Therapeutic Class Overview
Short-acting β_2-Agonists

Therapeutic Class

- **Overview/Summary:** Respiratory short acting β_2-agonists (SABAs) are Food and Drug Administration (FDA)-approved indications include asthma, chronic obstructive pulmonary disease, exercise-induced bronchospasm (EIB), 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.[1-15] 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 (ProAir HFA®, ProAir Respiclick®, Proventil HFA®, Proventil HFA®, Ventolin HFA®), levalbuterol (Xopenex®, Xopenex HFA®), metaproterenol and terbutaline. Respiratory β_2-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.[1-15] As a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing and sale of all albuterol metered dose inhalers (MDIs) containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008. These inhalers were replaced by MDIs which use hydrofluoroalkanes (HFAs). There is no difference in the safety or efficacy of the HFA inhalers compared to the CFC inhalers; however, there may small differences in taste and/or feel with the HFA inhalers. The deadline for removal of the pirbuterol (Maxair®) CFC inhaler is December 31, 2013.[16]

Table 1. Current Medications Available in the Therapeutic Class[1-15]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Short-Acting β_2-agonists			
Albuterol (AccuNeb®*, ProAir HFA®, ProAir Respiclick®, Proventil HFA®, Ventolin HFA®, VoSpire ER®*)	Relief of bronchospasm in patients with asthma†,‖, treatment or prevention of bronchospasm in patients with reversible obstructive airway disease†‡§, prevention of exercise-induced bronchospasm†‡	Dry Powder Inhaler: 90 µg Meter dose aerosol inhaler (HFA): 120 µg albuterol sulfate# 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:	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		2 mg/5 mL Tablet: 2 mg 4 mg	
Levalbuterol (Xopenex®*, Xopenex HFA®)	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease†	Meter dose aerosol inhaler (HFA): 59 µg¶ Solution for nebulization: 0.31 mg 0.63 mg 1.25 mg (3 mL vials)	a
Metaproterenol*	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg	a
Terbutaline*	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Injection: 1 mg/mL (2 mL vial) Tablet: 2.5 mg 5 mg	a

*Generic available in at least one dosage form or strength.
†Inhalation solution.
‡Metered-dose inhaler.
§Dry powder inhaler.
‖Oral formulations.
¶Delivering 45 µg levalbuterol base.
#Delivering 108 µg of albuterol (90 µg albuterol base).

Evidence-based Medicine

- Clinical trials have demonstrated the efficacy SABAs in providing relief from reversible bronchospasms and EIA.[21-41]
- Safety and efficacy of albuterol dry powder inhaler (ProAir Respiclick®) was evaluated in two 12-week randomized, double-blind, placebo-controlled studies. Forced expiratory volume in one second (FEV_1) was significantly improved with albuterol dry powder inhaler compared with placebo (no P value reported).[7]
- In clinical trials that comparing albuterol to levalbuterol, inconsistent results have been reported and have not consistently demonstrated improved outcomes with levalbuterol compared to albuterol. Moreover, studies have shown no significant differences between the two agents in the peak change in FEV_1 or the number and incidence of adverse events.[21-31]

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.[17-20]
  - Short-acting β_2-agonists should be used on an as-needed or "rescue" basis.[17-20]

- Anticholinergics may also be used for the treatment of acute exacerbations but are considered less effective than SABAs.[17-20]
- 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.[17-20]
- The use of LABAs to treat acute symptoms or exacerbations of asthma is not recommended.[17]

· Other Key Facts:
- 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 branded albuterol hydrofluoroalkanes (HFA) inhalers and one dry-powder inhaler; however, no generic equivalents are available.

References

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Therapeutic Class Review
Short acting β_2-Agonists

Overview/Summary

Respiratory short acting β_2-agonists are Food and Drug Administration (FDA)-approved for the prevention and treatment of bronchospasm associated with acute asthma exacerbations or other reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm (EIB). These agents are not approved for the chronic management of asthma or chronic obstructive pulmonary disease (COPD).[1-14] Activation β_2-adrenergic receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation, ultimately resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.[1-15] The short acting β_2-agonists (SABAs) consist of albuterol (ProAir HFA®, ProAir Respiclick®, Proventil HFA®, Ventolin HFA®), levalbuterol (Xopenex®, Xopenex HFA®), metaproterenol and terbutaline. Each SABA is available generically in at least one strength or formulation.

As a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing and sale of all albuterol metered dose inhalers (MDIs) containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008. These inhalers are to be replaced by MDIs which use hydrofluoroalkanes (HFAs). There is no difference in the safety or efficacy of the HFA inhalers compared to the CFC inhalers; however, there may small differences in taste and/or feel with the HFA inhalers. The deadline for discontinuation of production or dispensing of the pirbuterol CFC inhaler is December 31, 2013.[16]

Current clinical guidelines for the treatment of asthma and COPD state that SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations.[17-20] 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 National Heart, Lung, and Blood Institute (NHLBI), the use of LABAs to treat acute symptoms or exacerbations of asthma is not recommended.[17]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Albuterol (ProAir HFA®, ProAir RespiClick®, 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
Terbutaline*	β_2-agonist	a

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

Indications

Table 2. Food and Drug Administration-Approved Indications[1-15]

Indication	Albuterol	Levalbuterol	Metaproterenol	Terbutaline
Relief of bronchospasm in patients with asthma	a ‖			
Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease	a †‡§	a †		
Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema			a	a
Exercised-Induced Bronchospasm				
Prevention of exercise-induced bronchospasm	a †‡			

†Inhalation solution.
‡Metered-dose inhaler.
§Dry powder inhaler.
‖Oral formulations.

Pharmacokinetics

Table 3. Pharmacokinetics[1-15]

Generic Name	Onset of Action (minutes)	Duration of Action (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
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 (dry-powder inhalation)	5.7	2	80 to 100	Yes	5
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
Terbutaline	30 to 45	4 to 8	24 to 60	No	3.4

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

Clinical Trials

Clinical trials have demonstrated the efficacy of short acting β_2-agonists (SABAs) in providing relief from bronchospasm in patients with asthma or other reversible obstructive airway disease. Albuterol has also been shown to be safe and effective for the prevention of exercise-induced bronchospasm.[21-90]

Safety and efficacy of albuterol dry powder inhaler (ProAir Respiclick®) was evaluated in two 12-week randomized, double-blind, placebo-controlled studies involving 316 asthmatic patients 12 to 76 years of age. Both studies concluded that mean change from baseline to week 12 in forced expiratory volume in one second (FEV_1) was significantly improved with albuterol dry powder inhaler compared with placebo (no P value reported). A double-blind, randomized, placebo-controlled, crossover study evaluated albuterol dry powder inhaler and albuterol HFA inhaler (ProAir HFA®) in 71 adult and adolescent subjects ages 12 years and older with persistent asthma, albuterol dry powder inhaler had bronchodilator efficacy that was significantly greater than placebo at administered doses of 90 and 180 µg. In a randomized, single-dose, crossover study in 38 adult and adolescent patients with EIB, two inhalations of albuterol dry powder inhaler taken 30 minutes before exercise prevented EIB for the hour following exercise (defined as the maintenance of FEV_1 within 80% of post-dose, pre-exercise baseline values) in 97% (37 of 38) of patients as compared to 42% (16 of 38) of patients when they received placebo.[7]

In clinical trials evaluating these products for the treatment of mild asthma, all SABAs have been shown to be efficacious in improving forced expiratory volume in 1 second (FEV_1). Inconsistent result have been reported in trials comparing albuterol to levalbuterol.[21-31] In two studies (one retrospective, one prospective), levalbuterol resulted in a significantly lower hospitalization rate compared to albuterol.[21,22] When the two agents were administered in the emergency department, there was no significant difference in the time to discharge.[24] 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).[25] In an unpublished study, the difference in peak FEV_1 was statistically significant for albuterol hydrofluoroalkanes (HFA) compared to levalbuterol HFA (P=0.018).[30] In addition, studies have shown no significant differences between the two agents in the peak change in FEV_1 and the number or incidence of adverse events.[21-32]

For the treatment of EIA, albuterol and metaproterenol have demonstrated an improvement in FEV_1 compared to placebo.[39-41] In one study, albuterol- and metaproterenol- treated patients had a lower incidence of exercise induced bronchospasm compared to placebo.[39] 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).[40]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Asthma				
Carl et al[21] Albuterol 2.5 mg via nebulization (every 20 minutes for 2 hours) vs levalbuterol 1.25 mg via nebulization (every 20 minutes for 2 hours)	DB, PRO, RCT Individuals 1 to 18 years of age with asthma presenting to the ED (1 patient had been using levalbuterol the remainder albuterol as rescue prior to presenting to the ED)	N=547 Varying duration of hospitalizations	Primary: Hospital admission rate Secondary: LOS, ED LOS, intensification, number of aerosols, requirement for oxygen and adverse events	Primary: Compared to the albuterol group, the levalbuterol group had a significantly lower hospitalization rate (36 vs 45%; P=0.02). Secondary: There were no significant differences between the albuterol and levalbuterol group concerning secondary outcomes, including adverse events (P=0.26 to P=0.94). No significant adverse events occurred in either group.
Schreck et al[22] Albuterol 2.5 mg via nebulization (plus standard treatment) vs levalbuterol 1.25 mg via nebulization (plus standard treatment)	CR, OS, RETRO, Individuals ≥1 year of age with an acute asthma presenting to the ED requiring nebulization with a SABA	N=736 9 months	Primary: Patient disposition, ED LOS, and objective measures of patient upon arrival Secondary: Not reported	Primary: There was a significantly lower hospitalization rate in the levalbuterol group compared to the albuterol group (4.7 vs 15.1%; P=0.0016). The rate of 15.1% is comparable to the hospitals average admission rate of 16.4%. There was no significant difference between the two treatment groups concerning ED LOS and other objective measures upon patient presentation (P=0.762). Due to a decrease in hospitalizations, treatment costs were lower in the levalbuterol treatment group (P value not reported). Secondary: Not reported
Qureshi et al[23] Albuterol 2.5 to 5 mg via nebulization (plus standard treatment as needed)	DB, PRO, RCT Children 2 to 14 years of age with a known history of asthma presenting to a pediatric ED	N=129 Study was complete after patient received 5 doses, was admitted, or	Primary: Changes from baseline in clinical asthma score and the percent of predicted FEV_1 after the first, third, and	Primary: No significant differences between the treatment groups were found (P value not reported). Secondary: No significant differences between the treatment groups were found (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs levalbuterol 1.25 to 2.5 mg via nebulization (plus standard treatment needed)	with an acute moderate or severe asthma exacerbation	discharged	fifth treatment Secondary: Number of treatments, length of ED care, rate of hospitalizations, changes in pulse rate and oxygen saturation	No significant differences between the treatment groups concerning adverse event were reported (P value not reported).
Skoner et al[24] Albuterol 1.25 mg via nebulization vs albuterol 2.5 mg via nebulization vs levalbuterol 0.31 mg via nebulization vs levalbuterol 0.63 mg via nebulization vs placebo	DB, MC, PC, PG, RCT Children 2 to 5 years of age with asthma for at least 30 days and no other underlying medical condition	N=211 4 weeks	Primary: Change from baseline in the total score on the PAQ Secondary: PEF, rescue medication use, and the Child Health Status Questionnaire	Primary: Decrease in the PAQ score was demonstrated in all treatment groups (P value not reported). Secondary: All treatment groups demonstrated an improvement in PEF compared to placebo (P<0.01 for all treatment groups). All treatment groups, including the placebo group, demonstrated a decrease in rescue medication use. There were no significant differences between the treatment groups (P value not reported). All treatment groups demonstrated and improvement from baseline in the Child Health Status Questionnaire (P value not reported). Overall, the incidence of adverse events was similar for each treatment group during the study period. Adverse events were mild (68.0%) to moderate (28.1%) in severity. Among all patients, significant increases in ventricular heart rates were demonstrated in the levalbuterol 0.63 mg and racemic albuterol 2.5 mg groups compared to placebo (P value not reported).
Nowak et al[25] Albuterol 2.5 mg via	DB, MC, PG, PRO, RCT	N=627 1 month	Primary: Time to meet ED discharge criteria	Primary: For the levalbuterol and albuterol groups the median time to discharge (76.0 and 78.5 minutes) was not statistically different (P=0.74).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nebulization (up to 6 doses in 3 hours) with prednisone 40 mg tablet vs levalbuterol 1.25 mg via nebulization (up to 6 doses in 3 hours) with prednisone 40 mg tablet	Individuals ≥18 years of age presenting to the ED or clinic with an acute asthma exacerbation		Secondary: Comparisons of FEV_1 change from baseline, the proportion of patients hospitalized, effect of plasma concentration of (*S*)-albuterol at presentation on FEV_1 response and hospitalization	Secondary: There was no significant difference (P=0.28) in the admission rate between the albuterol (9.3%) and levalbuterol (7.0%) groups. After dose one and cumulative doses over time there was a greater FEV_1 improvement following levalbuterol compared to albuterol (P=0.021). For individuals not taking corticosteroids chronically before the trial, there were significantly fewer hospitalizations in the levalbuterol group compared to the albuterol group (3.8 vs 9.3%; P=0.03). There was no significant difference in the overall frequency of adverse event in the two treatment groups (P value not reported).
Nelson et al[26] Albuterol 1.25 mg TID via nebulization vs albuterol 2.5 mg TID via nebulization vs levalbuterol 0.63 mg TID via nebulization vs levalbuterol 1.25 mg TID via nebulization vs	DB, PC, PG, RCT Patients ≥12 years of age who did not smoke and had ≥6 month history of chronic and stable asthma, demonstrating at ≥15% improvement in FEV_1 to a single dose of albuterol 2.5 mg via nebulization	N=362 4 weeks	Primary: Peak change in FEV_1 after four weeks Secondary: AUC and use of rescue racemic albuterol MDI	Primary: Change in peak FEV_1 in the combined levalbuterol group was not significantly greater than the combined albuterol group (0.84 and 0.74; P value not reported). Secondary: A similar trend was noticed when evaluating the AUC; after the first dose, levalbuterol treatment was significantly better (P=0.02) compared to albuterol; however, at week four, even though the AUC values were higher in the levalbuterol groups, the difference was not significant. There was a significant improvement (P=0.006) in predose FEV_1 in the combined levalbuterol arm compared to the combined albuterol arm in the subset of patients not taking corticosteroids. There was significantly less rescue medication used in the active treatment groups compared to placebo. Compared to baseline, there was a significant decrease in rescue-medication use in both the levalbuterol 1.25 mg arm (P<0.001) and the albuterol 2.5 mg arm (P=0.056).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				All active treatments were well tolerated with the percent of patients reporting nervousness or tremor in the low dose groups being statistically significantly lower (P=0.003) compared to the high dose groups.
Gawchik et al[27] Albuterol 1.25 mg via nebulization (1 dose) vs albuterol 2.5 mg via nebulization (1 dose) vs levalbuterol 0.16 mg via nebulization (1 dose) vs levalbuterol 0.31 mg via nebulization (1 dose) vs levalbuterol 0.63 mg via nebulization (1 dose) vs levalbuterol 1.25 mg via nebulization (1 dose) vs	DB, PC, RCT, XO Patients 3 to 11 years of age with asthma for ≥6 months and reversibility of 12% or more 30 minutes after 2.5 mg of albuterol administered by nebulization	N=43 4 treatment visits (2 to 8 days apart)	Primary: Differences in peak change in FEV_1, peak percent change in FEV_1 and AUC Secondary: Not reported	Primary: Differences in peak change in FEV_1, peak percent change in FEV_1 and AUC were significantly improved in all treatment arms (with the exception of albuterol 1.25 mg in AUC) compared to placebo (P<0.05). No significant differences between the treatment groups were found (P<0.55). The medications were well tolerated and all adverse events reported were mild or moderate in severity, with no significant difference seen across the treatment groups (P values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				
Milgrom et al[28] Albuterol 1.25 mg via nebulization vs albuterol 2.5 mg via nebulization vs levalbuterol 0.31 mg via nebulization vs levalbuterol 0.63 mg via nebulization vs placebo	DB, MC, PC, PG, RCT Patients 4 to 11 years of age mild or worse asthma with a reversibility of ≥15% to albuterol	N=338 3 weeks	Primary: Peak percent change in FEV_1 from baseline Secondary: Change in pulmonary function, percent of responders within 30 minutes after dose, time to peak improvement in FEV_1, use of rescue medications, symptoms, symptom-free days, asthma control days and adverse event	Primary: A significant improvement was seen in peak percent change in FEV_1 from baseline in all active treatment arms compared to placebo on day 21 (P<0.019). Secondary: Immediately after nebulization on days zero and 21 there were clinically significant changes for all groups except placebo (P<0.02) and, with the exception of the albuterol 1.25 mg group, more patients responded to active treatment in comparison to the placebo group on both days (P<0.02). On day zero significantly more patients responded to levalbuterol 0.31 mg (62.9%) than to albuterol 1.25 mg (41.8%), immediately after nebulization (P=0.12). Levalbuterol 0.31 mg achieved a significantly greater change in asthma control days compared to levalbuterol 0.63 mg and albuterol 1.25 mg (P<0.04 for each comparison). Compared to all active treatments, levalbuterol 0.31 mg produced significantly smaller changes in heart rate (P<0.02). A significant decrease in potassium levels was seen in all treatment groups compared to placebo (P<0.002).
Data on file[29] Albuterol 180 µg QID via HFA-MDI vs levalbuterol 90 µg QID via HFA-MDI	DB, PC, PG, RCT Patients ≥12 years of age with moderate to severe asthma and FEV_1 45 to 75% of the predicted value	N=445 9 weeks	Primary: Mean percent change in peak FEV_1 Secondary: Not reported	Primary: Levalbuterol and albuterol demonstrated a significant improvement in mean peak FEV_1 during the study period compared to placebo (25.63, 28.98 vs 13.94%, respectively; P<0.001). The difference in peak FEV_1 was statistically significant for albuterol compared to levalbuterol (P=0.018). Overall, the incidences in adverse events were similar between all treatment groups. The most commonly reported adverse events were headache, viral infection and asthma. The most common adverse event

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				leading to discontinuation was asthma that occurred in 5.5, 2.5 and 1.8% of patients in the levalbuterol, albuterol and placebo groups, respectively. Secondary: Not reported
Data on file[30] Albuterol 180 µg QID via HFA-MDI vs levalbuterol 90 µg QID via HFA-MDI vs placebo	DB, PC, PG, RCT Patients ≥12 years of age with moderate to severe asthma with a FEV_1 45 to 75% of the predicted value	N=303 9 weeks	Primary: Mean percent change in peak FEV_1 Secondary: Percentage of responders (patients achieving a FEV_1 >15% over the visit predose value)	Primary: Levalbuterol and albuterol demonstrated a significant improvement in mean peak FEV_1 during the study period compared to placebo (25.30, 26.14 vs 12.45%, respectively; P<0.001). Secondary: The percentage of responders was greater in each active treatment group compared to placebo at each visit. The time to 15% response was also significantly shorter for each active treatment group compared to placebo at visits two and six (P<0.001). Overall, the incidences in adverse events were similar between each treatment group (50.0 to 56.5%). Serious adverse events were slightly less common in the levalbuterol group (5.7%) compared to the albuterol (10.0%) and placebo (8.5%) groups. Adverse events leading to discontinuation occurred in 5.7, 10.0, and 6.8% of patients in the levalbuterol, albuterol and placebo groups, respectively.
Nowak et al[31] Albuterol 2.5 mg via nebulization (3 doses) vs albuterol 5 mg via nebulization (3 doses) vs levalbuterol 0.63 mg via	OL, PRO Adult asthmatics presenting to the ED with an acute asthma exacerbation	N=93 2 hours	Primary: FEV_1 percent change from baseline following the third nebulization Secondary: Change and percent change from baseline FEV_1 at each time point, the percent of	Primary: The median percent change in FEV_1 was greater for 1.25 mg levalbuterol (74%), compared to 2.5 mg albuterol, (39%), 0.63 mg levalbuterol (37%), and 3.75 mg levalbuterol (26%) after three doses (P value not reported). Secondary: At 60 minutes posttreatment, levalbuterol 1.25, 2.5, and 5 mg improved the median percent predicted FEV_1 by 33 to 38% compared to 12 to 24% with 2.5 and 5 mg doses of albuterol and 0.63 and 3.75 mg doses of levalbuterol (P value not reported). (S) albuterol levels were found to be significantly inversely correlated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nebulization (3 doses) vs levalbuterol 1.25 mg via nebulization (3 doses) vs levalbuterol 2.5 mg via nebulization (3 doses) vs levalbuterol 3.75 mg via nebulization (3 doses) vs levalbuterol 5 mg via nebulization (3 doses)			responders, and the time to achieve a 15% and 50% increase from baseline	with baseline FEV_1 (P=0.004), and percent change in FEV_1 60 minutes post dose (P=0.006).
Jat et al[32] Albuterol (doses varied) vs levalbuterol (doses varied)	MA (7 RCT) Patients of all ages with acute asthma	N=1,625 Duration not reported	Primary: Respiratory rate, oxygen saturation, FEV_1, PEFR, retractions, air entry, wheezing and adverse events Secondary: Hospital admission rate, need for mechanical ventilation and duration of hospital stay	Primary: Overall, no significant difference was identified between levalbuterol and albuterol with regard to final respiratory rate (mean difference, 0.37; 95% CI, 0.80 to 1.54), change in respiratory rate (mean difference, -0.42; 95% CI, -9.28 to 8.46) or combined respiratory rate (mean difference, 0.35; 95% CI, 0.81 to 1.51). There was no statistically significant difference between the treatments in final oxygen saturation (mean difference, -0.29; 95% CI, -0.68 to 0.10) or the change in oxygen saturation (mean difference, -0.38; 95% CI, -2.98 to 2.23). No statistically significant difference was observed between patients treated with levalbuterol compared to albuterol with regard to FEV_1 (mean difference, -28.3; 95% CI, -59.95 to 3.33) and PEFR (mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				difference, 0.53; 95% CI, -13.85 to 14.91). There was no statistically significant difference between treatments with regard to asthma symptom scores (air entry, wheezing, retractions) (mean difference, -1.01; 95% CI, -5.30 to 3.28). Secondary: No statistically significant differences in adverse events were reported between the treatment groups. There was no statistically significant difference between levalbuterol and albuterol treatment with regard to changes in heart rate (mean difference, -2.87; 95% CI, -12.24 to 6.50). The hospital admission rate was significantly lower in levalbuterol group compared to the albuterol group (OR, 0.76; 95% CI, 0.58 to 0.98); however, the duration of ED care was not different between the groups (mean difference, 1.44; 95% CI, -4.39 to 7.27). There were no data available related to need for mechanical ventilation.
Wolfe et al[33] Albuterol syrup 2 mg TID vs metaproterenol syrup 10 mg TID	IB, MC, PG, RCT Individuals 5 to 9 years of age with chronic asthma	N=65 4 weeks	Primary: Time to maximal response, maximum percent increase from baseline, peak flow measurements, heart rate, blood pressure and adverse event Secondary: Not reported	Primary: There was a significantly greater degree of bronchodilation with albuterol compared to metaproterenol from two to eight hours post dose (P<0.05). The peak percent improvement in FEV_1 from baseline was significantly greater for albuterol compared to metaproterenol (29.3 vs 20.6%; P<0.05). There were no significant differences in the mean change from baseline in systolic blood pressure in either group; however, with metaproterenol the chronotropic effect was significantly greater (P<0.05) at one hour on day one and 28 and 1.5 hours on day 28 compared to albuterol. There was no significant difference in the frequency of adverse event between the two groups (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Martin et al[34] Salmeterol 42 µg two inhalations BID via DPI vs albuterol extended release tablets 4 mg in the morning and 8 mg in the evening	DB, DD, MC, RCT, XO Individuals 18 to 65 years of age with FEV_1 >50% and 12% improvement following inhaled albuterol	N=56 8 weeks	Primary: Morning peak flow, FEV_1 measurements Secondary: Nocturnal symptoms, nights without awakenings, rescue inhaler use, and safety	Primary: Improvements in PEF and FEV_1 were significantly improved in both groups (P<0.001) but did not differ significantly between groups (P value not reported). Secondary: A comparison of the adjusted treatment means for the percentage of nights without awakenings demonstrated a significant improvement with salmeterol compared to albuterol (84.6 vs 79.4; P=0.021). There was no statistical difference between the two groups concerning the percentage of patients who had no nocturnal awakenings (P value not reported). A significant decrease in baseline puffs/day of a rescue inhaler was observed in both the salmeterol group (4.57 to 1.85; P<0.001) and the albuterol group (4.57 to 2.66; P<0.001). The decrease with salmeterol was significantly greater (P<0.001). Seventy eight percent of the patients treated with albuterol and 75.9% of patients treated with salmeterol listed adverse event during the study (P value not reported).
Brambilla et al[35] 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	Primary: In the salmeterol group the mean number of awakening-free nights over the last week of treatment was significantly higher compared to the terbutaline group (5.3 vs 4.6; P=0.006). Secondary: No significant difference was found concerning the mean evening PEF; however, salmeterol was more efficacious than terbutaline on morning PEF (P=0.04) and PEF daily variations (P=0.01). A significantly greater percent of individuals in the salmeterol group compared to the terbutaline group stopped using rescue albuterol during

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			albuterol intake	the day (30 vs 9%; P=0.004); however, there was no significant difference at night (P value not reported). Significantly fewer patients in the albuterol group reported adverse events (16 vs 29%; P=0.04).
Tattersfield et al[36] Terbutaline 0.5 mg as needed via DPI vs formoterol 4.5 µg as needed via DPI	DB, PG, RCT Patients ≥18 years of age with asthma for ≥6 months and treated with a constant dose of ICS	N=362 12 weeks	Primary: Time to first severe exacerbation Secondary: Morning and evening peak flow rate, $FEV_{1,}$ symptoms, number of inhalations of relief medication and safety	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). It was documented that pre-bronchodilator FEV_1 was greater in the formoterol group than the terbutaline group (P value not reported). Both groups experienced a decrease in rescue inhalations but it was to a greater extent in the formoterol group (1.15 vs 0.40; P value not reported).
Hermansson et al[37] Terbutaline 500 µg QID via DPI vs salmeterol 50 µg BID via DPI	MC, OL, PG, RCT Patients ≥18 years of age with mild to moderate asthma	N=243 4 weeks	Primary: Morning, evening and diurnal PEF, daytime and nighttime symptoms, use of rescue inhaler and FEV_1 Secondary: Not reported	Primary: Over four weeks, salmeterol produced significant improvements over terbutaline in morning and evening PEF and diurnal variation (P<0.001, P=0.045 and P<0.001). After four weeks there was a statistically significant difference in favor of the salmeterol group in daytime and nighttime asthma score, and percent of days and nights when a rescue medication was needed (P<0.001, P=0.008, P=0.002 and P=0.007). After four weeks of treatment there were no significant differences in FEV_1 or FVC between the two groups (P=0.598 and P=0.916). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hancox et al[38] Terbutaline 1,000 µg QID via DPI vs budesonide 400 µg BID via DPI vs terbutaline 1,000 µg QID and budesonide 400 µg BID via DPI vs placebo	PC, RCT, XO Individuals 9 to 64 years of age with mild to moderate asthma with documented hyper-responsiveness	N=61 24 weeks	Primary: A rank order of treatment from worst [1] to best [4], and period of asthma control for each subject Secondary: PEF, nocturnal and daytime symptoms, use of rescue medication and compliance	Primary: Combined treatment was ranked significantly higher than each individual treatment and placebo (P<0.0001, P<0.0001 and P<0.01), budesonide ranked higher than placebo (P=0.025), and there was no significant difference between budesonide and terbutaline or terbutaline and placebo. Secondary: Mean morning peak flow was higher during combined treatment than budesonide alone (P<0.02), and both the combined treatment and budesonide were higher than either placebo or terbutaline (P<0.01). Mean evening peak flow was higher with all treatments (P<0.0003) and was higher with the combined treatment than either active medication alone (P<0.0002). No significant difference was seen between the two active medications alone. Nocturnal awakenings and percent of days during which wheeze was reported were reduced significantly in all treatment groups compared to placebo (P<0.0001 and P<0.001), but did not differ significantly between the groups. Rescue inhaler use significantly decreased in all groups compared to placebo (P<0.001), but did not differ significantly between the groups. The self-reported compliance was above 90% for all groups and did not differ significantly (P value not reported).
Exercise-Induced Bronchospasm				
Berkowitz et al[39] Albuterol 0.18 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 exercised-induced bronchospasm	N=18 4 days	Primary: Mean percentage increase in FEV_1 five minutes after medication, mean workload for exercise challenges, mean decrease in	Primary: Differences between mean baseline FEV_1 were not statistically significant between the treatment groups; however, five minutes post administration of albuterol or metaproterenol the mean increase in percentage of predicted FEV_1 was significantly higher compared to placebo (P<0.0005). A significantly greater increase (P<0.01) was also seen five minutes after the administration of metaproterenol when compared to albuterol. On the days when the subjects received the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
metaproterenol 1.3 mg, two inhalations 15 minutes prior to exercise via MDI vs placebo	(FEV_1 >20% of pre-exercise level) following a treadmill exercise test		FEV_1 from baseline, and the number of patients in whom bronchoconstriction was blocked over time Secondary: Not reported	active medications, the mean workloads were not found to be significantly different. Following the initial post-medication exercise test, a majority of patients in the placebo group experienced exercise-induced spasm compared to both active ingredient groups. This was a significant difference (P<0.0005) between the placebo and active ingredient groups but not between the active ingredient groups themselves. Following the two-hour exercise challenge, the remainder of the placebo group experienced exercise-induced spasm and a greater number in the remaining metaproterenol group compared to the albuterol group experienced exercise-induced spasm. There was a greater decrease in mean maximum decrease in FEV_1 in the placebo group compared to the active ingredient groups, which was found to be statistically significant (P<0.001). Albuterol prevented exercise-induced bronchospasm in more patients and for a significantly longer time than metaproterenol (P<0.05). Secondary: Not reported
Shapiro et al[40] 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	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
exercise challenge via DPI vs placebo				administration. Additionally, 71% of patients receiving formoterol were protected 12 hours after dosing compared to 26% of patients receiving albuterol, a percentage close to the 29% of patients receiving placebo (P values not reported). Nineteen percent of the patients treated with albuterol required a rescue inhaler at least once compared to zero patients receiving formoterol (P value not reported). There was no statistical difference in the percent of patients experiencing adverse event in all of the groups (no P value reported).
Richter et al[41] Formoterol 12 µg prior to exercise challenge via DPI vs salmeterol 50 µg prior to exercise challenge via DPI vs terbutaline 500 µg prior to exercise challenge via DPI vs placebo	DB, DD, PC, RCT, XO Nonsmoking patients 25 to 48 years of age with mild to moderate asthma, a history of exercise-induced bronchoconstriction and a documented hyper-responsiveness to inhaled methacholine	N=25 13 visits	Primary: Percent increase in FEV_1 between the inhalation of the study medication and the initiation of exercise (five, 30, or 60 minutes), and AUC of percent change in FEV_1 from end of exercise to 90 minutes Secondary: Not reported	Primary: At five minutes there was a significantly stronger response with terbutaline than salmeterol (P<0.001) and at five, 15, 30, and 60 minutes after inhalation, formoterol provided greater bronchodilation than salmeterol (P<0.05). There was no significant difference between terbutaline and formoterol at any of the time points. Mean pre-exercise FEV_1 was significantly larger in all active medication groups compared to placebo at 30 and 60 minute intervals (P<0.01) and was significantly larger after terbutaline and formoterol compared to salmeterol and placebo at the five-minute interval (P<0.05). A statistically significant (P<0.01) decrease was seen in AUC with increasing time between inhalation and exercise with terbutaline, formoterol, and salmeterol; however, there was no difference between treatments. Secondary: Not reported

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

Special Populations

Table 5. Special Populations[1-15]

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

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Approved for use in children six years of age and older.				
Terbutaline	Not sufficiently studied in patients 65 years of age and older. Approved in children 12 years of age and older.	Patients with moderate renal dysfunction should receive 50% of the usual dose. Avoid use in patients with severe renal impairment.	Not reported.	C	Unknown

HFA=hydrofluoroalkane

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-15]

Adverse Event(s)	Albuterol*,#	Albuterol†	Albuterol‡	Albuterol¶	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Terbutaline†	Terbutaline§
Cardiovascular										
Angina	a	a	-	a	-	a	a	-	-	-
Arrhythmias	a	-	-	a	a	a	a	-	-	-
Arteriosclerosis	-	-	-	-	-	-	-	-	-	-
Chest pain	<1	<1	0.9 to 1.7	<3	<2	a	-	0.2	-	1.3 to 1.5
Congestive heart failure	-	-	-	-	-	-	-	-	-	-
Electrocardiogram abnormal	-	-	-	-	<2	-	-	-	-	-
Electrocardiogram change	-	-	-	-	<2	-	-	-	-	-
Extrasystoles ventricular	-	-	-	<3	-	-	-	-	1.5	-
Heart block	-	-	-	-	-	-	-	-	-	-
Hypertension	a	a	1	a	<2	a	a	0.4	-	-
Hypotension	-	-	-	a	<2	-	a	-	-	-
Myocardial infarction	-	-	-	-	-	-	-	-	-	-
Pallor	1	-	-	-	-	-	-	-	-	-
Palpitations	<1	2.4 to 5.0	-	<3	-	-	a	3.8	5	7.8 to 22.9
QT prolongation	-	-	-	-	-	-	-	-	-	-
Syncope	-	-	-	-	<2	-	-	0.4	-	-
Tachycardia	1 to 2	2.7 to 5.0	1	3 to 7	2.7 to 2.8	a	6.1	17.1	3.5	1.3 to 1.5
Vasodilations	-	-	-	a	-	-	-	-	1	-
Central Nervous System										
Agitation	-	-	-	-	-	-	-	-	-	-
Anxiety	-	-	-	<3	2.7	-	-	-	1	-
Asthenia	-	-	-	-	3	-	-	-	2	-
Ataxia	-	-	-	<3	-	-	-	-	-	-
Cerebral infarct	-	-	-	-	-	-	-	-	-	-
Central nervous system stimulation	a	a	-	a	-	a	-	-	-	-
Confusion	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*,#	Albuterol†	Albuterol‡	Albuterol¶	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Terbutaline†	Terbutaline§
Depression	-	-	-	<3	-	-	-	-	-	-
Dizziness	3	1.5 to 2.0	4	3	1.4 to 2.7	2.7	a	2.4	3.5	1.3 to 10.2
Excitement	2 to 20	-	-	-	-	-	-	-	-	-
Fatigue	1	-	-	-	-	-	a	1.4	-	11.7-9.8
Hallucinations	-	-	-	-	-	-	-	-	<1	-
Headache	4	7.0 to 18.8	3	7	7.6 to 11.9	a	1.1	7	7.5	7.8 to 8.8
Hyperactivity	2	-	-	a	-	-	-	-	-	-
Hyperkinesia	4	-	-	<3	-	-	-	-	-	-
Hypokinesia	-	-	-	-	-	-	-	-	-	-
Insomnia	1.5	2.2	1	a	<2	a	a	1.8	1.5	-
Irritable behavior	<1	<1	-	-	-	-	-	-	-	-
Migraine	-	-	0.9 to 1.7	-	<2.7	-	-	-	-	-
Nervousness	9 to 15	8.5 to 20.0	-	7	2.8 to 9.6	a	4.8	20.2	35	16.9 to 30.7
Numbness in extremities	-	-	-	-	-	-	-	-	-	-
Paralysis	-	-	-	-	-	-	-	-	-	-
Paresthesia	-	-	-	-	<2	-	-	-	<1	-
Restlessness	-	<1	-	-	-	-	-	-	-	-
Rigors	-	-	-	<3	-	-	-	-	-	-
Sensory disturbances	-	-	-	-	-	-	-	0.2	-	-
Shakiness	9	-	-	-	-	-	-	-	-	-
Somnolence	1	<1	-	<3	-	-	-	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	6.8	a	1.6	16.9	15	7.8 to 38.0
Vertigo	a	a	-	a	-	a	-	-	-	-
Weakness	<1	2	-	-	-	-	-	0.2	-	0.5 to 1.3
Dermatological										
Acne	-	-	-	-	-	<2	-	-	-	-
Angioedema	a	a	-	a	a	a	-	-	-	-
Bruising	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*,#	Albuterol†	Albuterol‡	Albuterol¶	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Terbutaline†	Terbutaline§
Contact dermatitis	-	-	-	-	-	-	-	-	-	-
Dry skin	-	-	-	-	-	-	-	-	-	-
Eczema	-	-	-	-	-	-	-	-	-	-
Flushing	-	a	-	-	-	-	-	-	-	2.4
Herpes simplex	-	-	-	-	-	<2	-	-	-	-
Herpes zoster	-	-	-	-	-	-	-	-	-	-
Hives	-	-	-	-	-	-	-	0.2	-	-
Photodermatitis	-	-	-	-	-	-	-	-	-	-
Pruritus	-	-	-	-	-	-	-	0.4	-	-
Rash	a	a	-	<3	7.5	a	-	-	<1	-
Skin/appendage infection	-	-	1.7	-	-	-	-	-	-	-
Skin discoloration	-	-	-	-	-	-	-	-	-	-
Skin hypertrophy	-	-	-	-	-	-	-	-	-	-
Skin reaction	-	-	-	-	-	-	-	-	-	-
Urticaria	a	a	0.9 to 1.7	a	3	a	-	-	-	-
Endocrine and Metabolic										
Decrease glucose intolerance	-	-	-	-	-	-	-	-	-	-
Diabetes	-	-	-	<3	-	-	-	-	-	-
Hyperglycemia	-	-	-	a	-	-	-	-	-	-
Hypoglycemia	-	-	-	-	-	-	-	-	-	-
Hyperlipidemia	-	-	-	-	-	-	-	-	-	-
Metabolic acidosis	-	-	-	a	-	-	-	-	-	-
Weight gain	-	-	-	-	-	-	-	-	-	-
Gastrointestinal										
Abdominal pain	-	-	-	-	1.5	-	-	-	-	-
Anorexia	-	-	-	-	-	-	-	-	-	-
Constipation	-	-	-	-	-	<2	-	-	-	-
Diarrhea	-	-	-	<3	1.5 to 6.0	-	-	1.2	-	-
Dry mouth	-	-	-	<3	<2	-	a	0.4	1.5	-
Dyspepsia	-	-	1	-	1.4 to 2.7	-	-	-	-	-

Adverse Event(s)	Albuterol*,#	Albuterol†	Albuterol‡	Albuterol¶	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Terbutaline†	Terbutaline§
Dyspeptic symptoms	-	-	-	-	-	-	-	-	-	-
Epigastric pain	<1	-	-	-	-	-	-	-	-	-
Eructation	-	-	-	<3	-	-	-	-	-	-
Flatulence	-	-	-	<3	-	-	-	-	-	-
Gastritis	-	-	-	-	-	-	-	-	-	-
Gastroenteritis	-	-	0.9 to 3.4	-	<2	<2	-	-	-	-
Gastrointestinal infections	-	-	-	-	-	-	-	-	-	-
Gastrointestinal symptoms/ distress	2	-	-	-	-	-	-	3	-	-
Hyposalivation	-	-	-	-	-	-	-	-	-	-
Increased appetite	3	-	-	-	-	-	-	-	-	-
Loss of appetite	1	-	-	-	-	-	-	-	-	-
Melena	-	-	-	-	-	-	-	-	-	-
Nausea	-	2.0 to 4.2	0.9 to 1.7	10	<2	a	1.3	3.6	3	1.3 to 3.9
Oral candidiasis	-	-	-	-	-	-	-	-	-	-
Periodontal abscess	-	-	-	-	-	-	-	-	-	-
Rectal hemorrhage	-	-	-	-	-	-	-	-	-	-
Stomatitis	-	-	-	-	-	-	-	-	-	-
Taste changes	a	a	-	4	-	-	-	0.8	-	-
Vomiting	a	4.2	-	7	-	10.5	-	0.8	<1	1.3 to 3.9
Genitourinary										
Calcium crystalluria	-	-	-	-	-	-	-	-	-	-
Cystitis	-	-	-	-	-	-	-	-	-	-
Difficulty in micturition	-	<1	-	-	-	-	-	-	-	-
Glycosuria	-	-	-	-	-	-	-	-	-	-
Hematuria	-	-	-	-	-	<2	-	-	-	-
Kidney calculus	-	-	-	-	-	-	-	-	-	-
Nocturia	-	-	-	-	-	-	-	-	-	-
Prostate specific antigen increase	-	-	-	-	-	-	-	-	-	-
Pyuria	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*,#	Albuterol†	Albuterol‡	Albuterol¶	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Terbutaline†	Terbutaline§
Urinary tract infection	-	-	-	3	-	-	-	-	-	-
Urine abnormality	-	-	-	-	-	-	-	-	-	-
Vaginal moniliasis	-	-	-	-	-	<2	-	-	-	-
Hematologic										
Dysmenorrhea	-	-	-	-	-	<2	-	-	-	-
Leukocytosis	-	-	-	-	-	-	-	-	-	-
Laboratory Test Abnormalities										
Hyperkalemia	-	-	-	-	-	-	-	-	-	-
Hypokalemia	-	-	-	a	-	-	-	-	-	-
Liver enzyme elevation	-	-	-	-	-	-	-	-	a	-
Metabolic acidosis	-	-	-	-	-	-	-	-	-	-
Musculoskeletal										
Arthralgia	-	-	-	-	-	-	-	-	-	-
Arthritis	-	-	-	-	-	-	-	-	-	-
Articular rheumatism	-	-	-	-	-	-	-	-	-	-
Bone disorder	-	-	-	-	-	-	-	-	-	-
Clonus on flexing foot	-	-	-	-	-	-	-	0.2	-	-
Hypertonia	-	-	-	-	-	-	-	-	<1	-
Leg cramps	-	-	-	-	2.7	-	-	-	-	-
Muscle cramps	-	2.7 to 3.0	-	a	-	-	-	-	-	-
Muscle spasm	-	-	-	-	-	-	-	0.2	-	-
Muscle stiffness	-	-	-	-	-	-	-	-	-	-
Muscle tightness	-	-	-	-	-	-	-	-	-	-
Muscle rigidity	-	-	-	-	-	-	-	-	-	-
Musculoskeletal inflammation	-	-	-	-	-	-	-	-	-	-
Myalgia	-	-	-	-	<2	<2	-	-	-	-
Neck rigidity	-	-	-	-	-	-	-	-	-	-
Pain	-	-	-	3 to 5	1.4 to 3.0	4	-	0.2	-	-
Rheumatoid arthritis	-	-	-	-	-	-	-	-	-	-
Tendinous contracture	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Albuterol*,#	Albuterol†	Albuterol‡	Albuterol¶	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Terbutaline†	Terbutaline§
Respiratory										
Asthma exacerbation	-	-	11.1 to13	a	9.0 to 9.1	9.4	-	2	-	-
Bronchitis	-	-	0.9 to 1.7	-	-	2.6	-	a	-	-
Bronchospasm	a	a	-	a	-	-	-	a	-	-
Carcinoma of the lung	-	-	-	-	-	-	-	-	-	-
Chest infection	-	-	-	-	-	-	-	-	-	-
Chronic obstructive pulmonary disease	-	-	-	-	-	-	-	-	-	-
Cough	<1	-	-	5	1.4 to 4.1	a	-	0.2	-	-
Drying of oropharynx	a	a	-	a	-	a	-	-	-	-
Dysphonia	-	-	-	<3	-	-	-	-	-	-
Dyspnea	-	-	-	<3	a	a	-	a	-	2
Epistaxis	1	-	-	-	-	<2	-	-	-	-
Hoarseness	a	-	-	a	-	-	-	-	-	-
Increased sputum	-	-	-	-	-	-	-	-	-	-
Influenza	-	-	-	-	-	-	-	-	-	-
Laryngeal irritation	-	-	-	-	-	-	-	-	-	-
Laryngeal spasm	-	-	-	-	-	-	-	-	-	-
Laryngeal swelling	-	-	-	-	-	-	-	-	-	-
Laryngitis	-	-	-	<3	-	-	-	-	-	-
Lung disorder	-	-	-	-	-	<2	-	-	-	-
Nasal congestion	-	-	-	-	-	-	-	-	-	-
Nasopharyngitis	-	-	-	a	-	-	-	-	-	-
Oral mucosal abnormality	-	-	-	-	-	-	-	-	-	-
Oropharyngeal edema	a	a	-	<3	-	-	-	-	-	-
Oropharyngeal pain	-	-	-	-	-	-	-	-	-	-
Pharyngitis	-	-	-	14	3.0 to 10.4	6.6 to 7.9	-	-	-	-
Respiratory disorder	-	-	-	5	-	-	-	-	-	-
Rhinitis	-	-	-	16	2.7 to 11.1	7.4	-	-	-	-
Sinusitis	-	-	-	-	1.4 to 4.2	-	-	-	-	-

Adverse Event(s)	Albuterol*,#	Albuterol†	Albuterol‡	Albuterol¶	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Terbutaline†	Terbutaline§
Throat irritation	-	-	-	10	-	-	-	-	-	-
Turbinate edema	-	-	-	-	1.4 to 2.8	-	-	-	-	-
Upper respiratory tract infection	-	-	-	21	-	-	-	-	-	-
Viral respiratory infection	-	-	-	7	6.9 to 12.3	-	-	-	-	-
Voice alteration	-	-	-	-	-	-	-	-	-	-
Wheezing	-	-	-	-	-	-	-	-	-	-
Other										
Abnormal vision	-	-	-	-	-	-	-	-	-	-
Abscess	-	-	-	-	-	-	-	-	-	-
Accidental injury	-	-	-	-	2.7	9.2	-	-	-	-
Allergic reaction	-	-	0.9 to 3.4	-	-	-	-	-	-	-
Alopecia	-	-	-	-	-	-	-	-	-	-
Anaphylaxis	-	-	-	-	-	-	-	-	-	-
Back pain	-	-	-	4	-	-	-	-	-	-
Blurred vision	-	-	-	-	-	-	-	0.2	-	-
Chattiness	-	-	-	-	-	-	-	0.2	-	-
Chills	-	-	-	-	<2	-	-	0.2	-	-
Cold symptoms	-	-	3.4	-	-	-	-	-	-	-
Conjunctivitis	1	-	-	-	-	<2	-	-	-	-
Digitalis intoxication	-	-	-	-	-	-	-	-	-	-
Dilated pupils	<1	-	-	-	-	-	-	-	-	-
Ear pain	-	-	-	<3	-	<2	-	-	-	-
Ear signs	-	-	-	-	-	-	-	-	-	-
Edema	-	-	-	<3	-	-	-	-	-	-
Emotional lability	1	-	-	-	-	-	-	-	-	-
Eye itch	-	-	-	-	<2	-	-	-	-	-
Fever	-	-	-	6	3.0 to 9.1	-	-	0.4	-	-
Flu syndrome	-	-	2.6	-	1.4 to 4.2	-	-	0.2	-	-
Glaucoma	-	-	-	-	-	-	-	-	-	-
Glossitis	-	-	-	<3	-	-	-	-	-	-

Adverse Event(s)	Albuterol*,#	Albuterol†	Albuterol‡	Albuterol¶	Levalbuterol‡	Levalbuterol¶	Metaproterenol*	Metaproterenol†	Terbutaline†	Terbutaline§
Hernia	-	-	-	-	-	-	-	-	-	-
Hypersensitivity vasculitis	-	-	-	-	-	-	-	-	a	-
Keratitis	-	-	-	-	-	-	-	-	-	-
Lymphadenopathy	-	-	0.9 to 2.6	-	3	-	-	-	-	-
Malaise	-	-	-	-	-	-	a	-	-	-
Neoplasm	-	-	-	-	-	-	-	-	-	-
Otitis media	-	-	0.9 to 4.3	-	-	-	-	-	-	-
Pelvic pain	-	-	-	-	-	-	-	-	-	-
Peripheral edema	-	-	-	-	-	-	-	-	-	-
Retroperitoneal hemorrhage	-	-	-	-	-	-	-	-	-	-
Tonsillitis	-	-	-	-	-	-	-	-	-	-
Trauma	-	-	-	-	-	-	-	-	-	-
Viral infection	-	-	-	-	7.6 to 9.0	<2	-	-	-	-

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

Contraindications/Precautions

All β_2-agonists are contraindicated in patients with a history of hypersensitivity to any components of a particular product.[1-15]

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).[1-15]

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.[1-15]

Immediate hypersensitivity reactions may occur after administration of β_2-agonists as demonstrated by anaphylaxis, urticaria, angioedema, rash and bronchospasm.[1-15]

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.[1-15]

The use of β_2-agonists may produce significant hypokalemia in some patients. The decrease is usually transient.[1-15]

The use of β_2-agonists may aggravate preexisting diabetes mellitus and ketoacidosis and should be used with caution in patients with diabetes.[1-15]

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

Boxed Warning for Terbutaline[13, 14]

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

Drug Interactions

Table 7. Drug Interactions[1-15]

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	Potentiate the cardiovascular effects of β_2-agonists.

Dosage and Administration

Table 8. Dosing and Administration[1-15]

Generic Name	Adult Dose	Pediatric Dose	Availability
Albuterol	Relief of bronchospasm in patients with asthma, treatment or prevention of bronchospasm in patients with reversible obstructive airway disease: Meter dose aerosol inhaler (HFA), dry powder inhaler: 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations/day Solution for nebulization: 2.5 mg TID to QID times daily Sustained-release tablet: 4 to 8 mg BID; maximum, 32 mg/day Syrup, tablet: 2 to 4 mg TID to QID; maximum, 8 mg QID Prevention of exercise-induced bronchospasm: Meter dose aerosol inhaler (HFA), dry powder inhaler: 2 inhalations 15 to 30 minutes before exercise	Relief of bronchospasm in patients with asthma, treatment or prevention of bronchospasm in patients with reversible obstructive airway disease in patients four years of age and older: Meter dose aerosol inhaler (HFA): 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations/day Relief of bronchospasm in patients with asthma, treatment or prevention of bronchospasm in patients with reversible obstructive airway disease in patients two years of age and older: Solution for nebulization: 0.63 to 1.25 mg TID to QID; maximum, 2.5 mg TID to QID Syrup: 2 to 6 years of age: 0.1 mg/kg of body weight TID; maximum, 4 mg TID; 6 to 14 years of age: 2 mg TID to QID; maximum, 24 mg/day Relief of bronchospasm in patients with asthma, treatment or prevention of bronchospasm in patients with reversible obstructive airway disease in patients six years of age and older: Sustained-release tablet: 4 mg BID; maximum, 24 mg/day Tablet: 2 mg TID to QID;	Dry powder inhaler: 90 µg 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

Generic Name	Adult Dose	Pediatric Dose	Availability
		maximum 24 mg/day Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease in patients 12 years of age of or older: Dry power inhaler: 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations/day Prevention of exercise-induced bronchospasm in patients four years of age and older: Meter dose aerosol inhaler (HFA): 2 inhalations 15 to 30 minutes before exercise	
Levalbuterol	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease : Meter dose aerosol inhaler (HFA): 1 to 2 inhalations every 4 to 6 hours Solution for nebulization: 0.63 mg TID every 6 to 8 hours; maximum, 1.25 mg TID	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease in patients four years of age and older: Meter dose aerosol inhaler (HFA): 1 to 2 inhalations every 4 to 6 hours Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease in patients six years of age and older: Solution for nebulization: 0.31 mg TID; maximum, 0.63 mg TID	Meter dose aerosol inhaler (HFA): 59 µg‡ (80 or 200 inhalations) Solution for nebulization: 0.31 mg 0.63 mg 1.25 mg (3 mL vials)
Metaproterenol	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema: Syrup, tablet: 20 mg TID to QID	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema in children six years of age and older (or weight under 60 lbs): Syrup, tablet: 10 mg TID to QID	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg
Terbutaline	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema:	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and	Injection: 1 mg/mL (2 mL vial) Tablet: 2.5 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	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	emphysema: Injection: Safety and efficacy in children less than 12 years of age have not been established. Tablet: 12 to 15 years of age: 2.5 mg TID, 6 hours apart; maximum, 7.5 mg in 24 hours	5 mg

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

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guidelines	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2015)**[19]	Diagnosis · A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking and occupational exposure to dusts/chemicals. · A diagnosis of COPD should be confirmed by spirometry. · COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio. · The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ predicted confirms the presence of airflow limitation that is not fully reversible. · A detailed medical history should be obtained for all patients suspected of developing COPD. · Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications. · Bronchodilator reversibility testing should be performed to rule out the possibility of asthma. · Chest radiograph may be useful to rule out other diagnoses. · Arterial blood gas measurements should be performed in advanced COPD. · Screening for α_1-antitrypsin deficiency should be performed in patients who are from areas with a particularly high prevalence of the deficiency. Typical patients develop COPD at 45 years of age or younger and have lower lobe emphysema. · Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis. Therapeutic options · In patients who smoke, smoking cessation is the intervention with the greatest capacity to influence COPD. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates. · The management of COPD should be individualized to address symptoms and improve the patient's quality of life.

Clinical Guidelines	Recommendations
	· None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. · COPD patients should receive an annual influenza vaccine. · The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years of age or for patients <65 years of age with an FEV_1 <40% of the predicted value. · Patients who get short of breath while walking at their own pace on level ground should be offered rehabilitation. <u>Pharmacologic therapy for stable COPD</u> · Bronchodilators o Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations. o Principle bronchodilators include β_2-agonists, anticholinergics, and theophylline used as monotherapy or in combination. o The use of long-acting bronchodilators is more effective and convenient than short acting bronchodilators. o For single-dose, as needed use, there is no advantage in using levalbuterol over conventional bronchodilators. o Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators and is not recommended if those drugs are available and affordable. · Corticosteroids o Inhaled corticosteroids (ICSs) should be used in patients with an FEV_1 <60% of the predicted value. o Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. · Combination inhaled corticosteroid/ bronchodilator o An inhaled corticosteroid combined with a long-acting β_2-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to very severe COPD. · Nedocromil and leukotriene modifiers have not been adequately tested in COPD patients and cannot be recommended. <u>Management of stable COPD</u> · Identification and reduction of exposure to risk factors are important steps in the prevention and treatment of COPD. All individuals who smoke should be encouraged to quite. · The level of FEV_1 is an inadequate descriptor of the impact of the disease on patients and individualized assessment of symptoms and risk of exacerbation should also be considered. · Pharmacologic therapy is used to reduce symptoms, reduce frequency of exacerbations, and improve health status and exercise tolerance. Existing medications for COPD have not been conclusively shown to modify the long-term decline in lung function. · For both β_2-agonists and anticholinergics, long-acting formulations are preferred over short acting formulations. Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators. · Long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is recommended for patients at high risk of exacerbations.

Clinical Guidelines	Recommendations
	· Long-term monotherapy with oral or inhaled corticosteroids is not recommended in COPD. · The phosphodiesterase-4 inhibitor roflumilast may be useful to reduce exacerbations for patients with FEV_1 <50% predicted, chronic bronchitis, and frequent exacerbations. · Influenza vaccines can reduce the risk of serious illness and death in COPD patients. · Currently, the use of antibiotics is not indicated in COPD, other than for treating infectious exacerbations of COPD and other bacterial infections. <u>Management of exacerbations</u> · The most common causes of an exacerbation are viral upper respiratory tract infections and infection of the tracheobronchial tree. · Short acting inhaled β_2-agonists with or without short acting anticholinergics are usually the preferred bronchodilators for treatment of an exacerbation. · Systemic corticosteroids and antibiotics can shorten recovery time, improve lung function, and reduce the risk of early relapse, treatment failure, and length of hospital stay.
Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2015)**[18]	<u>General principles of asthma management</u> · The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of exacerbations, fixed airflow limitation, and side effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified. · Effective asthma management requires a partnership between the patient/caregiver and their healthcare providers. · Teaching communication skills to healthcare providers and taking into account the patient's health literacy may lead to increased patient satisfaction, better health outcomes, and reduced use of healthcare resources. · Control-based management means that treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk of exacerbations and side effects. · For population-level decisions about asthma management, the 'preferred option' at each step represents the best treatment for most patients, based on group mean data for efficacy, effectiveness, and safety from randomized controlled trials, meta-analyses, and observational studies, and net cost. · For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues. <u>Treatment overview</u> · At present, step 1 treatment is with as-needed short acting $beta_2$ agonist (SABA) alone. However, chronic airway inflammation is found even in patients with infrequent or recent-onset asthma symptoms, and there is a lack of studies of inhaled corticosteroids (ICS) in such populations. · Treatment with regular daily low dose ICS is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization, and death. · For patients with persistent symptoms and/or exacerbations despite low dose ICS, consider step up but first check for common problems such as

Clinical Guidelines	Recommendations
	inhaler technique, adherence, persistent allergen exposure, and comorbidities. o For adults and adolescents, the preferred step-up treatment is combination ICS/long-acting beta$_2$ agonist (LABA). o For adults and adolescents with exacerbations despite other therapies, the risk of exacerbations is reduced with combination low dose ICS/formoterol (with beclomethasone or budesonide) as both maintenance and reliever, compared with maintenance controller plus as-needed SABA. o For children six to 11 years, increasing the ICS dose is preferred over combination ICS/LABA. · Consider step down once good asthma control has been achieved and maintained for about three months to find the patient's lowest treatment that controls both symptoms and exacerbations. o Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit. o Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma. · For all patients with asthma: o Provide inhaler skills training. o Encourage adherence with controller medication, even when symptoms are infrequent. o Provide training in asthma self-management to control symptoms and minimize the risk of exacerbations and need for healthcare utilization. · For patients with one or more risk factors for exacerbations: o Prescribe regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients. o Identify and address modifiable risk factors (e.g., smoking, low lung function). o Consider non-pharmacological strategies and interventions to assist with symptom control and risk reduction. <u>Categories of asthma medications</u> · *Controller medications*: these are used for regular maintenance treatment. They reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and decline in lung function. · *Reliever (rescue medications)*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment. · *Add-on therapies for patients with severe asthma*: these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications and treatment of modifiable risk factors. <u>Stepwise approach for adjusting asthma treatment in adults, adolescents, and children six to 11 years of age</u> · Initial controller treatment: For best outcomes, regular daily controller treatment should be initiated as soon as possible after the diagnosis of asthma is made.

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
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Once treatment has been commenced (see table below), ongoing treatment decisions are based on a cycle of assessment, adjustment of treatment, and review of the response. Controller medication is adjusted up or down in a stepwise approach. Once good asthma control has been maintained for two to three months, treatment may be stepped down in order to find the patient's minimum effective treatment.
If a patient has persisting symptoms and/or exacerbations despite two to three months of controller treatment, assess and correct for the following common problems before considering any step up in treatment:

Incorrect inhaler technique.
Poor adherence.
Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as beta-blockers or (in some patients) non-steroidal anti-inflammatory drugs (NSAIDs).
Comorbidities that may contribute to respiratory symptoms and poor quality of life.
Incorrect diagnosis.

<table>
<tr><th colspan="6">Stepwise approach to control symptoms and minimize future risk</th></tr>
<tr><th></th><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td>Preferred controller choice</td><td></td><td>Low dose ICS</td><td>Low dose ICS/LABA*</td><td>Med/high ICS/LABA</td><td>Refer for add-on treatment (e.g., anti-IgE)</td></tr>
<tr><td>Other controller options</td><td>Consider low dose ICS</td><td>Leukotriene receptor antagonist (LTRA) or low dose theophylline*</td><td>Med/high dose ICS or low dose ICS+LTRA (or + theoph*)</td><td>High dose ICS + LTRA (or + theoph*)</td><td>Add low dose oral corticoste-roids</td></tr>
<tr><td>Reliever</td><td colspan="2">As-needed SABA</td><td colspan="3">As-needed SABA or low dose ICS/formoterol**</td></tr>
<tr><td colspan="6">*For children six to 11 years, theophylline is not recommended, and the preferred Step 3 treatment is medium-dose ICS.
**Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclomethasone/formoterol maintenance and reliever therapy.</td></tr>
</table>

<u>Management of worsening asthma and exacerbations</u>

Exacerbations represent an acute or sub-acute worsening in symptoms and lung function from the patient's usual status, or in some cases, the initial presentation of asthma.
Patients who are at an increased risk of asthma-related death should be identified and flagged for more frequent review.
The management of worsening asthma and exacerbations is part of a continuum, from self-management by the patient with a written asthma action plan, though to management of more severe symptoms in primary care, the emergency department, and the hospital.
All patients should be provided with a written asthma action plan appropriate for their level of asthma control and heath literacy, so they know how to recognize and respond to worsening asthma.

The action plan should include when and how to change reliever and controller medications, use oral corticosteroids, and access medical care if symptoms fail to respond to treatment.
Patients who deteriorate quickly should be advised to go to an acute care facility or see their doctor immediately.

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Clinical Guidelines	Recommendations
	o The action plan can be based on changes in symptoms or (in adults) peak expiratory flow. · For patients presenting with an exacerbation to a primary care or acute care facility: o Assessment of exacerbation severity should be based on the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation, and lung function, while starting SABA and oxygen therapy. o Immediate transfer should be arranged to an acute care facility if there are signs of severe exacerbation, or to intensive care if the patient is drowsy, confused, or has a silent chest. While transferring the patient, SABA therapy, controlled oxygen, and systemic corticosteroids should be given. o Treatment should be started with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer), early introduction of oral corticosteroids, and controlled flow oxygen if available. Response should be reviewed after one hour. o Ipratropium bromide treatment is recommended only for severe exacerbations not responding to initial treatment. o Chest X-ray is not routinely recommended. o Decisions about hospitalization should be based on clinical status, lung function, response to treatment, recent and past history of exacerbations, and ability to manage at home. o Before the patient goes home, ongoing treatment should be arranged. This should include starting controller treatment or stepping up the dose of existing controller treatment for two to four weeks, and reducing reliever medication to as-needed use. · Antibiotics should not be routinely prescribed for asthma exacerbations. · Arrange early follow-up after any exacerbation, regardless of where it was managed. o Review the patient's symptom control and risk factors for further exacerbations. o For most patients, prescribe regular controller therapy to reduce the risk of further exacerbations. Continue increased controller doses for two to four weeks. o Check inhaler technique and adherence. <u>Children five years and younger: assessment and management</u> · The goals of asthma management in young children are similar to those in older patients: o To achieve good control of symptoms and maintain normal activity levels. o To minimize the risk of asthma flare-ups, impaired lung development, and medication side effects. · Wheezing episodes in young children should be treated initially with inhaled SABAs, regardless of whether the diagnosis of asthma has been made. · A trial of controller therapy should be given if the symptom pattern suggests asthma and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe. · Response to treatment should be reviewed before deciding whether to continue it. If no response is observed, consider alternative diagnosis. · The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with a face mask for <4 years and mouthpiece for most four to five

Clinical Guidelines	Recommendations

year olds.

- Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children.

Stepwise approach to long-term management of asthma in children 5 years and younger				
	Step 1	**Step 2**	**Step 3**	**Step 4**
Preferred controller choice		Daily low dose ICS	Double 'low dose' ICS	Continue controller & refer for to specialist
Other controller options		Leukotriene receptor antagonist (LTRA) Intermittent ICS	Low dose ICS + LTRA	Add LTRA ↑ ICS frequency Add intermitt ICS
Reliever	As-needed SABA (all children)			

Consider this step for children with:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern consistent with asthma and asthma symptoms not well-controlled or ≥3 exacerbations per year	Asthma diagnosis, and not controlled on low dose ICS	Not controlled on double ICS
		Symptom pattern not consistent with asthma but wheezing episodes occur frequently, e.g. every 6 to 8 weeks. Give diagnostic trial for 3 months	First check diagnosis, inhaler skills, adherence, exposures	

<u>Management of worsening asthma and exacerbations in children five and younger</u>

- Early symptoms of exacerbations in young children may include increased symptoms, increased coughing (especially at night), lethargy or reduced exercise tolerance, impaired daily activities including feeding, and a poor response to reliever medication.
- Give a written asthma action plan to parents of young children with asthma so they can recognize a severe attack, start treatment, and identify when urgent hospital treatment is required.
  - Initial treatment at home is with inhaled SABA, with review after one hour or earlier.
  - Parents/carers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is worsening, especially in children less than one year of age.
  - Medical attention should be sought on the same day if inhaled SABA is needed more often that 3-hourly or for more than 24 hours.
  - There is only weak evidence to support patient-initiated oral corticosteroids.
- In children presenting to primary care or an acute care facility with an asthma exacerbation:
  - Assess severity of the exacerbation while initiating treatment with SABA (two to six puffs every 20 minutes for first hour) and oxygen (to maintain saturation 94 to 98%).
  - Recommend immediate transfer to hospital if there is no response to inhaled SABA within one to two hours; if the child is unable to speak or drink or has subcostal retractions or cyanosis; if resources are lacking in the home; or if oxygen saturation is <92% on room air.
  - Give oral prednisone/prednisolone 1 to 2 mg/kg/day for up to five days, up to a maximum of 20 mg/day for 0 to 2 years, and 30 mg/day for 3 to 5 years.

Clinical Guidelines	Recommendations
	o Children who have experienced an asthma exacerbation are at risk of further exacerbations. Follow up should be arranged within one week of an exacerbation to plan ongoing asthma management.
The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: **Guidelines for the Diagnosis and Management of Asthma (2007)**[17]	<u>Diagnosis</u> · To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction and alternative diagnoses must be excluded. · The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility and additional studies to exclude alternative diagnoses. · A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections and symptoms that occur or worsen at night. · Spirometry is needed to establish a diagnosis of asthma. · Additional studies such as pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. <u>Treatment</u> · Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations and reverse airflow obstruction. · The initial treatment of asthma should correspond to the appropriate asthma severity category. · Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. · Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing. · Quick relief medications include SABAs, anticholinergics and systemic corticosteroids. <u>Long-term control medications</u> · ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. · Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma. · When patients ≥12 years of age require more than a low-dose ICS, the addition of a LABA is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton. · Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventatively prior to exercise or unavoidable exposure to known allergens. · Omalizumab, an immunomodulator, is used as adjunctive therapy in patients 12 years of age and older who have allergies and severe persistent

<table>
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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 is a long-acting inhaled anticholinergic indicated once-daily for COPD and has not been studied in the long-term management of asthma.

<u>Quick-relief medications</u>
· 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.

<u>Assessment, treatment and monitoring</u>
· A stepwise approach to managing asthma is recommended to gain and maintain control of asthma.
· Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control.
· The stepwise approach for managing asthma is outlined below:
<table>
<tr><th>Inter-mittent Asthma</th><th colspan="5">Persistent Asthma: Daily Medication</th></tr>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th><th>Step 6</th></tr>
<tr><td><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>
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Clinical Guidelines	Recommendations
	Management of exacerbations · Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended. Special populations · For exercise-induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. Leukotriene receptor antagonists may also attenuate exercise-induced bronchospasm, and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention; however, they are not as effective as SABAs. · The addition of cromolyn to a SABA is helpful in some individuals who have exercise-induced bronchospasm. · Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery. · Albuterol is the preferred SABA in pregnant women because of an excellent safety profile. · ICSs are the preferred treatment for long-term control medication in pregnant women. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.
National Institute for Health and Clinical Excellence: **Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)**[20]	Diagnosis · Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze. · The primary risk factor is smoking. · Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1 <80% predicted and FEV_1/FVC <70%. Treatment · Smoking cessation should be encouraged for all patients with COPD. · Short acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation. · Long-acting bronchodilators (β_2 agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators. · Once-daily long-acting anticholinergic antagonists are preferred compared to four-times-daily short-acting anticholinergic antagonists in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with an anticholinergic antagonist. o FEV_1 ≥50% predicted: LABA or long-acting anticholinergic antagonist. o FEV_1 < 50% predicted: either LABA with an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist. · In patients with stable COPD and FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist when ICSs are not tolerated or declined. · Consider a long-acting anticholinergic antagonist in patients remaining breathless or having exacerbations despite therapy with LABA and ICSs

Clinical Guidelines	Recommendations
	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. <u>Management of exacerbations</u> · Patients with exacerbations should be evaluated for hospital admission. · Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial. · Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. · Oxygen should be given to maintain oxygen saturation above 90%. · Patients should receive invasive and noninvasive ventilation as necessary. · Respiratory physiotherapy may be used to help remove sputum. · Before discharge, patients should be evaluated by spirometry. · Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.

Conclusions

Respiratory short acting β_2-agonists are Food and Drug Administration (FDA)-approved for the prevention and treatment of bronchospasm associated with acute asthma exacerbations or other reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm. These agents are available in a variety of dosage forms, including solution for nebulization, aerosol 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. The short acting β_2-agonists are generally dosed multiple times per day for the relief of asthma related symptoms.[1-15]

Current clinical guidelines for the treatment of asthma and COPD state that SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations.[17-20] 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 National Heart, Lung, and Blood Institute (NHLBI), the use of LABAs to treat acute symptoms or exacerbations of asthma is not recommended.[17] Overall, short acting β_2-agonists have demonstrated similar efficacy and safety.[26-38]

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