to 3.5 and OR, 1.3; 95% CI, 0.4 to 3.7receiving formoterol, respectively). Among adults who reported using concomitant ICS at baseline, a trend toward fewer serious asthma exacerbations was seen in those receiving formoterol as compared with 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.
Salpeter et al[38] LABAs (formoterol via DPI) vs placebo	MA, 19 DD, PC, RCT Individuals diagnosed with asthma 15% of the participants were African American	N=33,826 All trials were at least 3 months	Primary: Severe asthma exacerbations requiring hospitalizations, life-threatening asthma exacerbations, and asthma-related deaths Secondary:	Primary: LABAs (formoterol and salmeterol) when compared to placebo 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), with similar risks seen in adults and children. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Not reported	
Boonsawat et al[60] 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 non-significant 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[61] 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 and older with a diagnosis of 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 with 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[62] Formoterol 12 µg via DPI and albuterol via MDI to use as needed (administered as separate	MC, OL, PG, RCT Individuals 18 years of age and older with moderate	N=259 3 months	Primary: The mean change in morning predose PEF for the entire treatment period	Primary: Over the 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). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
products) vs albuterol 100 µg via MDI to be used throughout the day as needed	persistent asthma		Secondary: Mean increase in evening predose PEF for the entire treatment period, day and night use of albuterol, and scores on the SGRQ	At visits three and five there was a significantly greater improvement in predose FEV_1 with formoterol compared to albuterol (P<0.01, P<0.05). At the conclusion of 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 significantly higher increase in symptom-free days and nights in the formoterol group when compared to albuterol (20, 30%; P<0.0001, P<0.003). A significantly higher decrease was seen in the SGRQ score with formoterol (-6.4) compared to albuterol (-3.5) (P=0.05).
Pleskow et al[63] 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, P<0.002) with no statistical difference between albuterol and placebo at this time. Secondary: Overall, at the last visit, both formoterol groups showed significant improvement at all time points vs 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, 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).
Bouros et al[64]	MC, OL, PG, RCT	N=132	Primary: Mean PEF during	Primary: There was a treatment effect of 20.36 L/minute in the combination group

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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	Individuals 18 years of age and older who were symptomatic on 500 µg daily of inhaled beclomethasone	12 weeks	final seven days of treatment Secondary: Overall PEF, asthma symptoms, rescue medication, and safety	over the patients receiving the double dose of corticosteroid (*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 corticosteroid (*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 corticosteroid (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[65] Metaproterenol via MDI vs pirbuterol via MDI	DB, MC, PG Asthmatic patients	N=133 12 weeks	Primary: Onset of action, peak effect, side effects, 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[66] Salmeterol 50 µg BID via DPI vs placebo Both groups received	DB, PC, PG, RCT Individuals 6 to 15 years of age with a documented history of reversible airway obstruction requiring β_2-agonist treatment for	N=426 12 months	Primary: Change from baseline in mean morning PEF Secondary: Percent of symptom-free nights and days, percent of nights and days with	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 salmeterol compared to 121 minutes for placebo (*P*<0.001). This

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
albuterol MDI to use as needed.	symptomatic control		no rescue inhaler, and incidence of asthma exacerbations	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[37] 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 and older with a diagnosis of 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 deaths or life-threatening	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%; *P*=0.022).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			experiences, and all-cause hospitalizations	
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 and older diagnosed with mild to moderate asthma requiring daily pharmacotherapy for at least 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[68] 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 inhaled corticosteroid dose.	DB, DD, MC, PG, RCT Individuals 18 years of age and older with chronic asthma currently receiving inhaled corticosteroids	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. This difference was statistically significant (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. There was no difference in the number of rescue-free days between the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				groups; however, there was an increase in percent of rescue-free nights in the salmeterol group (*P*<0.04).
Vervloet et al[69] Salmeterol 50 µg BID via DPI vs formoterol 12 µg BID via DPI	MC, OL, PG, RCT Individuals 18 years of age and older in the outpatient setting with moderate to severe reversible obstructive airway disease for at least 1 year and currently using regular inhaled corticosteroids (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[70] 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 inhaled corticosteroids	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[71] 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 inhaled corticosteroid dose.	MC, OL, PG, RCT Individuals 18 years of age and older with moderate to severe persistent asthma sub-optimally controlled on inhaled corticosteroids 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 effects between groups (*P* value not reported).
Martin et al[72] 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 (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 effects during the study. A difference that was not statistically significant (*P* value not reported).
Brambilla et al[73] 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 than with 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 (30%) compared to the terbutaline group (9%) stopped using rescue albuterol during the day (*P*=0.004), but 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[74] 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 effects	Primary: During months one to two of the study there was significantly less airway hyperresponsiveness with beclomethasone when 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, *P*=0.02) with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				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, 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[75] 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, quality of life 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 quality of life; 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[76] Terbutaline 0.5 mg as needed via DPI vs formoterol 4.5 µg as needed via DPI	DB, PG, RCT Individuals 18 years of age and older with asthma for at least six months and treated with a constant dose of inhaled corticosteroid for at	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
	least 4 weeks		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). Both treatments were well tolerated.
Hermansson et al[77] Terbutaline 500 µg QID via DPI vs salmeterol 50 µg BID via DPI	MC, OL, PG, RCT Individuals 18 years of age and older 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, *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, *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, *P*=0.916). Secondary: Not reported
Hancox et al[78] Terbutaline 1,000 µg QID via DPI vs budesonide 400 µg BID via DPI vs terbutaline 1,000 µg QID	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	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

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and budesonide 400 µg BID via DPI vs placebo			compliance	was higher with the combined treatment than either active medication alone (P<0.0002), but no significant difference was seen between the two 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, P<0.001), but did not differ significantly between the groups. Rescue inhaler use significantly decreased in all groups compared with 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[39] 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).

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				Secondary: The pooled result showed that there was no significant difference in 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 regard to the increase in FEV_1 with ICS compared to LABA treatment (MD, -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 (MD, -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 (MD, 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 versus salmeterol (OR 1.05; 95% CI 0.92 to 1.18) and budesonide versus formoterol (OR 0.96; 95% CI 0.76 to 1.20) were observed.
Hanania et al[79] (abstract) Arformoterol 15 µg BID via nebulizer (ARF 15)	DB, DD, MC, RCT Patients with COPD	N=443 6 months	Primary: Post-treatment adverse events, COPD exacerbations,	Primary: Proportion of patients with post-treatment adverse events in the ARF 15, ARF 25 and FORM groups was 67.8, 76.2 and 66.7% respectively (*P* value not reported).

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vs arformoterol 25 µg BID via nebulizer (ARF 25) vs formoterol 12 µg BID via DPI (FORM)			pulmonary function, dyspnea, use of rescue SABAs and ipratropium, SGRQ Secondary: Not reported	The proportion of patients with COPD exacerbation in the ARF 15, ARF 25 and FORM 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. Mean change from baseline in peak FEV_1 in the ARF 15, ARF 25 and FORM groups was 0.30, 0.34 and 0.26 L respectively (*P* value not reported). Mean change from baseline in mean 24 hour trough FEV_1 in the ARF 15, ARF 25 and FORM groups was 0.10 L, 0.14 L and 0.09 L respectively (*P* value not reported). Mean change from baseline in respiratory capacity in the ARF 15, ARF 25 and FORM 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.
Baumgartner et al[50] Arformoterol 15 µg BID via nebulizer vs arformoterol 25 µg BID via nebulizer vs arformoterol 50 µg QD via	DB, MC, PC, RCT Men and women 35 years of age and older with primary diagnosis of COPD and FEV_1 ≤65% predicted and >0.70 L, with Medical Research Council Dyspnea Scale Score ≥2, an FEV_1/FVC ratio	N=717 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 averaged over time	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 $AUC_{0\text{-}12\ h}$ vs placebo (*P*<0.001). Greater improvement in FEV_1 $AUC_{0\text{-}12\ h}$ was also observed for the arformoterol group compared to the salmeterol group over the 12 week period (*P*<0.024).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
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.	≤70%, and a minimum smoking history of 15 pack-years at baseline		zero to 12 hours after study drug administration	Compared with 15 µg, 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[51] arformoterol 15 µg BID via nebulizer vs arformoterol 25 µg BID via nebulizer vs arformoterol 50 µg QD via nebulizer vs salmeterol 42 µg BID via MDI	DB, PC, MC, RCT Men and women 35 years of age and older with a primary diagnosis 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 averaged over time zero to 12 hours after study drug administration	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 $AUC_{0\text{-}12\ h}$ vs 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 placebo Patients were allowed to use albuterol MDI as a rescue therapy and ipratropium MDI as a supplemental medication as needed.				
Benhamou et al[80] Formoterol 24 µg via DPI (1 dose) vs albuterol 400 µg inhaled via DPI (1 dose) vs placebo	DB, PC, RCT, XO Individuals 40 to 75 years of age with stable, reversible COPD	N=25 1 dose	Primary: AUC (zero to30 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 (-0.32; *P*<0.0001). Secondary: There were no statistical differences between the two active medication groups in secondary endpoints, and each had a similar onset (5 minutes; *P* value not reported). No serious adverse effects or clinically relevant changes in vital sign were observed in any of the groups (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cote et al[52] Formoterol 12 µg BID via DPI vs salmeterol 50 µg BID via MDI	AC, MC, OL, PG, RCT Patients ≥40 years of age who were current or previous smokers (>10 pack-years) with a diagnosis of COPD according to the ATS guidelines, and a prebronchodilator FEV_1 >35% of predicted normal, an FEV_1 ≤70% of forced vital capacity within the last 6 months, use of salmeterol 50 µg BID for ≥4 weeks before screening and able to perform the six-min walk test	N=270 28 days	Primary: Change from baseline in FEV_1 five minutes postdose on day 28 Secondary: Changes from baseline in FEV_1 at 30 and 60 min postdose on day 28, in distance walked in the six-minute walk test on day 28, and changes in Borg scores for perception of breathlessness after the six-minute walk test	Primary: Changes from baseline in FEV_1 at five min postdose on day 28 favored treatment with formoterol over salmeterol (approximately 0.13 vs 0.07 L, respectively; *P*=0.022). Secondary: Changes from baseline in FEV_1 on day 28 were significantly greater with formoterol compared to salmeterol at 30 and 60 min 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[89] Formoterol 9 µg single dose via DPI vs salmeterol 50 µg single dose via MDI vs	DB, DD, MC, PC, RCT, XO Patients ≥40 years of age with a diagnosis of COPD, current or previous smoker with a smoking history equivalent to ≥10 pack years and post-	N=109 3 weeks	Primary: Change in FEV_1 at five minutes postdose Secondary: Proportion of patients achieving ≥12% increase in FEV_1 at five minutes postdose; proportion of patients who	Primary: The increase in FEV_1 with formoterol at five minutes postdose was significantly higher compared to salmeterol (7.2 vs 4.1%; *P*=0.009) and placebo (0.7%; *P*<0.001. This corresponded to an increase of 127, 73 and 12 mL, respectively. Secondary: The proportion of patients with a ≥12% increase in FEV_1 at five minutes postdose was significantly higher with formoterol compared to salmeterol and placebo (23.1% vs 9.2 and 6.4%, respectively; *P*<0.05 for both). The difference in the proportion of patients achieving a ≥12% increase in FEV_1 at five minutes postdose was not statistically significant

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placebo There was a two to seven day washout period between treatment administrations.	bronchodilator FEV_1/FVC <70% and post-bronchodilator FEV_1 in the range ≥50 to ≤80% of predicted normal		achieved ≥12% increase in FEV_1 at each time point between 10 and 120 minutes postdose; time to reach ≥12% increase in FEV_1; average FEV_1 during the first 15 minutes postdose (AUC_{15}]); and average FEV_1 during 120 minutes postdose (AUC_{120}) and adverse events	between salmeterol and placebo (*P*=0.549). The cumulative proportion of patients achieving a ≥12% increase in FEV_1 at each time point between 10 and 120 minutes postdose was larger in the formoterol group compared to the salmeterol and placebo treatment groups (*P* values not reported). In addition, the proportion of patients achieving this increase was higher with salmeterol compared to placebo (*P* value not reported). The time to achieve a ≥12% increase in FEV_1 was significantly shorter for formoterol compared to salmeterol (HR, 2.09; 95% CI, 1.31 to 3.35; *P*=0.002) and placebo (HR, 6.53; 95% CI, 3.55 to 12.02; *P*<0.001). The time for salmeterol was also significantly shorter compared to placebo (HR, 3.13; 95% CI, 1.77 to 5.55; *P*<0.001). The average increase in FEV_1 during the first 15 minutes postdose was significantly higher with formoterol compared to salmeterol and placebo (6.4% vs, 4.1 and 1.2%, respectively; *P*<0.005 for both). In addition, salmeterol significantly increased FEV_1 during the first 15 minutes compared to placebo (*P*<0.001). At 120 minutes postdose, there was no statistically significant difference in FEV_1 between formoterol and salmeterol (9.6 vs 8.2%, respectively; *P*=0.245); however, both treatments significantly increased FEV_1 relative to placebo (*P*<0.001 for both). The number of adverse events was low, given the single-dose administration of each agent. No serious adverse events were reported. There were no changes in blood pressure or pulse rate with any of the treatments.
Cazzola et al[81] Formoterol 12 µg, 12, and 24 µg via DPI vs	RCT, SB, XO Patients 51 to 77 years of age with COPD, having an acute exacerbation defined as	N=16 2 days	Primary: Maximum FEV_1 value during the dose-response curve Secondary:	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

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albuterol 200 µg, 200, and 400 µg via MDI Doses administered on two consecutive days.	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		Spirometric data (inspiratory capacity and FVC), pulse rate, SpO_2 values	after 48 µg of formoterol and 800 µg of albuterol. There was a significant increase in change 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[82] Formoterol 20 µg via nebulizer vs formoterol 12 µg via DPI vs placebo	DB, MC, PC, PG, RCT Patients 40 years of age and older diagnosed with COPD, including persistent cough, sputum, production, and/or shortness of breath on effort, a current or prior 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	N=351 12 weeks	Primary: Percent change from baseline in the standardized absolute AUC_{0-12} for FEV_1 measured over 12 hours following the morning dose at week 12 Secondary: Change in the quality of life from baseline in the total SGQR, symptom and impact scores, and rescue medication use	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). 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). 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). All groups had similar amounts of albuterol usage, approximately 2.7 puffs/day, at baseline. Albuterol use remained consistent throughout the study for the placebo group. There was a 42% decrease in albuterol use

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				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[83] (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 disease control, and dyspnea	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 ($P \leq 0.0001$). Patient satisfaction and perception of disease control were significantly 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[84] Levalbuterol 1.25 mg via nebulizer vs albuterol 2.5 mg via nebulizer vs albuterol/ipratropium 2.5/0.5 mg via nebulizer	DB, RCT, XO Patients with a diagnosis of COPD, mean age of 69 years, 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	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	COPD medications in previous month), and the ability to withhold bronchodilator medications for the washout period prior to each testing			FEV_1) was significantly increased in all three active groups compared to placebo at 0.5 hours ($P \leq 0.03$) and this persisted at 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 ($P<0.05$) and 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 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).

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Hanania et al[85] 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, transition dyspnea index, CRDQ, CBSQ, exacerbations, and supplemental albuterol use	Primary: 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. 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: 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 dyspnea index observed 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. Statistically significant reduction in supplemental albuterol use in the fluticasone/salmeterol group compared to the fluticasone monotherapy group (P=0.036) and placebo (P=0.002). Numerical reduction in supplemental albuterol use in the fluticasone/ salmeterol group compared to the salmeterol monotherapy group. Statistically significant increase in CRDQ scores in the fluticasone/ salmeterol group compared to placebo (P=0.006). Statistically significant increase in CRDQ scores in the fluticasone monotherapy group compared to placebo (P=0.002). Statistically significant increase in CBSQ scores in the fluticasone/

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				salmeterol group and the fluticasone monotherapy group compared to placebo ($P \leq 0.017$).
Vogelmeier et al[86] Salmeterol 50 µg BID vs tiotropium 18 µg QD Patients receiving a fixed-dose ICA/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-	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 antibiotics or hospitalization	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; $P<0.001$). The annual rate of exacerbations was 0.64 in the tiotropium group and

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blind treatment phase.	within the previous year			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[40] 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. The following medications were prohibited: long and short acting anticholinergics, LABA/ICS combination products, SABA/short	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 5 minutes to 4 hours, 5 minutes to 1 hour and 1 hour to 4 after last dose hours 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 significantly higher peak FEV_1 compared to placebo at day 1 and week 12, with least-squares 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 least-squares mean differences of 170±24, 180±24 and 170±24 mL, respectively (*P*<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
acting anticholinergic combination products, LABA, SABA, xanthine derivatives and parenteral and oral corticosteroids.				
Kornmann et al[41] 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 ICS monotherapy at an equivalent dose. Salbutamol was provided for use as needed.	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 vs placebo Secondary: Trough FEV_1 at 12 weeks vs salmeterol, FEV_1 at day 2 and weeks 12 and 26, health status, diary assessments, dyspnea; 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 (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 significantly "superior" at weeks 12 and 26 compared to salmeterol (*P*<0.001 for both). Throughout the trial, 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 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 (≥4 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 (±SE) percentage days of poor COPD control over 26 weeks was 34.10±1.82% with both indacaterol and salmeterol compared to 38.10±1.85% with placebo (*P*=0.058 and *P*=0.057). In addition, compared to patients receiving salmeterol, patients receiving indacaterol

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				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. 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[42] INVOLVE Indacaterol 300 µg QD vs indacaterol 600 µg QD vs formoterol 12 µg BID vs placebo Patients previously on LABA/ICS combination	DB, DD, 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=129 1 year	Primary: Trough FEV_1 at 12 weeks Secondary: Days of poor COPD control, SGRQ score, time to first exacerbation, spirometry, TDI score, exacerbation rates, BODE index, safety	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 (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. Secondary: Both doses of indacaterol were significantly "superior" to placebo (least-squares mean, 38.3) 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 (least-squares mean, 41.3 and 41.3) 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%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
products were switched to ICS monotherapy at an equivalent dose. Salbutamol was provided for use as needed. Other bronchodilators or corticosteroids were not allowed unless to treat a COPD exacerbation.				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 (least-squares mean, 1.7 and 2.9 L/minute) 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 (least-squares mean, 1.22 and 1.57) 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; 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-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[43] INSIST Indacaterol 150 µg QD vs salmeterol 50 µg BID 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.	DB, DD, MC, PG, RCT 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=1,123 12 weeks	Primary: Change in FEV_1 AUC from 5 minutes post dose to 11 hours and 45 minutes postdose at 12 weeks Secondary: Trough FEV_1; FEV_1 AUC5 minutes-4 hour, 5 mininutes-8 hour and 8 hour-11 hours45 minutes at 12 weeks; FEV_1 on day ½ and week 12; FVC at 12 weeks; dyspnea; safety	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: 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). FEV_1 at day ½ with

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Salbutamol was provided for use as needed.				indacaterol was higher compared to salmeterol at most time points, with significance only achieved at six of the 11 assessments (*P* values not reported). 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 (≥1 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 frequently reported (1.1 vs 0.4%; *P* values not reported).
Magnussen et al[44] INPUT Indacaterol 300 µg QD, administered in the morning (AM) vs indacaterol 300 µg QD,	DB, DD, PC RCT, XO Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, post-	N=96 12 weeks	Primary: Trough FEV_1 at 14 days Secondary: FEV_1 at individual time points on day 1 of each treatment period, trough FVC at 14 days, patient-	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
administered in the evening (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, if the dose and regimen were stable for 1 month prior to screening.	bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%		reported symptom assessment, safety	Secondary: For individual time point FEV_1 values on day 1, 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 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[45] INSURE Indacaterol 150 or 300 µg, administered as a single dose	DB, MC, RCT, XO Patients ≥40 years of age with moderate to severe COPD,	N=89 5 single dose treatment periods, separated by a 4	Primary: FEV_1 at five minutes vs placebo Secondary: FEV_1 at five minutes	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
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 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	smoking history ≥20 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%	to 7 day washout period	vs 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	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). 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
acting anticholinergic combination products, other LABAs, SABAs, xanthine derivatives and parenteral or oral corticosteroids.				
Donohue et al[46] INHANCE Indacaterol 150 µg QD vs indacaterol 300 µg QD vs tiotropium 18 µg QD vs placebo Patients randomized to tiotropium received OL treatment. Albuterol was permitted for use as needed.	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 vs placebo Secondary: Trough FEV_1 at 12 weeks vs tiotropium, FEV_1 at five minutes on day 1, TDI, diary card-derived symptom variables, SGRQ, time to first COPD exacerbation, safety	Primary: The difference between both doses of indacaterol and placebo in trough FEV_1 was 180 mL, which exceeded the prespecified minimum clinically important difference 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 1 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 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 ($P \leq 0.001$ 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 ($P \leq 0.001$). The changes in baseline in morning and evening PEF (L/minute) were significantly greater with both doses of indacaterol compared to placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(*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. Aside from this, cough within five minutes was observed in an average of 16.6 and 21.3% of patients per visit who were receiving indacaterol 150 and 300 µg, 0.8% of patients receiving tiotropium and 2.4% of patients receiving placebo (*P* values not reported). This cough typically had a median duration of six seconds and was not associated with bronchospasm or with increased discontinuation rates. Otherwise, adverse events were similar across treatment.
Vogelmeir et al[47] INTIME Indacaterol 150 µg QD vs indacaterol 300 µg QD vs tiotropium 18 µg QD	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	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,	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 least-squares mean difference of 50 mL; this did not meet the requirement for superiority.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo The trial consisted of three 14 day treatment periods, each of which was 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, 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. The following medications were not permitted after the screening visit: long and short acting anticholinergics, LABAs, SABAs, xanthine	≥30% predicted and FEV_1/FVC <70%		safety	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 both the first day and after 14 days of treatment, 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 1, 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
derivatives and parenteral or oral corticosteroids.				
Buhl et al[48] INTENSITY Indacaterol 150 µg QD 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.	DB, DD, MC, PG, RCT 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=1,593 12 weeks	Primary: Trough FEV_1 at 12 weeks Secondary: FEV_1 and FVC at individual time points, TDI, SGRQ, use of rescue medication, diary card-derived symptom variables, safety	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). Subsequent criteria for superiority were not met. Secondary: After five minutes on day 1, 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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).
Chapman et al[49] 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 with 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 with 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 with to placebo (*P*<0.001 for both comparisons). The

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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). 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.
Kinoshita et al[90] Indacaterol 150 µg QD vs indacaterol 300 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with moderate to severe COPD and a smoking history of ≥20 pack-years were enrolled if post-bronchodilator FEV_1 ≤80% and ≥30% predicted and FEV_1/FVC <70%	N=347 12 weeks	Primary: 24 hour postdose trough FEV_1 Secondary: Trough FEV_1 after two, four and eight weeks, individual time-point FEV_1 and FVC on day one and peak FEV_1 on day one, health status, diary card assessments, dyspnea, rescue medication use, safety and tolerability	Primary: The trough FEV_1 at week 12 for indacaterol 150 µg, indacaterol 300 µg and placebo were 1.34 L, 1.37 L and 1.17 L, respectively (*P*<0.001 for both compared to placebo). Secondary: Both indacaterol 150 µg and 300 µg treatment groups had significantly greater trough FEV_1 values at weeks two, four and eight compared to placebo (*P*<0.001). The FEV_1 values for both indacaterol doses were significantly greater at all post-baseline time points on day one compared to placebo (*P*<0.001 for all time points). Similarly, both indacaterol doses provided statistically significant increases in FVC compared with placebo at all post-baseline time points on day one (*P*<0.001). The TDI total scores for both indacaterol doses were significantly greater than placebo at 12 weeks (*P*<0.05). Similarly, TDI total scores were significantly greater with both indacaterol doses compared to placebo at weeks four (*P*<0.001) and eight (*P*<0.05). A greater proportion of patients in both indacaterol groups had a TDI total score ≥1 at weeks 4, 8 and 12 compared to placebo (*P*<0.05 for both indacaterol doses compared to placebo). The SGRQ total scores at week 12 were significantly improved compared to placebo for indacaterol 150 µg (*P*=0.005) and indacaterol 300 µg (*P*=0.001). This improvement was consistent across all components of the SGRQ, with scores for symptoms, activity and impacts all significantly lower for both indacaterol doses than placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Both doses of indacaterol were associated with a greater proportion of patients reporting "nights with no night time awakenings" (P<0.05) and "days able to perform usual daily activities" (P<0.001) compared to the placebo group. There was no statistically significant difference in albuterol use between either indacaterol dosage and placebo. The overall incidence of adverse events was 49.1% with both indacaterol doses and 59.0% with placebo. The most common adverse events were COPD worsening, followed by nasopharyngitis. No cardiac adverse events were reported in the indacaterol treatment groups.
Lee et al[87] Exposure to inhaled corticosteroids, 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, inhaled corticosteroids and LABAs were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for inhaled corticosteroids 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 with 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 inhaled corticosteroids (OR, 0.88; 95% CI, 0.79 to 1.00), however this also did not reach statistical significance. 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 inhaled corticosteroids 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:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 inhaled corticosteroids, 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 inhaled corticosteroids 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, inhaled corticosteroids 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[53] Albuterol 0.18 mg, two inhalations 15 minutes prior to exercise via MDI vs metaproterenol 1.3 mg, two inhalations 15 minutes prior to exercise via MDI vs	RCT, SB, XO Patients 12 to 17 years of age with bronchial asthma and found to have exercised-induced bronchospasm (FEV_1 >20% of pre-exercise level) following a treadmill exercise test	N=18 4 days	Primary: Mean percentage increase in FEV_1 five minutes after medication, mean workload for exercise challenges, mean decrease in FEV_1 from baseline, and the number of patients in whom bronchoconstriction was blocked over time	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 with placebo (*P*<0.0005). A significantly greater increase (*P*<0.01) was also 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			Secondary: Not reported	(*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[54] Albuterol 180 µg prior to exercise challenge via MDI vs formoterol 12 µg prior to exercise challenge via DPI vs formoterol 24 µg prior to exercise challenge via DPI vs placebo	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: 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*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				value not reported). There was no statistical difference in the percent of patients experiencing adverse effects in all of the groups (no *P* value reported).
Richter et al[55] 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 Non smoking 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 with 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[56] Montelukast 10 mg orally once in the evening vs salmeterol 100 µg, two inhalations BID via DPI	DB, PG, RCT Patients 15 to 45 years of age who had been nonsmokers for at least 1 year and had a smoking history of less than 15 pack-years; patients had a	N=191 8 weeks	Primary: Change from baseline in the maximal percentage decrease in FEV_1 at the end of eight weeks of treatment Secondary: Change from baseline for maximal	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 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	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		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%	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[57] Montelukast 10 mg orally QD in the evening vs salmeterol 50 µg BID via DPI vs placebo	DB, MC, PG, RCT Patients 15 to 45 years of age with at least a 1-year history of asthma, documentation of exercise-induced bronchospasm in the past year, and were uncontrolled on inhaled corticosteroid for at least 2 months	N=122 4 weeks	Primary: Effect on the maximum FEV_1 after β_2-agonists administered to patients with four weeks of treatment with placebo, montelukast, or salmeterol Secondary: Effects of treatment on pre-exercise	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 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			FEV_1, exercise exacerbation, rescue bronchodilation, time to recovery to pre exercise FEV_1 level and average CEAQ	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[88] 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 as partly defined by the American Thoracic Society, stable chronic airway obstruction with no hospital admissions for an exacerbation and no major change in medication for at least 4 weeks prior to screening visit,	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 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and an initial FEV_1 of ≥40% of the predicted value when not receiving a bronchodilator			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, 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, SB=single blinded, XO=crossover
Miscellaneous abbreviations: AUC=area under the curve, 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, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, HFA=hydrofluoroalkane, LABA=long acting β_2-agonists, LOS=length of stay, MDI=metered dose inhaler, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, SABA=short acting β_2-agonists, SGRQ=St. George's Hospital Respiratory Questionnaire

Special Populations

Table 5. Special Populations[1-18]

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 (HFA inhaler dosage form). 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. Approved for use in children six 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
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.	B	Unknown
Long Acting β_2-agonists					
Arformoterol	Dosage adjustment not required in the elderly population. Safety and efficacy in children have not been established.	No dosage adjustment required.	Use with caution in patients with hepatic dysfunction.	C	Unknown
Formoterol	Dosage adjustment not required in the elderly population. 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. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	No dosage adjustment required; not studied in severe hepatic dysfunction.	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
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

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-19]

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol *	Metaproterenol †	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Cardiovascular																
Angina	a	a	-	a	a	a	a	-	-	a	a	-	-	-	-	-
Arrhythmias	a	-	-	a	<2	a	a	-	a	a	a	-	-	a	-	-
Arteriosclerosis	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Chest pain	<1	<1	0.9 to 1.7	<3	7	1.9 to 3.2	-	-	<2	a	-	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	a	a	1	a	a	a	a	-	<2	a	a	0.4	-	4	-	-
Hypotension	-	-	-	a	a	a	a	-	<2	-	a	-	<1	-	-	-
Myocardial infarction	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Pallor	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Palpitations	<1	2.4 to 5.0	-	<3	a	a	a	-	-	-	a	3.8	1.3 to 1.7	a	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	a	a	a	-	2.7 to 2.8	a	6.1	17.1	1.2 to 1.3	a	3.5	1.3 to 1.5
Vasodilations	-	-	-	a	-	-	-	-	-	-	-	-	-	-	1	-
Central Nervous System																
Agitation	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Anxiety	-	-	-	<3	-	1.5	-	-	2.7	-	-	-	<1	≥1	1	-
Asthenia	-	-	-	-	≥2	-	-	-	3	-	-	-	-	-	2	-
Ataxia	-	-	-	<3	-	-	-	-	-	-	-	-	-	-	-	-
Cerebral infarct	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Central nervous system stimulation	a	a	-	a	a	-	-	-	-	a	-	-	-	-	-	-
Confusion	-	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol *	Metaproterenol †	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Depression	-	-	-	<3	-	-	-	-	-	-	-	-	<1	-	-	-
Dizziness	3	1.5 to 2.0	4	3	a	1.6	2.4	-	1.4 to 2.7	2.7	a	2.4	0.6 to 1.2	4	3.5	1.3 to 10.2
Excitement	2 to 20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fatigue	1	-	-	-	a	a	a	-	-	-	a	1.4	<1	-	-	11.7-9.8
Hallucinations	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Headache	4	7.0 to 18.8	3	7	≥2	a	a	5.1	7.6 to 11.9	a	1.1	7	1.3 to 2.0	13 to 17	7.5	7.8 to 8.8
Hyperactivity	2	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-
Hyperkinesia	4	-	-	<3	-	-	-	-	-	-	-	-	<1	-	-	-
Hypokinesia	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Insomnia	1 to 2	2.0 to 2.4	1	a	a	1.5	2.4	-	<2	a	a	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	a	a	-	2.8 to 9.6	a	4.8	20.2	4.5 to 6.9	a	35	16.9 to 30.7
Numbness in extremities	-	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-
Paralysis	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Paresthesia	-	-	-	-	<2	-	-	-	<2	-	-	-	-	a	<1	-
Restlessness	-	<1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rigors	-	-	-	<3	-	-	-	-	-	-	-	-	-	-	-	-
Sensory disturbances	-	-	-	-	-	-	-	-	-	-	-	0.2	-	a	-	-
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	a	-	6.8	a	1.6	16.9	1.3 to 6.0	a	15	7.8 to 38.0
Vertigo	a	a	-	a	-	-	-	-	-	a	-	-	-	-	-	-
Weakness	<1	2	-	-	-	-	-	-	-	-	-	0.2	<1	-	-	0.5 to

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol *	Metaproterenol †	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
																1.3
Dermatological																
Acne	-	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-
Angioedema	a	a	-	a	-	-	-	-	a	a	-	-	-	a	-	-
Bruising	-	-	-	-	-	-	-	-	-	-	-	-	0.6	-	-	-
Contact dermatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Dry skin	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Eczema	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Flushing	-	a	-	-	-	-	-	-	-	-	-	-	<1	-	-	2.4
Herpes simplex	-	-	-	-	<2	-	-	-	-	<2	-	-	-	-	-	-
Herpes zoster	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Hives	-	-	-	-	-	-	-	-	-	-	-	0.2	-	-	-	-
Injection site pain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.5 to 2.6
Photodermatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	>1	-	-
Pruritus	-	-	-	-	-	1.5	-	-	-	-	-	0.4	<1	-	-	-
Rash	a	a	-	<3	4	1.1	-	-	7.5	a	-	-	<1	4	<1	-
Skin/appendage infection	-	-	1.7	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin discoloration	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Skin hypertrophy	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Skin reaction	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urticaria	a	a	0.9 to 1.7	a	-	-	-	-	3	a	-	-	-	3	-	-
Endocrine and Metabolic																
Decrease glucose intolerance	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diabetes	-	-	-	<3	-	-	-	>2	-	-	-	-	-	-	-	-
Hyperglycemia	-	-	-	a	a	a	a	>2	-	-	-	-	-	≥1	-	-
Hypoglycemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hyperlipidemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Metabolic acidosis	-	-	-	a	a	a	a	-	-	-	-	-	-	-	-	-
Weight gain	-	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-
Gastrointestinal																
Abdominal pain	-	-	-	-	-	a	-	-	1.5	-	-	-	<1	-	-	-
Anorexia	-	-	-	-	-	-	-	-	-	-	-	-	<1	-	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol *	Metaproterenol †	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
Constipation	-	-	-	-	<2	-	-	-	-	<2	-	-	-	-	-	-
Dental discomfort	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Diarrhea	-	-	-	<3	6	-	4.9	-	1.5 to 6.0	-	-	1.2	1.3	-	-	-
Dry mouth	-	-	-	<3	a	1.2	3.3	-	<2	-	a	0.4	1.3	-	1.5	-
Dyspepsia	-	-	1	-	-	a	-	-	1.4 to 2.7	-	-	-	-	-	-	-
Dyspeptic symptoms	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Epigastric pain	<1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Eructation	-	-	-	<3	-	-	-	-	-	-	-	-	-	-	-	-
Flatulence	-	-	-	<3	-	-	-	-	-	-	-	-	-	-	-	-
Gastritis	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Gastroenteritis	-	-	0.9 to 3.4	-	-	a	-	-	<2	<2	-	-	-	-	-	-
Gastrointestinal infections	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Gastrointestinal symptoms/ distress	2	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-
Hyposalivation	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Increased appetite	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Loss of appetite	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Melena	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Nausea	-	2.0 to 4.2	0.9 to 1.7	10	a	a	4.9	2.4	<2	a	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	a	a	-	4	-	-	-	-	-	-	-	0.8	0.6	-	-	-
Vomiting	a	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	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol *	Metaproterenol †	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
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	-	-	-	-	-	-	-	-	-	-	-
Hypokalemia	-	-	-	a	a	a	a	-	-	-	-	-	-	-	-	
Liver enzyme elevation	-	-	-	-	-	a	-	-	-	-	-	-	-	-	a	-
Metabolic acidosis	-	-	-	-	-	a	-	-	-	-	-	-	-	-	-	-
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	-	a	a	1.7	a	>2	-	-	-	-	-	3	-	-
Muscle spasm	-	-	-	-	-	-	-	-	-	-	-	0.2	-	3	-	-
Muscle stiffness	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Muscle tightness	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Muscle rigidity	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Musculoskeletal inflammation	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Myalgia	-	-	-	-	-	a	-	-	<2	<2	-	-	-	≥1	-	-
Neck rigidity	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol *	Metaproterenol †	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
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	a	-	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	-	a	-	7	-	-
Bronchospasm	a	a	-	a	-	-	-	-	-	-	-	a	-	a	-	-
Carcinoma of the lung	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Chest infection	-	-	-	-	-	2.7	-	-	-	-	-	-	-	-	-	-
Chronic Obstructive pulmonary disease	-	-	-	-	≥2	-	-	-	-	-	-	-	-	-	-	-
Cough	<1	-	-	5	-	-	-	6.5	1.4 to 4.1	a	-	0.2	1.2	5	-	-
Drying of oropharynx	a	a	-	a	-	-	-	-	-	a	-	-	-	-	-	-
Dysphonia	-	-	-	<3	-	1	-	-	-	-	-	-	-	-	-	-
Dyspnea	-	-	-	<3	4	2.1	-	-	a	a	-	a	-	-	-	2
Epistaxis	1	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-
Hoarseness	a	-	-	a	-	-	-	-	-	-	-	-	-	-	-	-
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	-	-	-	a	-	-	3.3	5.3	-	-	-	-	-	-	-	-
Oral mucosal abnormality	-	-	-	-	-	-	-	-	-	-	-	-	-	≥1	-	-
Oropharyngeal edema	a	a	-	<3	-	-	-	-	-	-	-	-	-	-	-	-
Oropharyngeal pain	-	-	-	-	-	-	-	2.2	-	-	-	-	-	-	-	-
Pharyngitis	-	-	-	14	-	3.5	-	-	3.0 to	6.6 to	-	-	-	6	-	-

Adverse Event(s)	Albuterol*	Albuterol†	Albuterol‡	Albuterol¶	Arformoterol‡	Formoterol#	Formoterol‡	Indacaterol#	Levalbuterol‡	Levalbuterol¶	Metaproterenol *	Metaproterenol †	Pirbuterol§	Salmeterol#	Terbutaline†	Terbutaline**
									10.4	7.9						
Respiratory disorder	-	-	-	5	-	-	-	-	-	-	-	-	-	-	-	-
Rhinitis	-	-	-	16	-	a	-	-	2.7 to 11.1	7.4	-	-	-	4	-	-
Sinus headache	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Sinusitis	-	-	-	-	5	2.7	-	>2	1.4 to 4.2	-	-	-	-	4	-	-
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	-	-
Cyst	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Digitalis intoxication	-	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Dilated pupils	<1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear pain	-	-	-	<3	-	-	-	-	-	<2	-	-	-	-	-	-
Ear signs	-	-	-	-	-	-	-	-	-	-	-	-	-	4	-	-

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

a 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.[1-18]

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).[1-18]

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.[1-18]

Immediate hypersensitivity reactions may occur after administration of β_2-agonists as demonstrated by anaphylaxis, urticaria, angioedema, rash and bronchospasm.[1-18]

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.[1-18]

The use of β_2-agonists may produce significant hypokalemia in some patients. The decrease is usually transient.[1-18]

The use of β_2-agonists may aggravate preexisting diabetes mellitus and ketoacidosis and should be used with caution in patients with diabetes.[1-18]

Indacaterol has not been evaluated in patients with acutely deteriorating chronic obstructive pulmonary disease (COPD), 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 (SABA).[1]

There have been rare reports of seizures in patients taking terbutaline. Seizures did not recur after the drug was discontinued.[13,14]

Black Box Warning for Brovana® (arformoterol)[91]

WARNING
Asthma-related death: Long-acting β_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 β_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 β_2 agonists, including arformoterol. The safety and efficacy of arformoterol in patients with asthma have not been established. All long-acting β_2 agonists, including arformoterol, are contraindicated in patients with asthma without use of a long-term asthma control medication.

Black Box Warning for Foradil® and Perforomist® (formoterol)[91]

WARNING
Asthma-related death: Long-acting β_2 adrenergic agonists, such as formoterol, increase the risk of asthma-related death. Data from a large placebo-controlled United States study that compared the safety of another long-acting β_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 β_2 adrenergic agonists, including formoterol.

WARNING
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 β_2 adrenergic agonists. Because of this risk, use of formoterol 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. Children and adolescent patients: Available data from controlled clinical trials suggest that long-acting β_2 adrenergic agonists increase the risk of asthma-related hospitalization in children and adolescents. For children and adolescents with asthma who require the addition of a long-acting β_2 adrenergic agonist to an inhaled corticosteroid, a fixed-dose combination product containing an inhaled corticosteroid and long-acting β_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 β_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 β_2 adrenergic agonist is recommended.

Black Box Warning for Arcapta® (indacaterol)[91]

WARNING
Asthma-related death: Long-acting β_2 adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting β_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 LABA, including indacaterol, the active ingredient in Arcapta Neohaler®. The safety and efficacy of Arcapta Neohaler® in patients with asthma have not been established. Arcapta Neohaler® is not indicated for the treatment of asthma.

Black Box Warning for Serevent® (salmeterol)[91]

WARNING
Asthma-related death: Long-acting β_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 versus 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 β_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 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.

WARNING
Children and adolescents: Available data from controlled clinical trials suggest that long-acting β_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 β_2 adrenergic agonist to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a long-acting β_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 β_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 β_2 adrenergic agonist is recommended.

Drug Interactions

Table 7. Drug Interactions[1-20,91]

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[1-20,91]

Generic Name	Adult Dose	Pediatric Dose	Availability
Short Acting β_2-agonists			
Albuterol	Treatment or prevention of bronchospasm in patients with asthma: 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 Exercise-induced bronchospasm: Aerosol inhaler (HFA): 2	Treatment or prevention of bronchospasm in patients with asthma: Meter dose aerosol inhaler (HFA):4 years of age and older: 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations/day Solution for nebulization: 2 to 12 years of age: 0.63 to 1.25 mg TID to QID; maximum, 2.5 mg TID to QID Sustained-release tablet: 6 to 12 years of age: 4 mg BID; maximum, 24 mg/day	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

Generic Name	Adult Dose	Pediatric Dose	Availability
	inhalations 15 to 30 minutes before exercise	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 Tablet: 6 to 12 years of age: 2 mg TID to QID; maximum 24 mg/day Exercise-induced bronchospasm: Meter dose aerosol inhaler (HFA): 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise	Syrup: 2 mg/5 mL Tablet: 2 mg 4 mg
Levalbuterol	Treatment or prevention of bronchospasm in patients with asthma: 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 asthma: Meter dose aerosol inhaler (HFA): 4 years of age and older: 1 to 2 inhalations every 4 to 6 hours Solution for nebulization: 6 to 11 years of age: 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	Treatment or prevention of bronchospasm in patients with asthma and treatment of reversible bronchospasm occurring in association with emphysema and bronchitis: Syrup, tablet: 20 mg TID to QID	Treatment or prevention of bronchospasm in patients with asthma: Syrup, tablet: 6 to 9 years of age (or weight under 60 lb): 10 mg TID to QID	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg
Pirbuterol	Treatment or prevention of bronchospasm in patients with asthma: 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	Treatment or prevention of bronchospasm in patients with asthma: 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	Treatment or prevention of bronchospasm in patients with asthma: Injection: Safety and efficacy in children less than 12 years of age have not been established. Tablet: 12 to 15 years of	Injection: 1 mg/mL (2 mL vial) Tablet: 2.5 mg 5 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Tablet: 2.5 to 5 mg TID, 6 hours apart; maximum, 15 mg in 24 hours Treatment of reversible bronchospasm occurring in association with emphysema and bronchitis: 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	age: 2.5 mg TID, 6 hours apart; maximum, 7.5 mg in 24 hours	
Long Acting β_2-agonists			
Arformoterol	Maintenance treatment of bronchoconstriction in COPD: Solution for nebulization: 15 µg BID	Safety and efficacy in children have not been established.	Solution for nebulization: 15 µg (2 mL)
Formoterol	Treatment or prevention of bronchospasm in patients with asthma: Capsule for inhalation: 12 µg capsule inhaled BID; maximum, 24 µg/day (Foradil®) Exercise-induced bronchospasm: Capsule for inhalation: 12 µg capsule inhaled at least 15 minutes before exercise (Foradil®) Maintenance treatment of bronchoconstriction in COPD: 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 or prevention of bronchospasm in patients with asthma: Capsule for inhalation: 5 years of age and older: 12 µg capsule inhaled BID; maximum, 24 µg/day (Foradil®) Exercise-induced bronchospasm: Capsule for inhalation: 5 years of age and older: 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	Maintenance treatment of airway obstruction in COPD: Capsule for inhalation: 75 µg QD	Safety and efficacy in children have not been established.	Capsule for inhalation: 75 µg
Salmeterol	Treatment or prevention of bronchospasm in patients with asthma: Dry powder inhaler: 1 inhalation	Treatment or prevention of bronchospasm in patients with asthma: Dry powder inhaler: 1	Dry powder inhaler: 50 µg (28 or 60 inhalations)

Generic Name	Adult Dose	Pediatric Dose	Availability
	BID Exercise-induced bronchospasm: Dry powder inhaler: 1 inhalation at least 30 minutes before exercise Maintenance treatment of bronchoconstriction in COPD: Dry powder inhaler: 1 inhalation BID	inhalation BID Exercise-induced bronchospasm: 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
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 additional 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 inhaled corticosteroids (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 short-acting β_2-adrenergic agonists (SABAs), anticholinergics and systemic corticosteroids.

Clinical Guidelines	Recommendations
	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 low-dose ICSs, the addition of a long-acting β_2-adrenergic agonists (LABAs) 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 preventativly 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 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 bromide is a long-acting inhaled anticholinergic indicated once-daily for chronic obstructive pulmonary disease 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.

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>· 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><u>Preferred</u>
SABA as needed</td><td><u>Preferred</u>
Low-dose ICS

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

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

<u>Alternative</u>
Medium-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td><u>Preferred</u>
High-dose ICS+ LABA and consider omalizu-mab for patients who have allergies</td><td><u>Preferred</u>
High-dose ICS+LABA+ oral steroid and consider omalizumab for patients who have allergies</td></tr>
</table>
<u>Management of exacerbations</u>
· Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended.

<u>Special populations</u>
· 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.</td></tr>
<tr><td>Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention (2010)[23]</td><td><u>Diagnosis</u>
· A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough and chest tightness.
· Measurements of lung function (spirometry or peak expiratory flow) provide an assessment of the severity, reversibility and variability of airflow limitation and provide confirmation of the diagnosis of asthma.

<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</td></tr>
</table>

Clinical Guidelines	Recommendations
	include inhaled and systemic glucocorticosteroids, leukotriene receptor antagonists, LABAs in combination with ICS, sustained-released theophylline, cromones and anti-immunoglobulin E (IgE). · Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include SABAs, inhaled anticholinergics and short-acting theophylline. 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. · To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of ICS. · Leukotriene receptor antagonists are generally less effective than ICSs and therefore may be used as an alternative treatment in patients with mild persistent asthma. · Some patients with aspirin-sensitive asthma respond well to leukotriene receptor antagonists. · Leukotriene receptor antagonists used as add-on therapy may reduce the dose of 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 ICS. · Several studies have demonstrated that leukotriene receptor antagonists 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 ICS fails to achieve control, the addition of a LABA is the preferred treatment. · Controlled studies have shown that delivering a LABA and an ICS 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 budesonide and formoterol may be used for rescue and maintenance therapy, this use is not approved by the Food and Drug Administration (FDA). · Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on ICS alone. · Cromolyn and nedocromil are less effective than a low dose of an ICS. · 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 effects. · Other anti-allergic compounds have limited effect in the management of asthma. Reliever medications · SABAs are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise induced

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
bronchospasm in patients of all ages.
· SABAs should be used only on an as-needed basis at the lowest dose and frequency required.
· Although the guidelines states that formoterol, a LABA, is approved for symptom relief because of its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with ICS, the use of this agent as a rescue inhaler is not approved by the FDA.
· Ipratropium bromide, an inhaled anticholinergic, is a less effective reliever medication in asthma than SABAs.
· Short-acting theophylline may be considered for relief of asthma symptoms.
· Short-acting oral β_2- adrenergic 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 effects.
· Systemic corticosteroids are important in the treatment of severe acute exacerbations.

<u>Assessment, treatment, and monitoring</u>
· 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, treatment can be stepped down to the lowest step and dose of treatment that maintains control.
· Asthma control is defined as: no (twice or less/week) daytime symptoms; no limitations of daily activities, including exercise; no nocturnal symptoms or awakening because of asthma; no (twice or less/week) need for reliever treatment; normal or near-normal lung function results and no exacerbations.
· 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:
<table>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td colspan="5">Asthma Education and Environmental Control</td></tr>
<tr><td>As Needed SABAs</td><td colspan="4">As Needed SABAs</td></tr>
<tr><td rowspan="4">Controller Options*</td><td>Select One</td><td>Select One</td><td>To Step 3 Treatment, Select One or More</td><td>To Step 4 Treatment, Add Either</td></tr>
<tr><td><u>Low-dose ICS</u></td><td><u>Low-dose ICS+LABA</u></td><td><u>Medium- or high-dose ICS+LABA</u></td><td>Oral cortico-steroid</td></tr>
<tr><td>Leukotriene receptor antagonists</td><td>Medium- or high-dose ICS

Low-dose ICS + leukotriene receptor antagonists</td><td>Leukotriene receptor antagonists

Sustained release theophylline</td><td>Anti-IgE treatment</td></tr>
<tr><td>-</td><td>Low-dose ICS + sustained-release theophylline</td><td>-</td><td>-</td></tr>
</table>
*Preferred controller options are underlined.
</td></tr>
</table>

Clinical Guidelines	Recommendations
	· Patients who do not reach an acceptable level of control at Step 4 can be considered to have difficult-to-treat asthma. In these patients, a compromise may need to be reached focusing on achieving the best level of control feasible, with as little disruption of activities and as few daily symptoms as possible, while minimizing the potential for adverse effects. Consideration of utilizing an asthma specialist should occur. Management of exacerbations · Repeated administration of SABAs 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 SABAs or if the episode is severe. Special populations · LABAs may also be used to prevent exercise induced bronchospasm and because of a more rapid onset of action, formoterol is more suitable for symptom relief as well as symptom prevention over salmeterol. · Appropriately monitored use of theophylline, ICS, β_2- adrenergic agonists and leukotriene receptor antagonists, specifically montelukast, are not associated with an increased incidence of fetal abnormalities. · ICS has been shown to prevent exacerbations of asthma during pregnancy. · Acute exacerbations during pregnancy should be treated with nebulized SABAs and oxygen. Systemic corticosteroids should be instituted when necessary.
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2010)**[24]	Diagnosis · A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors for the disease. · A diagnosis of COPD should be confirmed by spirometry. · The presence of a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <0.70 confirms the presence of airflow limitation that is not fully reversible. · Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality and the presence of complications. · A detailed medical history should be obtained for all patients suspected of developing COPD. · Severity of COPD is based on the patient's level of symptoms, the severity of the spirometric abnormality and the presence of complications such as respiratory failure, right heart failure, weight loss and arterial hypoxemia. · Chest radiograph may be useful to rule out other diagnoses and to establish the presence of significant comorbidities such as cardiac failure. · Arterial blood gas tension measurements should be considered for all patients with FEV_1 <50% predicted or clinical signs suggestive of respiratory failure or right heart failure. · COPD is typically a progressive disease; therefore, lung function can be expected to worsen over time, even with the best available care. · Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy. In addition, symptom monitoring is used to determine when to modify therapy and to identify any complications that may develop.

Clinical Guidelines	Recommendations
	· Comorbidities are common in COPD and should be actively identified. Comorbidities often complicate the management of COPD, and vice versa. · Screening for α_1-antitrypsin deficiency may be valuable in patients of Caucasian decent who develop COPD at a young age (<45 years of age) or who have a strong family history of the disease. · In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques and it is assumed that asthma and COPD coexist in these patients. In these instances, current management is similar to that of asthma. Other potential diagnoses (e.g., congestive heart failure, bronchiectasis, tuberculosis, obliterative bronchiolitis, and diffuse panbronchiolitis) are usually easier to distinguish from COPD. Treatment · The management of COPD should be individualized to address symptoms and improve the patient's quality of life. · None of the medications for COPD have been shown to modify the long term decline in lung function that is hallmark of this disease. Treatment should be focused on reducing symptoms and complications. · Choice of agent within each medication class depends on the availability of medication and the patient's response. · Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms. · Inhaled therapy is preferred. · When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential. COPD patients may have more problems in effective coordination with a metered dose inhaler compared to healthy patients; alternative breath-activated or spacer devices are available for most formulations. Dry powder inhalers may be more convenient and possibly provide improved drug deposition, although this has not been established in COPD. · Principle bronchodilators include β_2-agonists, anticholinergics and methylxanthines used as monotherapy or in combination. · Regular treatment with long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. · The choice between β_2-agonists, anticholinergics, theophylline or combination therapy depends on availability and individual response in terms of symptom relief and side effects. · The order in which the bronchodilator medications are normally introduced into patient care (based on the level of disease severity and clinical symptoms) is: β-agonists, anticholinergics and methylxanthines. · Regular use of LABAs or short- or long-acting anticholinergics improves health status. · Long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. · Theophylline is effective in COPD, but due to its potential toxicity inhaled bronchodilators are preferred when available. All theophylline studies were performed with slow-release preparations. · Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

Clinical Guidelines	Recommendations
	· For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators. · The addition of regular treatment with ICSs to bronchodilator treatment is appropriate for symptomatic COPD patients with an FEV_1 <50% predicted and repeated exacerbations. · Regular treatment with ICSs has been shown to reduce the frequency of exacerbations and thus improve health status for symptomatic patients with an FEV_1<50% of the predicted value and repeated exacerbations. · Treatment with ICSs increases the likelihood of pneumonia and does not reduce overall mortality. · An ICS combined with a LABA is more effective than the individual components in reducing exacerbations and improving lung function and health status. · Combination ICS/LABA therapy increases the likelihood of pneumonia. · Addition of an ICS/LABA to an anticholinergic appears to provide additional benefits. · There is insufficient evidence to recommend a therapeutic trial with systemic corticosteroids in patients with Stage II, Stage III or Stage IV COPD and poor response to an inhaled bronchodilator. · Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. · In COPD patients influenza vaccines can reduce serious illness. · 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. · Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. Management of exacerbations · The most common causes of an exacerbation are tracheobronchial tree infections and air pollution. · Inhaled β_2-agonists (particularly inhaled β_2-agonists with or without anticholinergics) and systemic corticosteroids are effective treatments for exacerbations of COPD. · Patients experiencing COPD exacerbations with clinical signs of airway infection may benefit from antibiotic treatment.
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 ($beta_2$ agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators.

Clinical Guidelines	Recommendations
	· Once-daily long-acting muscarinic antagonists are preferred compared to four-times-daily short-acting muscarinic 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 a muscarinic antagonist. o FEV_1 $\geq$50% predicted: long-acting β_2-agonist or long-acting muscarinic antagonist. o FEV_1 < 50% predicted: either long-acting β_2-agonist with an inhaled corticosteroid in a combination inhaler or a long-acting muscarinic antagonist. · In patients with stable COPD and FEV_1 $\geq$50% who remain breathless or have exacerbations despite maintenance therapy with a long-acting β_2-agonist, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting muscarinic antagonist when inhaled corticosteroids are not tolerated or declined. · Consider a long-acting muscarinic antagonist in patients remaining breathless or having exacerbations despite therapy with long-acting β_2-agonist and inhaled corticosteroids and vice versa. · Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects 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. Management of exacerbations · 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.[91] 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.[3,9-19]

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.[22,23] 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.

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.[25-35,48,62] 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.[35-57,70,77,78,80,81,84-87] 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.[37-38]

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